ISSN: 1220-3173; E-ISSN: 2457-7618

EFFECTS OF *CRATAEGUS MONOGYNA* ADMINISTRATION ON SOME BIOCHEMICAL PARAMETERS IN DOGS WITH CARDIOVASCULAR DISEASE

EFECTELE ADMINISTĂRII DE *CRATAEGUS MONOGYNA* ASUPRA UNOR PARAMETRI BIOCHIMICI LA CÂINI CU AFECȚIUNI CARDIOVASCULARE

Marina Corina KRAČUNOVIĆ[1)], S. ORĂȘAN-ALIC[1)], R.T. CRISTINA[1)], Roberta TRIPON[1),2)],D. MORAR[1)], S. BĂRĂITĂREANU[3)], F. SIMIZ[1)], Eugenia DUMITRESCU[1),*)]

ABSTRACT

Crataegus monogyna (hawthorn) is a plant from the Rosaceae family, recognised in traditional medicine for various pharmacological and pharmacodynamic effects, including antioxidant, antiarrhythmic, vasodilator, positive inotropic, hypotensive, and anti-inflammatory effects. The aim of this study was to evaluate the effects of hawthorn (*Crataegus monogyna*), on some enzymes of diagnostic significance in cardiovascular diseases. The study was performed on a number of 20 dogs (10 males and 10 females) aged between 7 and 10 years, diagnosed with cardiovascular diseases. The biochemical parameters monitored during the study were aspartate aminotransferase (AST), creatine phosphokinase (CK-MB), alanine aminotransferase (ALT), and alkaline phosphatase (ALP). The study protocol included the administration of 430 mg standardised *Crataegus monogyna* capsules orally for a period of 6 months, and the serum activity of the enzymes investigated was evaluated serially at one, three, and six months. Favourable effects were found on the mean values of the biochemical parameters investigated, probably due to the vasodilator effect, leading to an increase in blood flow in the subendocardial and coronary vessels. Serum activity of liver enzymes was also found to be improved, due to the antioxidant and anti-inflammatory effects, more eloquent in females in the study group.

Keywords: *Crataegus monogyna*, cardiac dysfunction, phytotherapy, liver dysfunction

REZUMAT

Crataegus monogyna (păducel) este o plantă din familia *Rosaceae*, recunoscută în medicina tradițională pentru diverse efecte farmacologice și farmacodinamice, printre care efectele antioxidant, antiaritmic, vasodilatator, inotrop pozitiv, hipotensiv și antiinflamator. Scopul acestui studiu a constat in evaluarea efectelor Păducelului (*Crataegus monogyna*), asupra unor enzime cu semnificație de diagnostic în afecțiuni cardiovasculare . Studiul a fost efectuat pe un număr de 20 de câini (10 masculi și 10 femele) cu vârsta cuprinsă între 7 și 10 ani, diagnosticați cu afecțiuni cardiovasculare. Parametri biochimici monitorizați pe parcursul studiul au fost aspartat-aminotransferaza (AST), creatinfosfokinaza (CK-MB), alanin-aminotransferaza (ALT) și fosfataza alcalină (ALP). Protocolul studiului a prevăzut administrarea de capsule standardizate de *Crataegus monogyna* de 430 mg, pe cale orală, pe o perioadă de 6 luni și evaluarea seriată la una, trei și șase luni a activității serice a enzimelor investigate. Au fost constate efecte favorabile privind valorile medii ale parametrilor biochimici investigați, probabil datorită efectului vasodilatator, determinând o creștere a fluxului sanguin la nivelul vaselor subendocardice și coronariene. De asemenea s-a constatat îmbunătățirea activității serice a enzimelor hepatice, datorită efectului antioxidant și antiinflamator, aspect mai elocvent la femelele din lotul studiat.

Cuvinte cheie: *Crataegus monogyna,* disfuncție cardiacă, fitoterapie, disfuncție hepatică

Scientific studies have shown that many synthetic drugs that act on the cardiovascular system can cause adverse effects, such as digestive disorders, cardiac arrhythmias, and blood pressure fluctuations. Recently, there has been a growing interest in the use of natural therapeutic agents with minimal side-effects, in particular edible and medicinal plants, which have been widely used both in nutrition and in the treatment of certain diseases. *Crataegus monogyna* (hawthorn) is an essential plant of the *Rosaceae* family, recognized in traditional medicine for various pharmacological and pharmacodynamic effects due to some of the bioactive compounds it contains. Among these, the main compounds are chlorogenic acid, epicatechin, hyperoside, quercetin, rutin, vitexin, and procyanidins (21,22,27). Flavonoids, especially flavonols and flavones, are found in abundance, with the highest level of flavonoids being rutin, vitexin, vitexin-2''-O-rhamnoside, and hyperoside (18). According to numerous data in the literature, Hawthorn has antioxidant, antiarrhythmic, vasodilator, positive inotropic, hypotensive, and anti-inflammatory effects. (3, 5, 8, 11, 12, 14-16, 19, 23, 25, 26)

In the present study, the dogs were monitored from

1) University of Life Sciences "King Michael I of Romania", Faculty of Veterinary Medicine, Timișoara, Romania
2) University of Life Sciences "King Michael I of Romania", Research Institute for Biosecurity and Bioengineering, Timișoara, Romania
3) University of Agronomic Sciences and Veterinary Medicine, Faculty of Veterinary Medicine, Bucharest, Romania
*) *Corresponding author: eugeniadumitrescu@usvt.ro*

a blood biochemical point of view, the selected parameters being aspartate aminotransferase (AST), creatine phosphokinase (CK-MB) for humoral identification of subendocardial and/or myocardial ischaemia, alanine aminotransferase (ALT), and alkaline phosphatase (ALP), respectively, because in these dogs' liver damage was also found, with repercussions on the cardiovascular system. The association of the two pathologies is reported in multiple scientific studies in both human and veterinary medicine. (2,20,23).

MATERIALS AND METHODS

Animals and experimental design

The study was performed on a total of 20 dogs (one group of 10 males and one group of 10 females). The dogs included in the study ranged in age from 7 to 13 years and showed cardiovascular symptoms such as exertional fatigue, dyspnoea, nocturnal cough, syncopal states, and blood pressure oscillations. All dogs underwent electrocardiograms, cardiac ultrasonography, haematologic and biochemical analysis, and blood pressure measurement. The study protocol included the administration of standardised *Crataegus monogyna* 430 mg capsules orally in the following doses, depending on the weight of the dogs: up to 20 kg - 1 capsule/day, 20-40 kg - 2 capsules/day, over 40 kg - 3 capsules/day, for a period of 6 months. A serial evaluation was performed at one, three, and six months of the presented parameters.

The biochemical parameters monitored during the study were aspartate aminotransferase (AST), creatine phosphokinase (CK-MB), alanine aminotransferase (ALT), and alkaline phosphatase (ALP).

In this study, only the changes observed in these biochemical parameters during administration of the hawthorn product were evaluated.

Biochemical investigations

The blood biochemical analyses were performed in the Laboratory of Metabolic and Functional Explorations of the University of Life Sciences " Regele Mihai I of Romania" Timisoara. Blood biochemical parameters were determined from blood serum by standard methods with an automatic biochemistry analyser: Randox - Rx Daytona+. From all dogs, blood samples were collected in the morning after a 12-hour fasting period from the cephalic vein in plain or gel tubes for biochemical examination of blood. Serum was separated from the erythrocyte mass within approximately 1 hour of sample collection and refrigerated until analysis.

Statistical analysis

Statistical analysis was performed with the IMB-SPSS program, using the Turkey Anova test to calculate within-plot differences between sampling intervals. Student's t-test was used for differences between males and females. Values were expressed as mean values ± SD (standard deviation).

Statistical values were considered as follows: $p < 0,05$*, $p < 0,01$**; $p < 0,001$***; ns: not significant.

The statistical program used to produce the graphs was Graph Pad Prism 6.0 for Windows (Graph Pad Software, San Diego, U.S.A.). Only significant differences between the four periods of sampling were highlighted in the graphs.

RESULTS AND DISCUSSION

Aspartate aminotransferase (AST) catalyses the transfer of the amino group from L-aspartic acid to ketoglutaric acid, leading to the synthesis of oxaloacetic and L-glutamic acid, with a role in energy and proteinogenesis. AST shows increased concentrations in the myocardium and liver, with 60% found in the cytoplasm and 40% in the mitochondria (4,9).

In the context of cardiac disease in dogs, the determination and visualisation of the evolution of blood biochemical values of aspartate aminotransferase is necessary, being associated with intrinsic aspects of ischaemic phenomena in myocardiocytes (24).

In a clinical context in which the advanced age of the dogs in the study group, in addition to cardiac symptoms, showed exertional fatigue, dyspnoea, nocturnal cough, syncopal states, and dyspeptic disorders secondary to hepatocellular dysfunction, we decided to evaluate serum enzyme activity of alanine aminotransferase (ALT) and alkaline phosphatase (ALP). The advanced age of the dogs under study is associated with changes in vascular elasticity and the ability to adapt to variations in blood flow, leading inevitably to subendocardial and/or myocardial distress, materialised by subendocardial and/or myocardial ischaemic injury, including heart rhythm disturbances.

Considering the above mentioned, the determination of the biochemical value of serum creatine kininephosphokinase (CK-MB) represented, together with the other dosed parameters, firstly, a protocol for monitoring the morpho-functional integrity of the cardiovascular system and secondly, of the liver.

As for hawthorn (*Crataegus monogyna*), according to data from specialised literature (6,10,11), it has an antioxidant role and converts, at hepatic level, LDL cholesterol into HDL cholesterol with beneficial effects on the vascular and coronary systems, in particular, cardiac functions, being also protective and tonic on the liver. In our study, the effect of administration of Hawththorn - 430 mg capsules, doses ranging from 1 to 3 capsules per day, depending on the weight of the dogs, for six months was followed. Determinations of blood biochemical parameters ALT, AST, ALP, CK-MB were carried out, and their changes were monitored.

Table 1 shows the mean values and dispersion indices of AST and CK, and Table 2 the mean values and dispersion indices of ALT and ALP, in 20 dogs, 10 males and 10 females, following oral administration of hawthorn, once daily, in the form of standardised 430 mg capsules. The data presented in the Table 1 reflect the fact that in the males in the study, statistically, the mean serum aspartate aminotransferase (AST) level before *C. monogyna* administration was 9.79% higher than after one month of administration.

Table 1

Mean values and dispersion indices for biochemical parameters AST and CK in dogs with cardiovascular disease

Specify		Male		Female		P
		Media±SD*	SEM**	Media±SD	SEM	
AST (U/L)	0	63.52±12.385^{aA}	3.917	86.36±11.329^{bAC}	3.583	0.000
	1	56.01±9.639^{aA}	3.048	77.11±8.901^{bA}	2.815	0.000
	3	53.86±9.616^{aA}	3.041	72.86±8.445^{bBC}	2.670	0.000
	6	51.71±9.821^{aA}	3.106	67.26±7.559^{bBC}	2.390	0.001
	p	0.081		0.000		
CK-MB/ CPK2 (U/L)	0	172.24±56.413^{aA}	17.839	271.49±55.185^{bA}	17.451	0.001
	1	152.48±42.660^{aA}	13.490	237.66±42.037^{bAC}	13.293	0.000
	3	147.62±43.481^{aA}	13.750	230.30±38.668^{bAD}	12.228	0.000
	6	126.91±39.356^{aA}	12.446	197.06±34.292^{bBCD}	10.844	0.000
	p	0.197		0.005		

$^{a-a}$p>0.05; $^{a-b}$p<0.05; Differences between males and females were performed with the student t-test
$^{A-A,B-B,C-C,D-D}$ p>0.05; $^{A-B,A-C,A-D,B-C.B-D}$ p<0.05; Differences between sampling days were performed with the Anova test with Tukey; *SD – standard deviation; ** SEM- mean error of the mean

Regarding the AST value, as a sensitive marker of myocardial and hepatic distress, it was found that before *Crataegus monogyna* administration, its mean serum values were above the physiological limit of the species of 10-40 U/L. Females were more affected by 0.76%, compared to males, which suggests the possibility of a more advanced degree of subendocardial and/or myocardial ischaemia, possibly hepatic, being of diagnostic and prognostic importance, since in cardiac ischaemic syndromes the growth time is early (6-12 hours).

Analysing the mean values obtained for serum aspartate aminotransferase (AST), it was found that, in the male dogs in the study, after one month of treatment, there was a decrease of 11.82%.

The same downward trend was observed at 3 and 6 months of treatment with *C. monogyna*, respectively, where the decrease in mean AST values was 15.20% and 18.59%, respectively, with no statistically significant differences, p>0.05.

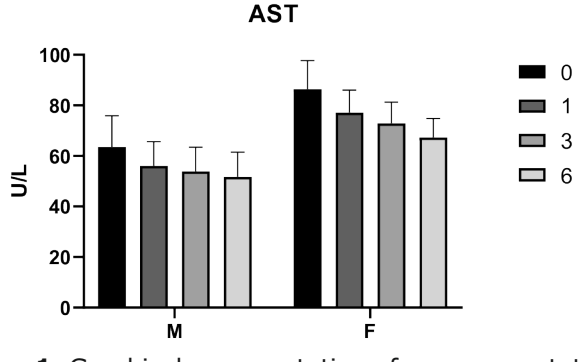

Fig. 1. Graphical representation of mean aspartate aminotransferase values in dogs with heart disease receiving *C. monogyna*

In the case of female dogs of the studied group, in which also the mean values of aspartate aminotransferase were higher than in males, at 1 month after administration the decrease was 10.71%, statistically insignificant, p>0.05, on the other hand, at 3 months of hawthorn administration, the mean value of AST decreased by 15.63%, being significant differences, at a significance threshold p<0.05.

The favourable effect of *C. monogyna*, on aspartate aminotransferase, was recorded after 6 months of continuous administration of the product, when the decrease was 22.11%, a statistically significant difference between the initial and final phases of the study, at a p<0.001, as shown graphically in Figure 1.

Serum creatine kinase (CK) activity, in general, being closely related to cellular energy metabolism, the determination of the CK-MB fraction in the cardiac dogs of the studied group was useful to determine the existence of a protective action of the *C. monogyna*-based product on the heart and, implicitly, on the coronary system. From the analysis of the tabulated values presented above, it was found that before the administration of hawthorn, the serum level of this enzyme recorded average serum values higher than the physiological ones, as reported in the specialised literature, namely 172.24 U/L in males and 271.49 U/L in females. In male dogs of the studied group, following treatment with hawthorn for 1, 3, and 6 months, mean values decreased by 11.47%, 14.29%, and 26.31%, respectively, with no significant differences at a significance level of p>0.05.

In the female dogs in the study group, mean serum CK-MB ions decreased by 12.46% after 1 month and by 15.17% after 3 months of treatment, and there were no statistically significant differences, p>0.05, plotted in Figure 2.

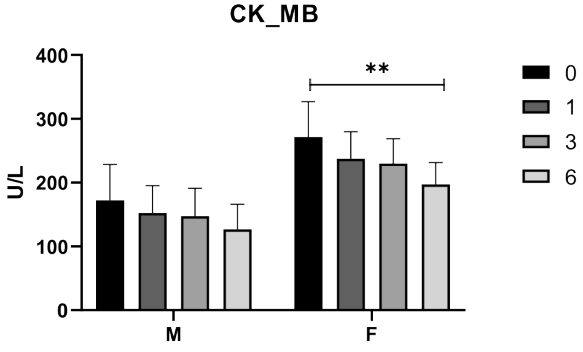

Fig. 2. Graphical representation of creatine phosphokinase-MB mean values in dogs with heart disease receiving *C. monogyna*

An eloquent aspect was, in the case of females, the mean value of CK-MB after 6 months of treatment when there was a reduction of 27.41%, a significant decrease, recording a significance threshold $p < 0.05$.

The decrease in serum enzymatic activity of the parameters that may indicate cardiac injury, CK-MB and AST, during the administration of hawthorn, indicates a positive action on the cardiovascular system in the dogs taken in the study. This action is also confirmed in another scientific study in which, following administration of a Crategus extract, the values of these two parameters were significantly reduced (13).

In accordance with other studies showing a positive correlation between liver and cardiovascular health (24), serum alanine aminotransferase (ALT) and alkaline phosphatase (ALP) enzymes were determined according to the established protocol.

Statistical analysis of ALT and ALP values in the dogs studied showed that serum alanine aminotransferase values decreased by 9.79% in males after one month of treatment and by 13.88% after 3 months, with no significant differences between the three periods studied at $p>0.05$. After 6 months of hawthorn capsules administration, the mean value was found to be lower by 18.85%, being a significant difference between the beginning of treatment and the end of the study period, at a $p<0.05$.

From the analysis of the alkaline phosphatase (ALP), in the males of the studied group, the evolution of the mean values showed a similar aspect to ALT, decreasing by 15.03% after the first month of administration and by 16.02% at the end of three months of treatment with Hawthorn, with no statistically significant differences, $p>0.05$. At the end of 6 months of continuous administration of paducel capsules, a reduction of the serum value by 22.11% was observed with significant differences, $p<0.05$.

Female dogs in the study group showed a more favourable evolution compared to males. Regarding mean values of ALT and ALP, there were no significant differences after the first month of treatment, at a significance level $p>0.05$. A noteworthy aspect is that after 3 and, respectively, 6 months of treatment, there was a reduction in mean serum ALT by 16.49% and 18.28%, respectively, statistically significant differences at a threshold $p<0.01$ at three months and $p<0.001$ at six months, plotted in Figure 3.

The situation was similar in the case of alkaline phosphatase, where the decrease of 24.25% was the most eloquent after 6 months of administration of the *C. monogyna*-based product, with a statistically significant difference at a significance level $p>0.05$, as shown in Figure 4. Alkaline phosphatase shows elevations, especially in liver disease and in muscle disease. In the present study, it was used as a liver biochemical parameter by correlating with a concomitant increase

Table 2

Mean values and dispersion indices for biochemical parameters ALT and ALP in dogs with cardiovascular disease

Specify		Male		Female		P
		Media±SD*	SEM**	Media±SD	SEM	
ALT (U/L)	0	$79.64±14.363^{aAC}$	4.542	$80.25±10.201^{aA}$	3.226	0.914
	1	$71.84±15.500^{aAD}$	3.953	$73.43±7.821^{aAC}$	2.473	0.737
	3	$68.58±12.099^{aAD}$	3.826	$67.01±4.959^{aBC}$	1.568	0.709
	6	$64.62±10.493^{aBD}$	3.318	$65.58±6.540^{aB}$	2.068	0.794
	p	0.045		0.000		
ALP (U/L)	0	$148.87±27.222^{aA}$	8.608	$189.52±36.048^{bA}$	11.399	0.011
	1	$126.48±18.466^{aAC}$	5.840	$170.02±27.140^{bAC}$	8.583	0.001
	3	$125.01±17.702^{aAD}$	5.598	$160.57±24.290^{bAD}$	7.681	0.001
	6	$115.95±14.907^{aBCD}$	4.714	$143.56±18.076^{bBCD}$	5.716	0.002
	p	0.006		0.005		

$^{a-a}p>0.05$; $^{a-b}p<0.05$; Differences between males and females were performed with the student t-test
$^{A-A,B-B,C-C,D-D}p>0.05$; $^{A-B,A-C,A-D,B-C.B-D}p<0.05$; Differences between sampling days were performed with the Anova test with Tukey; *SD – standard deviation; ** SEM- mean error of the mean

in ALT and AST. By the results observed for this parameter, correlated with the decrease in the other transaminases, we can discuss the hepatoprotective effect of *C. mono-gyna*, as also shown in the study by Zjwan Mohamman (28) in which, after a 5-week administration of haw-thorn in a high triglyceride diet, significant decreases in ALP were observed compared to the values in the group not receiving hawthorn.

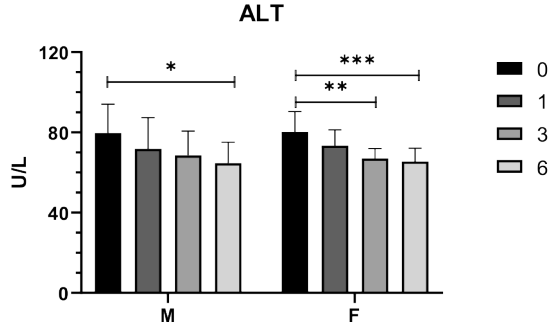

Fig. 3. Graphical representation of mean values of alanine aminotransferase in dogs with heart disease receiving *C. monogyna*

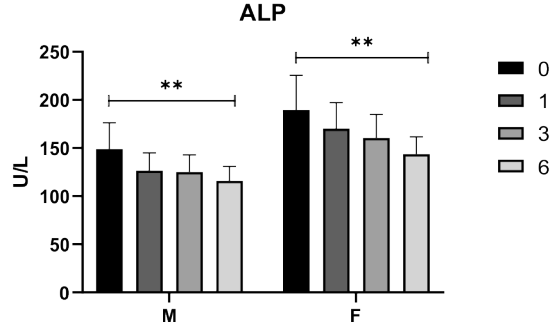

Fig. 4. Graphical representation of mean values of alkaline phosphatase in dogs with heart disease receiving *C. monogyna*

In terms of hepatocellular integrity and the parameters under study, serum transaminase levels (AST and ALT) are frequently elevated in liver injury, because they reach the peripheral blood in cases of hepatocellular integrity damage, being important markers of hepatocellular damage (7). The results obtained regarding the evolution of liver enzymes (AST, ALT) followed a similar evolution of values as that obtained by Fatima Ex-Zahhra Amrati et al. (1) following the induction of liver stress in rats in order to verify the existence of the hepatoprotective effect of *Crataegus monogyna*. Also, a concomitant decrease in the serum values of the two parameters as indicators of hepatocellular integrity was obtained in another scientific study (16), thus highlighting once again the hepatoprotective function of hawthorn.

CONCLUSIONS

Due to the increased bioavailability, pharmacodynamics, and pharmacokinetics of the active principles contained in *Crataegus monogyna*, the administration of this biopreparation improved the biochemical parameters studied, materialised by the improvement of the biological status in the dogs studied. Female dogs recorded lower serum levels of AST and CK-MB compared to males, starting from the third month of administration of hawthorn capsules, probably due to the vasodilator effect, improving coronary and microvascular blood flow, with beneficial effects on the myocardium. The evolution of the serum enzymatic activity of ALT and ALP in female dogs was higher than in males after the first month of administration, due to the antioxidant and cholesterol metabolism-regulating effect. The significant decrease in serum AST and CK-MB suggests a vasorelaxant effect, especially after 6 months of administration of *Crataegus monogyna*.

REFERENCES

1. *Allen L.A., Felker G.M., Pocock S.,* (2009), Liver function abnormalities and outcome in patients with chronic heart failure: data from the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM) program. Eur J Heart Fail, 11:170e7
2. *Amrati F.E.Z., Mssillou I., Boukhira S., Bichara M.D., El Abdali Y., Azevedo R.G., Mohamed C., Slighoua M., Conte R., Kiokias S., Pontes G.S., Bousta D.,* (2024), Phenolic composition of *Crataegus monogyna Jacq*. extract and its anti-inflammatory, hepatoprotective, and antileukemia effects. *Pharmaceuticals, 17(6):786*
3. *Braslasu M.C., Braslasu E.D., Verman I.G., Savulescu-Fiedler I.M,* (2004), Veterinary cardiology. Diagnosis of cardiovascular diseases in animals, Ed. I (in Romanian), (Ed.) Artprint, Bucharest, Romania
4. *Brixius K., Willms S., Napp A., Tossios P., Ladage D., Bloch W., Mehlhorn U., Schwinger R.H. G.,* (2006), *Crataegus* special extract WS 1442 induces an endothelium-dependent, NO-mediated vasorelaxation via eNOS-phosphorylation at serine 1177. Cardiovasc Drugs Ther, 3:177-184
5. *Busse R., Edwards G., Félétou M., Fleming I., Vanhoutte P.M., Weston A.H.,* (2002), EDHF: bringing the concepts together. Trends Pharmacol Sci, 8:374-380
6. *Chang W.T., Dao J., Shao Z.H.*, (2005), Hawthorn: potential roles in cardiovascular disease. Am J Chin Med, 1:1-10
7. *Eujin K., Eungyeong J., Jang-Hoon L.,* (2022), Potential roles and key mechanisms of hawthorn extract against various liver diseases. Nutrients, 4(4):867
8. *Garjani A., Nazemiyeh H., Maleki N., Valizadeh H.,* (2000), Effects of extracts from flowering tops of *Crataegus meyeri* on ischaemic arrhythmias in anaesthetized rats. Phytother Res, 6:428-431
9. *Gong K.Z., Song G., Spiers J.P., Kelso E.J., Zhang Z.G.*, (2007), Activation of immune and inflammatory systems in chronic heart failure: novel therapeutic approaches. Int J Clin Pract Suppl, 4:611-621

10. *Heber D.,* (2001), Herbs and atherosclerosis, Curr Atheroscler Rep, 1:93-96
11. *Jie W., Xiong X., Feng B.,* (2013), Effect of *Crataegus* Usage in Cardiovascular Disease Prevention: An Evidence-Based Approach. Evid Based Complement Alternat Med, 2013:149363
12. *Li C., Wang M.H.,* (2011), Anti-inflammatory effect of the water fraction from hawthorn fruit on LPS-stimulated RAW 264.7 cells. Nutr Res Pract, 2:101-106
13. *Mombouli J.V., Vanhoutte P.M.,* (1999), Endothelial dysfunction: from physiology to therapy, J Mol Cell Cardiol, 1:61-74
14. *Mona A.S., Sahar M., Shimaa E.M., Amira M.D.,* (2018), Influence of Hawthorn (*Crataegus oxyacantha*) leaves extract administration on myocardial infarction induced by isoproterenol in rats. Cardiology and Angiology: An International Journal, 7(1):1-12
15. *Müller A., Linke W., Klaus W.*, (1999), *Crataegus* extract blocks potassium currents in guinea pig ventricular cardiac myocytes. Planta Med, 4:335-339
16. *Rezaei-Golmisheh A., Malekinejad H., Asri-Rezaei S., Farshid A.A., Akbari P., (*2015), Hawthorn ethanolic extracts with triterpenoids and flavonoids exert hepatoprotective effects and suppress the hypercholesterolemia-induced oxidative stress in rats. Iran J Basic Med Sci, 18(7):691-699
17. *Rodrigues S., Calhelha R.C., Barreira J.C., Dueñas M., Carvalho A.M., Abreu R.M., Santos-Buelga C., Ferreira I.C.,* (2012), *Crataegus monogyna* buds and fruits phenolic extracts: Growth inhibitory activity on human tumor cell lines and chemical characterization by HPLC–DAD–ESI/MS. Food Res Int, 49:516-523
18. *Rodriguez M.E., Poindexter B.J., Bick R.J., Dasgupta A.,* (2008), A comparison of the effects of commercially available hawthorn preparations on calcium transients of isolated cardiomyocytes, J Med Food, 4:680-686
19. *Schwinger R.H.G., Pietsch M., Frank K., Brixius K.*, (2000), *Crataegus* special extract WS 1442 increases force of contraction in human myocardium cAMP-independently. J Cardiovasc Pharmacol, 5: 700-707
20. *Shinagawa H., Inomata T., Koitabashi T.,* (2008), Prognostic significance of increased serum bilirubin levels coincident with cardiac decompensation in chronic heart failure. Circ J, 72:364e9
21. *Sokół-Łętowska A., Oszmiański J., Wojdyło A.*, (2007), Antioxidant activity of the phenolic compounds of hawthorn, pine and skullcap. Food Chem, 103:853-859
22. *Tadić V.M., Dobrić S., Marković G.M., Đorđević S.M., Arsić I.A., Menković N.A.R., Stević T.,* (2008), Anti-inflammatory, gastroprotective, free-radical-scavenging, and antimicrobial activities of hawthorn berries ethanol extract. J Agric Food Chem, 56:7700-7709
23. *Taimor G., Hofstaetter B., Piper H.M.,* (2000), Apoptosis induction by nitric oxide in adult cardiomyocytes via cGMP- signaling and its impairment after simulated ischemia. Cardiovasc Res, 3:588-594
24. *Van Deursen V.M., Damman K., Hillege H.L., Van Beek A.P., Van Veldhuisen D.J., Voors A.A.,* (2010), Abnormal liver function in relation to hemodynamic profile in heart failure patients, J Card Fail, 16(1):84-90
25. *Vijayan N.A., Thiruchenduran M., Devaraj S. N.*, (2012), Anti-inflammatory and anti-apoptotic effects of *Crataegus oxyacantha* on isoproterenol-induced myocardial damage. Mol Cell Biochem, 367(1-2):1-8
26. *Yndestad A., Damås J.K., Øie E., Ueland T., Gullestad L., Aukrust P.,* (2007), Role of inflammation in the progression of heart failure. Curr Cardiol Rep, 3:236-241
27. *Zhang Z., Chang Q., Zhu M., Huang Y., Ho W.K., Chen Z.Y.,* (2001), Characterization of antioxidants present in hawthorn fruits. *J Nutr Biochem,* 12:144-152
28. *Zjwan M.I.H., Goran Q.O., Twana A. M.,* (2017), The liver protectiv role of hawthorn (*Crataegus* sp.) in hypertriglyceridimic induced rats. Polytech J, 7 (2):111-118.