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Evaluation of Histopathological Changes of Osteoarthritis on the Cardiovascular System by Gavage of Hydro Alcoholic Extract of Wild Anemone (Papaver Rhoeas L.) in Male Rats

Sareh Sangy[1*], Aminollah Bahaoddini[2], Alireza Tavassoli[3]

[1]Department of biology, Faculty of science, Shiraz University, Shiraz. Iran
[2]General practitioner Asmanagazi university medical school, Eskishhir, Turkey
[3]MD Assistant prof. of pathology, Pathology ward, Fasa medical sciences university, Fasa, Fars province, Iran

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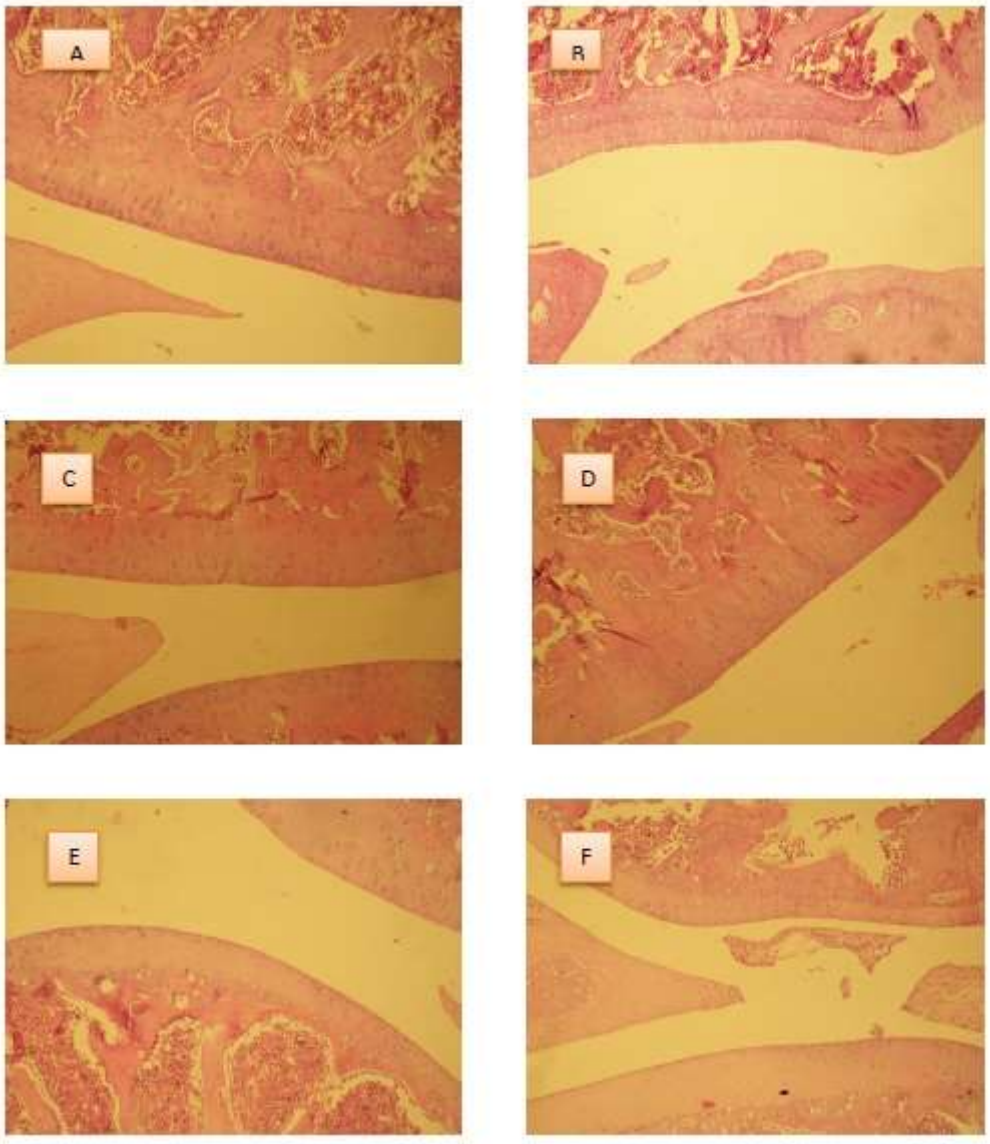
ABSTRACT

Since synovial inflammation is involved in the early stages of OA, one of the most appropriate methods for osteoarthritis is the development of CVD. The treatment of this disease is the use of medicinal plants. Among these plants is wild anemone with the scientific name. The aim of this study was to investigate the effect of wild anemone extract on the cardiovascular system of rats with osteoarthritis. 35. Immature male rats were instilled by injection of monosodium iodostat into the right knee joint of the osteoarthritis model. After one week, wild anemone was gavaged for 14 days with alcoholic aqueous extract and on day 30 after recording blood pressure parameters (systolic pressure, diastolic pressure). Histopathological examination was performed on rat heart and knee. The results were analyzed using SPSS software. In the study of histopathological changes, indicators Joint membrane by gavage of wild anemone extract in ras with osteoarthritis mesh Healthy control group was reported and chronic inflammation and congestion and perivascular changes of the heart were higher in rats with arthritis ($P < 0.05$). Based on the results, it can be said that in rats receiving doses Effective wild anemone extract has been observed to have the least joint damage and the best physiological function of the heart.

* Corresponding author: Sareh Sangy
✉ E-mail: sareh.sangy@gmail.com

GRAPHICAL ABSTRACT



INTRODUCTION

Hypertension is one of the most common and important diseases of today. The disease often grows covertly and unknowingly, and may eventually lead to cardiovascular disease or acute heart failure. Therefore, hypertension must be controlled and carefully treated. Cardiovascular disease (CVD) is one of the leading causes of death worldwide [1]. In Western countries, more than one third and in Iran, 50% of the causes of death are included and is in the top causes of death in the country. Studies have shown that systemic and chronic inflammation can increase the risk of CVD. Osteoarthritis (OA), or arthritis, is a common degenerative disorder of the articular cartilage, with hypertrophic changes in the subchondral bone, which cause 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. Because synovial inflammation is involved in the early stages of osteoarthritis, one of the side effects of OA is CVD 9. In addition, the first line of OA treatment is the use of no steroidal anti-inflammatory drugs (NSAIDs). Which has dangerous side effects in the development of cardiovascular disease 10. Therefore, it may be appropriate to use alternative methods, such as the use of herbs that have a modifying effect on blood pressure. Wild anemone (Papaver rhoeas L.) is one of the dark poppy plants (Papaveraceae) is one of these plants that has a variety of alkaloids and has a family affinity and effects similar to poppy. Due to the very small amounts of morphine in the extract of this plant, it is called "harmless opium" and so far various medicinal properties have been reported from them and the active compounds in wild sap include: papaverine, anthocyanin, radin, radic acid, acid Papaverine and roagenin Papaverine is one of the opium alkaloids used in the treatment of vascular congestion, especially coronary arteries. Papaverin reduces the activity of the sodium-potassium pump. As well as study by Marco et al. showed that another benefit inhibition is its effect on left ventricular diastolic function [2-5].

Another major alkaloid of wild anemone is anthocyanin, which is known for its antithrombotic effects, endothelial dilatation, arterial stiffness, and protective effect on the heart by suppressing increased phosphorylation hypertrophy in protein kinase C and activating protein kinase B Coronary heart disease is the leading cause of death in most industrialized countries. In addition, coronary heart disease is associated with significant complications and disability. Clinical spectrum of coronary heart disease from asymptomatic and asymptomatic anemia (ischemia) to chronic persistent angina, unstable angina, acute myocardial infarction (myocardium), ischemic heart disease (ischemic cardiomyopathy) and sudden death the heart is changeable. In recent decades, due to the use of newer coronary heart disease drug treatment methods as well as new intervention and surgical methods, the mortality rate due to coronary heart disease has gradually decreased [6-9].

However, about 900,000 people each year have a heart attack in the United States, of which about 225,000 die, most of whom die from coronary heart disease due to irregularity or heart failure.

Clinical signs of coronary heart disease are strongly caused by hardening of the arteries (atherosclerosis) of the coronary artery. (The epicardium, the visceral part of the pericardium or fibrous-serous sac that surrounds the heart and the roots of the great arteries) [10-12].

Coronary heart disease and hardening of the arteries are present at almost any age and can occur in both sexes. However, the severity of arteries in coronary heart disease depends in part on genetic background, risk factors, and local hemodynamic conditions. Vascular endothelial injury in coronary heart disease is the initiating event. Hypertension High blood cholesterol, smoking, and local hemodynamic abnormalities cause vascular endothelial damage, resulting in endothelial dysfunction and endothelial dysfunction, resulting in macrophages (originating from blood monocytes in the neck), and lipids (mainly bad cholesterol (LDLs), i.e. low-density lipoproteins) accumulate at the site of vascular injury [13].

Coronary heart disease produces foam-like cells due to oxidation of LDLs and their ingestion by macrophages. Accumulation of these cells forms the first visible lesion of atherosclerosis (atherosclerosis), the fat vein. The release of enzymes and toxins by macrophages exposes the endothelium, causing platelets to adhere to the site of injury. With the onset of atherosclerotic plaque, the developmental effects of plaque and macrophage stimulate the migration and proliferation of smooth muscle cells and fibroblasts, resulting in fibrotic antima (inner

vein layer).Coronary heart disease as plaque grows, the arteries become blocked and blood flow through the arteries becomes impaired. Usually a 70% reduction in the diameter of a coronary artery is sufficient to restrict blood flow in the presence of an increased need for blood to the heart muscle (for example, during exercise or physical activity), and a 90% stenosis can limit resting blood flow [14-18].

The inability of coronary arteries with coronary heart disease to enhance blood flow in this condition leads to the clinical pattern of stable angina. Numerous factors increase the risk of coronary heart disease and hardening of the arteries (atherosclerosis) in people [19-22].

Aging, male gender and family history of premature atherosclerosis are irreversible risk factors for coronary heart disease. The incidence of coronary heart disease increases with age. Considering that no study has been reported on the effect of oral anemone extract (gavage) on blood pressure and, arthritis so in the present study we decided to investigate the histopathological effect of wild anemone extract on blood pressure [23-26].

MATERIALS AND METHODS

Method was used to prepare the flower extract of wild anemone. The collection of this plant was done from the cities around Shiraz and was scientifically identified by the professor of botany of the Faculty of Science of Shiraz University. The collected plant was then dried and pulverized by an electric grinder and transferred to a human 1,800 ml containing 70% ethanol for 72 hours. And placed in an incubator at 37 ° C for 72 hours until completely dry and powdered [27-29].

Grouping

35 male rats were tested in the following groups:

- Control group (healthy rats(
- Group of healthy and treated rats with a dose of 200 mg / kg daily wild anemone (up to 14 days)
- Control group: Rats with OA injected with 50 mg of monosodium iodostat (MIA, MIA; sigma-ALDRICH, USA) in the amount of 50 µL (single Dose containing 1 mg MIA in 0.9% saline) [30].
- Positive control group: Rats with OA similar to group 3 but treated with Celebrex gavage (10 mg / kg).
- OA group of rats treated with gavage at a dose of 200 mg / kg wild anemone.

Test method

35, 30-day-old male Wistar race weighing between 150-100 g for one week in controlled light conditions (12 hours of light and 12 hours of darkness) and a temperature of 22 +,-3 ° C with access to water and food [31-33].

They were adequately maintained. To model osteoarthritis, the animal was first anesthetized by intraperitoneal injection of ketamine-xylazine (dose 60-60) g/kg, respectively, and the right knee joint was sterilized with 100% ethanol and then induced cartilage defect by dose injection. 1 mg monosodium iodostat (MIA, MIA; sigma-ALDRICH, USA) in the amount of 50µL (single dose containing 1 mg MIA in 0.9% saline) It was performed with a G 27 sterile needle in the knee joint at maximum flexion. However, there was no damage to the subchondral bone. One week after osteoarthritis model, wild anemone extract (dose 200 mg / kg equivalent to 0.46 g / kg extract powder) and Celebrex (10 mg / kg) were dissolved in 300 µl of solvent (water and alcohol) and Gauze was given to rats for 14 days. At the end of the fourth week, each animal was anesthetized by intraperitoneal injection of urethane (Sigma-Aldrich, St. Louis, MO, USA) at a dose of 1.2 g / kg.

Histopathological assessment

On day 30, swollen joint capsule, ligament and synovial tissue and heart tissue were removed from the tested rats. It was kept in 10% formalin, then in 5% formic acid for 72 hours the samples

were then dehydrated in ethanol, then placed in paraffin. Stained with hematoxylin, eosin and toluidine blue. Histopathological changes for each sample was placed. Samples were examined by a pathologist.

Statistical analysis of data

The recorded graphs were converted to numbers using Lab chart software and these numbers were confirmed by SPSS version 19 using Paired-samples T test. Then for comparison between the groups used one-way ANOVA test and the data were analyzed considering the significance level (P <0.05). LSD test was used to compare the mean of the data. Data were presented as mean (+,-), mean standard error and were used to measure changes in histopathological variables of Lones test and T test.

Findings

Assessment of knee pathology

Compared with control and control groups, according to the mean of the data, the most changes in changes in articular membrane and articular cartilage (P = 0.016), IFP (infrapatellar fat pad) and number of tibial chondrocytes (P = 0.166) was observed in rats with (control OA). Compared to the control and positive control groups, according to the mean data, changes in articular cartilage (P = 0.374), Erosion, IFP (P = 1.000) and Brusa (P = 0.029) were reported and showed a decrease in changes in the Celebrex recipient group.

The group receiving wild anemone extract (dose 200 mg / kg) is less than the control in cartilage membrane indices (P = 0.016) and also changes in articular cartilage indices in levels Tibial thickness (P = 0.892), femoral thickness (P = 0.385), joint destruction (P = 0.242), corrosion (0.374) = 0 (P), the number of tibial chondrocytes (P = 0.094) and the number of femoral chondrocytes (P = 1.000) are the same.

Comparison of wild anemone extract group (with doses of 100, 200 and 400) mg / kg and control

The overall result of the group comparison tests is that the changes in the articular membrane and articular cartilage of the arthritic and drug-receiving rats at the dose of (100 and 400) mg / kg are the same as the control group. Also, these changes were less in arthritic and drug-receiving rats at a dose of 200 mg / kg compared to the control group. (**Fig.1**)

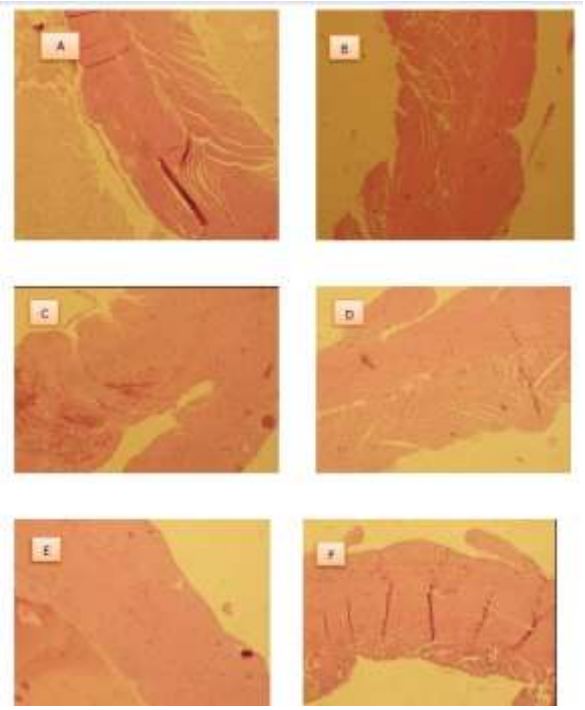


Fig. 1. Knee histology after H&E rusting A) Control group, B) control group, C) positive control group, D) dose mg / kg 100, E) dose 200 mg / kg y) dose 400 mg / kg

Assessment of cardiac pathology

Compared to healthy and control rats with OA, according to the mean data, there are fewer cardiac changes (acute inflammation, necrosis, congestion and PV) (P = 0.014). Also, the rate of these changes in the positive control group compared to the control group is the same at the chronic level (P = 0.089).

Comparison of wild anemone extract group (with doses of 100, 200 and 400) mg / kg and control

In the group of rats with orthodontic medication at a dose of 100 mg / kg with the control group, according to the mean data, cardiac changes in the levels of acute inflammation, necrosis and PV and chronic inflammation (P <0.052) And congestion (P = 0.078) are the same in these two groups, but the levels of chronic inflammation and congestion are in the groups receiving 200 mg / kg (P = 0.000) and (614), respectively. P = 0) and in the group receiving 400 mg / kg (P = 0.000) and (P = 0.771) the dose was higher than the control group, but the mean difference in The group receiving 200 mg / kg is lower than the 400 mg / kg dose.

In fact, cardiac changes in the group of rats with arthritis receiving a dose of 400 mg / kg were greater than the dose of 200 mg / kg and at a dose of 100 mg / kg compared to the dose groups (200 and 400) Mg / kg was lower (**Fig. 2**).

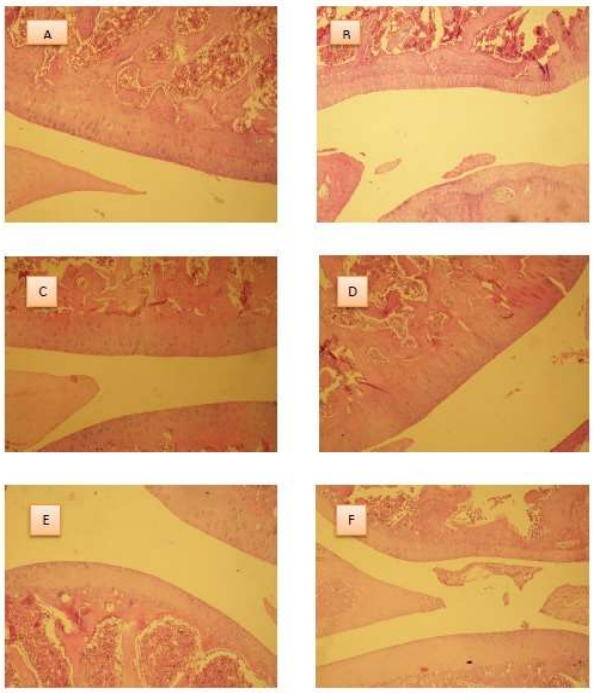


Fig. 2. Histology of the heart after rinsing with H&E**,** Control group, B) control group, C) positive control group, D) dose mg / kg 100, E) dose 200 mg / kg y) dose 400 mg / kg.

Comparison of systolic, diastolic blood pressure and mean arterial pressure

The mean systolic pressure in the control group (with OA) increased significantly compared to the control group (healthy). Also, the mean arterial pressure, systolic pressure in the 200 dose group compared to the group the control has a significant decrease (**Fig. 1**). Also, the mean heart rate in the group receiving 200 mg / kg decreased compared to the control group, but this decrease was not significant.

RESULT AND DISCUSSION

The histopathological results of this study showed that changes in articular cartilage and articular cartilage were more common in rats with osteoarthritis, which is consistent with previous studies. On the other hand, systole, diastole, mean arterial pressure and heart rate in rats with osteoarthritis Increased compared to the control group. Consistent with the results of the present study, Veronese et al. (2019) [25] showed a linear relationship between the severity of osteoarthritis and cardiovascular disease. Wang et al. (2016) [26], in a meta-analysis, also stated that there is strong evidence that OA is an important risk factor for CVD 16 and 17.18, and as noted in the pathology results of this study, chronic inflammation and Cardiac congestion and perivascular changes have been higher in rats with arthritis, which confirms the findings of previous studies. On the other hand, increased blood pressure (mean arterial pressure, systolic and diastolic pressure) was seen in rats with orthosis can be related to wag nerve activity, which causes a significant reduction in heart rate and decreased contractile strength of the heart. Also, 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. On the other hand, nicotinic receptor (α7 (α7nAChR) is present in the synovial tissue of the knee joint of patients with OA, which can be attributed to the production of local acetylcholine in the regulation of arthritis, to the cholinergic anti-inflammatory pathway that inhibits cytokine production. It becomes inflammatory. It also stimulates articular chondrocytes by IL-1β or TNF-α to transmit the N65-κB p65 nucleus, a wide range of catabolic genes such as nitric oxide synthase (iNOS) and cyclooxygenase-2 (COX-2). It is contained in chondrocytes, which leads to the production of destructive proteases and attenuation of the extracellular matrix30. The cholinergic system in the arteries also causes a nitric oxide-dependent relaxant effect. Previous studies have shown that inhibition of NO production in blood vessels leads to high blood pressure. However, the most changes in articular membrane (at IFP level) and articular cartilage (number of tibial chondrites) were seen in the group of rats with arthritis, and since NO has different roles, so that in chronic inflammation It has an anti-inflammatory role and a pro-inflammatory role in acute joint inflammation, this finding can be justified. Decreased changes in articular cartilage have also been observed in the rat group of arthritis receiving Celebrex.

However, in the present study, no significant cardiac microscopic changes were reported with oral administration of Celebrex in the heart, which is not consistent with the study of Fable et al. (2014) and Moncada (2006).On the other hand, it is hypothesized that vascular changes may have caused cardiac complications in rats. The previous study is consistent with the fact that the COX-2 inhibitor causes an imbalance, which causes platelets to accumulate in COX-1, from the production of COX-2 dependent prostacyclin by It blocks endothelial cells and can affect blood vessels and cause vasoconstriction and inhibition of COX by NSAIDs reduces the effect of systemic vasodilation on prostaglandins such as PGI2 and PGE2.On the other hand, this can be attributed to the short oral administration time in the present study, and it is hypothesized that long-term use of Celebrex may cause cardiac microscopic complications that require further research in this area. As shown in the present findings, the oral extract of wild anemone (Papaver rhoeas. L.) at a dose of 200 mg / kg reduces the mean arterial pressure, systolic and diastolic pressure and increases heart rate compared to rats with arthritis. Cardiac pathological results also confirm this finding and this can be attributed to the effect of oral extract on cardiac output or changes in peripheral vascular resistance, and since oral extract of wild anemone reduced systolic pressure compared to the control state.

Therefore, it can be concluded that it has reduced cardiac output, which has occurred through a reduction in stroke volume and ultimately a decrease in cardiac contractile strength. This effect may be due to the presence of papaverine and various active compounds in the extract. The results of previous research have shown that papaverine in wild anemone reduces the activity of the sodium-potassium pump and inhibits the enzyme phosphodiesterase. The study of Marco et al. Also showed that one of the benefits of inhibiting phosphodiesterase 2 is the effect on left ventricular diastolic function, which is present in the present study. The results also showed that changes in articular membrane indices by gavage of wild anemone extract (200 mg/kg) in rats with osteoarthritis similar to healthy controls were reported that the reduction of these changes could be due to the presence of anthocyanins as Another active ingredient in wild anemone was found to be in line with the present study by Cassidy et al. (2015), which showed that anthocyanins have anti-inflammatory properties and high anthocyanin consumption is associated with decreased levels of proinflammatory cytokines and regulation of inflammatory mediators. Other

effects of anthocyanins are on inflammation. In addition, anthocyanin has the ability to reduce the risk of CVD and dilate the endothelium, improve arterial stiffness and have a protective effect on the heart by suppressing increased phosphorylation hypertrophy in protein kinase C, and activate Akt protein kinase B. The findings of the present study are consistent with the research of Farrokhi et al. (2017) and Redi et al. (2007). Based on the results, it can be said that chronic inflammation and congestion and perivascular changes of the heart were higher in rats with arthritis and rats receiving wild anemone extract had the least joint damage and the best physiological function of the heart.

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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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