Original Article

The Effect of Royal Jelly and Exercise on Liver Enzymes in Addicts

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Abstract

Introduction: Addiction or substance dependence is one of the major health problems. It damages liver tissues through free radical production and, consequently, increased lipid peroxidation. The present study aimed to compare the effect of royal jelly supplementation, resistance band exercise, and a combination of these two methods on serum levels of liver enzymes in opium addicts undergoing methadone maintenance therapy (MMT). Materials and Methods: This is a quasi-experimental study with pre-test and post-test design conducted on 80 men. The mean age and BMI of participants were 36.06±4.37 years and 21.45±1.62 kg/m^2. Theses individuals were randomized into four groups: resistance band exercise (consisting of 3 sessions per week for 8 weeks), royal jelly supplementation, combined group (resistance band + royal jelly), and control. Body composition and serum levels of liver enzymes (AST, ALT, ALP) were measured in all groups before and after the intervention. Covariance and paired t-test were used to analyze data. Throughout, P <0.05 was considered statistically significant. Results: The results revealed a significant decrease in AST, ALT, and ALP levels in the three experimental groups compared to the control group. Similarly, body composition increased significantly [in the three experimental groups] (P = 0.264) compared to the control group. Conclusion: Eight weeks of royal jelly supplementation and resistance band exercise reduced serum levels of liver enzymes in opium addicts undergoing MMT.

Keywords: royal jelly, resistance band, heart injury, oxidative stress, opium, methadone

Introduction

Substance abuse is associated with hepatic disorders, and methadone is a synthetic opioid that is commonly administered to relieve acute pain [1]. Methadone can affect the natural function of liver enzymes in animals and humans [2, 3]. It is used as an alternative treatment to prevent or mitigate withdrawal symptoms [4]. Aspartate aminotransferase (AST), alanine aminotransferase (ALT), and alkaline phosphatase (ALP) enzymes are considered the major indicators for liver status assessment [5]. The liver is the largest gland in the body and is responsible for producing, modifying, storing, and removing certain substances. It is one of the most important organs which serves to detoxify drugs, excrete substances resulting from destruction and remodeling of erythrocytes, produce coagulants, store glucose as glycogen, and regulate glucose and lipid [6]. Elevated levels of ALT in the blood can indicate damage to the main liver tissue, whereas AST increases in the case of liver parenchyma damage as well as cardiac and muscle injuries [7]. Early, Kreek (1973) observed that abnormal liver function is one of the adverse effects of methadone administration. Also, another study performed on the effect of methadone on liver enzymes in patients treated with methadone suggested that methadone exerts a significant impact on ALP, which is a possible indication of cholestatic (obstructive) injury pattern of methadone on the liver [2]. Studies have also proposed that exercise can have positive effects on the hepatic enzymes of both healthy and sick people [8, 9]. During exercise, the liver is exposed to stimuli such as body temperature, formation, circulation interruption, and glycogen reduction. Doing certain exercises helps support the liver against various environmental and physiological stresses such as cold, heat, hypoxia, ischemia, and energy depletion, hence playing a major role in the prevention of liver diseases [6]. Short-term exercise reduces circulating markers of liver enzymes in obese patients with non-alcoholic fatty liver disease (NAFLD) [10]. Nabizadeh Haghighi and Shabani (2016) reported that aerobic exercise 3 times a week (every 90 minutes) for 8 weeks reduced liver enzymes in people with NAFLD [11]. However, studies have also suggested that doing

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exercise does not [positively] affect liver enzymes in addicts. For example, Asad et al. (2013) found that endurance exercise for 8 weeks had no effect on AST and ALT levels in female addicts undergoing MMT [12]. Similarly, Haddadi et al. (2015) proposed that endurance training does not have a significant impact on the level of ALP in women under MMT [13]. Khodabandeh et al. (2017) explored the protective effect of royal jelly on the adipose tissue of adult female rats under nicotine treatment. In this research, royal jelly improved the status of oxidative stress, serum levels of AST, ALT, ALP, as well as hepatic tissue damage in nicotine-treated rats. Royal jelly is a highly active antioxidant with a great capacity to inhibit free radicals. The authors in the above study also showed that lipid peroxidation heightened in the subjects which were treated with nicotine compared to the control group. Lipid peroxidation can be used as an indicator to measure damage to membrane tissues as a result of free radical production. It could be inferred that high levels of lipid peroxidation products in the liver of nicotine-treated rats could be due to the excessive generation of free radicals by nicotine itself. Royal jelly reduces the production of reactive oxygen species by lowering leukocytes' response and improving the mitochondrial respiratory chain. Royal jelly thus reduced the level of lipid peroxidation [14]. Nejati et al. (2016) investigated the protective effect of royal jelly on oxymetholone-induced liver injury in adult rats. The results indicated that royal jelly could lessen liver damage [15]. Anbara et al. (2016) studied the antioxidant effect of royal jelly with vitamin C on enzymes, histomorphometry, and apoptosis of hepatocytes in adult rats with hemolytic anemia. The results showed that co-administration of royal jelly and vitamin C decreased alkaline phosphatase, aspartate transaminase, and alanine transaminase by reducing apoptosis, Kupffer cells, and the nucleus diameter of hepatocytes. Royal jelly and vitamin C, as free radical inhibitors, are capable of reducing oxidative damage and apoptosis resulting from hemolytic anemia caused by phenylhydrazine on the liver of rats [16].

BehzadMoghadam (2017) confirmed that eight weeks of resistance band exercise and low-calorie diet both improved plasma levels of hepatic enzymes and liver fat content in patients with NAFLD. Thus, the AST level dropped considerably in both groups. However, the plasma level of ALT decreased significantly only in the low-calorie diet group [17]. Douglas et al. (2018) explored the effect of royal jelly on the liver of rats exposed to chronic stress and concluded that cold-restraint stress can heighten corticosterone and glycemia, resulting in oxidative damage to the liver tissue. In this study, the effects of royal jelly supplementation on the levels of corticosterone, glycemia, plasma enzymes, and hepatic antioxidant systems were investigated in restraint and cold stressed. The results revealed that royal jelly supplementation could improve corticosterone levels and hepatic antioxidant system in hypertensive rats, suggesting the adaptation and protection potential of royal jelly against hepatitis [18]. Nagai et al. (2006) found that royal jelly proteins display high antioxidant activity and that these proteins are capable of inhibiting free radicals such as superoxide anion and diphenyl picrylhydrazyl radical [19]. Taghizadeh et al. (2014) addressed the impact of royal jelly as an antioxidant on oxidative stress reduction induced by chronic immobilization stress (CIS) in the liver of mice. The results showed that lipid peroxidation and liver enzyme levels decreased significantly in mice receiving CIS and royal jelly, especially at the dose of 100 mg/kg, compared to the group which received CIS alone [20]. The research by Gholie Pour et al. (2014) illustrated that royal jelly, thanks to its being rich in biologically active compounds, is an effective antioxidant against oxidative stress caused by polycystic ovary syndrome (PCOS) and its daily oral intake can diminish the adverse effects of this syndrome on liver tissue, reduce the amount of fat accumulation in the liver, and prevent secondary complications of polycystic ovaries, including fatty liver [21]. Administering royal jelly with vitamin C amended the observed changes in liver enzyme levels. Royal jelly and vitamin C, as free radical inhibitors, can mitigate oxidative damage and apoptosis caused by hemolytic anemia associated with phenylhydrazine in rat liver [16]. Hepatocyte nucleus diameter and Kupffer cells (liver macrophages) in the liver shrink by royal jelly [22]. It has also been proposed that royal jelly, due to its anti-inflammatory property and antioxidant activity, reduces liver enzyme levels by enhancing antioxidant defense, inhibiting lipid peroxidation [23], and suppressing inflammatory responses. Royal jelly exhibits a high antioxidant activity and can inhibit free radicals such as superoxide anion and hydroxyl radicals; besides, owing to its rich biologically active compounds, it can be protective against oxidative stress and lower damage to the liver tissue of rats [19].

However, there is a relatively small body of literature that is concerned with the combined effects of these two types of interventions. Similarly, there are few studies on the effect of royal jelly supplementation on serum levels of liver enzymes in addicts. Moreover, no study has so far addressed the impact of doing exercise with resistance band on serum levels of liver enzymes in addicts. The present study explores the effect of eight weeks of royal jelly supplementation and resistance band exercise on serum levels of liver enzymes in opium addicts under MMT.

Methods:

This is a quasi-experimental study with a pre-test and post-test design. It includes three experimental groups and one control group. The study population consisted of 25-45-year-old men addicted to opium who underwent MMT at Naji Addiction Treatment Center in Zahedan, southeast Iran. The researchers first referred to the center to review the medical records of participants and to provide the center with the required information about the research. Eligible individuals were selected based on the inclusion criteria. being male; opium addiction; methadone maintenance therapy; no cardiovascular disease, musculoskeletal disease, chronic renal/pulmonary disease, and chronic/acute inflammatory disease; no use of lipid and blood pressure medications,

aspirin, and vitamin supplements; no specific diet; no history of participation in any exercise program in the last one year; and no drug or dietary sensitivity. The exclusion criteria, on the other hand, included allergy to royal jelly supplementation, hypotension, absence for more than three sessions, and unwillingness to continue the study. A total of 80 qualified addicts were finally recruited. The subjects were randomly divided into 4 groups: resistance band exercise (n = 20), royal jelly supplementation (n = 20), exercise+royal jelly (n = 20), and control (n = 20). They were familiarized with the type of study, its goals and method of implementation, as well as its benefits and potential risks. Informed consent was obtained from each subject.

This study was approved by the Ethics Committee on Biomedical Research of Zahedan University of Medical Sciences (IR.ZAUMS.REC.1397.458). Subjects' weight was measured by a digital scale (Seca, Germany) with an accuracy of 100 g. The height of participants was calculated using a Seca gauge (Germany) with an accuracy of 0.1 cm. Body mass index (BMI) was calculated through dividing weight (kg) by the square of height (m2).

Exercise program

The subjects performed resistance band exercises for 8 weeks (3 non-consecutive sessions per week, each lasting 60 minutes). Each training session consisted of 10 minutes of warm-up, 40 minutes of core exercise, and 10 minutes of cool-down. The main workout included the movements of the biceps, triceps, chest press, lateral lifting of the hands, lower abdominal crunch, hip flexion, hip abduction, squat, and trunk elevation. For each movement, the subjects performed 10-15 repetitions at three sets. They rested 60-90 seconds after each set and 120 seconds after each movement. To determine the intensity of the exercise, each subject was given a brown resistance band before starting the program. The subjects used this band to perform more than 12 repetitions of each movement. If a person was able to do more than 12 repetitions using the same band, another band with a different color was provided to be used for performing the same movements [24].

Supplementation

Every day for 8 weeks, the subjects orally received royal jelly at a dose of 100 mg/kg [15].

Biochemical measurement

Intravenous blood sampling was carried out in two stages (before resistance band exercise and royal jelly supplementation; eight weeks afterward). Samples (10 ccs) were taken from the antecubital vein at a 12-hour fasting state (at 8 a.m.) while the subjects sat on a chair. Blood samples were immediately poured into tubes containing an anticoagulant (EDTA). They were then centrifuged at a speed of 3,000 rpm for 10 minutes at 4 °C. The obtained plasma was stored at -80 °C for subsequent measurements. To separate serum from plasma, the samples were kept at laboratory temperature for 30 minutes. Then, they were centrifuged (Dlasent-12, UK) for 5-10 min at a speed of 2,000 rpm. All measurements were performed by a laboratory expert who was unaware of the status (group distribution) of the subjects. AST, ALT, and ALP measurements were performed using the alpha-classical BT-1500 Autoanalyzerand Pars AzmunBiochemistry Kit.

Statistical method

Covariance analysis was used to compare the effect of the intervention in the study groups while considering the effect of pre-test scores. A paired t-test was employed to compare the mean difference between pre-test and post-test scores. Before the tests, the assumptions of data normality and homogeneity of error variance between the two groups were assessed and confirmed using Shapiro-Wilk and Levene tests, respectively. The assumption of homogeneity of regression slope was also tested and verified. $P < 0.05$ was considered statistically significant.

Findings:

This study was conducted on 80 male opium addicts receiving MMT at Naji Addiction Treatment Center in Zahedan. Table 1 presents the central indicators related to the general characteristics of the subjects in the pre-test and post-test.

Table 1. The mean and standard deviation of age, height, and weight of participants in the four study groups

Variable	Royal jelly		Exercise		Exercise + Royal jelly		Control	
	Mean	SD	Mean	SD	Mean	SD	Mean	SD
Age	35.60	5.45	34.85	3.62	37.30	4.39	36.50	4.02
Height	1.72	.07	1.74	.08	1.71	.04	1.70	.03
Weight	66.30	9.01	65.00	8.38	63.30	4.33	59.70	4.34

The mean age of the subjects was 35.60±5.45 years in the royal jelly group, 34.85±3.62 years in the exercise group, 37.30±4.39 years in the exercise+royal jelly group, and 36.50±4.04 years in the control group.

The mean height of subjects was 1.72±0.07 m in the royal jelly group, 1.74±0.08 m in the exercise group, 1.71± 0.04 m in the exercise+royal jelly group, and 1.70±0.03 m in the control group.

Finally, the mean weight of the subjects was 66.30±9.01 kg in the royal jelly group, 65.00±8.38 kg in the exercise group, 63.30±4.33 kg in the exercise+royal jelly group, and 59.70±4.34 kg in the control group.

Table 2. Results of covariance analysis

Variable	Stage	Royal jelly	Exercise	Exercise + Royal jelly	Control	Intergroup F-value	Intergroup P-value	Intergroup Eta-squared
AST	Pretest	85.30±16.19	54.85±10.57	74.55±5.42	78.90±9.04	203.264	<.001	.890
	Posttest	60.90±11.15	47.35±10.09	52.60±4.97	87.35±8.83			
ALT	Pretest	82.70±16.67	49.30±4.01	90.65±7.96	81.45±6.79	260.569	<.001	.912
	Posttest	68.60±11.45	42.80±3.21	78.85±5.23	90.50±6.44			
ALP	Pretest	1082.20±184.37	871.00±129.59	955.15±111.60	861.80±129.88	49.663	<.001	.665
	Posttest	890.15±160.25	761.75±95.87	765.95±98.71	893.10±139.35			

After the pretest effect was taken into account, a significant difference was observed between the four groups in terms of ALP, ALT, and ALP.

Table 3. Posttest results of the four study groups

Exercise - royal jelly	Exercise - royal jelly	Exercise - royal jelly	Control - exercise+royal jelly	Control - exercise	Control - royal jelly		Variable
8.709*	.683	-8.026*	31.668*	22.959*	30.985*	Mean	AST
1.750	1.558	2.079	1.483	1.873	1.500	Standard error	
<.001	1.000	.001	<.001	<.001	<.001	Significance level	
-8.805	-5.012	3.793	17.712	26.517	22.724	Mean	ALT
1.697	.982	1.479	.995	1.447	.945	Standard error	
<.001	<.001	.074	<.001	<.001	<.001	Significance level	
63.882*	21.409	-42.473	202.676*	138.793	181.267*	Mean	ALP
17.535	18.027	19.492	17.625	17.146	19.687	Standard error	
.003	1.000	.195	<.001	<.001	<.001	Significance level	

The mean AST in the royal jelly group was significantly lower than that in the control ($p < 0.001$) and exercise ($p = 0.001$) groups; however, it was not significantly different from the royal jelly+exercise group ($p = 0.001$). The mean AST in the exercise group was significantly lower than that in the control group ($p < 0.001$), but it was significantly higher compared to the royal jelly group ($p = 0.001$) as well as the exercise+royal jelly group ($p < 0.001$). The mean AST in the exercise+royal jelly group was significantly lower than that in the control group ($p < 0.001$) but higher than that in the exercise group ($p < 0.001$); however, it showed no significant difference from the royal jelly group ($p = 0.00$). On the other hand, ALT in the royal jelly group was significantly lower compared to the control group ($p < 0.001$) as well as the royal jelly+exercise group ($p < 0.001$), but it did not differ significantly from the exercise group ($p = 0.074$). The mean ALT in the exercise group was significantly lower than those in the control and exercise+royal jelly groups ($p < 0.001$), yet it was not significantly different from the royal jelly group ($p = 0.074$). The mean ALT in the exercise+royal jelly group was significantly lower than that in the control group ($p < 0.001$) but higher than those in the royal jelly and exercise groups ($p < 0.001$).The mean ALP was significantly lower in individuals who received royal jelly compared to the control group ($P < 0.001$), but it exhibited no significant difference from the exercise group ($p = 0.195$) and exercise+royal jelly ($p = 0.001$). The mean ALP in the exercise group was significantly lower than that in the control group ($p < 0.001$) but higher than that in the exercise+royal jelly group ($p = 0.003$); meanwhile, it did not show a significant difference from the royal jelly group ($p = 0.195$). Eventually, the results indicated that the mean ALP in the exercise+royal jelly group was significantly lower than those in the control ($p < 0.001$) and exercise ($p = 0.003$) groups, but it did not vary significantly from the royal jelly group ($p = 1.00$).

Discussion and Conclusion:

The results of this study suggest that 8 weeks of royal jelly supplementation and resistance band exercise may considerably, though at different degrees, reduce serum levels of AST, ALT, and ALP in opium addicts under MMT.

The results of the present research are in line with the findings obtained by Khodabandeh et al. (2017), who investigated the protective effect of royal jelly on the nicotine-treated liver of adult female rats. In this study, royal jelly improved oxidative stress and serum levels of AST, ALT, and ALP as well as liver tissue damage in nicotine-treated subjects. The authors concluded that royal jelly can have a protective effect on the liver tissue of rats treated with nicotine. Royal jelly is a highly active antioxidant that has the potential to inhibit free

radicals. The above study showed that lipid peroxidation was greater in nicotine-treated groups than in controls. Lipid peroxidation can be adopted as an indicator to measure the damage occurring to the tissues due to free radical production. Thus, high levels of lipid peroxidation products in the liver of nicotine-treated rats could be related to free radical overproduction due to nicotine. Royal jelly helps bring down the level of lipid peroxidation and the production of reactive oxygen species by reducing the leukocyte response and enhancing the mitochondrial respiratory chain [14]. The results of the present study are in good agreement with those of Nejati et al. (2016), who explored the protective effect of royal jelly on oxymetholone-induced liver injury in adult rats. The results of this research demonstrated that, due to its abundance of biologically active compounds, royal jelly can serve as a potent factor against oxidative stress caused by PCOS. Furthermore, they suggested that daily oral administration of royal jelly can significantly alleviate the effects of this syndrome on liver tissues, shorten the extent of fat accumulation in hepatocytes, and prevent secondary complications of PCOS such as the fatty liver and type 2 diabetes. Royal jelly produces a protective effect against the toxicity of Lambda-cyhalothrin on the liver tissue and significantly elevates the liver enzymes to the control group. Hypocholesterolemic activity of royal jelly is closely associated with decreased expression of squalene epoxidase, a key enzyme in cholesterol synthesis, and increased lipoprotein receptors in mice. Being rich in neopterin, royal jelly can bring about a special protective effect on the liver. On the other hand, royal jelly stimulates DNA synthesis in hepatocytes and prevents apoptosis in the liver. Thus, examining the effect of royal jelly on the liver affected Oxymetholone- Induced Liver Injury, Nejati et al. (2016) found that apoptosis was significantly reduced in subjects treated by royal jelly [15].

Anbara et al. (2016) assessed the antioxidant property of royal jelly and vitamin C on enzymes, histomorphometry, and apoptosis of hepatocytes in adult rats with experimental hemolytic anemia. The results illustrated that the administration of royal jelly with vitamin C helps lower the concentration of alkaline phosphatase, aspartate transaminase, and alanine transaminase by reducing apoptosis, Kupffer cells (liver macrophages), and the nucleus diameter of hepatocytes [22]. Royal jelly also seems to have anti-inflammatory and antioxidant properties which decrease liver enzymes by reinforcing antioxidant defense, restricting lipid peroxidation [23], and suppressing inflammatory reactions. Royal jelly shows high antioxidant activity and can inhibit free radicals such as superoxide anion and hydroxyl radicals; additionally, it can be protective against oxidative stress and reduce destructive effects on the liver tissue of rats thanks to its biologically active compounds.

In another research by Behzadi Moghaddam (2017), it was noted that resistance band exercise, as a result of modifying lipid profile, was effective in improving liver fat content and plasma levels of liver enzymes. It was found that the decrease in plasma triglyceride concentration is associated with a drop in the plasma concentration of hepatic enzymes. The fall in hepatic enzymes observed in the present study can be partly attributed to the improvement of the lipid profile, which is a classical risk factor. There is evidence suggesting that exercise helps treat fatty liver by decreasing fat mass and improving atherogenic lipid disorders associated with metabolic syndrome [17].

Douglas et al. (2018) probed the adaptogenic property of royal jelly in the liver of rats subjected to chronic stress. They reported that cold-restraint stress increases corticosterone and glycemia, resulting in oxidative damage to the liver tissue. In this study, the impact of royal jelly supplementation on the levels of corticosterone, glycemia, plasma enzymes, and the hepatic antioxidant system was addressed in restraint and cold stressed rats. The results substantiated that royal jelly supplementation could improve corticosterone levels and the hepatic antioxidant system in hypertensive rats, indicating adaptogenic as well as the protective potential of royal jelly against hepatitis B. In a study aimed at determining the effects of royal jelly on oxidative stress induced by cisplatin (CDDP) in the kidneys and liver, biochemical and antioxidant parameters were measured and immunohistochemical apoptosis was assessed. Based on the results, royal jelly played a significant protective role for these organs by decreasing lipid peroxidation (MDA), increasing GSH level, and promoting GST, GSH-Px, and SOD activities. Besides, royal jelly led to increased activity of hepatocytes and tubular epithelium. As a result, royal jelly can be used in combination with cisplatin to improve oxidative stress parameters induced by cisplatin and apoptotic activity [18]. Nagai et al. (2006) suggested that royal jelly proteins have high antioxidant activity and can inhibit free radicals such as superoxide anion and DPPH radical [19].

Taghizadeh et al. (2014) investigated the effect of royal jelly as an antioxidant on decreasing oxidative stress caused by CIS in mice. They observed that rats receiving both CIS and royal jelly, especially at a dose of 100 gm/kg, had significantly lower levels of liver enzymes and lipid peroxidation compared to the group which underwent CIS alone [20].

Gholie Pour et al. (2014) examined the protective effect of royal jelly on the liver tissue of adult female rats with experimental PCOS. They confirmed that royal jelly significantly reduced the levels of liver enzymes in the subjects. The results of this study established that royal jelly, comprising rich biological components, is an effective antioxidant against oxidative stress induced by PCOS and its daily oral intake can minimize the adverse effects of this condition on liver tissues. It was also revealed that royal jelly can help decrease fat accumulation in hepatocytes and avoid secondary complications of polycystic ovaries, including fatty liver. Using royal jelly alongside vitamin C improved changes in liver enzyme levels. Inhibiting free radicals, vitamin C and royal jelly can reduce the oxidative damage

and apoptosis of hemolytic anemia caused by phenylhydrazine in mice [21].

The results of the current study are inconsistent with those of Asgari et al. [25], which could be because of the difference in the type of subjects and liver enzymes status at the beginning of each research. The limitations of our study include the emotional vulnerability of the subjects due to being away from the family while staying at the treatment center, the effect of fatigue on the participants, and individual differences in terms of genetic and hereditary characteristics, which were beyond our control.

Conclusion:

Eight weeks of royal jelly supplementation and resistance band exercise reduced serum levels of hepatic enzymes in opium addicts under methadone maintenance therapy. This was achieved by empowering the antioxidant defense system, inhibiting lipid peroxidation, and suppressing inflammatory reactions. It is recommended that similar studies be designed on other types of addiction (nervous system depressants, hallucinogens, etc.) and their associated treatment methods like buprenorphine.

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