Isolating and studying the effect of natural products isolated from the Alhagi maurorum Medik on the level of sirtuin7 and some biochemical variables in mice with cardiovascular diseases

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KEYWORDS
Cardiovascular disease, isolation, mice, natural products

ABSTRACT
The study included the isolation and diagnosis of various natural products from Aqul. The oily substance, its fatty acids, and the flavonoid compounds were isolated and diagnosed by means of high performance liquid chromatography. Also, alkaloids were isolated. It was observed that the products elevated the level of enzyme sirtuin7, and it positively reflected along with their positive effects on all other measured biochemical variables. It also checked the influence of these products on some biochemical variables related to the cardiovascular disease in the serum of the diseased mice. Among these biochemical variables were sirtuin7 (SIRT7), tumor necrosis factor-alpha (TNF-a), glutathione peroxidase (GPx), glutathione (GSH), and malondialdehyde (MDA). For example, the level of SIRT7, GPx, and GSH significantly decreased in the infected mice compared to healthy mice, while TNF-a and MDA levels showed.

Introduction

Cardiovascular diseases (CVDs) refer to a big group of issues and disorders in the cardiovascular system that lead to death all around the world [1]. The problem with mitochondrial dysfunction is closely associated with CVDs [2] because, being the major site where production of reactive oxygen species occurs, these excess levels significantly accentuate oxidative stress [3]. In the case where the rate of ROS generation exceeds the antioxidant capacity, oxidative stress is produced [4], and this forms one of the greatest risk factors for cardiovascular diseases [5].

Aqul perennial is a plant of wide distribution, common in dry lands with low rainfall, high salinity, alkaline, and rocky areas. It is native to North Africa, the Middle East, and Southeastern Europe [6],[7]. The botanical name of the plant is Alhagi maurorum Medik [8]., commonly Camelthorn [9]. Alhagi is claimed as one of the world's three traditional medicines, in practice since more than 2500 years [10] ago. It has been an ancient medicinal remedy under Uyghur traditional medicine system to treat ailments like colds, rheumatic pains, diarrhea, stomach aches, headaches, toothache, and dental pain. The pharmacologic studies have confirmed the antioxidant, anti-tumor, anti-inflammatory, and neuroprotective effects; hepatoprotective, nephroprotective, immunomodulatory effects [11]; and also it is used in the treatment of diabetes [12]. Belonging to Plantae kingdom, Fabales order, Fabaceae family, and Alhagi genus, people have been using Alhagi since ancient times for the treatment of diseases related to the respiratory, liver, heart, blood vessels, digestive, immune, urinary, and reproductive systems [13]. Up to now, 178 chemical compounds have been identified in Alhagi, including flavonoid compounds, the natural substances found in various parts of the plant. Their exceptional medical properties make them very useful to animals and humans since flavonoids have a multitude of biological properties, which allow them to be used as antioxidants, anti-tumors, anti-inflammatories, anti-mutagens, anti-ulcers, and anti-obesity agents [14]. They are also helpful for protecting the heart, as they can prevent high blood pressure and arteriosclerosis, reduce atrial pressure, enhance vasodilation, and prevent ventricular dysfunction (that is the cause of 1/3 death cases of cardiovascular diseases and a significant complication of arteriosclerosis and arterial thrombosis) [15]. The Aqul also contains alkaloids used as anticancer drugs, vasodilators, and antiarrhythmic agents [16]. Additionally, Aqul contains phenolic acids, important phytochemicals for maintaining health. It has been shown in animal and human studies that phenolic acids own anti-hypertensive, anti-hyperlipidemic, antifibrotic, and anti-inflammatory activities [17], which all confer cardioprotection. Apart from that, Aqul contains 19 polysaccharides, glycosides, volatile oils, and several other chemical compounds [18]. The present study would investigate the impact of such chemical compounds obtained from Aqul in case of cardiovascular diseases.

Materials and Methods

The Aqul plant was collected from the area surrounding Beiji town, in Salah al-Din Governorate. The roots were cleaned away from the leaves, stems, and fruits separately. Then, the stems and thorned leaves were cleaned from impurities and left in the shade for three days to dry. Afterward, it was milled into a finer state using a Turkish company 'Baron' blender; it was placed in the shade for five days, given time to completely dry in order to extract it.

Fatty acids and oils from the Aqul plant are extracted from the stems and leaves through taking 200 grams of the powdered plant and placed in petroleum ether (60-80 °C) for 3 days; after that, the solvent was decanted off and the process repeated. The extraction was then carried out by a Soxhlet apparatus for three days, followed by solvent evaporation through rotary evaporation and cooling of the oil, extracted from the plant [19]. The product thus obtained was diagnosed within a closed tube with its cap tightly closed. The fatty acids and volatile oils were diagnosed with high-performance liquid chromatography using colorimetric analysis technique (HPLC) [20]. Flavonoids were isolated after soaking the residue, which was left from oil extraction, in 99% ethanol for three days in the dark. Then they were extracted using a Soxhlet apparatus and the ethanol evaporated using a rotary evaporator. The resulting residue was placed in a sealed tube for analysis [21]. HPLC techniques were employed to identify the flavonoids [22]. The oil and flavonoids were isolated first, and then separation of the plant powder was done to obtain alkaloids. The remaining substance was extracted in extraction equipment using the distilled water for three days to ensure that all ethanol was removed. This was followed by soaking the substance in distilled water for one day and an extraction process. The extract was later dried to remove the water and thus obtain a dry extract for storage and future testing [23].

Experimental Animals: This study was conducted on 25-30 adult male white mice, aged between 9 and 12 weeks, with an average weight of 20-25 grams. The animals were randomly divided into five equal groups and placed in special plastic cages with dimensions of 10 × 20 × 40 cm, covered with stainless steel wire. Five animals were placed in each cage. The cages were prepared for cleanliness and sterilization and filled with wood shavings. The cages were cleaned and washed weekly. Continuous provision of food and water was ensured for the animals, in addition to exposing all animals to the same natural light and temperature conditions. The study was conducted at the University of Mosul / College of Veterinary Medicine. Ethical Provel no UM.VET.2024 dated March 3, 2024

Induction of Cardiovascular Disease: Hydrogen peroxide (H2O2) was used to induce cardiovascular diseases. The solution was prepared by taking 1 ml of the 25% standard solution and diluting it in 1 litter of distilled water, with the solution being changed every three days. The mice were treated with hydrogen peroxide for six weeks at a dose of 0.1 ml. The new disease condition was diagnosed through clinical examinations and histological diagnosis of the heart and aorta [24]. Blood and tissue samples were collected from all healthy and affected mice.

Injection of animals with cardiovascular disease: The animals were divided into five groups, each consisting of 5 mice.

Group 1: Healthy control group

Group 2: Received only 1% hydrogen peroxide throughout the treatment period and considered an untreated diseased group

Groups 3, 4, and 5: After treatment with peroxide and induction of the disease, they were injected with plant extracts (oil, flavonoids, and alkaloids) successively and at doses of (1.25, 61.28, and 7.80) mg per kilogram of body weight of the animal, respectively.

Sample collection (blood and tissues): The animals were then anesthetized slightly in ether [25], and blood samples were obtained from the eye socket. Blood was collected in dry, clean, and sterilized tubes (gel tubes), which were centrifuged for serum separation to conduct the needed biochemical analyses. Other heart and liver tissues were also isolated and stored in 10% formalin in tubes for histological studies [26].

The levels of Sirtuin7 and TNF-a were estimated by using ELISA. The ELISA method used was the sandwich-ELISA assay using ELISA kit [27] and [28]. Activity of GPx was calculated based on the technique used in the study [29]. The glutathione concentration in serum was determined with a modified method using an Ellman's reagent [30]. The concentration of malondialdehyde in serum was also determined based on the method used by the researchers in the study [31]. The compounds in the Astragalus plant were identified by using high performance liquid chromatography (HPLC). Statistical analysis: The data obtained from the clinical examination was analyzed using statistical package SPSS 19 to describe mean and measure of dispersion using one-way analysis of variance, where p-value was considered an indicator of significant difference at ($p \leq 0.05$).

Statistical analysis: The clinical examination data were analyzed using the statistical software SPSS 19 to determine the mean and measure of dispersion using one-way analysis of variance. A p-value of ($p \leq 0.05$) was used as an indicator of significant difference [32].

Results

The active principles of Astragalus plant drug were determined by the use of colorimetric assays or physical techniques. Major components are flavonoids and alkaloids; besides, their biological activity was assayed for therapeutic effect on mice with experimentally induced cardiovascular disease through peroxide. HPLC techniques were used for the determination of fatty acid composition in the extract. The results, on the other hand, showed the detection of palmitic acid, oleic acid, stearic acid, lenolic acid, and linolenic acid in oil extract, and the detection of gallic acid, ferulic acid, qurcetine acid, kaempferol acid, caffeic acid, syringeic acid, p-coumaric acid in flavon.

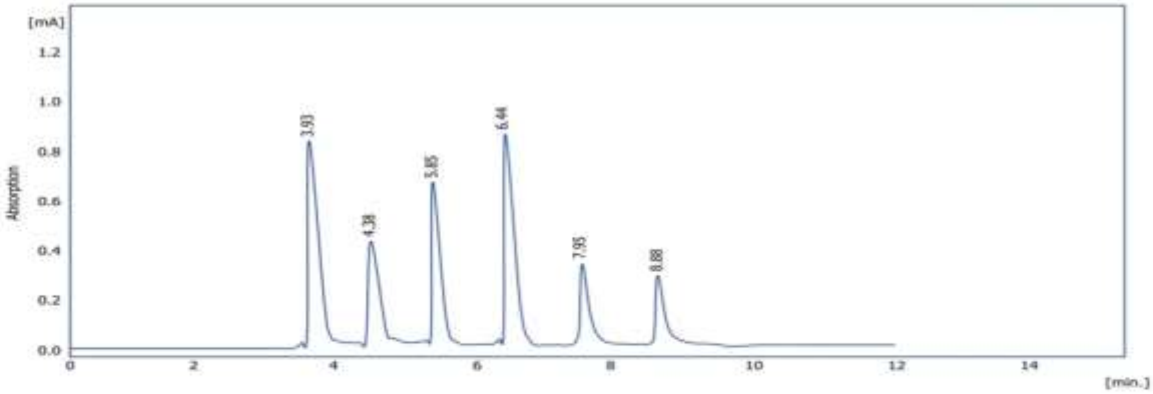

Figure (1): HPLC chromatogram of oils isolated from Aqul plant

Table (1): Chromatographic Analysis Results for Identified Peaks

No.	Reten Time [min]	Area [MAU.s]	Height [Mau]	Area [%]	Height [%]	W05 [min]	Compound Name
1	3.93	244598.80	805.98	24.00	24.00	0.15	Oleic acid
2	4.38	136985.44	245.66	11.00	11.00	0.08	Stearic acid
3	5.85	195247.15	689.80	17.00	17.00	0.10	Palmatic acid
4	6.44	355214.41	809.11	24.00	24.00	0.15	Lenolic acid
5	7.95	99652.21	353.65	12.00	12.00	0.05	Linolenic acid
6	8.88	85202.55	319.88	12.00	12.00	0.05	
	Total	1116900.30	4022.14	100.00	100.00		

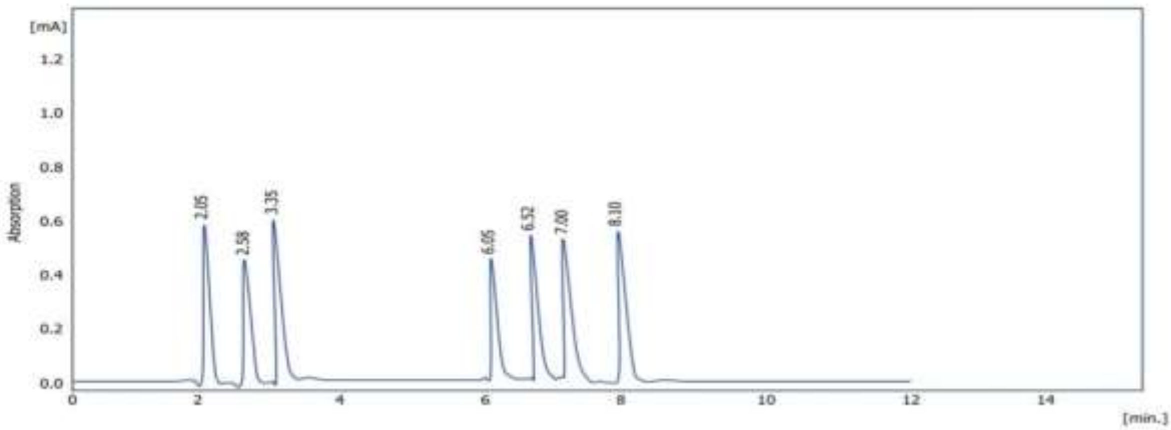

Figure (2): HPLC chromatogram and standard retention time for flavonoids isolated from Aqul plant

Table (2): Chromatographic Analysis Results for Identified Peaks

NO	Reten Time [min]	Area [MAU.s]	Height [Mau]	Area [%]	Height [%]	W05 [min]	Compound Name
1	2.05	25642.56	580.65	14.00	14.00	0.10	Gallic acid
2	2.58	20658.90	500.12	12.00	12.00	0.08	Ferulic acid
3	3.35	33621.47	580.98	15.00	15.00	0.10	Qurcetine acid
4	6.05	21451.79	500.36	12.00	12.00	0.08	p-coumaric acid
5	6.52	25996.98	560.51	17.00	17.00	0.10	Kaempferol acid
6	7.00	40214.56	554.74	15.00	15.00	0.10	Caffeic acid
7	8.10	41202.11	570.95	15.00	15.00	0.10	Syringeic acid
	Total	208788.15	3848.31	100.00	100.00		

Table 3: The effects of the natural constituents of Aqul plant on the biochemical parameters in the mice groups

Biochemical Variables	*Group 1* Control		*Group 2* Untreated Infected (2.5mg/kg)		*Group 3* Oil treatment (0.1mg/kg)		*Group 4* Flavonoids treatment (0.1mg/kg)		*Group 5* Alkaloids treatment (0.1mg/kg)	
	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D	Mean	S.D
SIRT7 (ng/ml)	E 15.63	.543	A 2.562	.388	B 9.740	.505	D 14.204	.177	C 12.344	.258
TNF-α (pg/ml)	A 10.63	.403	E 291.76	5.561	C 114.756	3.806	B 58.596	1.884	D 147.08	5.77
GPx (u/l)	C 139.25	.403	A 64.602	5.562	AB 97.864	3.806	B 103.582	1.884	AB 96.63	5.773
GSH (μmol/l)	D 12.398	.171	A 4.496	.2812	B 8.21600	.5005	D 12.3975	.508	C 9.788	.344
MDA (μmol/l)	A 1.145	.057	D 6.214	.229	C 5.4720	.3279	A 1.3200	.090	B 4.196	.161

The horizontal arrangement of various letters (average ± standard error) indicates a significant difference at a probability level of $P < 0.05$ accord.

Histological changes in experimental animals' organs

Based on histological analysis, the animals in the control group had cardiac and epicardial structures that appeared structurally normal. Figure 3 illustrates the typical tissue features of the heart, represented by the cells (black arrow), cardiac muscle fibers (blue arrow), and blood vessels (yellow arrow). Meanwhile, Figure 4 demonstrates the typical tissue landmarks of the epicardial layers (↔), the mesothelial cells (⟶), and the smooth muscle cells and fibres (⟶).

Histological examination of the animals with experimentally induced heart and vascular disease using 1% hydrogen peroxide for six weeks revealed pathological tissue changes in the heart and epicardial artery compared to healthy mice. Figure 5 illustrates myocardial cell necrosis (black arrow), glassy degeneration (blue arrow), and severe edema among the cardiac muscle fibres (yellow arrow). Additionally, Figure 6 shows the tissue landmarks of the epicardial artery, revealing the presence of atherosclerotic lesions in the inner and middle layers (↔), characterized by the presence of foam cells (⟶), smooth muscle cell hypertrophy (⟶), and intimal thickening (⟶).

The treatment of animals with cardiovascular disease using natural extracts from the Aqul plant for 21 days led to tissue restoration and improvement in the structure of both the heart and the aorta in the treated animals, especially those treated with flavonoids, compared to tissues taken from untreated animals. Animals in group 3 treated with the oil extract showed a significant improvement in both heart and aortic tissues. Figure 7 illustrates the natural tissue features of cardiac muscle fibres (black arrow) with mild vacuole degeneration of some fibers (blue arrow). Figure 8 represents a tissue section of the aorta of an oil-treated mouse from the treated group, showing foam cells in the intima (↔) and thickening of the media (⟶).

Group 4, treated with flavonoids, showed a significant improvement, and this extract had the most excellent therapeutic effect on both heart and aortic tissues. Figure 9 illustrates the natural tissue landmarks of cardiac muscle fibers (black arrow) with mild hyalinosis (blue arrow) and the presence of edema (yellow arrow). Figure 10 represents a tissue section of the aorta of a mouse from the flavonoid-treated group, demonstrating the natural tissue landmarks of the aortic layers (↔), endothelial cells (⟶), and smooth muscle cells and fibres (⟶).

Similarly, Group 5, treated with alkaloids, improved both heart and aortic tissues. Figure 11 illustrates the natural tissue landmarks of cardiac muscle fibres (black arrow) with mild edema (blue arrow), and Figure 12 represents a tissue section of the aorta of a mouse from the alkaloid-treated group, demonstrating the presence of foam cells in the intima (↔) and hypertrophy of smooth muscle fibres (⟶).

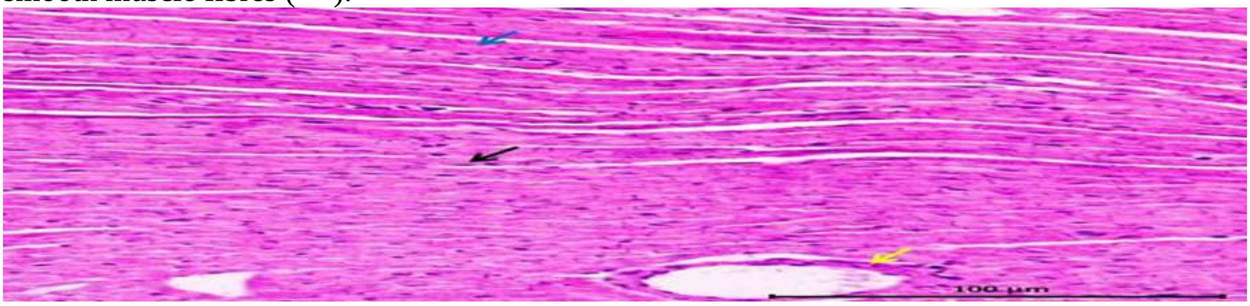

Fig.3: Histological section of a mice heart from the control group illustrating the natural histological features of the heart tissue, represented by the cells (black arrow), cardiac muscle fibres (blue arrow), and blood vessels (yellow arrow). Haematoxylin and eosin stain, 400X.

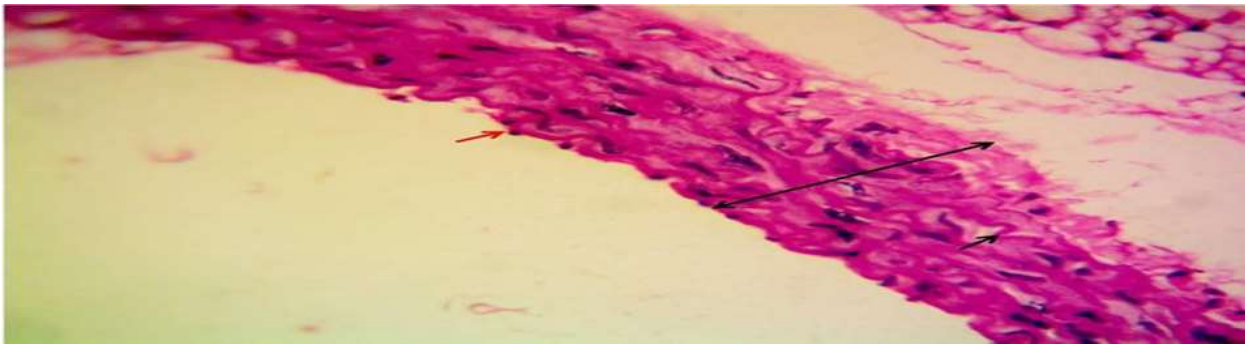

Fig. 4: Histological section of the abdominal aorta of a mice from the control group , illustrating the normal tissue features of the aortic layers (↔), endothelial cells (⟶), and smooth muscle cells and fibres (⟶). Haematoxylin and eosin stain, 400X.

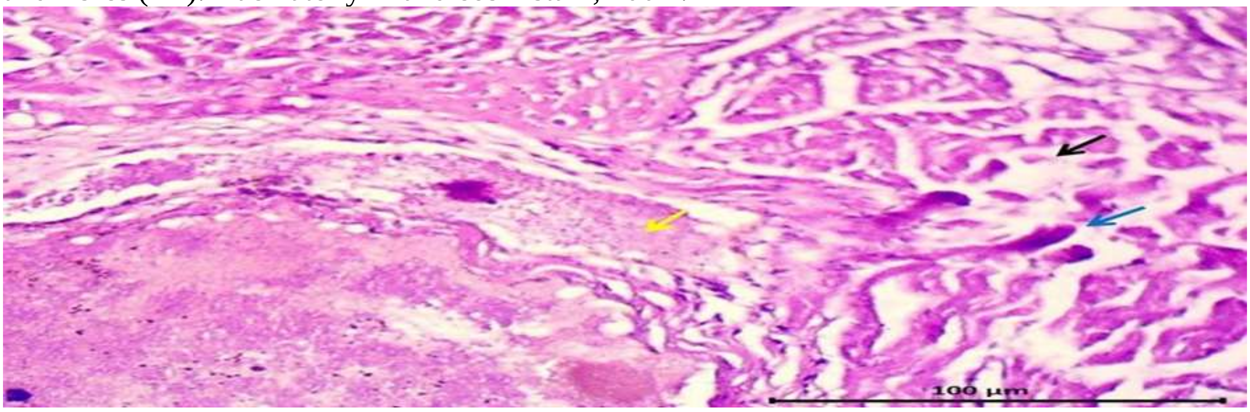

Fig. 5: A histological section of a mice heart from the affected Patient group showing myocardial cell necrosis (black arrow), glassy degeneration (blue arrow), and severe edema between the cardiac muscle fibres (yellow arrow). Haematoxylin and eosin stain, 400X.

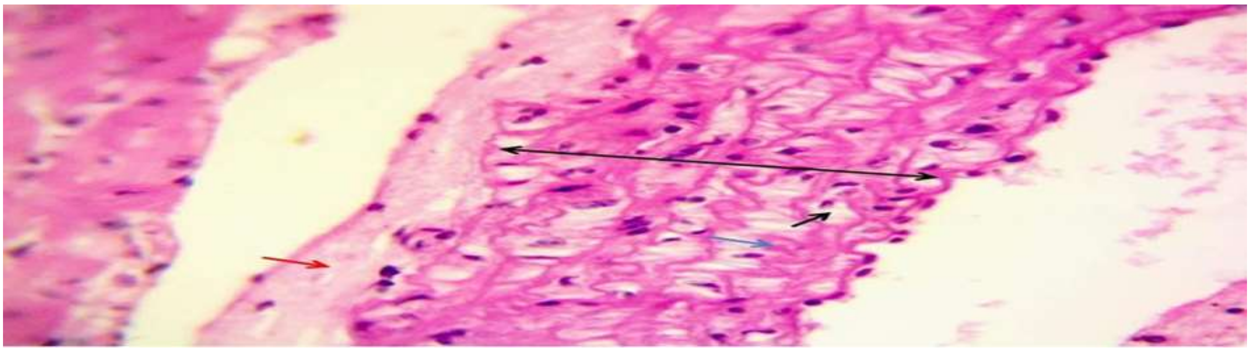

Fig 6: Histological section of the abdominal aorta of a patient group demonstrates the presence of atherosclerotic lesions in the intimal and medial layers (↔), characterized by the presence of foam cells (⟶), smooth muscle cell hypertrophy (⟶), and thickening of the adventitial layer (⟶). Haematoxyl in and eosin stain, 400X

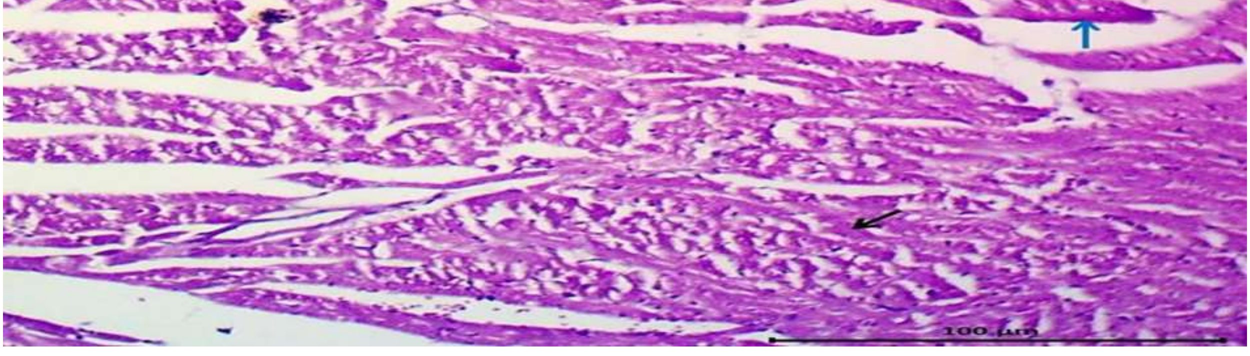

Fig. 7: Histological section of a mice heart from the oil-treated group showing the natural histological features of cardiac muscle fibres (black arrow) with mild interstitial edema (blue arrow). Haematoxylin and eosin stain, 400X.

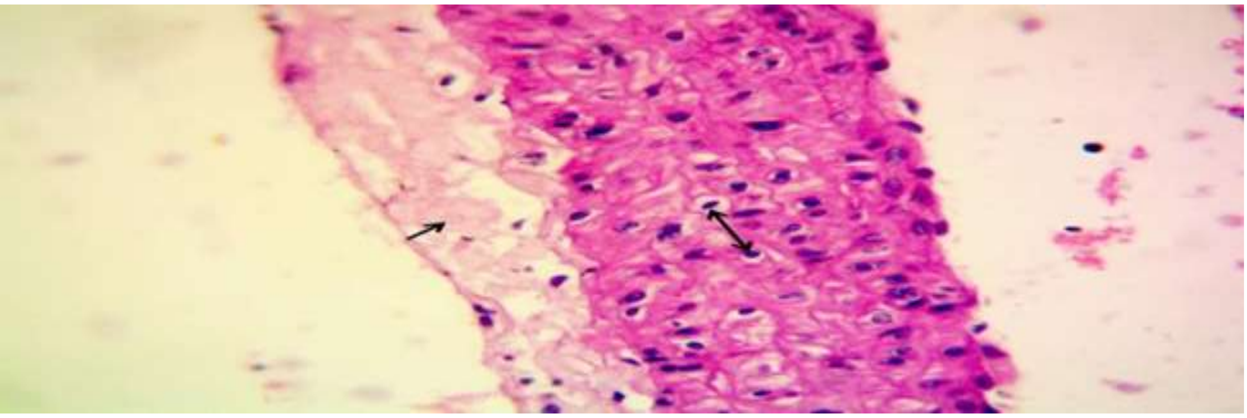

Fig. 8: A histological section of the aortic artery of a mouse from the oil treated group with demonstrates the presence of foam cells in the intima (↔) and thickening of the tunica media (⟶). Haematoxylin and eosin stain, 400X.

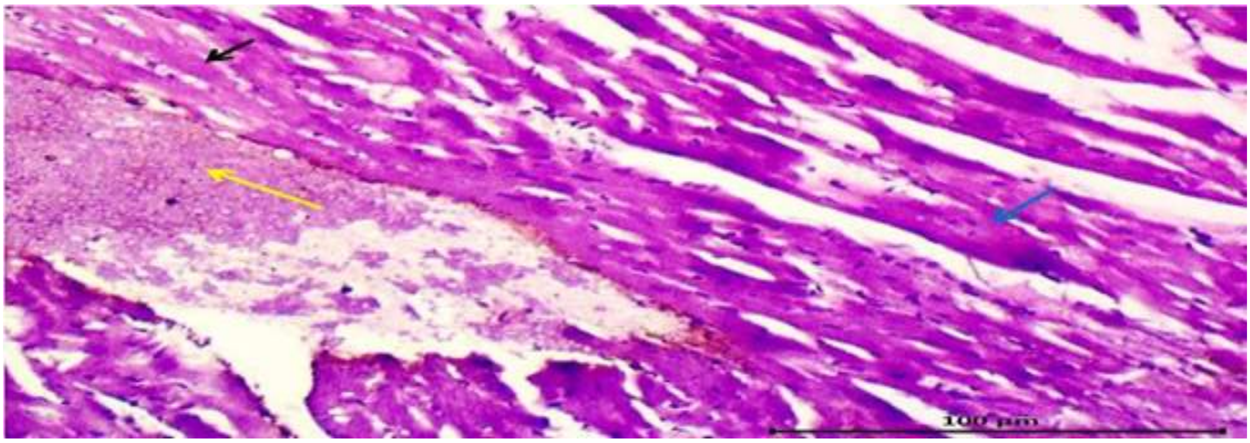

Fig. 9: A histological section of a mice heart from the group treated with flavonoids illustrates the natural histological features of cardiac muscle fibres (black arrow) with mild interstitial fibrosis (blue arrow) and the presence of edema (yellow arrow). Hematoxylin and eosin stain, 400X.

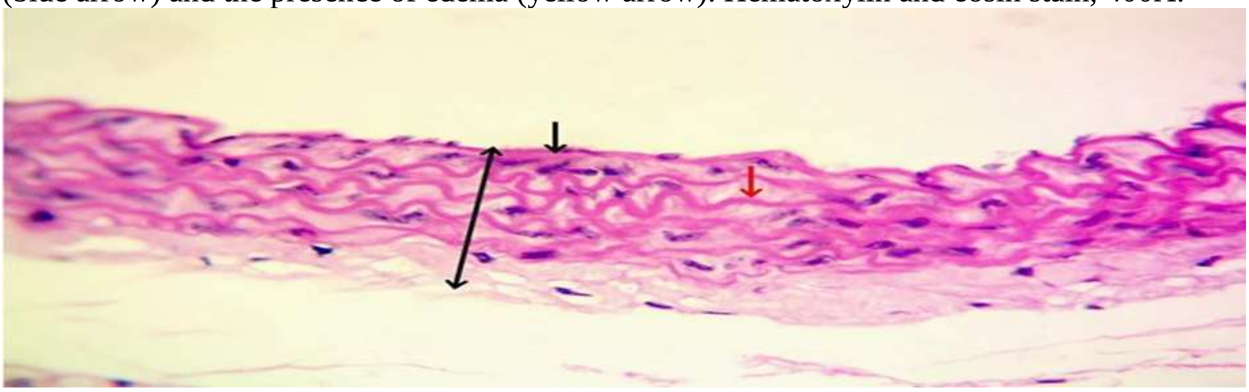

Fig.10: A histological section of the aortic artery of a mouse from the group treated wit flavonoids shows the natural histological features of the intima (↔) and the endothelial cells (⟶), smooth muscle cells, and fibres (⟶). Haematoxylin and eosin stain, 400X

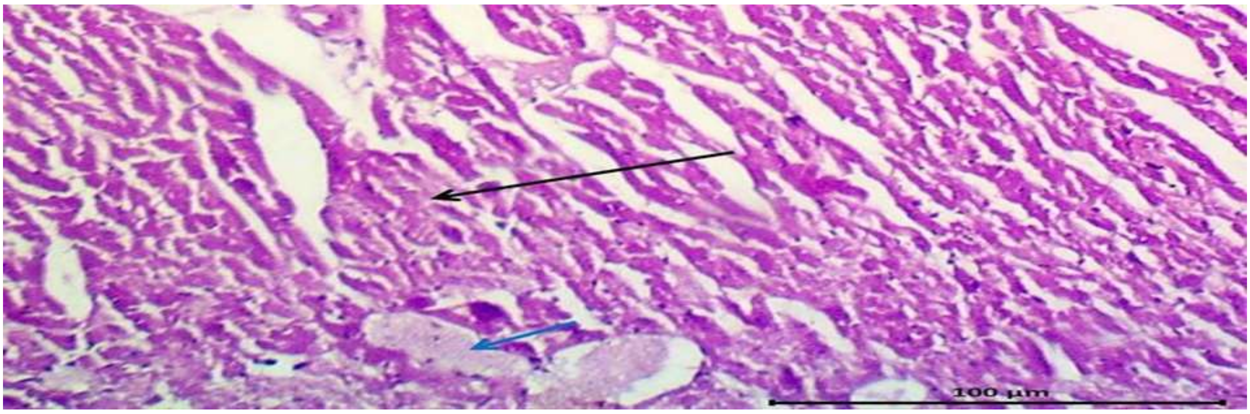

Fig. 11: Histological section of a mice heart from the group treated with alkaloids showing the natural histological features of cardiac muscle fibres (black arrow) with mild edema (blue arrow). Haematoxylin and eosin stain, 400X.

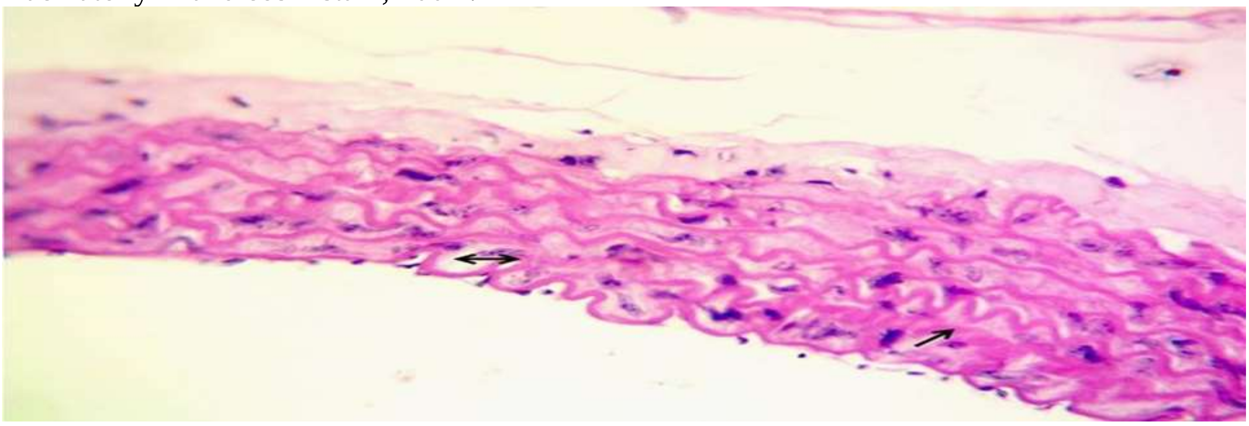

Fig. 12: A histological section of the aortic artery of a mouse from the alkaloid-treated group demonstrates the presence of foam cells in the intima (↔) and hypertrophy of smooth muscle fibres (⟶). Haematoxylin and eosin stain, 400X.

Discussion

Fatty acids are essential in our bodies and are found in oils and natural fats in various structures. They are vital for energy storage and cellular fuel, obtained solely from dietary sources. Algae oil is rich in linoleic acid, and consuming more linoleic acid has been linked to a reduced risk of cardiovascular diseases. It is an essential fatty acid with significant benefits for heart and vascular health through its anti-inflammatory effects, lipid-lowering properties, and blood pressure regulation [33]. Gallic acid is a potent phenolic compound with significant protective effects on the heart and blood vessels. Its antioxidant, anti-inflammatory, and anti-proliferative properties contribute to reducing the risks and development of cardiovascular diseases. By preventing LDL oxidation, reducing inflammation, improving endothelial function, and regulating blood pressure and lipid profiles, gallic acid plays a crucial role in maintaining heart and vascular health [34].

The effect of natural products isolated from the Aqul plant on specific biochemical parameters:

In this research, the influence of different compounds extracted from the Aqul plant, which consists of oil, flavonoids, and alkaloids, on rats that have cardiovascular disease was checked in addition to the effect on the biochemical variables measured as in Table 3 in case these products were injected at doses (1.25, 61.28, 7.80 mg/kg) respectively per body weight. It was noticed that the presence of the sirtuin7, glutathione peroxidase, and glutathione became much less in amount. Conversely, significant increase in tumor necrosis factor was observed in the mice suffering from cardiovascular disease compared to the healthy ones. Additionally, the level of malondialdehyde in these mice was considerably high compared to healthy ones. The level of SIRT7 in these affected mice was also low compared to the control group. This decrease may be principally caused by the effects of oxidative stress, which causes many problems including poor mitochondrial function and cell aging; however, this is all about what causes cardiovascular disease, as hydrogen peroxide is one of the types of oxygen-harmful interactions [35]. The results in Table (3) indicated that the natural products isolated from the Aqul plant led to an increase in the level of SIRT7. Flavonoids were the most effective in increasing the level of Sirtuin7. In this regard, an increase can be attributed to the antioxidant-rich flavonoids, which have the ability to alleviate oxidative stress evoked by reactive oxygen species through increasing SIRT7 levels and reducing incidences of cardiovascular disease [36]. Flavonoids promote mitochondrial biogenesis and function [37]. This way, better functioning mitochondria provide for higher cellular energy levels and more sirtuins expression, such as SIRT7, which is related to the regulation of mitochondria [38] .

The serum concentration of TNF-α in the infected mice was much higher than in the control group. This increase is mainly caused by the inflammatory responses and oxidative stress, since hydrogen peroxide is a reactive oxygen species that elicits oxidative stress in cells [39]. The results also showed that TNF-α in the mice serum was generally decreased by natural products isolated from the Aqul plant, with flavonoids being the most effective at decreasing the level of TNF-α, in which a significant decrease in the level of TNF-α was found in the infected treated with flavonoids compared to the diseased one. Without treatment, the reduction is mediated by the antioxidant effects of flavonoids and consequent reduction in oxidative stress. Flavonoids are generally anti-inflammatory, including reducing the serum levels of TNF-α [40].

A decrease in the serum concentration of GPx in the infected mice compared to the control was identified. This decline could be as a result of several factors in relation to the physiologic response to oxidative stress caused by hydrogen peroxide. When there is excessive oxidative stress, it may damage proteins, including GPx, thus dropping its concentration in blood serum [41]. The results pointed out that natural products isolated from the Aqul plant increased the level of GPx in the blood serum of mice treated with them compared to infected, untreated mice. It was demonstrated that flavonoids had a better impact on the elevation of GPx level, with the reason that flavonoids raise content and activity of glutathione peroxidase in serum with the aid of their antioxidant [42] and anti-inflammatory activity [43].

It is witnessed that the concentration of glutathione in serum in infected mice was reduced if compared with its concentration in the control group. This fall could be attributed to the oxidative stress of the hydrogen peroxide, and the oxidative stress greatly augments the rate at which the hormone GSH is used up since it is among the main antioxidants that are very key in the scavenging of a range of toxins emanating from high rates of increased oxidative stress and increased free radicals. As a result, this high usage eventually depletes the GSH reserves hence the reduced serum levels [44]and [45]. Results showed that natural products isolated from the Aqul plant increased the serum level of GSH in infected and treated mice as compared to the untreated infected mice. Flavonoids act to have an effect on the increment of the GSH hormone. This increase may be due to the reason that flavonoids promote the synthesis of GSH by up-regulating it through the control of enzymes like GSH synthesizing expression and activity. Flavonoids were also known to stimulate the activity of glutamate cysteine ligase (CL) enzyme involved in GSH biosynthesis [46].

Further, it was noticed that the concentration of MDA in serum of infected mice increased when compared to the control group. An increase of major magnitude was found in stimulation of oxidative stress leading to lipid peroxidation. The process involves the generation of reactive oxygen species that attack polyunsaturated fatty acids in cell membranes, leading to the formation of MDA as a by product and hence increasing its levels in serum [47]. The results also showed that natural products isolated from Aqul plant led to a lower level of MDA in serum of infected and treated mice compared to untreated infected mice. Among the three treatments, it was flavonoids that achieved the greatest reduction in MDA levels, with a marked reduction in its quantity content in infected mice treated with flavonoids compared with that in the untreated infected group. This is because flavonoids have potent antioxidant activities that reduce lipid peroxidation through the reduction of oxidative stress [48].

Acknowledgement:
To University of Mosul, College of Science, Department of Chemistry for providing the required chemicals.

Conclusions

This research has isolated the natural products from the Aqul plant, where it was observed to have a positive effect on cardiovascular diseases through their therapeutic effect as they led to the reduction of inflammatory factors, oxidative stress, and other oxidation factors. The relationship which can be seen in the study is that of a reduction of the concentration of the Sirtuin7 and their association with the non-coronary artery disease population.

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تقييم مستوى السرتوين7 وبعض المتغيرات الكيموحيوية لدى مرضى القلب والأوعية الدموية

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الخلاصة

تضمنت الدراسة عزل وتشخيص النواتج الطبيعية المختلفة من نبات العاقول , Aqul plant حيث تم فصل المادة الزيتية وأحماضها الدهنية بالإضافة إلى مركبات الفلافونويدات التي تم تشخيصهم باستخدام تقنية كروماتوغرافيا السائل عالي الأداء .(HPLC)كما تم عزل القلويدات, ودرس تأثير هذه المنتجات على مستوى إنزيمSirtuin7 ، حيث كشفت عن تأثير إيجابي في رفع مستوىSIRT7 ، إلى جانب تأثيراتها الإيجابية على المتغيرات البيوكيميائية الأخرى المقاسة. اضافة إلى ذلك، تناولت الدراسة تأثير هذه المنتجات الطبيعية على بعض المتغيرات الكيموحيوية ذات العلاقة بأمراض القلب والأوعية الدموية في مصل الفئران المستحثة بالمرض. وشملت هذه المتغيرات البيوكيميائية كل من السرتوين7 (SIRT7)، وعامل نخر الورم ألفا -TNF) (α، الكلوتاثايون بيروكسيديز (GPx)، الكلوتاثايون (GSH)، والمالونديالدهيد (MDA). أظهرت النتائج أن مستويات SIRT7 وGPx وGSH انخفضت بشكل ملحوظ في الفئران المريضة مقارنة بالفئران السليمة، في حين أظهرت مستويات TNF-α وMDA زيادة ملحوظة.

الكلمات المفتاحية: أمراض القلب والأوعية الدموية، الفصل، الفئران، المنتجات الطبيعية.