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Hypolipidemic and hepatoprotective effects of corn silk extract in nicotine-administered male mice

Anahita Mohammadi[1], Ali Akbar Oroojan[2], Mehdi Hashemi[3], Seyedeh Mahsa Poormoosavi[4], Mojtaba Dolatshahi[2], Fatemeh Golshokouh[1]

[1]School of Medicine, Student Research Committee, Dezful University of Medical Sciences, Dezful, Iran
[2]Department of Physiology, School of Medicine, Dezful University of Medical Sciences, Dezful, Iran
[3]Department of General Surgery, School of Medicine, Dezful University of Medical Sciences, Dezful, Iran
[4]Department of Histology, School of Medicine, Research and Clinical Center for Infertility, Dezful University of Medical Sciences, Dezful, Iran

ABSTRACT

Aim: This study is done to investigate the hypolipidemic and hepatoprotective effects of corn silk extract in nicotine-administered male mice.
Background: Nicotine can induce pathophysiological effects in the liver tissue through oxidative stress and damage cells. Corn silk can improve liver function with its antioxidant effects.
Methods: In this experimental study, 30 male NMRI mice (25-30 gr) were divided into 5 groups: controls, sham, nicotine 2.5 mg/kg, nicotine+aqueous extract of corn silk 400 mg/kg, and nicotine+methanolic extract of corn silk 400 mg/kg for 1 month. One day after the last nicotine and extracts consumption, the serum samples were performed for biochemical measurement, and the supernatant of the homogenized liver was administered for antioxidant variables assessment.
Results: There was no significant difference in the body weight of different groups. Liver weight and GSH decreased in the nicotine group compared to the control group ($P<0.05$). Triglycerides, total cholesterol, HDL-C, LDL-C, liver enzymes, and MDA increased in the nicotine group compared to the control group ($P<0.05$). Also, the expansion of sinusoids, the presence of inflammatory cells, and necrosis of liver cells were observed in the nicotine group compared to the control group. Using aqueous and methanolic extracts of corn silk in mice receiving nicotine led to the improvement of the mentioned variables ($P<0.05$).
Conclusion: The results of this study showed that the use of nicotine can lead to the induction of hepatotoxicity. The use of aqueous and methanolic extracts of corn silk improved them through its antioxidant activity.

Keywords: Corn silk, Liver, Nicotine, Mouse.

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Introduction

Nicotine is an alkaloid that is produced in the nightshade family. In 2012, it has been determined that 30% of men and 6% of women are tobacco users worldwide. Smoking is the largest preventable cause of premature death and accounts for 18.5% of all deaths in economically developed countries. Nicotine is a stimulant in low doses and an inhibitor of nerve activity in high doses (1). Nicotine plays a significant role in the development of cardiovascular, lung, and many other diseases. It is also known that nicotine causes oxidative stress by creating reactive oxygen species (ROS), reducing glutathione content, catalase (CAT), and superoxide dismutase (SOD) in various tissues (2, 3). It seems that the liver is the main place for the biological transfer of nicotine, and this compound can cause many adverse physiological effects in this tissue. During smoking, nicotine is absorbed through the lungs and quickly metabolized in the liver, causing three major side effects, including toxicity, reduced immune response, and carcinogenesis (4). Nicotine increases the

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Reprint or Correspondence: **Ali Akbar Oroojan,** *Assistant Professor of Physiology, Department of Physiology, School of Medicine, Dezful University of Medical Sciences, Dezful, Iran.*
E-mail: aliakbar_oroojan@yahoo.com
ORCID ID: 0000-0001-5249-3239

activity of serum aminotransferase enzymes in male rats treated with this compound. Chronic nicotine consumption causes liver damage through a significant increase in serum total cholesterol (TC) and triglyceride (TG), which may be due to the effect of oxidative stress and the production of free radicals (5).

Corn silk is an important traditional medicine in China. In the past years, various components have been discovered in corn silk, such as alkaloids, flavonoids, terpenes, saponins, and carbohydrates, which, through the reduction of free radicals, lead to the prevention of diseases such as cancer, high blood pressure, and nervous system disorders (6). Corn silk contains sodium, potassium, magnesium, calcium salts, proteins, and vitamins. It has been used to treat kidney stones, nephritis, prostatitis, cystitis, edema, and gout worldwide. This part of the corn plant has antioxidant, anti-diabetic, anticoagulant, anti-inflammatory, anti-cancer, anti-obesity, and lipid peroxidation-reducing functions (7). In an antioxidant study, the ethanolic extract of corn silk showed a good reduction power in the number of free radicals comparable to the antioxidant effect of vitamin C. Therefore, this extract can act as an electron donor that leads to the termination of free radical chain reactions (8). In addition, the content of flavonoids and tannins in corn silk plays an important role in protecting the liver against toxic substances, which is observed in the morphology of the liver tissue (9). The results of one study on the hypolipidemic activity of corn silk in rats fed a high-fat diet have shown that the total flavonoids extracted from corn silk have a hypolipidemic effect so that the administration of flavonoids from corn silk extract leads to a decrease in the levels of TC, TG and low-density lipoprotein cholesterol (LDL-C) (8). Therefore, considering the prevalence of nicotine consumption in humans and its negative effect on the liver through increasing oxidative stress and the effect of corn silk on improving the antioxidant defense system in different parts of the body, the present study investigated the hypolipidemic and hepatoprotective effects of corn silk extract in nicotine-administered male mice.

Methods

Plant extraction

To prepare corn silk aqueous extract, 100 gr of the powder of this part of the plant was poured into 1 liter of distilled water and mixed in a shaker for 48 hours. After passing through the filter, it was centrifuged at 3500 rpm for 20 minutes (10). In the preparation of methanolic extract, 250 gr of corn silk powder in 1 liter (20-80%) of distilled water and methanol for 72 hours, similar to the method of preparing aqueous extract, after passing through a filter, it was centrifuged at 3500 rpm for 20 minutes (7). Finally, after drying the supernatant solution of both extracts in a 37°C incubator, the resulting powder was kept at 4°C until use.

Animals' preparation

In the current experimental study, 30 male NMRI mice (25-30 gr), were obtained from the Animal Reproduction and Maintenance Center of Dezful University of Medical Sciences and kept in a 12-hour light-dark cycle, with free access to tap water and commercial food. Then the animals were divided into 5 groups (n=6): control, sham (received an intraperitoneal injection (IP) and gavage of normal saline), nicotine (2.5 mg/kg) (IP) (11), nicotine (2.5 mg/kg) + aqueous extract of corn silk 400 mg/kg (orally) (10), nicotine (2.5 mg/kg) + methanolic extract of corn silk 400 mg/kg (7). The duration of using nicotine and extracts was 1 month at the same time (12).

Hormonal, biochemical, and antioxidant measurement

Twenty-four hours after the last dose of the extract administration, the serum samples of the animals were separated through cardiac puncture blood drawing under deep anesthesia with the ketamine-xylazine combination (70 mg/kg - 10 mg/kg). Then, the amount of TG, TC, high-density lipoprotein (HDL- C), alanine aminotransferase (ALT), aspartate aminotransferase (AST), and alkaline phosphatase (ALP) was analyzed using biochemical methods and specific commercial kits. On the other hand, a part of the liver was homogenized using phosphate buffer saline. After centrifugation at 5000 rpm for 10 minutes, the supernatant sample was used to measure malondialdehyde (MDA) and glutathione (GSH) levels by specific commercial kits (Novin Navand Salamat Pishtaz Co., Iran). To measure very low-density lipoprotein (VLDL) and LDL-C, the following formulas were used (13, 14).

$$VLDL = TG/5$$

$$LDL\ (mg/dL) = TC/1.19 + TG/1.9 – HDL/1.1 – 38$$

Histological assessment

The liver tissue samples were removed and fixed in 10% formalin. After tissue processing, 5 to 7-micron paraffin sections were prepared. Sections were stained with hematoxylin and eosin, and tissue changes were examined under a light microscope. From each animal, at least 6 slides were taken for each tissue. Finally, the expansion of sinusoids, the presence of inflammatory cells, and an increase in the necrosis of liver cells were examined by light microscope. (15).

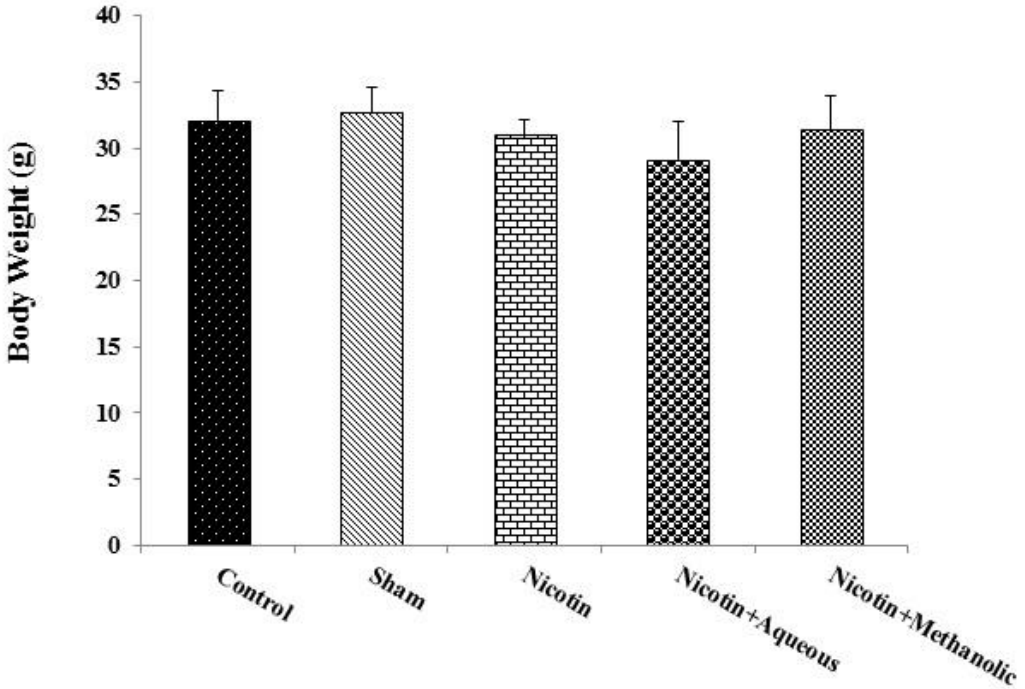

Figure 1. Effect of aqueous and methanol extracts of corn silk on body weight. The results are mean±SEM (n=6).

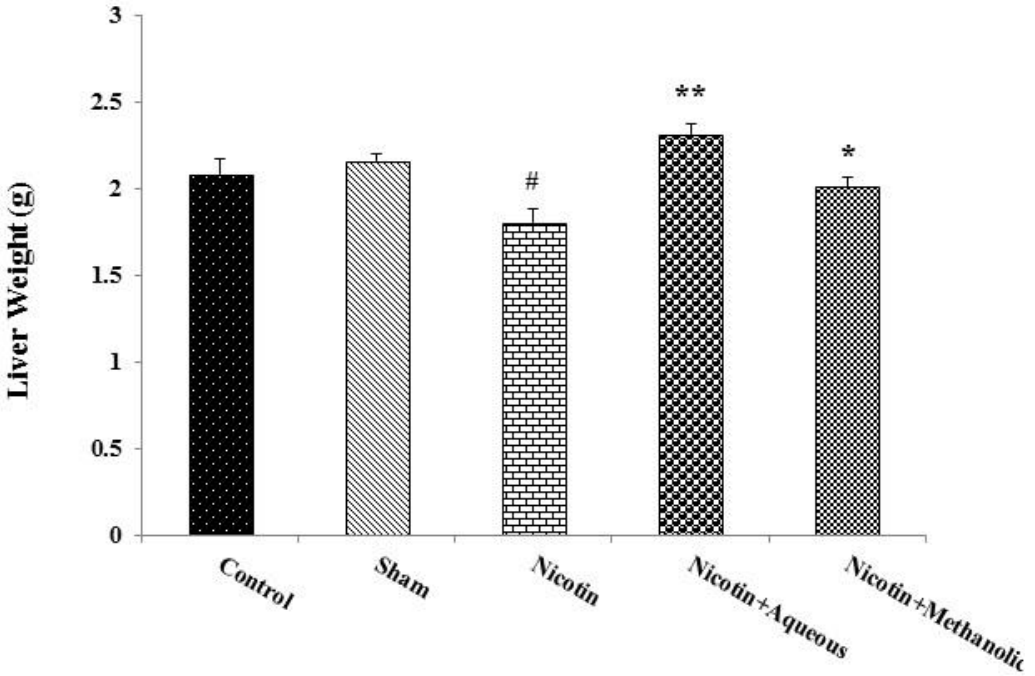

Figure 2. Effect of aqueous and methanol extracts of corn silk on liver weight. The results are mean±SEM (n=6). #: P<0.05 compared to the control and sham groups; *: P<0.05 and **: P<0.01 compared to the nicotine group.

Statistical analysis

Data were compared using SPSS (version 22; SPSS Inc., Chicago, Ill) software and the one-way ANOVA statistical method. Data were presented as mean±SEM (mean±standard error of the mean), and P less than 0.05 was considered statistically significant.

Results

Effect of aqueous and methanol extracts of corn silk on body weight

The present study's results showed no significant difference in body weight in the different groups (Figure 1).

Effect of aqueous and methanol extracts of corn silk on liver weight

Liver weight in mice receiving nicotine significantly decreased compared to the control and sham groups (P<0.05). The use of aqueous (P<0.01) and methanol (P<0.05) extracts of corn silk in mice receiving nicotine led to the improvement of this variable compared to the nicotine group (Figure 2).

The effect of aqueous and methanol extracts of corn silk on lipid profile

TG levels increased significantly in the nicotine-treated group compared to the control and sham groups (P<0.05). Also, this lipid factor decreased in nicotine-receiving groups treated with aqueous and methanol extracts of corn silk compared to the nicotine group (P<0.05). The amount of TC increased in the nicotine-receiving group compared to the control and sham groups (P<0.05). Although this variable tended to decrease in the group receiving nicotine plus aqueous extract of corn silk, but this decreasing effect was significant in the methanolic extract group compared to the nicotine group (P<0.05). The results of HDL-C measurement showed that this factor increased significantly in the nicotine group (P<0.01) and nicotine plus aqueous extract of corn silk (P<0.05) compared to the control and sham groups. This lipid variable showed a significant decrease in rats receiving nicotine plus aqueous (P<0.05) or methanolic (P<0.05) extracts of the mentioned plant compared to the nicotine group. The results of LDL-C calculation showed an increase in the nicotine group compared to the control and sham groups (P<0.01). Also, treatment with aqueous and methanolic extracts of corn silk in groups receiving nicotine led to a significant reduction of LDL-C compared to the nicotine group (P<0.01). The ratio of LDL-C to HDL-C in the nicotine group did not change compared to the control group. In addition, this ratio showed a significant decrease in the groups receiving nicotine plus aqueous or methanol extracts of corn silk compared to the control and nicotine groups (P<0.05). VLDL values increased significantly in the nicotine-receiving group compared to the control and sham groups (P<0.05). Also, this lipid factor decreased in the groups receiving nicotine plus aqueous and methanol extracts of corn silk compared to the nicotine group (P<0.05; Table 1).

The effect of aqueous and methanol extracts of corn silk on liver enzymes

The ALT measurement results showed that nicotine can increase the serum level of this enzyme compared to the control and sham groups (P<0.05). On the other hand, this enzyme showed a significant decrease in the groups receiving nicotine plus aqueous or methanol extracts of corn silk compared to the nicotine group (P<0.05; Figure 3). Serum AST assessment showed a significant increase of this enzyme in the nicotine group compared to the control and sham groups (P<0.05).

Table 1. The effect of aqueous and methanolic extracts of corn silk on lipid profile

Variables / Groups	TC (mg/dL)	TG (mg/dL)	LDL-C (mg/dL)	HDL-C (mg/dL)	LDL-C/HDL-C	VLDL (mg/dL)
Control	90.66±3.84	55.00±1.73	33.03±2.33	43.00±1.15	0.76±0.010	10.40±0.34
Sham	90.25±3.97	63.25±4.55	32.82±2.53	44.66±1.76	0.74±0.015	13.05±0.91
Nicotine	110.33±3.28$^{\#}$	89.00±7.68$^{\#}$	45.21±3.65$^{\#\#}$	60.33±3.71$^{\#\#}$	0.75±0.019	17.80±1.87$^{\#}$
Nicotin+ Aqueous extract	102.75±3.61	64.33±6.06*	32.82±3.12**	52.66±1.45$^{\#*}$	0.62±0.022$^{\#*}$	12.40±1.31*
Nicotin+ Methanolic extract	90.33±3.36*	60.00±5.69*	31.12±2.89**	47.33±1.45*	0.65±0.018$^{\#*}$	12.10±1.53*

The results are mean±SEM (n=6). #: P<0.05 and ##: P<0.01 compared to the control and sham groups; *: P<0.05 and **: P<0.01 compared to the nicotine group.

Also, the protective effect of aqueous and methanol extracts of corn silk led to a significant decrease of AST in mice receiving nicotine compared to the nicotine group (P<0.01; Figure 4). Serum ALP levels increased in the nicotine group compared to the control and sham groups (P<0.05). This enzyme showed a significant

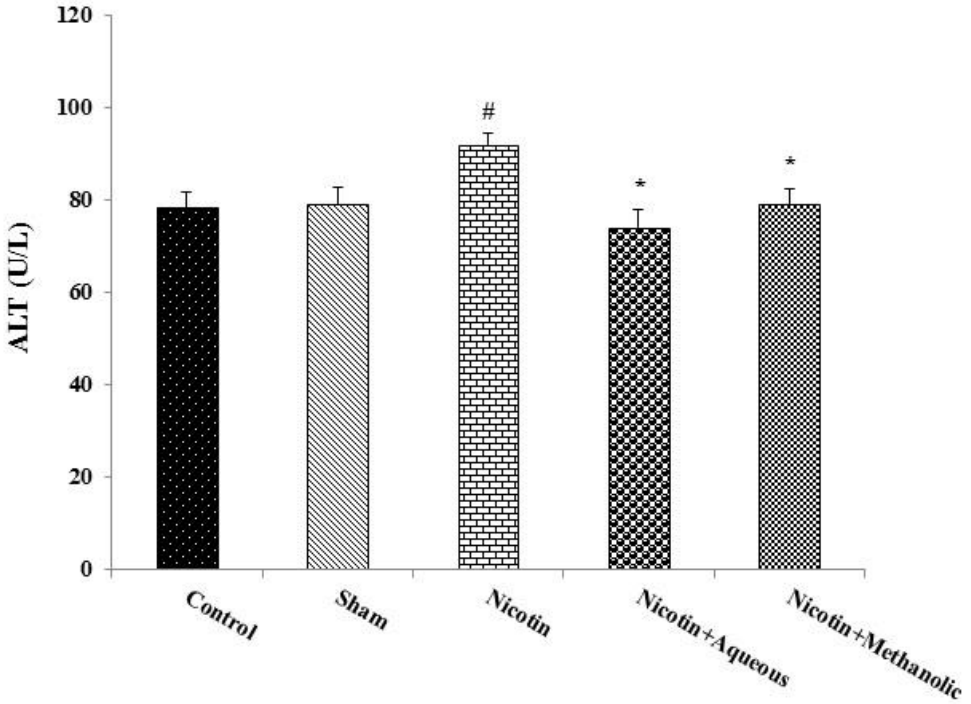

Figure 3. Effect of aqueous and methanol extracts of corn silk on serum ALT. The results are mean±SEM (n=6). #: P<0.05 compared to the control and sham groups; *: P<0.05 compared to the nicotine group.

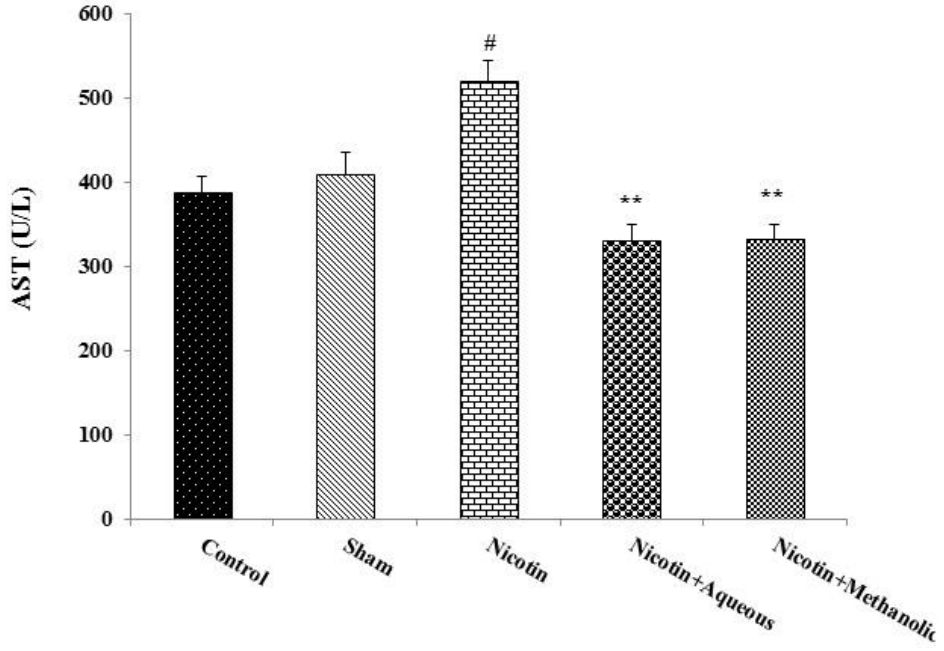

Figure 4. Effect of aqueous and methanol extracts of corn silk on serum AST. The results are mean±SEM (n=6). #: P<0.05 compared to the control and sham groups; **: P<0.01 compared to the nicotine group.

decrease in mice receiving nicotine plus aqueous or methanol extracts of corn silk compared to the nicotine group (P<0.01; Figure 5).

Effect of aqueous and methanol extracts of corn silk on MDA and GSH of liver tissue

Measuring MDA as a variable of lipid peroxidation in the liver tissue of the nicotine group showed a significant

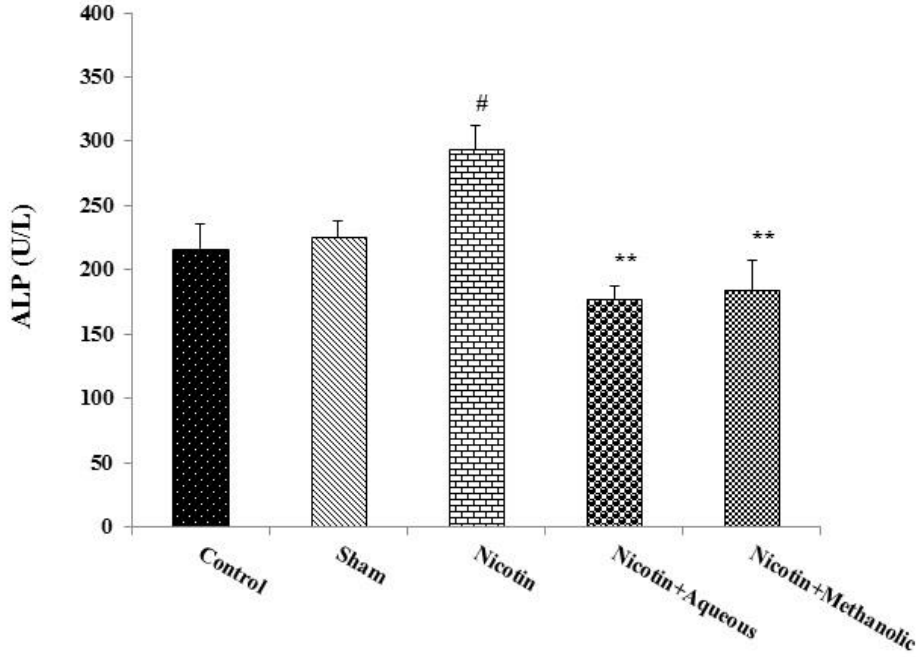

Figure 5. Effect of aqueous and methanol extracts of corn silk on serum ALP. The results are mean±SEM (n=6). #: P<0.05 compared to the control and sham groups; **: P<0.01 compared to the nicotine group.

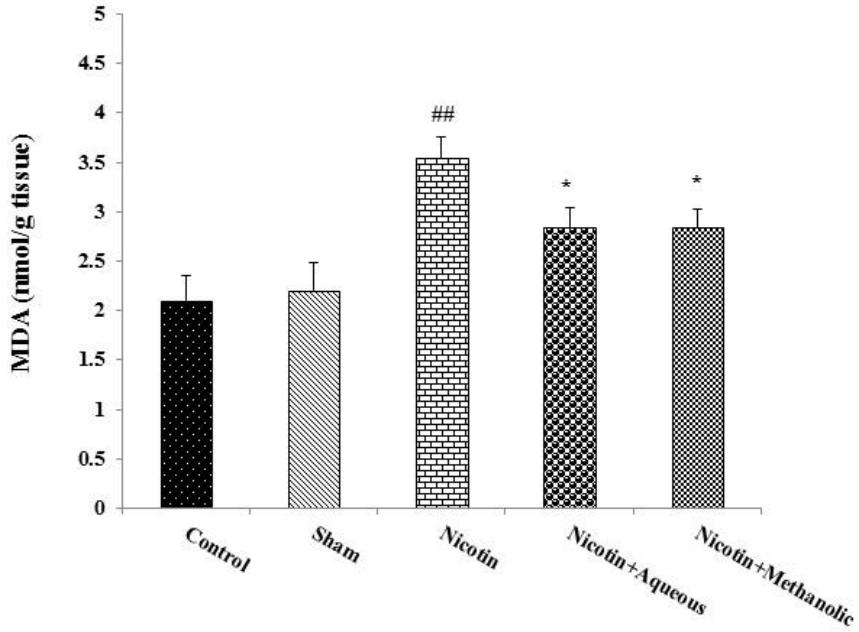

Figure 6. Effect of aqueous and methanol extracts of corn silk on MDA content of liver tissue. The results are mean±SEM (n=6). ##: P<0.01 compared to the control and sham groups; *: P<0.05 compared to the nicotine group.

increase compared to the control and sham groups (P<0.01). Treatment of animals with nicotine plus aqueous or methanol extracts of corn silk caused a significant decrease in this variable compared to the nicotine group (P<0.05; Figure 6). The measurement of GSH as a variable of liver tissue glutathione in the group receiving nicotine (P<0.001) and nicotine plus aqueous or methanol extracts of corn silk (P<0.01) caused a significant decrease compared to the control and sham groups. Also, this antioxidant factor showed a significant increase in the groups receiving nicotine plus aqueous or methanol extracts of corn silk compared to the nicotine group (P<0.05; Figure 7).

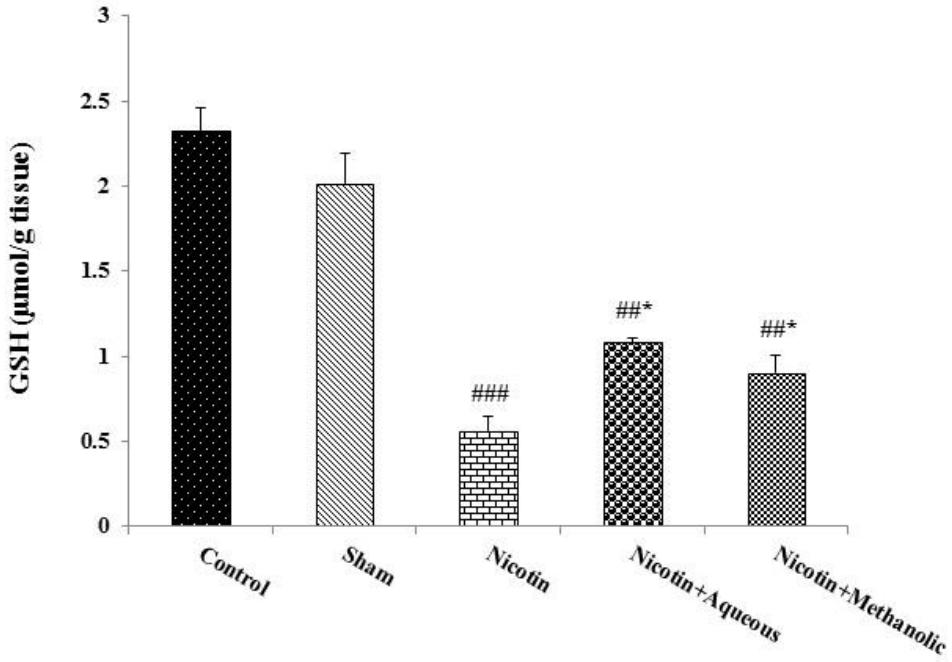

Figure 7. Effect of aqueous and methanol extracts of corn silk on GSH content of liver tissue. The results are mean±SEM (n=6). ##: P<0.01 and ###: P<0.001 compared to the control and sham groups; *: P<0.05 compared to the nicotine group.

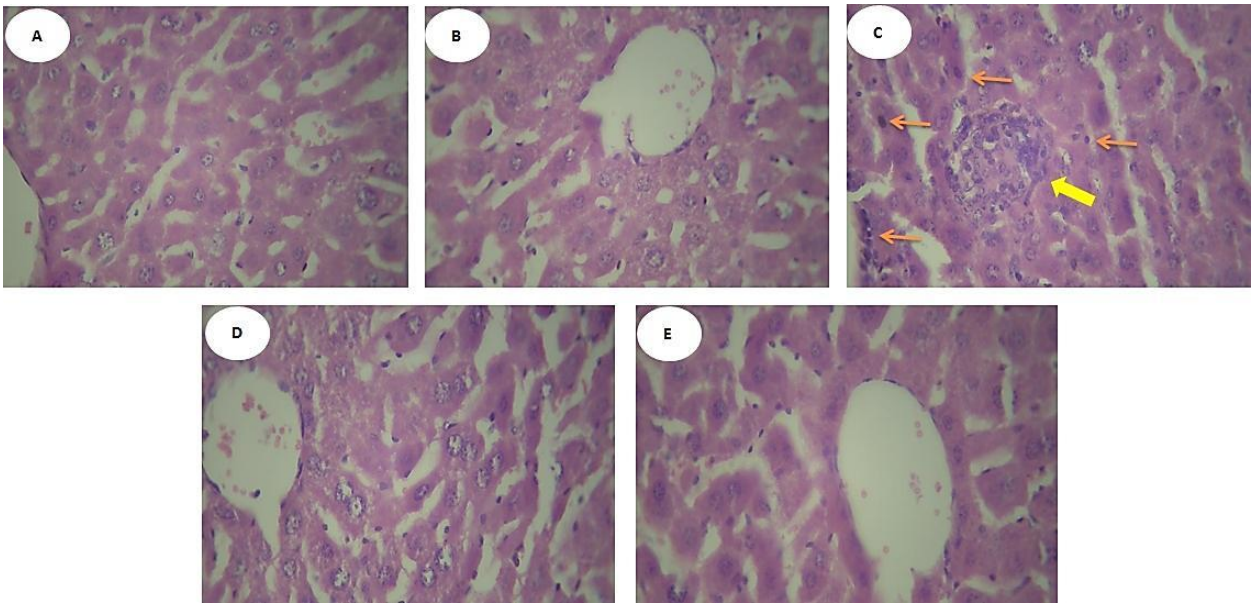

Figure 8. The effect of aqueous and methanol extracts of corn silk on liver tissue changes. A: Control; B: Sham; C: Nicotine; D: nicotine + corn silk aqueous extract; E: Nicotine group + corn silk methanolic extract.

The effect of aqueous and methanol extracts of corn silk on liver tissue changes

The results of the liver tissue examinations showed an increase in the expansion of sinusoids, the presence of inflammatory cells, and an increase in the necrosis of liver cells in the nicotine group compared to the control group. Also, these variables were reduced in the groups receiving aqueous and methanol extracts of corn silk compared to the nicotine group, and these changes were more evident in the groups of nicotine plus methanol extract of corn silk (Figure 8).

Discussion

The results of the present study showed that IP injection of nicotine leads to the induction of oxidative stress through increasing lipid peroxidation and decreasing glutathione levels. Along with this imbalance of the oxidant system and antioxidant defense, the induction of liver toxicity and hyperlipidemic conditions were created by increasing liver enzymes ALT, AST, and ALP and harmful fats, including TG, TC, VLDL, and LDL.

MDA is one of the most widely used biomarkers of lipid peroxidation, which indicates tissue damage caused by free radicals in biological fluids. The Khademi et al. study showed that MDA levels increased in endometrial cells exposed to nicotine (16). This variable also increased in the liver tissue and plasma of mice treated with nicotine, which is consistent with the present study (17, 18). Also, the increase of MDA in the human liver HepG2 cell line following nicotine treatment has been observed in Yarahmadi et al. findings (19). According to the findings of the present study, the research of Khademi et al., revealed that GSH levels decreased simultaneously with the increase of MDA in all nicotine-administered concentrations. This finding shows that compared to other antioxidant enzymes, GSH is more susceptible to oxidative damage caused by increased ROS/free radicals, and nicotine showed a significant negative correlation between glutathione reduction and MDA increase (16). Also following chronic nicotine administration, a decrease of GSH in the liver and testis tissues of rats has been observed in Husain et al. findings (20). Therefore, present nicotine injection causes its damage by reducing the level of antioxidant enzymes and induction of oxidative stress.

According to the results of hepatotoxicity alterations through liver enzyme assessment in the present study, El-Sherbeeny et al. determined that nicotine administration causes specific liver damage, which is accompanied by changes in liver biochemical markers in the form of a significant increase in AST and ALT values (21). Also, the induction of liver damage and increases liver enzymes by nicotine may occur as a result of nicotine itself or one of its metabolites, especially cotinine. The reason of this event is that the liver is the main site of nicotine biotransformation, and it is exposed to its metabolites (22). Previous studies by Chattopadhyay et al. showed that nicotine exposure increases plasma and tissue lipid levels and accelerates lipid peroxidation in rats. The authors of this study concluded that nicotine increases blood lipids by increasing the synthesis and secretion of triglyceride-enriched lipoproteins (17). Hyperlipidemia is considered as an important risk factor for liver diseases such as cirrhosis, hepatocellular carcinoma, and liver failure (23). In addition to liver cell damage and lipid profile abnormalities caused by nicotine, it induces oxidative liver damage through increased lipid peroxidation and decreased tissue antioxidants (24). Therefore, according to the data of the present study and based on the mentioned studies, it can be suggested that nicotine has significantly increased the level of MDA along with decreasing the levels of GSH in mice, leading to an increase in ALT, AST, and ALP enzymes and inducing liver damage.

Changes in the concentration of major lipids such as TC, HDL-C, LDL-C, and TG can provide useful information about lipid metabolism and the predisposition of the heart to atherosclerosis and related cardiovascular diseases. TG, LDL-C, and HDL-C are associated with lipolysis, plasma cholesterol transport, and atherosclerotic propensity. Saheed et al. showed that a reduction of serum levels of TC, TG, and LDL-C was occurred in rats receiving all doses of 100, 200, and 400 mg/kg of corn silk aqueous extract, which expresses that this extract decrease the risk of cardiovascular disease in animals. Moreover, the significant improvement in the lipid profile shows that the extract of this part of the corn plant has hypolipidemic effects (10). The results of a

systematic review and meta-analysis have shown that the aqueous extract of corn silk may be useful in reducing the serum concentration of TC, TG, and LDL-C and improving HDL-C (25). The ratio of LDL-C to HDL-C is clinically used to predict the risk of cardiovascular diseases in patients with dyslipidemia and expresses the effectiveness of lipid-lowering agents in patients (26). Therefore, according to the effect of nicotine on this variable, it may be suggested that nicotine increases HDL-C in response to increased LDL-C. Thus, it is hard to interpret the overall of nicotine consumption on the risk of cardiovascular diseases because high concentrations of HDL-C are associated with greater protection from coronary artery disease. Therefore, the overall effect on the lipoprotein profile must be considered when assessing cardiovascular risk with nicotine. However, corn silk extracts may have a protective effect against this risk disorder by improving the ratio of LDL-C to HDL-C.

A lot of evidence show that nicotine and its main metabolite, cotinine, induce hepatotoxicity and hepatocellular necrosis through direct inflammatory or immunological effects. The direct toxic effect of nicotine and cotinine on the liver may be related to increased oxidative stress, lipid peroxidation, and DNA damage by free radicals produced in mitochondria (20). Also, Helen et al showed that ROS, superoxide, and hydrogen peroxide are the main free radicals induced by nicotine, which decrease the antioxidant defense of cells. They also demonstrated that GSH is critical for protecting the liver and kidney against oxidative stress and exerts this effect by detoxifying exogenous toxins and scavenging ROS (27). Therefore, according to the results of previous studies, in the present study, nicotine-induced liver tissue damage through increasing lipid peroxidation, and the use of aqueous and methanolic extracts of corn silk protected liver tissue from nicotine-induced stress damage via increasing GSH levels in this tissue.

Conclusion

In conclusion, the results of this study showed that the use of nicotine leads to an increase in liver enzymes (ALT, AST, and ALP) and lipid profile, including TG, TC, VLDL, LDL-C, and HDL-C. That these changes can lead to the induction of hepatotoxicity. It was also found that one of the mechanisms involved in these changes is an increase in lipid peroxidation and a decrease in the amount of glutathione in the liver tissue. Moreover, using aqueous and methanol extracts of corn silk led to the improvement of all the changes induced by nicotine, which expresses that the use of corn silk extracts has been able to produce a balance in the antioxidant defense system.

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Conflict of interests

The authors declare no conflict of interest.

References

1. Fagerström K. Nicotine: pharmacology, toxicity and therapeutic use. J Smok Cessat 2014;9:53-59.

2. Ni G, Zhang X, Afedo SY, Rui R. Evaluation of the protective effects of icariin on nicotine-induced reproductive toxicity in male mouse -a pilot study. Reprod Biol Endocrinol 2020;18:65.

3. Salahipour MH, Hasanzadeh S, Malekinejad H. Ameliorative effects of Achillea millefolium inflorescences alcoholic extract against nicotine-induced reproductive failure in rat. Exp Toxicol Pathol 2017;69:504-516.

4. Salahshoor M, Mohamadian S, Kakabaraei S, Roshankhah S, Jalili C. Curcumin improves liver damage in male mice exposed to nicotine. J Tradit Complement Med 2016;6:176-183.

5. Abushofa FA, Azab AE, Alkadrawy S. Hepatic pathophysiological changes induced by nicotine and/or sodium nitrite injection in male albino rats. East African Scholars J Med Sci 2019;2:184-196.

6. Jia Y, Gao X, Xue Z, Wang Y, Lu Y, Zhang M, et al. Characterization, antioxidant activities, and inhibition on α-glucosidase activity of corn silk polysaccharides obtained by different extraction methods. Int J Biol Macromol 2020;163:1640-1648.

7. Wans EM, Ahmed MM, Mousa AA, Tahoun EA, Orabi SH. Ameliorative effects of corn silk extract on acetaminophen-induced renal toxicity in rats. Environ Sci Pollut Res Int 2021;28:1762-1774.

8. Hasanudin K, Hashim P, Mustafa S. Corn silk (Stigma maydis) in healthcare: a phytochemical and pharmacological review. Molecules 2012;17:9697-9715.

9. Nessa N, Ifmaily I, Putri Y, Asra RJAJoPR, Development. Hepatoprotector effect of corn silk ethanol extract (stigma maydis) on paracetamol-induced white male rats. Asian J Pharm Res Dev 2021;9:10-16.

10. Saheed S, Oladipipo AE, Abdulazeez AA, Olarewaju SA, Ismaila NO, Emmanuel IA, et al. Toxicological evaluations of Stigma maydis (corn silk) aqueous extract on hematological and lipid parameters in Wistar rats. Toxicol Rep 2015;2:638-644.

11. Salahshoor MR, Khazaei M, Jalili C, Keivan M. Crocin improves damage induced by nicotine on a number of reproductive parameters in male mice. Int J Fertil Steril 2016;10:71-78.

12. Ernst C, Eling N, Martinez-Jimenez CP, Marioni JC, Odom DT. Staged developmental mapping and X chromosome transcriptional dynamics during mouse spermatogenesis. Nat Commun 2019;10:1251.

13. Ahangarpour A, Oroojan AA, Badavi M. Exendin-4 protects mice from D-galactose-induced hepatic and pancreatic dysfunction. Pathol Aging Age Relat Dis 2018;8:1418593.

14. Ahangarpour A, Shabani R, Farbood Y. The effect of betulinic acid on leptin, adiponectin, hepatic enzyme levels and lipid profiles in streptozotocin–nicotinamide-induced diabetic mice. Res Pharm Sci 2018;13:142-148.

15. Oroojan AA, Ahangarpour A, Paknejad B, Zareian P, Hami Z, Abtahi SR. Effects of myricitrin and solid lipid nanoparticle-containing myricitrin on reproductive system disorders induced by diabetes in male mouse. World J Mens Health 2021;39:147.

16. Khademi F, Totonchi H, Mohammadi N, Zare R, Zal F. Nicotine-induced oxidative stress in human primary endometrial cells. Int J Toxicol 2019;38:202-208.

17. Chattopadhyay K, Chattopadhyay BD. Effect of nicotine on lipid profile, peroxidation & antioxidant enzymes in female rats with restricted dietary protein. Indian J Med Res 2008;127:571-576.

18. Chattopadhyay K, Mondal S, Chattopadhyay B, Ghosh S. Ameliorative effect of sesame lignans on nicotine toxicity in rats. Food Chem Toxicol 2010;48:3215-3220.

19. Yarahmadi A, Zal F, Bolouki A. Protective effects of quercetin on nicotine induced oxidative stress in 'HepG2 cells'. Toxicol Mech Methods 2017;27:609-614.

20. Husain K, Scott BR, Reddy SK, Somani SM. Chronic ethanol and nicotine interaction on rat tissue antioxidant defense system. Alcohol 2001;25:89-97.

21. El-Sherbeeny NA, Nader MA, Attia GM, Ateyya H. Agmatine protects rat liver from nicotine-induced hepatic damage via antioxidative, antiapoptotic, and antifibrotic pathways. Naunyn-Schmiedeberg's Arch Pharmacol 2016;389:1341-1351.

22. Jalili C, Tabatabaei H, Kakaberiei S, Roshankhah S, Salahshoor MR. Protective role of Crocin against nicotine-induced damages on male mice liver. Int J Prev Med 2015;6:92.

23. Xia X, Ma Y, Xing X, Huang C, Li L, Gui G, et al. Antioxidant and hepatoprotective effect of different extracts of guizhencao (herba bidentis bipinnatae) against liver injury in hyperlipidemia rats. J Tradit Chin Med 2013;33:518-523.

24. Dey S, Roy S. Role of reduced glutathione in the amelioration of nicotine-induced oxidative stress. Bull Environ Contam Toxicol 2010;84:385-389.

25. Shi S, Yu B, Li W, Shan J, Ma T. Corn silk decoction for blood lipid in patients with angina pectoris: a systematic review and meta-analysis. Phytother Res 2019;33:2862-2869.

26. Chu ZS, Yu ZL, Pan SY, Jia ZH, Wang XY, Zhang Y, et al. A comparative study between Wuweizi seed and its post-ethanol extraction residue in normal and hypercholesterolemic mice. Lipids Health Dis 2015;14:93.

27. Helen A, Krishnakumar K, Vijayammal P, Augusti K. Antioxidant effect of onion oil (Allium cepa. Linn) on the damages induced by nicotine in rats as compared to alpha-tocopherol. Toxicol Lett 2000;116:61-68.