eISSN 2255-0569

ORIGINAL

The effect of inflammation in MIA-induced osteoarthritis on physiological cardiovascular function in male rats

El efecto de la inflamación en la osteoartritis inducida por MIA sobre la función cardiovascular fisiológica en ratas macho

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Received: 19 - VII - 2021
Accepted: 22 - VII - 2021

doi: 10.3306/AJHS.2021.36.04.88

Abstract

This study investigates the effect of inflammation in MIA-induced osteoarthritis on cardiovascular physiological function in male rats Osteoarthritis (OA) is the most common joint disease in adults worldwide and osteoarthritis of the knee is the most common type. The most common symptom of osteoarthritis is joint pain. Osteoarthritis is a common degenerative disorder of articular cartilage, accompanied by hypertrophic changes in the subchondral bone, which causes inflammation of the surrounding tissues. Studies have shown that systemic and chronic inflammation can increase the risk of cardiovascular disease. Because synovial inflammation is involved in the early stages of OA, one of the side effects of OA is CVD. OA is associated with mild to moderate pain symptoms and the first line of treatment for this disease is the use of nonsteroidal anti-inflammatory drugs (NSAIDs) such as celecoxib. However, the dangerous side effects of NSAIDs in the development of cardiovascular disease in these individuals limit the long-term use of NSAIDs. Using alternative methods such as the use of herbs can prevent side effects. Among these plants is Papaver rhoeas with the scientific name (Papaver rhoeas L.) which has anti-inflammatory properties and is effective in vascular congestion.

Keywords: Papaver rhoeas, osteoarthritis, inflammation, cardiovascular disease, celecoxib.

Resumen

Este estudio investiga el efecto de la inflamación en la osteoartritis inducida por MIA sobre la función fisiológica cardiovascular en ratas macho. La osteoartritis (OA) es la enfermedad articular más común en adultos en todo el mundo y la osteoartritis de rodilla es el tipo más común. El síntoma más común de la osteoartritis es el dolor articular. La osteoartritis es un trastorno degenerativo común del cartílago articular, acompañado de cambios hipertróficos en el hueso subcondral, que causa inflamación de los tejidos circundantes. Los estudios han demostrado que la inflamación sistémica y crónica puede aumentar el riesgo de enfermedad cardiovascular. Debido a que la inflamación sinovial está involucrada en las primeras etapas de la OA, uno de los efectos secundarios de la OA es la ECV. La OA se asocia con síntomas de dolor leve a moderado y la primera línea de tratamiento para esta enfermedad es el uso de medicamentos antiinflamatorios no esteroideos (AINE) como celecoxib. Sin embargo, los peligrosos efectos secundarios de los AINE en el desarrollo de enfermedades cardiovasculares en estas personas limitan el uso a largo plazo de los AINE. El uso de métodos alternativos, como el uso de hierbas, puede prevenir efectos secundarios. Entre estas plantas se encuentra la anémona silvestre de nombre científico (Papaver rhoeas L.) que tiene propiedades antiinflamatorias y es eficaz en la congestión vascular.

Palabras clave: Extracto acuoso alcohólico de anémona salvaje, osteoartritis, inflamación, enfermedad cardiovascular, celecoxib.

Introduction

New evidence suggests that inflammation is a major mediator of joint pathology in osteoarthritis and that NF κ-B signaling pathway regulation plays an important role in causing this inflammation[1&2]. The proinflammatory cytokines involved in osteoarthritis are TNF-α and β1-IL, which are considered to be the main problem[3]. TNF-α, which is derived from damaged endothelial cells, also causes inflammation in the walls of blood vessels and regulates leukocyte activity, leading to the maturation and release of cytokines and chemokines[4]. On the other hand, there is a lot of evidence that inflammatory markers play an important role in the formation of atherogenesis and arterial thrombosis. Studies have also shown that systemic inflammation can increase the risk of CVD. Chronic inflammation is another risk factor for CVD. 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[5]. Because synovial inflammation is involved in the early stages of OA, one of the side effects of OA is CVD[6]. Cardiovascular diseases include ischemic heart disease, congestive heart failure, transient ischemic attacks, and stroke[7].Several studies have shown that the inflammatory reflex is associated with an increased risk of atherosclerosis 8. Epidemiological studies have also shown an association between increased levels of inflammatory markers and a high prevalence of CVD9.

Steroid anti-inflammatory drugs, including cyclooxygenase 2 inhibitors (celecoxib or celebrex), which are recommended as first-line treatment for OA, are associated with an increased risk of CVD. Study in 2014 found that taking NSAIDs increases the risk of myocardial infarction, stroke, hypertension, heart failure, and atrial fibrillation10. To date, much information has been obtained about the cardiovascular toxicity of NSAIDs, and often conflicting results have been obtained, especially for aspirin and naproxen, as well as similar results for patients taking ibuprofen[11&12]. To date, clinical research on the effect of NSAIDs in patients with cardiovascular disease has been limited to experimental studies with flurbiprofen, meloxicam, and parecoxib / valdecoxib.

The mechanism of cardiovascular effects of aspirin, naproxen and other non-selective NSAIDs and COX-2 inhibitors is still debated. Although non-selective NSAIDs inhibit both COX-1 and COX-2, selective COX-2 inhibitors, including lumiracoxib, have no effect on COX-1 at therapeutic concentrations. The initial hypothesis explaining the increased risk of cardiovascular disease associated with COX-2 inhibitors is that the inhibitor of this enzyme causes an imbalance resulting in platelet aggregation due to COX-1, while in COX-2-dependent prostacyclin is inhibited by endothelial cells that can affect blood vessels[13].

Inhibition of COX by NSAIDs reduces the effect of systemic vasodilation on prostaglandins such as PG I2, PG E2, and group (CINOD), which are prescribed to treat patients with OA and are more widely used to reduce the complications of CVD than NSAIDs.[14] Extensive clinical and experimental evidence suggests that NSAIDs and COX-2 inhibitors may cause vasoconstriction[15]. Due to the tendency of people to use herbal medicines and also to reduce the cardiovascular effects of OA chemotherapy drugs, so the use of alternative methods such as the use of medicinal plants seems necessary, including Papaver rhoeas plants. Papaver rhoeas (scientifically named Papaver rhoeas L.) is a dark poppy plant 77 and has a variety of alkaloids and has a family affinity and similar effects with poppy[16]. Due to the very small amounts of morphine in the extract of this plant, it is called “harmless opium”[17]. So far, various medicinal properties of this plant have been reported.

The active ingredients in Papaver rhoeas cracking include: papaverine, radin, radic acid, papauric acid[18], roagenin and anthocyanin. Papaverine is one of the opium alkaloids that is used in the treatment of clogged arteries, especially the coronary arteries. It has also been used in a wide range of treatments for diseases such as inflammation[18], labor pain and pain relief and as a sedative and sedative. In addition, it is useful in the treatment of urinary incontinence and pruritic fever[19]. Another major herb is anthocyanin, which has the ability to reduce the risk of CVD[20] and to improve platelet function and antithrombotic effects. Endothelial dilation, improvement of arterial stiffness and protective effect on the heart[21] by suppressing hypertrophy Phosphorylation of protein kinase C and activation of Akt protein kinase B. Study in 2017 also showed that anthocyanins have anti-inflammatory properties, and high anthocyanin consumption is associated with decreased levels of proinflammatory cytokines, such as C-reactive protein (CRP) and the regulation of inflammatory mediators. Other effects of anthocyanins on inflammation include:[22]. The effect of cholinergic and nitrogenic systems in osteoarthritis is as follows.

Because acetylcholine (Ach), the main neurotransmitter of the vagus nerve, is a major mediator of the cholinergic anti-inflammatory pathway and nicotinic receptor α7 (α7nAChR) is present in the synovial tissue of the knee joint of patients with OA, local acetylcholine production can be used to regulate arthritis. Attributed to the cholinergic anti-inflammatory pathway which inhibits the production of inflammatory cytokines, such as IL-6, TNF-α, and the matrix metalloproteinase 9[23].

Stimulation of articular chondrocytes by IL-1β or TNF-α to transmit NF-κB p65 nucleus also includes a wide range of

catabolic genes such as nitric oxide synthase (iNOS) and COX-2 in chondrocytes, which lead to the production of proteases. Destructive attenuation of the extracellular matrix[24] However, studies have shown that systemic treatment with nicotine agonists reduces the severity and prevalence of osteoarthritis in mice. The most important effect of the cholinergic system in the circulatory system is the regulation of heart rate, which is applied through the parasympathetic fibers in the vagus nerves, which significantly reduces the heart rate and reduces the contractile strength of the heart. Acetylcholine released from nerve terminals by M2 muscarinic receptors opens a bunch of potassium channels and increases potassium excretion and hyperpolarization of nodes that produce action potential in the heart. The cholinergic system does not expand much in the arteries, and in the skeletal muscle and coronary arteries of the endocrine vessels, it causes a nitric oxide-dependent relaxant effect[25].

Preparation and maintain of rats

The present study is experimental and of a fundamental type. In this study, according to the regulations of the Medical Ethics Committee, 70 adults male Wistar rats in 14 groups of 5 with a weight range of 100 to 200 grams were purchased from Razi Serum Institute of Shiraz. In the animal house of Shiraz University, Faculty of Science, under light-controlled conditions, the dark cycle of light and food was maintained so that 12 hours before the start of the experiment, their access to food was cut off but they had free access to water.

Preparation of extract

First of all the leaves of Papaver rhoeas, Osteoarthritis, Inflammation, Cardiovascular Disease, Celecoxibwere collected from the cities around Shiraz and transferred to the Faculty of Science by the professor of botany of the Faculty of Science of Shiraz University, were scientifically identified. Then the collected plant was healthy in a shady environment without dry moisture and by Electric powder mill was transferred to human 1800 ml to prepare the extract and then enough 70% ethanol was added to it and it remained in the same condition for 12 hours. After 12 hours, the solution was filtered on the surface of the powder with a funnel filter paper and transferred to Petri dishes and placed in an incubator at 37°C for 12 hours to dry completely and become a powder.

Preparation of extract in oral and injectable groups

For this purpose, first the required dose for each mouse was calculated according to its weight. The weight calculated by the scales was then weighed, then 300 µl of solvent was added and dissolved on a vortex machine. In the oral groups, the extract at doses of 100, 200 and 400 mg / kg was given to the animal by gavage for 2 weeks, and in the injected groups, the extract was injected through a venous cannula on the day of surgery.

Osteoarthritis Induction Method

The animal was initially anesthetized by intraperitoneal injection of urethane (1.2 mg / kg) and osteoarthritis was induced in the knee joint of 35 30-day-old rats injected with monosodium iodoacetate (MIA; sigma-ALDRICH, USA). For this purpose, first the animal's right knee joint was sterilized with 100% ethanol and after induction of cartilage defect by injecting 1 mg of monosodium iodostat in 50µL (as a single dose containing 1 mg of MIA in 0.9% saline) by a The G 27 sterile needle was inserted into the longitudinal groove of the right knee joint at maximum flexion. Of course, in situations where no damage was done to the subchondral bone[26].

Surgical protocol and prescription of drugs

Thirty days after the MIA injection, animals whose access to food but had free access to water were excluded 12 hours before the start of the experiment. The surgical procedures are as follows: Each animal in the experimental groups was anesthetized by intraperitoneal injection of urethane (1.2 mg / kg) and then a tracheostomy was performed to prevent aspiration and suffocation during anesthesia. Cannulation was performed to access the femoral arteries. The venous cannula was used for injections during the test and the arterial cannula was connected to the power lab, which recorded the mean arterial pressure, systolic pressure, diastolic pressure, and heart rate as follows:

Prescription of Drugs

After surgery, the animal was rested for one hour to relieve the effects of surgical stress and keep the animal in a stable position. A total of 70 adult male Wistar rats were randomly divided into 14 groups of 5 with a weight range of 150-100 g and in all groups, cardiac parameters were recorded and then blood plasma of all samples for troponin, Tnf-alfa and CK was collected.

Group receiving injectable and oral extract of Papaver rhoeas

In the injection group: At first, the blood pressure of the animals in this group was recorded for 30 minutes without receiving any treatment. Then 300 µl of solvent extract was injected intravenously over 15 seconds and blood pressure was recorded. After blood pressure returned to normal, 300 µl of Papaver rhoeas, Osteoarthritis, Inflammation, Cardiovascular Disease, Celecoxibextract

at a dose of 2 mg / kg (equivalent to 0.005 gr / kg of extract powder), dose of 5 mg / kg (equivalent to 0.01 g / kg of extract powder), dose of 10 mg / kg (equivalent 0.025 extract powder) and a dose of 25 mg / kg (equivalent to 0.07 g / kg extract powder) were injected and blood pressure was recorded.

In the oral group: After creating the OA model (by MIA injection), Papaver rhoeas extract was gavaged for two weeks, so that in the experimental groups, different doses of Papaver rhoeas extract were 100 mg / kg (equivalent to 0.23 gr / kg). Extract powder), dose 200 mg / kg (equivalent to 0.46 g / kg extract powder), dose 400 mg / kg (equivalent to 0.1 g / kg extract powder) and in the positive control group, Celebrex (10 mg / kg) in 300 microliters of solvent (water and alcohol Percent 70) Was dissolved and given to the animals by gavage. Blood pressure was recorded on day 30 similar to the injection group.

Measuring research variables

How to measure blood pressure changes

For this purpose, cannulation was performed to access the femoral arteries. The venous cannula was used for injections during the experiment and the arterial cannula was connected to the power lab, which recorded the mean arterial pressure, systolic, diastolic and heart rate. This device is equipped with an A-to-D system that converts and records analog data into numbers.

Method of measuring the weight of a mouse foot

Measure the volume of edema by placing the right foot (with OA by injection of MIA and the left foot (healthy) of the animal up to the wrist (to measure the difference in weight between the two feet) in a water container placed on a scale and record the weight of the rat's foot in Days (1,7,14,21,28) (Xu.et al, 2017) and the weight distribution of rats were calculated

Method of measuring knee thickness

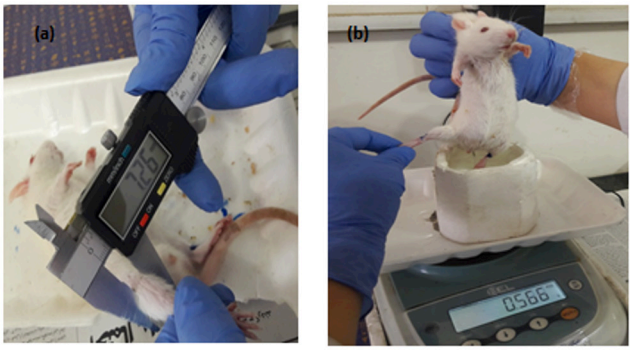
Knee thickness in rats with osteoarthritis was assessed using a caliper with an accuracy of 0.02 mm and was evaluated on days (1,7,14,21,28). According to Janet's description, the animal's knee diameter was scored this way.

1 / 0-2 mm score (01)
1 / 2-0 / 4 score (02)
1 / 4-6 score (03)
1 / 6-8 score (04) (Janet et al., 2004)

Creatine kinase (ck) measurement method

ELISA Kits were used to analyze creatine kinase (coat number: CUBEK06774). CK enzyme contains CK-M isoenzyme, which produces CK-MB and CK-MM isoenzymes. Measurement of CK-MB activity is a test. It is completely dedicated to diagnosing heart muscle damage and thus diagnosing and evaluating a heart attack.
TNF-α: A cytokine is a polypeptide made by monocytes

Figure 1: a) Measurement of rat knee thickness b) Weight measurement of rat foot with osteoarthritis.



and macrophages. This factor plays an important role in many diseases, including inflammatory diseases. The body responds to stimuli such as infection or tissue damage. This factor creates inflammation and this factor leads to the activation of neutrophils and changes in the permeability of vascular endothelial cells. To measure TNF-α by ELISA solid phase sandwich method 1 and the kit made by the French company Diaclone (coat number: 872.010 .001) was used.

Troponin measurement method

ELISA Kits (coat number: MBS727624) were used for troponin analysis.

Information analysis method

Data were analyzed using SPSS software using Independent T-test to examine the differences between groups and Paired sample T-test to examine the differences between different stages of a group with $p < 0.05$ as a significant level. Was analyzed.

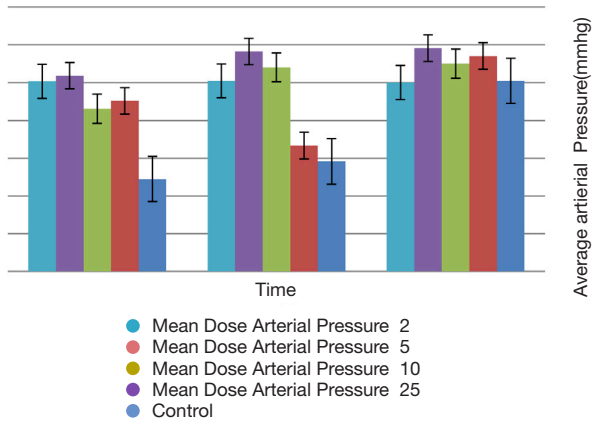
Research Findings

In this study, in order to evaluate the obtained data, first the initial results of the data have been reported through statistical indices of mean and standard deviation of mean. Through one-way analysis of variance and pairwise comparison tests by LSD method, we investigated the differences between the experimental groups. Significance level was considered $P < 0.05$ and all statistical methods were performed using SPSS software version 19.

Hypothesis 1
Determining the effective dose of Papaver rhoeas extract injection:

Mean arterial pressure in response to different doses of Papaver rhoeas extract in both control and experimental groups in the injection group (doses 2, 5, 10 and 25 mg / kg) As shown in Chart 1, among the different doses tested, in response to the injected extract at a dose of 5 mg / kg, the fastest arterial pressure drop was observed, which returned to the optimal position compared to the control group over time.

Figure 2: Comparison of mean arterial pressure changes (Beat / min) in response to different doses of Papaver rhoeas extract in the injected group compared with the control group. a indicates a significant difference between the extract group and the control group and control P = 0.000. b indicates no significant difference between control and control group P≤0.05.



Hypothesis 2
Cardiovascular effect of effective dose of Papaver rhoeas injectable extract:

Mean arterial pressure, systolic, diastolic and heart rate in the presence of 5 mg / kg injection of Papaver rhoeas extract. According to Chart 2 and 3, in the group receiving Papaver rhoeas extract, systolic, diastolic pressure and mean arterial pressure in the experimental mode were significantly reduced compared to the control and control modes.

Figure 3: Mean arterial pressure, systolic, diastolic and heart rate in the presence of 5 mg / kg injection of Papaver rhoeas extract. According to Chart 2 and 3, in the group receiving Papaver rhoeas extract, systolic, diastolic pressure and mean arterial pressure in the experimental mode were significantly reduced compared to the control and control modes.

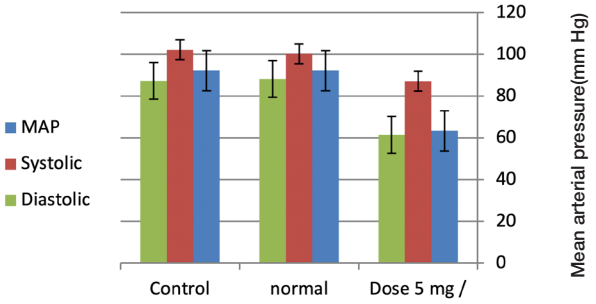
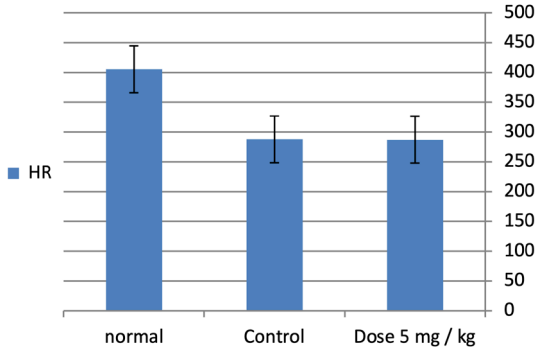


Figure 4: Comparison of heart rate in control, solvent and 5 mg / kg dose groups of Papaver rhoeas extract injection. a indicates a significant difference between the group receiving the extract and the control group and control P = 0.000
b indicates no significant difference between control and control group P≤0.05.



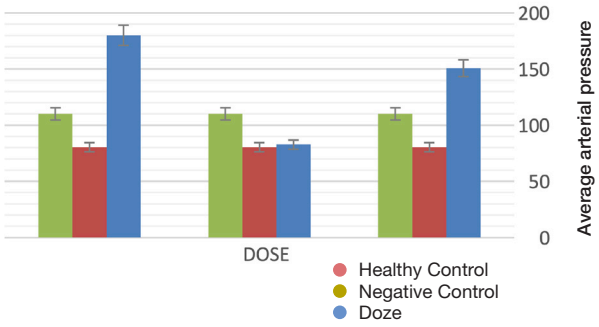
Discussion

Hypothesis 1: Determining the effective dose of oral extract of Papaver rhoeas.

Mean arterial pressure in response to different doses of Papaver rhoeas extract in both control and experimental groups in the oral group (200, 100 and 400) mg/kg

As shown in **Figure 5**, between different doses tested, the mean arterial pressure in response to the oral extract at a dose of 200 mg / kg had a significant decrease compared to the negative control group and doses of 100 and 400 (mg/kg).

Figure 5: Comparison of changes in blood pressure in response to different doses of Papaver rhoeas extract in the oral group compared with the control and negative control groups. a: Indicates a significant difference between the experimental and negative control groups P <0.05
b: Indicates the difference in meaning between in the experimental and healthy control groups P <0.05.



Hypothesis 2: Cardiovascular effects of oral anemone extract

Systolic, diastolic pressure, mean artery and heart rate in the presence of 200 mg / kg oral extract of Papaver rhoeas. As you can see in **table I**, mean arterial mean pressure, systolic pressure, and diastolic pressure are significantly lower in the 200-dose group compared with the orthosis or OA (negative control) group. Also, all parameters of mean arterial pressure, systolic pressure, diastolic pressure and heart rate (**Figure 6**) increased in the negative control group compared to the control group.

Figure 6: Comparison of systolic and diastolic blood pressure and mean arterial pressure (mmHg) of control, solvent and 200 mg/kg dose groups of injected Papaver rhoeas extract

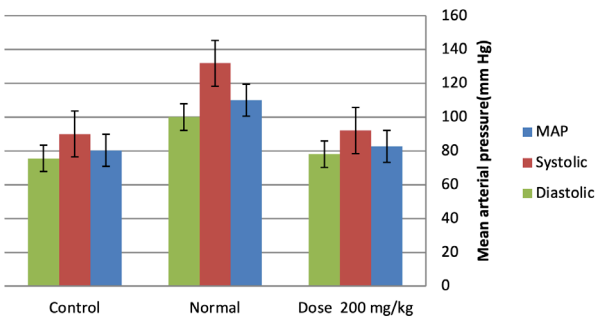


Table I: Comparison of systolic, diastolic blood pressure and mean arterial pressure (mmHg), heart rate (Beat / min) in control groups (healthy), with (negative control) and rats with OA receiving a dose of 200 oral anemone extract Papaver rhoeas (N = 5)
a: shows a significant difference between the negative control group and the control group P <0.05
b: shows a significant difference between the 200-dose group and the negative control group P <0.05.

Parameters / Group	Heart beat	Average arterial pressure	Systolic pressure	Diastolic pressure
Control	364.39±25.81	110.07±5.75	131.9±4.76	100.10±3.88
With OA (negative control)	364.39±12.41	110.07±5.46	131.9±5.55[a]	100.10±4.88
	316.97±27.21	82.75±7.36[b]	92.09±5.44[b]	78.09±3.88

The Effect of Papaver rhoeas on the Improvement of Cardiovascular Complications Caused by Osteoarthritis

Measurement of Rat knee Diameter and Weight

The effect of Celebrex and oral extract of Papaver rhoeas at a dose of 200 mg / kg on knee inflammation has been investigated in **table II**.

According to the table, rat knee diameter (right foot) in the experimental group receiving Celebrex

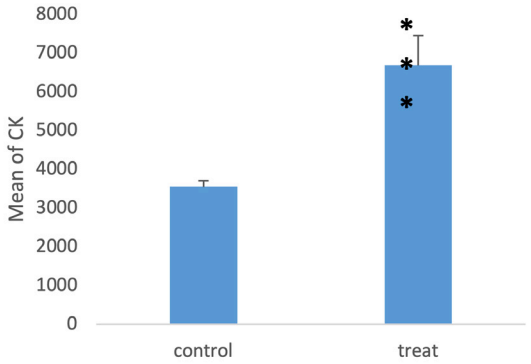
From day 1 to day 14 and then on day 21 compared to the control group (left foot) had a similar amount. And rat knee weight from day 1 to 7 and then on day 14 had a similar amount compared to the control group.

Creatine Kinase (CK) Assay Results

To measure the level of creatine kinase (CK) in rat serum according to different concentrations of standard solutions and their absorption, draw a standard diagram and then using a standard diagram (**Figure 7**), the concentration (CK) of each the sample was identified using its adsorption rate.

The mean of the control group was 3552.17 2. 162.331 and the mean of the experimental group was 6691.8 76 766.025 and the independent t-test in unequal variance showed that the difference between the mean observed between the two groups was significant (p = <0.0001) Has increased significantly.

Figure 7: Standard curve of creatine kinase



TNF-α assay results

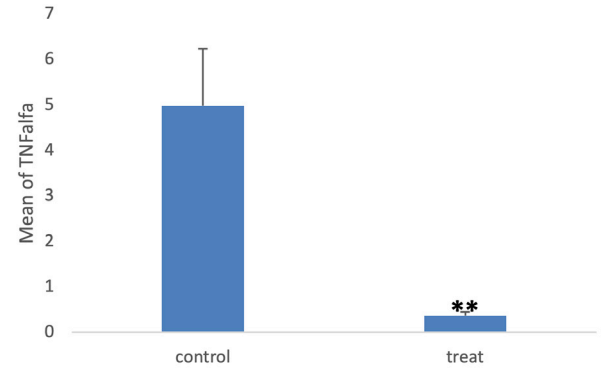
To measure the amount of TNF-α in the rat knee joint according to the different concentrations of standard solutions and their absorption, draw a standard diagram and then using a standard diagram (**Figure 8**), the concentration of TNF-α for each sample using Its absorption was determined.

The mean of the control group was 4.98 1. 1.25 and the mean of the experimental group was 0.085 ± 0.364 and the independent t-test in unequal variance showed that the mean difference between the two groups was significant (p <0.0001) Significance has decreased. (**Figure 9**).

Table II: Table of diameter and weight of rat knee in Celebrex group and dose 200 mg / kg
Paired t-test results were used for all comparisons.
a: Indicates significant difference between right and left foot diameters, P <0.05
b: Indicates significant difference between right and left foot weights, P <0.05

Group		Day	-1	1	7	14	21
Control	(ml) Knee diameter	right left	6.05±0.40 6.03±0.26	6.08±0.31 6.03±0.16	6.04±0.33 6.07±0.15	6.03±0.20 6.04±0.10	6.04±0.28 6.01±0.14
	Weight of Knee	right left	1.49±0.50 1.44±0.33	1.47±0.44 1.48±0.34	1.44±0.33 1.44±0.31	1.48±0.31 1.42±0.41	1.46±0.33 1.43±0.44
Arthritis control	Weight of Knee (ml)	right left	6.05±0.40 6.03±0.26	6.08±0.31 6.03±0.16	6.04±0.33 6.07±0.15	6.03±0.20 6.04±0.10	6.04±0.28 6.01±0.14
	Weight of Knee	right left	1.49±0.50 1.44±0.33	1.47±0.44 1.48±0.34	1.44±0.33 1.44±0.31	1.48±0.31 1.42±0.41	1.46±0.33 1.43±0.44
Selberks	(ml) Knee diameter	right left	6.08±0.21 6.09±0.22	6.16±0.30[a] 6.08±0.17	7.01±0.30[a] 6.35±0.14	6.86±0.22[a] 6.34±0.13	6.23±0.26 6.21±0.15
	Weight of Knee	right left	1.46±0.34[b] 1.45±0.44	1.47±0.54[b] 1.49±0.54	1.73±0.43 1.54±0.41	1.82±0.41 1.62±0.40	1.64±0.43 1.49±0.42
200 Doze/kg	(ml) Knee diameter	right left	6.10±0.33 6.08±0.26	6.19±0.20 6.09±0.27	7.14±0.25 6.30±0.27	6.79±0.22 6.31±0.26	6.47±0.19 6.13±0.25
	Weight of Knee	right left	1.48±0.54[b] 1.36±0.04	1.48±0.40 1.35±0.18	1.79±0.37 1.46±0.17	1.81±0.37 1.52±0.19	1.60±0.38 1.44±0.18

Figure 8: TNF assay results

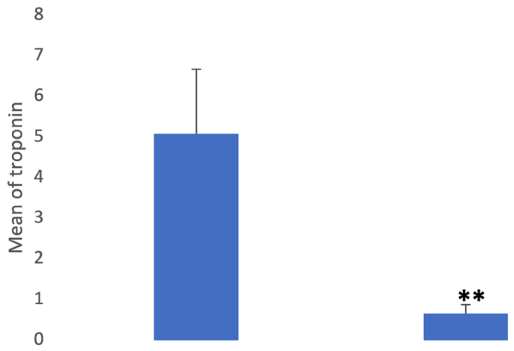


8. Tropenin assay results

To measure the amount of troponin in the rat knee joint according to different concentrations of standard solutions and their absorption, draw a standard diagram and then using a standard diagram (**Figure 9**), the concentration of troponin for each sample using its absorption was found.

The mean of the control group was 5.08 1.5 1.592 and the mean of the experimental group was 0.223 ± 0.651 and the independent t-test in unequal variance showed that the mean difference between the two groups was significant (p = 0.018) and the amount of troponin in the experimental group was significant. Significance has decreased.

Figure 9: Troponin assay results



Conclusion

The results of this study showed that Papaver rhoeas extract can significantly inhibit the OA process in rats with arthrosis of monosodium iodostat (especially at a dose of 200 mg/kg) and reduce edema and foot weight in infected rats. Oral extract of Papaver rhoeas showed that anthocyanin (active substance in Papaver rhoeas) had an anti-inflammatory effect through the mechanism of action in inhibiting the activity of inflammatory cells and proinflammatory cytokines in monosodium iodoacetate mice. Also, the decrease in creatine kinase-MB level in coronary fluid in the group receiving Papaver rhoeas confirms that the presence of anthocyanin can reduce the risk of CVD and cause endothelial dysplasia and by increasing the phosphorylation of hypertrophy protein kinase C and activation of protein kinase B Improves vascular stiffness, which has a protective effect on the heart. since the Papaver rhoeas used in this study has been shown in previous studies to significantly reduce the proliferation of monkey kidney cancer cell line (IC50 7.80 = µg / ml) and the effect of extract inhibition on DPPH radical (74.7) 5 µg / ml) The extract also had a phenolic content higher than the flavonoid content, which makes its use relatively safe. On the other hand, hypertension (moderate arterial pressure, systolic and diastolic pressure) can be related to vagal nerve activity, which causes There is a significant reduction in heart rate and decreased contractile strength of the heart[9]. Also, the serological findings of the present study showed that troponin levels decreased with the consumption of Papaver rhoeas. On the other hand, acetylcholine released from nerve terminals through muscarinic M2 receptors causes the opening of a group of potassium channels and increases potassium outflow and hyperpolarization of nodes that produce action potential in the heart. There is also a nicotinic receptor (α7 (α7nAChR) in synovial tissue. It has been shown for synovial tissue in the knee joint of patients with OA that it can produce local acetylcholine in arthritis attributed to the cholinergic system[27]. Which inhibits the production of inflammatory cytokines[23&28].

Stimulation of articular chondrocytes by IL-1β or TNF-α to transport p65 NF-κB nuclei also involves a wide range of catabolic genes such as nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2) in chondrocytes, leading to the production of proteases. Destroys and weakens the extracellular matrix[29]. In this study, Papaver rhoeas reduced TNF-α in rat knee joint, which is in line with the study[30] on the other hand, epidemiological studies have shown that there is a relationship between increased levels of inflammatory markers and high prevalence of CVD. Based on the obtained results, it can be said that in the rats receiving the effective dose, the least joint damage and the best physiological function of the heart were observed.

Interests conflict

The researchers declare that they have no conflict of interest.

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