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Potential Ameliorative Effect of Melissa Officinalis Ethanolic Extract on Bleomycin-Induced Cardiotoxicity in Rats

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Abstract:
Melissa officinalis has antioxidant and anti-inflammatory activities and is used in various diseases. This study aimed to elucidate the ability of Melissa officinalis ethanolic extract to lessen cardiotoxicity in male rats after being injected with bleomycin to infect them with cardiotoxicity. Forty adults male Wister albino rats weighing (150–200g) were placed into four groups at random after acclimatization (10 rats each); The first group, which functioned as the control group, was composed of healthy rats, the second group included ordinary rats orally administered with 450 mg/kg/day of Melissa officinalis extract (MEE) for six weeks, Rats in the third group were given bleomycin intraperitoneally at a dose of 15 mg/kg/week for the same duration, and the fourth group included rats poisoned with bleomycin for six weeks while being concomitantly ingested with MEE orally for six weeks. The findings showed that MEE significantly reversed the cardiological declines brought on by bleomycin; this was demonstrated by a large increase in cardiac GSH and CAT and a significant reduction in cardiac MDA. Additionally, despite increased HDL, serum levels of CK, LDH, TNF-α, IL-1β, cholesterol, triglycerides, and LDL have been significantly lowered. Additionally, the histopathology results demonstrated significant regrowth. In conclusion, MEE contains a high concentration of antioxidants like phenolic compounds that can decrease bleomycin-induced cardiotoxicity. So, these results recommend using Melissa officinalis as a food supplement as it effectively reduces cardiotoxicity.

***Keywords**: Cardiotoxicity, phenolic compounds, antioxidant enzymes, histopathology*

Introduction

Coronary heart disease are among the major causes of morbidity and mortality around the world that predispose to disability, economic problems and health more than any other disease [1]. Cardiomyopathy, in general, means reduced pumping strength of the heart, and

hence, can cause heart failure. It is the third reason for heart failure after coronary insufficiency and hypertension [2].

The bacteria *Streptomyces verticillus* produces the chemotherapeutic drug bleomycin [3]. Animal models of pulmonary fibrosis use bleomycin since it has fibrosis as one of its main side effects when treating human cancer. Treatment for malignant pleural effusion, lymphoma, squamous cell carcinomas, and germ cell tumors often involves the intrapleural injection of bleomycin. In order to stop the cell cycle in tumor cells, bleomycin is believed to cause single and double strand DNA breaks in those cells. This is accomplished through the chelation of metal ions and the production of DNA-crushing superoxide and hydroxide free radicals as a result of the reaction between the produced pseudo enzyme and oxygen [4]. Overproduction of ROS can result in an inflammatory response that is harmful to the lungs, activates fibroblasts, and leads to fibrosis [5] & [6]. The effects of this medication on unique tissues are strongly impacted by the bleomycin hydrolase enzyme, which inactivates bleomycin. Low enzyme levels in the lungs make them more susceptible to bleomycin-induced tissue damage [7].

The role of medicinal plants in maintaining human health is enormous. Larvicidal, antibacterial, antifungal, antiviral, anti-helminthic, anti-allergic, and anti-carcinogenic are only a few of their many properties [8]. These therapeutic properties are caused by the presence of chemical elements such as tannins, oils, and gums. Additionally, due to their understanding of the chemical components of plants, pharmacologists, microbiologists, botanists, and natural product chemists are searching the world for phytochemicals that may have developed for the treatment of various illnesses. Many drugs used today are derived from plants [9]. *Melissa officinalis L* (*Lamiaceae*), also known as lemon balm, is a famous medicinal plant species used in the remedy of numerous diseases; it is widely used as a vegetable, including flavor to dishes [10]. *M. Officinalis* is a rich source of natural antioxidants; its leaves incorporate many phytochemicals, together with polyphenolic compounds, consisting of caffeic acid derivatives [11], numeric compounds [12], flavonoids [13], essential oil, and considerable citral [14]. In addition, leaves incorporate vitamins E and C which have crucial activity as free radical inactivators [11]. *M. Officinalis* has antispasmodic, anti-histaminic, and antibacterial properties [15]. Additionally, it is used to treat anxiety, neurosis, nervousness, palpitations, and headaches [16]. Also, it's also thought to have useful effects on people with Alzheimer`s disease [17] and has healing efficiency with the modulation of temper and cognitive performance [18].

The aim of the study was to investigate the possible benefits of an ethanolic extract of *Melissa officinalis* on rat cardiotoxicity induced on by bleomycin using several cytokine and antioxidant markers.

Materials and methods

Chemicals

Bleomycin was purchased from Sigma Aldrich Company (St. Louis, MO, USA). As stated by Zaghloul *et al*., (2017) [19].

Plant materials and extraction

Melissa officinalis obtained from a local market (Abd El-Rahman Harraz, Bab El-Khalk zone, Cairo, Egypt), grinded and soaked in ethanol (1: 10 w/v) for three days for extraction process under non-stop shaking. After filtration, the solvent was evaporated with the use of a rotary evaporator using (Rotavapor® R-300) it at 35 to 40 °C. under decreased stress till dryness was achieved, after which the yield percent was calculated as gram (extract)/a hundred g (crude powdered herb). Then, the in-vitro antioxidant activity of the extract, after which the extract was saved at -20°C till similar use Sulieman (2007) [20].

Determination of total extract yield

The extract was added to a quick-fit round bottom flask with a known weight (W1), freeze-dried, and weighted again (W2); the yield was then calculated using the following formula:

Extract yield (g/ g crude herb) = (W2 −W1)/W3

Where,

W1 is the weight of a clear and dry quick-fit flask in grams,

W2 is the weight of the flask after lypholization in grams

W3 is the weight of the crude powdered herb in grams

Determination of total phenolic content

The phenolic content of the MEE was determined according to the method of Jayaprakasha and Rao (2000) [21].

DPPH radical scavenging activity

The ability of antioxidants in CEE to quench DPPH radicals was established, as previously mentioned by Nogala-Kalucka *et al*., (2005) [22].

Experimental design

From the Animal Colony at the National Research Centre in Giza, Egypt, 40 male Wister albino rats weighing 150–200g had been purchased; The rats were cared for by humans in accordance with the institution's established standards for the handling and use of experimental animals, which were approved by the faculty's ethics committee at Al-Azhar University in Assiut, Egypt; however, the same ethical committee decided to approve this trial. Prior to the test, the rats were kept in suitable plastic cages with free access to food and water for a week so they could get used to the environment. When the rats were acclimated to the conditions in the testing room, they were divided into 4 groups at random (10 rats each).

Healthy rats in the first group were given a basal diet according to Reeves *et al*., (1993) [23] and an intraperitoneal injection of 1 ml of isotonic saline without any other treatments, the second group was made up of healthy rats that had received MEE orally every day for six weeks at a dose of 450 mg/kg, the third group included rats that had received intraperitoneal bleomycin at a rate of 15 mg/kg/week for six weeks and the fourth group included rats that had been given MEE orally every day.

Blood and tissue sampling

After diethyl ether anesthesia and an overnight fast, 3-5 ml of blood were drawn from the rat's retro-orbital plexus using heparinized, sterile glass capillaries at the conclusion of the treatment session. Blood sample's sera were separated, and they were kept at -80°C until as soon as it was practical to conduct biochemical studies. Blood sample was centrifuged for 15

minutes at 3000 rpm. The rats were promptly butchered. After blood was obtained from the rats, they were promptly killed, and the hearts were extracted, cleansed in saline, dried, rolled in aluminum foil, and chilled at -80°C for homogenization and biochemical evaluations. The nuclear and mitochondrial fractions of the homogenate were subsequently separated by centrifugation at 5000 rpm for 20 minutes.

Biochemical determinations

With the aid of a Shimadzu spectrophotometer, all of the biochemical measurements were performed (UV–vis 1201, Japan).

Using kits obtained from Germany's DiaSys Diagnostic systems GmbH, the serum lipid profile was determined according to the colorimetric method described by Roeschlau *et al*., (1974) [24] & Fossati and Principe, (1982) [25]. Making use of reagent kits purchased from BioVision, South Milpitas, California, USA, LDH and CK-total were measured calorimetrically according to the method of Van der Heiden *et al*., (1994) [26] & IFCC. (1989) [27].

Oxidative stress markers of heart tissue

Heart GSH, CAT, and MDA kits from Biodiagnostic, Dokki, Giza, Egypt. All parameters were determined by Montgomery and Dymock (1961) [28], Ruiz-Larrea (1994) [29] & Koracevic *et al*., (2001) [30].

Determination of pro-inflammatory cytokine (TNF-α & IL-1β)

The concentrations of TNF-α and IL-1β in the serum were determined according to the method of Allan *et al*., (2005) [31] using rat ELISA kits from Sino Gene Clon Biotech Co., Ltd., No. 9 BoYuan Road, YuHang District 311112, Hang Zhou, China (Dynatech Microplate Reader Model MR 5000, 478 Bay Street, Suite A213, Midland, ON, Canada).

Histopathology

Hematoxylin and eosin was used to stain 5 m thick paraffin sections, which were then examined under a light microscope as described by Drury and Wallington (1980) [32].

Statistical analysis

Analysis of variance (ANOVA) was used to compare means, followed by the post hock (Tukey) multiple comparisons test at $p \leq 0.05$. The statistical analysis system (SAS) computer software was used for this; copyright (c) 1998 by SAS Institute Inc., Cary, North Carolina, USA according to Steel and Torrie (1960) [33].

Results and Discussion

The Melissa officinalis ethanolic extract's yield, total phenolic content (TPC), and radical scavenging activity (RSA) are depicted in Table (1). MEE was shown to have a higher total phenolic content (20.1mg/g) and significant radical scavenging activity (58.3%). These data agree with Dehelean *et al*., (2006) [34], Awad *et al*., (2007) [35], Pereira *et al*., (2009) [36] and Ibarra *et al*., (2010) [37] they mentioned that both artificial and organic free radicals may be scavenged by the lemon balm extract in either their early or late stages of production. The researchers also point out that *Melissa officinalis* extracts (MOE) protect against oxidative stress-related illnesses including diabetes, cardiovascular disease (CVD), or neurological diseases like Parkinson's and Alzheimer's. All of these beneficial effects can also be attributed to the herb's significant amounts of rosmarinic, oleanolic, ursolic, and triterpenoids, assuming that each of these active components can inhibit-aminobutyric acid

(GABA) transport activity and elevate the level of this neurotransmitter in the brain. In animal models of myocarditis, the flavonoids quercetin, luteolin, and apigenin have been shown to be beneficial. They modulate the immune response, reduce inflammation, and may subsequently suppress cardiac tissue remodeling that happens in dilative cardiomyopathy, Zhang *et al*., (2016) [38], Wu *et al*., (2020) [39]. Also, Kennedy *et al*., (2016) [40] reported that the *M. officinalis* extracts represent ongoing efforts to look into novel substances with possible antibacterial properties. Additionally, numerous studies have demonstrated that various herbal remedies are sources of a variety of compounds, many of which have antibacterial and radical scavenger capabilities that can protect the human body from pathogens as well as cellular oxidation events. Due to their potential for generating herbal medicines with antibacterial, antiviral, and antioxidant properties, these materials are important Jahanban-Esfahlan *et al*., (2015) [41], Miraj *et al*., (2017) [42], Saratale *et al*., (2018) [43].

Approximately 27 and 8 mg/g, respectively, of phenolic compounds and flavonoids were discovered to be present in substantial excess in dried extracts of *M. officinalis* leaves. Additionally, consumption of flavonoids and mortality from coronary artery disease may be negatively correlated Nijveldt *et al*., (2001) [44] & Tavafi (2015) [45]. The antioxidant action of flavonoids is their main advantage. This might be caused by xanthine oxidase inhibition, interference with inducible nitric oxide synthase activity, and free radical scavenging Nijveldt *et al*., (2001) [44].

Table (1): Total phenolic content, radical scavenging activity of Melissa officinalis ethanolic extracts*

Parameter / Sample	Yield (%)	TPC (mg/g)	RSA (%)
Melissa officinalis ethanolic extract (MEE)	18.1±0.51	20.1±0.71	58.3±3.1

** Mean of three replicates*

As compared to the control group and bleomycin group the resulted showed that the significantly higher serum cholesterol, triglyceride, and LDL levels as well as significantly lower HDL levels. Intriguingly, the administration of MEE to bleomycin-poisoned rats led to a considerable evolution of lipid profile parameters as evidenced by marked increases in HDL levels and significant decreases in cholesterol, triglycerides, and LDL levels when compared to bleomycin-treated rats Table (2). These statistics are consistent with Bolkent *et al*., (2005) [46] & Zarei *et al*., (2015) [47], not only does lemon balm have an excellent background in traditional medicine, but recent research has shown that it can both lower and increase total lipid levels. confirmed that it is widely effective in cardiovascular diseases. Decreases HDL (High Density Lipoprotein) levels and liver cholesterol synthesis. The major cause of death in the modern world is cardiometabolic illness. This term's definition has been broadened to cover chronic renal failure, diabetes, and CVD de Waard *et al*., (2019) [48].

When established risk factors are present, cardiotoxicity may be to blame for the direct effects of medication on heart function and structure or it may speed up the onset of cardiovascular disease. There have been several research and publications of data on various

forms of pharmaceutical and/or radiation-induced cardiotoxicity to date. There are three forms of cardiotoxic action of antineoplastic agents Lenneman *et al*., (2016) [49] & López-Sendón *et al*., (2020) [50].

Acute cardiotoxicity is uncommon and typically presents with no symptoms. It happens throughout or right after chemotherapy (a few hours). Acute myocarditis or myocarditis, which very infrequently results in a rapid myocardial infarction or death, non-specific alterations in the terminal region of the ventricular complex, transitory heart failure, an asymptomatic decrease in ejection fraction, and acute myocarditis are all examples of arrhythmias. In this sense, polyphenol-rich plants are recognized as dietary supplements that are safe and have significant health benefits, especially with respect to lipid status and blood glucose levels, thus dietary supplements with plant extracts may be useful in cardiometabolic disease Cicero *et al*., (2017) [51].

Table (2): Effect of MEE and bleomycin on serum cholesterol, triglycerides, LDL and HDL levels in rats.

	Control	MEE	Bleomycin	Bleomycin ~ MEE
CHO (mg/dl)	65.4±2.0	68.5±4.4	160±13.5*	102±7.7#
TG (mg/dl)	105±8.6	107±1.9	226±10.4*	129±11.2#
HDL-C (mg/dl)	45.7±2.7	45.6±1.9	35.6±1.9*	42.6±1.3#
LDL-C (mg/dl)	22.5±1.7	22.5±1.4	79.3±15.2*	36.5±3.6#

Values are expressed as mean ±SD

** and # Means there are a significant difference compared with the control group and bleomycin group at (p≤ 0.05).*

Regarding Table (3), the considerable increase in cardiac MDA together with a large decrease in the activity of CAT as well as GSH level during bleomycin intoxication caused a marked deterioration in the cardiac oxidative stress status. In contrast to the bleomycin-intoxicated group, MEE therapy of bleomycin-intoxicated rats significantly reduced cardiac MDA levels while also significantly increasing GSH levels and CAT activities. These data agree with Draginic *et al*., (2021) [52] who found that the MOEs from *Melissa officinalis* significantly reduced the production of prooxidants (O_2-, H_2O_2, and TBARS) and enhanced the antioxidant defense system by increasing GSH, SOD, and CAT in comparison to EAM, with the medium and high doses (100 and 200 mg/kg) being more effective than the low dose (50 mg/kg) at (p≤0.05) Also, *M. Officinalis* extract may be connected, at least in part, to the antioxidant benefits of this herbal extract that were previously discussed. This is corroborated by the fact that the serum of rats given *M. officinalis* (100 mg/kg) extract had increased antioxidant enzymes and SOD activity, as well as lower serum MDA levels. It should be mentioned that the serum MDA level has been employed as a gauge for tissue harm brought on by in-vivo free oxygen radicals Kim *et al*., (2000) [53] & Sahin *et al*., (2011) [54]. In addition, 5 days after reperfusion, the extract significantly increased blood superoxide dismutase (SOD) activity and significantly decreased serum cardiac troponin I (CTnI), lactate dehydrogenase (LDH), and malondialdehyde (MDA) levels. The dosage that was effective was MOE-100mg/kg.

Table (3). Effect of MEE and bleomycin on cardiac MDA, GSH and CAT in rats.

	Control	MEE	Bleomycin	Bleomycin ~ MEE
MDA (µmol/g tissue)	15.5±1.1	14.5±1.5	28.4±5.5*	18.8±2.1#
GSH (nmol/g tissue)	55.9±5.5	57±4.6	19.9±1.9*	47.4±7.4#
CAT (U/g tissue)	370±16.1	375±27.6	212±11.2*	326±7.1#

Values are expressed as mean ±SD

** and # Means there are a significant difference compared with the control group and bleomycin group at (p≤ 0.05).*

The obtained data showed a significant increase in TNF-α, IL-1β, LDH and CK levels in the bleomycin group compared with the control group. Interestingly, administration of bleomycin rats containing MEE significantly reduced TNF-α, IL1β, LDH and CK levels compared to bleomycin animals, thus bringing all inflammatory cytokines and cardiac enzymes within normal limits improved (Fig. 2a–d).

The inflammatory response results in increased endothelial cell permeability, the influx of blood leukocytes into the stroma, oxidative burst, and release of cytokines (interleukins and tumor necrosis factor α (TNF-α). At the same time, the activity of several enzymes (oxygenase, nitric oxide synthase, and peroxidase) and arachidonic acid metabolism are induced. During the inflammatory process, cell adhesion molecules such as intercellular adhesion molecule (ICAM) and vascular cell adhesion molecule (VCAM) are also expressed Gomes *et al*., (2008) [55].

That is, chronic 3-week quercetin supplementation inhibited the pro-inflammatory cytokines TNF-α and IL-1β and upregulated IL-10 in an experimental autoimmune myocarditis rat model, resulting in a dose-dependent showed protective effect Milenkovic *et al*., (2010) [56]. The primary component of Stapf Cymbopogon Citrate essential oil is Citral. Her IL-1β and IL-6 were demonstrated to be suppressed by this Her EO in normal mouse peritoneal macrophages was activated by Her LPS Abe *et al*., (2003) [57] & Sforcin *et al*., (2009) [58]. Some of the primary components of essential oils, such as citral, geraniol, citronellol, and carvone, can suppress the formation of TNF-α induced neutrophils even though some essential oils can inhibit the synthesis of pro-inflammatory cytokines like TNF-α. Additionally, it can prevent adhesion reactions Abe *et al*., (2003) [57]. Citral reduced TNF-α in lipopolysaccharide-stimulated RAW 264.7 cells, according to a different study by Lin *et al*., (2008) [59].

The presence of Citral as a significant ingredient in the *M. officinalis* essential oil that used may be connected with anti-inflammatory effects.

Amina *et al.,* (2013) [60] reported that *M. officinalis* essential oil decreased and prevented early and late edema of carrageenan-induced inflammation at doses of 200 and 400 mg/kg ($p<0.001$). The extract also dramatically decreased ($p<0.001$) and prevented edema at various stages of the inflammatory response in rat tests with trauma-induced edema. The essential oil of *M. officinalis* can successfully prevent the growth of leg mass during the inflammatory phase, according to the data. This suggests that the essential oil of *M. officinalis* possesses potent anti-inflammatory properties, probably via preventing the release of inflammatory mediators. Prostaglandins and cytokines are additionally inhibited by serotonin and histamine.

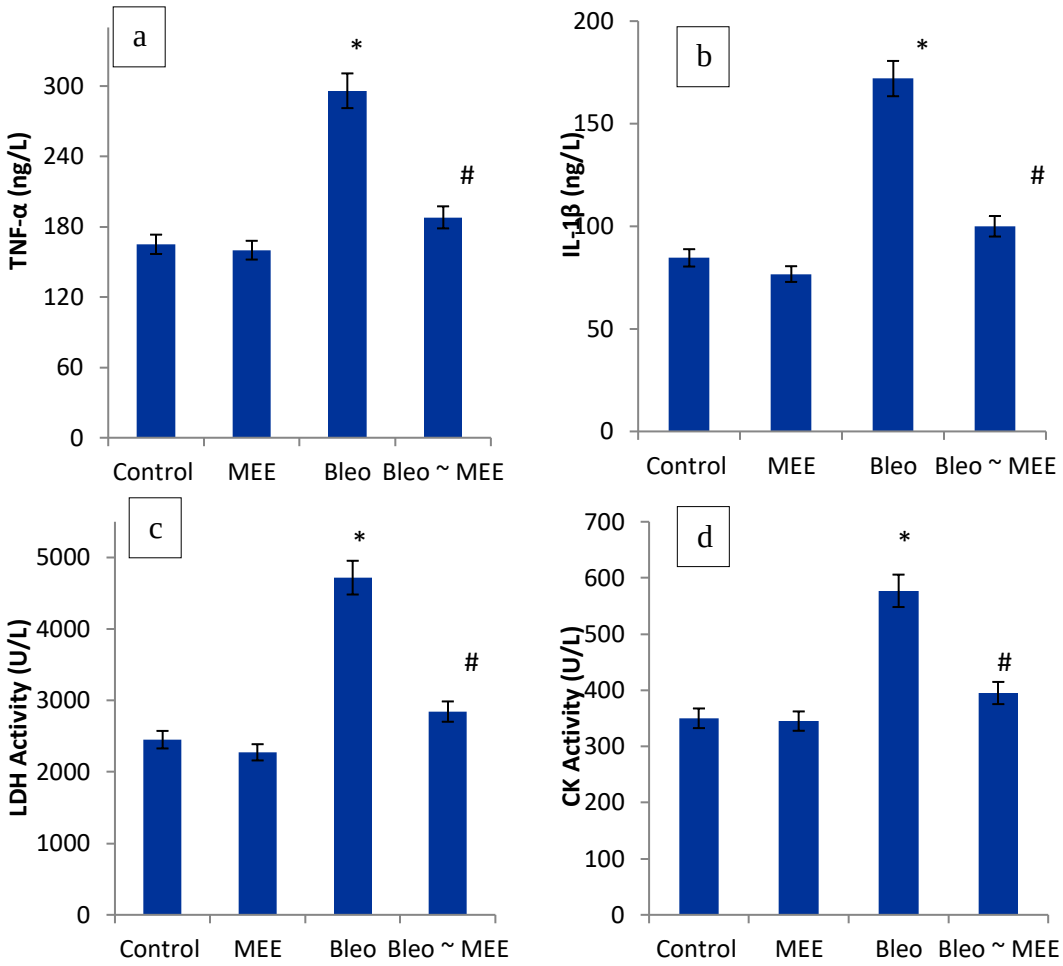

Figure (1a – d). Effect of MEE and bleomycin on TNF-α, IL-1β, LDH and CK activity

Histopathological investigation

Rats from several groups were studied for their cardiac tissues using histopathology. Indicated that control rats' cardiac tissues had normal architecture and histology (Fig. 3A), and rats that had received MEE had normal cardiomyocytes similar to those in the control group (Fig. 3B). Rats given bleomycin, however, displayed cytoplasmic vacuolization and obvious deterioration (Fig. 4C).

It's interesting to note that rats are given bleomycin and MEE therapy revealed cardiac muscle cells that appeared normal (Fig. 3D). Gozhenko *et al*., (2021) [61] reported that a single injection of bleomycin into the body of rats causes severe morphological changes in the structures of the heart. Changes, first of all, develop in vessels of heart (veins, arteries, vessels of MCR) with formation of sludges, stasis, microthrombi. This demonstrates the presence of bleomycin, in addition to cardio-and pulmotoxic also endotheliotoxic effects. With increasing frequency of administration of the drug increases the severity and prevalence of the described changes, necrosis of the cardiomyocytes (CM). Also, after the second administration of the drug there were contractual degenerations of CM and marginal

lysis of individual CM, damage to the microcirculatory tract of all heart vessels with increasing necrosis of CM both due to ischemia and due to apoptosis. Thus, there was both direct and indirect cardiotoxic effect, and its severity increased in proportion to the duration of exposure.

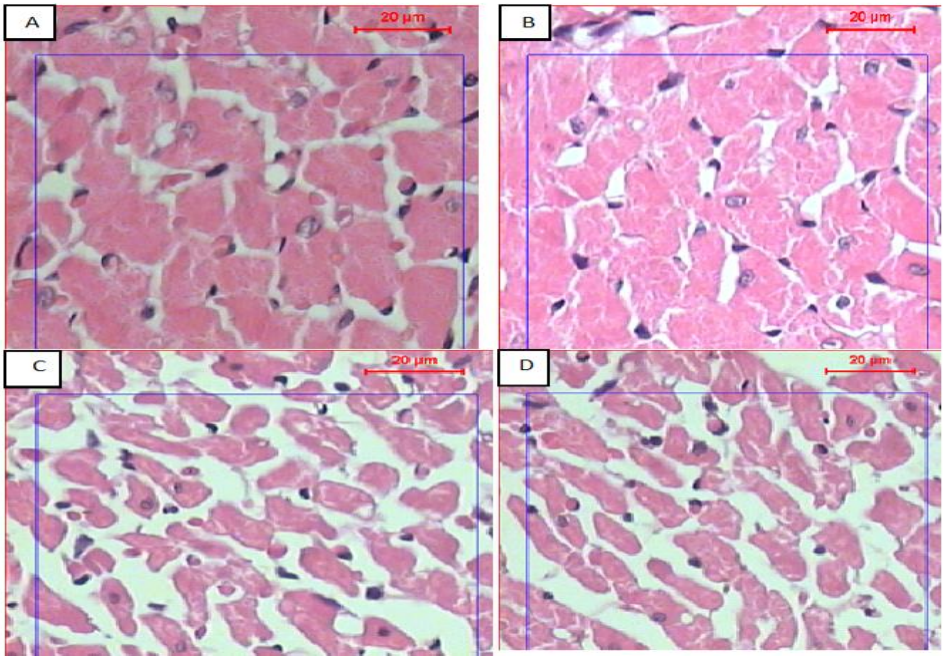

Figure (3A-D): Histological examination of the heart tissue of rats (H&E, X400)
(A) The normal ultrastructure of the heart belongs to a group (1) the control group, showing cardiac myocytes with normal myofibrils.
(B) Light micrograph of the heart belongs to a group (2) MEE group, showing cardiac muscle cells with normal appearance.
(C) Light micrograph of the heart belongs to a group (3) bleomycin group, showing cardiac myocytes with cytoplasmic vacuoles and loss of myofibrils.
(D) Light micrograph of the heart belongs to a group (4) bleomycin combines with MEE group, showing cardiac muscle cells with normal appearance.

Conclusion

The ethanolic extract of *Melissa officinalis* can enhance histopathology, lipid profile, pro-inflammatory parameters, and antioxidant parameters. All of these effects can be attributed to particular plant components' high phenolic concentration, which provides them potent antioxidant properties. These findings lend credence to MEE's prospective use in the management of cardiotoxicity.

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التأثيرات التحسينية المحتملة لمستخلص الميلسيا الايثانولي على السمية القلبية المستحثة بالبلوميسين في الجرذان

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الملخص العربي:

الميلسيا لها أنشطة مضادة للأكسدة وللالتهابات وتستخدم في العديد من الأمراض. لذلك كان الهدف من هذه الدراسة توضيح قدرة مستخلص الميليسيا الايثانولي على تقليل السمية القلبية لذكور الجرذان بعد حقنهم بالبلوميسين لاصابتهم بالتسمم القلبي. تم تقسيم أربعون من ذكور الجرذان البيضاء البالغة بشكل عشوائي والتي تزن (150 ــ 200 جم) إلى أربع مجموعات (10 جرذان لكل مجموعة) تتكون المجموعة الأولى من الجرذان السليمة كمجموعة ضابطة. أما المجموعة الثانية قد اشتملت على جرذان سليمة تتناول عن طريق الفم 450 مجم/ كجم / يوم من مستخلص الميلسيا الايثانولي لمدة 6 أسابيع. والجرذان في المجموعة الثالثة تم حقنهم بالبلوميسين بالبطن بجرعة (15 مجم / كجم / أسبوع) لفترة مماثلة. وتضمنت المجموعة الرابعة الجرذان التي تم حقنها بالبلوميسين وتتناول مستخلص الميلسيا الايثانولي لمدة 6 أسابيع عن طريق الفم. أظهرت النتائج أن مستخلص الميلسيا الايثانولي استعاد بشكل كبير التدهور القلبي الناجم عن البلوميسين. وقد ظهر ذلك من خلال الزيادة الكبيرة في GSH و CAT والزيادة في الكوليسترول المرتفع الكثافة HDL والانخفاض في MDA القلبي ومصل الدم في الكوليسترول و IL-1β ، TNF-α، LDH، CK والجليسريدات الثلاثية والكوليسترول منخفض الكثافة (LDL) بشكل ملحوظ بالإضافة إلى ذلك أظهرت نتائج الفحص الهستولوجي تجدداً في الأنسجة. في الختام مستخلص الميلسيا الايثانولي يحتوي على تركيزات عالية من مضادات الأكسدة كالمركبات الفينولية مما قلل السمية القلبية المحدثة بالبلوميسين. لذلك توصي الدراسة باستخدام الميلسيا كمكمل فعال لخفض السمية القلبية.

الكلمات المفتاحية: السمية القلبية . المركبات الفينولية . أنزيمات مضادات الأكسدة . الهستوباثولوجي