

## Protective Effect of Honey and Grape Juice against Cisplatin-Induced Peripheral Neuropathy in Mice

### Abstract

Cisplatin, a potent chemotherapeutic agent, is widely used in the treatment of different types of solid tumors, and its neurotoxicity remains a major problem in clinical use. This study was designed to investigate the protective effect of honey and grape juice (GJ) against cisplatin-induced peripheral neuropathy.

A total of 40 mice were randomly divided into 5 equal groups (n = 8) including the control group; cisplatin group; GJ group; honey group; honey + GJ group. Cisplatin (2 mg kg<sup>-1</sup> i.p.) was given twice a week six times. GJ (10%, 10 ml kg<sup>-1</sup>) and honey (10%, 10 ml kg<sup>-1</sup>) were orally given to mice every day. The tail-flick test was used to evaluate the neuroprotective properties of GJ and honey. Malondialdehyde (MDA) and total antioxidant capacity (TAC) were determined in the serum using colorimetric methods. Intraperitoneal injection of cisplatin meaningfully reduced the latency time in the tail-flick test as well as TAC in serum while increasing MDA. Orally treatment of mice with GJ, honey, and a combination of them increased latency time in the tail-flick test and TAC in serum, while decreasing the MDA levels. GJ, honey, and a combination of them can have protective effects against cisplatin-induced neuropathy, which may be due to the antioxidant properties of these substances.

**Keywords:** Cisplatin; Grape Juice, Honey, Peripheral Neuropathy

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## Introduction

Cisplatin (Cis-diaminodichloroplatinum II), a well-known antineoplastic agent approved by FDA in 1978, is commonly used in the treatment of different solid tumors, including bladder, cervical, colorectal, endometrial, head, lung, ovarian, neck, ovarian, and testicular cancers (1, 2).

Cisplatin creates highly reactive charged platinum complexes that bind to nucleophilic groups in GC-rich regions in DNA, inducing intra-strand and inter-strand cross-links in DNA, as well as between DNA and proteins, which leads to cell-cycle arrest and apoptosis (3).

One of the major side effects of this drug is peripheral neuropathy (PN, in 80 to 90% of cisplatin-treated patients), which limited its clinical use at the desired dosage and duration (4). Due to the absence of a blood-brain barrier (BBB) in the peripheral nervous system (PNS), nerve cells, especially in the dorsal root ganglion (DRG), are easily exposed to the toxic effects of cisplatin (1). Several mechanisms have been proposed for cisplatin-induced peripheral neuropathy (CIPN), among which oxidative stress has a more important and prominent role (5). Cisplatin disrupts mitochondrial function by impairing mitochondrial DNA replication and transcription, causing ATP depletion (one of the causes of PN) and increased oxygen-reactive species (ROS) production (6). The produced ROS react with DNA to form 8-hydroxy guanine, causing DNA damage, activation of caspases, and ultimately apoptosis of neurons (7). In addition, excess generation of ROS increases lipid peroxidation and cellular membrane damage (8).

Antioxidants play an important role in inhibiting the production and neutralization of free radicals. Several antioxidant agents including vitamin E (9), selenium (10), curcumin (11), caffeic acid phenethyl ester (12), and rutin (1) have been shown to reduce cisplatin-induced neurotoxicity.

Honey is a complex natural product composed of fructose (38%) and glucose (31%) as the major ingredients and a series of other minor ingredients such as flavonoids, phenolic acids (chrysin, caffeic acid, quercetin), carotenoid-like substances, organic acids, ascorbic acid, Millard reaction products, and certain antioxidant enzymes (e.g. glucose oxidase and catalase) (13, 14), and as a potent antioxidant, it's hepatoprotective, nephroprotective, sperm-protective properties against cisplatin toxicity have been reported in several studies (15-17). Interestingly, it has been shown that honey increases the cytotoxic effects of cisplatin on cancer cells (18, 19).

Grape is one of the most popular fruits in the world, which is rich in vitamins, minerals, carbohydrates, dietary fiber, flavonoids, polyphenols, tannins, proanthocyanidins, and resveratrol (20). Grape juice and its derivatives, both have antioxidant properties that have been extensively studied in

animals, humans, and in vitro conditions (21-23). Ko et al. showed that oral administration of whole grape juice prevents cisplatin-induced dyspepsia (20). Proanthocyanidins and resveratrol isolated from grape skins and red wine are polyphenols that have nephroprotective properties against cisplatin-induced toxicity in rats (23, 24). Oral feeding of grape juice (10 ml/kg of body weight) for 17 days led to improved liver function in pentylenetetrazole-induced oxidative damage in rats (25).

Although there have been several studies on grape juice and honey, no study has been conducted to investigate whether whole grape juice and crude honey are protective against CIPN. Therefore, this study aimed to examine the possible neuroprotective effect of honey and grape juice against cisplatin-induced neuropathy in mice.

## Materials and Methods

### Drugs and Chemicals

Cisplatin, Thiobarbituric acid (TBA), Trichloroacetic acid (TCA), and 1,1,3,3 - tetraethoxypropan (TEP) were purchased from Sigma Chemical Co. (Sigma, Germany). Metmyoglobin, 2,2'-Azino-bis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt (ABTS), 6-Hydroxy-2,5,7,8-tetramethylchromane-2-carboxylic acid (Trolox), Hydrogen peroxide, and Phosphoric acid were obtained from Merck (Darmstadt, Germany).

### Experimental Animals

A total of 40 male Swiss albino mice, weighing 25 to 35 g, were purchased from the Pasteur Institute of Iran, Tehran, Iran. The animals were fed with standard mice food pellets and tap water ad libitum and acclimatized in a well-ventilated room with a 12 hours light/12 hours dark cycle and a normal temperature of  $22 \pm 3^\circ\text{C}$ . The animal handling procedures were conducted in conformity with the international guidelines for the care and use of experimental animals and approved by the local Research Ethical Committee at Tabriz University of Medical Sciences, Iran (Approval No.: IR.TBZMED.VCR.REC.1398.159)

### Experimental Procedures

In this experiment, mice were treated daily with NS, grape juice (GJ), honey, and a combination of honey and grape juice (Honey + GJ) based on their group throughout the study. To induce peripheral neuropathy, CDDP was injected Intraperitoneally (i.p) on the seventh day of the study and then twice a week at regular intervals until the end of the fourth week (26). CDDP doses were adjusted weekly for each animal according to their weight change. Grape juice and honey were used with a concentration of 10% (w/w, 1 ml of

GJ or honey was dissolved in 10 ml of NS). Animals were randomly divided into five equal groups (n=8) as follows:

Group I (Control): Mice received NS (10 ml.kg<sup>-1</sup> p.o)

Group II: Mice received NS (10 ml.kg<sup>-1</sup>p.o) and CDDP (2 mg.kg<sup>-1</sup>, i.p, 6 times)

Group III: Mice received GJ (10 ml.kg<sup>-1</sup>, p.o) and CDDP (2 mg.kg<sup>-1</sup>, i.p, 6 times)

Group IV: Mice received honey (10 ml.kg<sup>-1</sup>, p.o) and CDDP (2 mg.kg<sup>-1</sup>, i.p, 6 times)

Group V: Mice received GJ and honey (10 ml.kg<sup>-1</sup>, p.o), and CDDP (2 mg.kg<sup>-1</sup>, i.p, 6 times).

## **Behavioral Assessment**

### **Tail flick test**

To evaluate the protective effects of GJ, honey, and their combination (GJ + honey) on cisplatin-induced neuropathy, before cisplatin injection tail Flick test was performed on days 0, 7, 15, 22, and 29<sup>th</sup> according to the method described by D'Amour and Smith (1941). Briefly, the animal was lightly restrained and infrared thermal stimuli (20 W/cm<sup>2</sup>) were applied to the middle one-third of the animal's tail. The time of tail-flick is measured and recorded. The cut-off time of the latency to tail flick was set up to 30 s to prevent any further tissue damage (27).

### **Sample Collection**

After the final measurements, the mice were anesthetized with xylazine/ ketamine (i.p) and the blood samples were collected by cardiac puncture, centrifuged at 3000 rpm for 20 min at +4 °C, and the separated sera were stored at - 80 °C for TAC and MDA measurement.

## **Biochemical Assays**

### **Malondialdehyde (MDA) measurement in serum**

Serum MDA levels were determined spectrophotometrically using a thiobarbituric acid reactive substance (TBARS) assay (28). Briefly, 500 µL of serum or TEP standard was mixed with 3 ml of the 1% phosphoric acid. After vortexing, 1 mL of 0.67% TBA solution was added, and the mixture was heated at 100 °C for 45 minutes and cooled using the cold-water bath. Next, the mixture was centrifuged at 3000 rpm for 10 min, and the pink color was extracted using 3 mL of normal butanol. Finally, the absorbance of the supernatant was measured at 532 nm, and the results were expressed as µmol/mL in serum.

### **Total Antioxidant Capacity**

Serum total antioxidant capacity (TAC) was measured by a colorimetric method. In this technique, ABTS radical is incubated with methemoglobin (HX-Fe<sup>+</sup>) and hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) to produce ABTS + radical. This cation

radical is relatively stable and is green-blue, which can be measured in the range of 660 nm. The antioxidants in the sample in proportion to their concentration can inhibit the formation of this green-blue color. TAC was expressed as mmol Trolox (a vitamin E analog, as a standard) equivalent/L using the standard calibration curve (29).

## **Statistical analysis**

The differences between obtained values (mean ± S.E.M) were tested by one-way analyses of variance (ANOVA) followed by the Tukey posthoc test, graph pad 8.0 prism software (GraphPad Software, Inc., La Jolla, CA, USA). P values of 0.05 or less were considered to show significant differences for all comparisons made.

## **Results**

### **Induction of peripheral neuropathy and the effect of grape juice and honey**

As shown in Table 1, i.p. injection of cisplatin (2 mgkg<sup>-1</sup>; twice a week) meaningfully reduced the latency time in the tail-flick test at the end of the second, third, and fourth weeks compared with the control group (P < 0.001), indicates that cisplatin at the mentioned dose induced neuropathy in these animals. The decrease in latency time was significantly inhibited by pre-treatment with grape juice (P < 0.001) and honey (P < 0.01) compared to the cisplatin group on the 15th day, but their combination had no significant inhibitory effect (P > 0.05). In addition, continued treatment with grape juice, honey, and a combination of them caused a significant increase in latency time compared to the cisplatin group in the third and fourth weeks (P < 0.05). In the last week of the study, there was no significant difference in latency time between the groups of grape juice, honey, and their combination (P > 0.05) (Table 1).

### **Effect of cisplatin alone and in combination with grape juice or honey on lipid peroxidation in serum**

As illustrated in Fig. 1, serum MDA content, an indicator of lipid peroxidation, was increased in Cisplatin-treated mice compared to control groups (P< 0.001). Grape juice, honey, and their combination inhibited elevation in the serum MDA levels due to cisplatin injection (P < 0.001).

### **Effect of cisplatin alone and in combination with grape juice or honey on total antioxidant capacity in serum**

Intraperitoneal injection of cisplatin (2 mg kg<sup>-1</sup> × 6 times) induced a noticeable decrease in total antioxidant capacity (TAC) compared to control groups (P < 0.001). Oral treatment with grape juice, honey, and grape juice + honey enhanced the TAC compared to the cisplatin group (P < 0.001). In addition, the TAC mean in the grape juice group was significantly higher than in the honey group (P < 0.001). (Fig. 2.)

## Discussion

Neurotoxicity is one of the major side effects of cisplatin, which has limited its use in effective doses in the treatment of cancer (4). Several mechanisms have been proposed for the neurotoxicity of cisplatin, one of the most likely of which is the increase in free radical production and the resulting oxidative stress. By increasing the production of reactive oxygen species, cisplatin causes lipid membrane peroxidation, DNA damage, and ultimately extensive tissue damage (5). Various studies have shown that concomitant use of cisplatin with an antioxidant agent reduces the severity of drug-induced toxicity (9, 10, 12).

The current study examined the neuroprotective effect of honey and grape juice against cisplatin-induced neuropathy via measurement of the serum levels of MDA and TAC, as well as the tail Flick test was performed.

In the present study, repeated i.p administration of cisplatin caused the development of peripheral neuropathy as well as increased the MDA and decreased the TAC levels in the serums of mice. These results are in good agreement with the findings of an earlier study about the neurotoxicity of cisplatin in experimental animals (30).

Our tail-flick test results showed that cisplatin caused significant hyperalgesia on day 15. We observed that oral administration of honey and grape juice increased the pain threshold It was in the third and fourth weeks. Similar to the findings of this study, Mohajjel Nayebi et al. also showed that oral administration of Carbamazepine increased the pain threshold in cisplatin-treated animals. Furthermore, our findings showed that oral administration of grape juice, honey, and grape juice + honey partially reduced cisplatin-induced peripheral neuropathy and reversed the changes in MDA and TAC to their normal levels as in the control group. Previous studies showed that purple grape juice has a neuroprotective against temozolomide (31) and carbon tetrachloride (32) in rats via increasing enzymatic antioxidant defenses and preventing lipid peroxidation. Similarly, Kiyumarsi et al. showed that honey can reduce MDA and enhance TAC levels in cisplatin-treated mice (33). Honey and grape juice are potent antioxidant agents; therefore, they may prevent lipid peroxidation in cell membranes by increasing serum antioxidant capacity and eliminating oxygen free radicals.

## Conclusion

In conclusion, grape juice and honey showed a neuroprotective effect against cisplatin neurotoxicity, which may be due to the antioxidant properties of these natural products. Further studies are needed to identify the exact

mechanism of the protective effect of grape juice and honey against cisplatin-induced neurotoxicity.

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## References

1. Almutairi MM, Alanazi WA, Alshammari MA, Alotaibi MR, Alhoshani AR, Al-Rejaie SS, et al. Neuroprotective effect of rutin against Cisplatin-induced neurotoxic rat model. *BMC complementary and alternative medicine*. 2017;17(1):1-9.
2. Saadati H, Noroozadeh S, Esmacili H, Amirshahrokhi K, Shadman J, Niapour A. The Neuroprotective Effect of Mesna on Cisplatin-Induced Neurotoxicity: Behavioral, Electrophysiological, and Molecular Studies. *Neurotoxicity Research*. 2021;39(3):826-40.
3. Manohar S, Leung N. Cisplatin nephrotoxicity: a review of the literature. *Journal of Nephrology*. 2018;31(1):15-25.
4. Aldossary SA. Review on the pharmacology of cisplatin: clinical use, toxicity, and mechanism of resistance of cisplatin. *Biomedical and Pharmacology Journal*. 2019;12(1):7-15.
5. Kanat O, Ertas H, Caner B. Platinum-induced neurotoxicity: a review of possible mechanisms. *World journal of clinical oncology*. 2017;8(4):329.
6. Santos N, Catao C, Martins N, Curti C, Bianchi M, Santos A. Cisplatin-induced nephrotoxicity is associated with oxidative stress, redox state unbalance, impairment of energetic metabolism and apoptosis in rat kidney mitochondria. *Archives of toxicology*. 2007;81(7):495-504.
7. Turan M, Cayir A, Cetin N, Suleyman H, Turan IS, Tan H. An investigation of the effect of thiamine pyrophosphate on cisplatin-induced oxidative stress and DNA damage in rat brain tissue compared with thiamine: thiamine and thiamine pyrophosphate effects on cisplatin neurotoxicity. *Human & experimental toxicology*. 2014;33(1):14-21.
8. Sadeghi H, Soltani M, Kokhdan EP, Abbasi R, Sadeghi H, Mostafazade M, et al. Renoprotective effect of *Otostegia persica* on vancomycin-induced nephrotoxicity in rats. *Comparative Clinical Pathology*. 2021:1-9.
9. Argyriou AA, Chroni E, Koutras A, Iconomou G, Papapetropoulos S, Polychronopoulos P, et al. A randomized controlled trial evaluating the efficacy and safety of vitamin E supplementation for protection against cisplatin-induced

peripheral neuropathy: final results. *Supportive Care in Cancer*. 2006;14(11):1134-40.

10. Erken HA, Koç ER, Yazıcı H, Yay A, Önder GÖ, Sarıcı SF. Selenium partially prevents cisplatin-induced neurotoxicity: a preliminary study. *Neurotoxicology*. 2014;42:71-5.

11. Al Moundhri MS, Al-Salam S, Al Mahrouqee A, Beegam S, Ali BH. The effect of curcumin on oxaliplatin and cisplatin neurotoxicity in rats: some behavioral, biochemical, and histopathological studies. *Journal of Medical Toxicology*. 2013;9(1):25-33.

12. Özyurt B, Güleç M, Özyurt H, Ekici F, Atı Ö, Akbaş A. The effect of antioxidant caffeic acid phenethyl ester (CAPE) on some enzyme activities in cisplatin-induced neurotoxicity in rats. 2006.

13. Ariefdjohan MW, Martin BR, Lachcik PJ, Weaver CM. Acute vs. chronic effects of honey and its carbohydrate constituents on calcium absorption in rats. *Wiley Online Library*; 2006.

14. Hamad R, Jayakumar C, Ranganathan P, Mohamed R, El-Hamamy MM, Dessouki AA, et al. Honey feeding protects the kidney against cisplatin nephrotoxicity through suppression of inflammation. *Clinical and Experimental Pharmacology and Physiology*. 2015;42(8):843-8.

15. Bhalchandra W, Alqadhi YA. Administration of Honey and Royal Jelly Ameliorate Cisplatin Induced Changes in Liver and Kidney Function in Rat. *Biomedical and Pharmacology Journal*. 2018;11(4):2191-9.

16. Ibrahim A, Abd Eldaim MA, Abdel-Daim MM. Nephroprotective effect of bee honey and royal jelly against subchronic cisplatin toxicity in rats. *Cytotechnology*. 2016;68(4):1039-48.

17. Waykar BB, Alqadhi YA. Protective role of royal jelly and honey against cisplatin-induced sperm function parameters in male rats. *EXECUTIVE EDITOR*. 2020;11(7):158.

18. Alizadehnohi M, Nabiuni M, Nazari Z, Safaeinejad Z, Irian S. The synergistic cytotoxic effect of cisplatin and honey bee venom on human ovarian cancer cell line A2780cp. *Journal of venom research*. 2012;3:22.

19. Shiassi Arani F, Karimzadeh L, Ghafoori SM, Nabiuni M. Antimutagenic and synergistic cytotoxic effect of cisplatin and honey bee venom on 4T1 invasive mammary carcinoma cell line. *Advances in pharmacological sciences*. 2019;2019.

20. Ko J, Tsai C, Liu T, Lin M, Lin H, Ou C. Differential effects of grape juice on gastric emptying and renal function from cisplatin-induced acute adverse toxicity. *Human & experimental toxicology*. 2016;35(8):808-17.

21. Burin VM, Falcão LD, Gonzaga LV, Fett R, Rosier JP, Bordignon-Luiz MT. Colour, phenolic content, and

antioxidant activity of grape juice. *Food Science and Technology*. 2010;30(4):1027-32.

22. VINSON JA, YANG J, PROCH J, LIANG X. Grape juice, but not orange juice, has in vitro, ex vivo, and in vivo antioxidant properties. *Journal of medicinal food*. 2000;3(4):167-71.

23. Zhu M, Huang Y, Wang Y, Shi T, Zhang L, Chen Y, et al. Comparison of (poly) phenolic compounds and antioxidant properties of pomace extracts from kiwi and grape juice. *Food chemistry*. 2019;271:425-32.

24. Yousef M, Saad A, El-Shennawy L. Protective effect of grape seed proanthocyanidin extract against oxidative stress induced by cisplatin in rats. *Food and Chemical Toxicology*. 2009;47(6):1176-83.

25. Rodrigues AD, Scheffel TB, Scola G, Dos Santos MT, Fank B, Dani C, et al. Purple grape juices prevent pentylene tetrazol-induced oxidative damage in the liver and serum of Wistar rats. *Nutrition Research*. 2013;33(2):120-5.

26. Öztürk G, Anlar Ö, Erdoğan E, Kösem M, Özbek H, Türker A. The effect of Ginkgo extracts EGb761 in cisplatin-induced peripheral neuropathy in mice. *Toxicology and applied pharmacology*. 2004;196(1):169-75.

27. Lutfy K, Cai SX, Woodward RM, Weber E. Antinociceptive effects of NMDA and non-NMDA receptor antagonists in the tail flick test in mice. *Pain*. 1997;70(1):31-40.

28. Ohkawa H, Ohishi N, Yagi K. Assay for lipid peroxides in animal tissues by the thiobarbituric acid reaction. *Analytical biochemistry*. 1979;95(2):351-8.

29. Erel O. A novel automated direct measurement method for total antioxidant capacity using a new generation, more stable ABTS radical cation. *Clinical biochemistry*. 2004;37(4):277-85.

30. Asadpour Y. Evaluation of the effect of Dexamethasone and Citicoline on Cisplatin-induced pain (neuropathy) in Mice: Tabriz University of Medical Sciences, Faculty of Pharmacy; 2019.

31. Gabardo T, Frusciant MR, Pereira Marinho J, Dos Santos M, Abujamra AL, Dani C, et al. In Vitro Antioxidant Activity of Purple Grape Juice (*Vitis Labrusca*) against Temozolamide Treatment in Rat Brains. *Beverages*. 2018;4(4):99.

32. Dani C, Pasquali MA, Oliveira MR, Umezu FM, Salvador M, Henriques JA, et al. Protective effects of purple grape juice on carbon tetrachloride-induced oxidative stress in brains of adult Wistar rats. *Journal of medicinal food*. 2008;11(1):55-61.

33. Kiyumarsi P. Evaluation of prophylactic effects of Olanzapine and Honey on neuropathic pain induced by Cisplatin in mice: Tabriz University of Medical Sciences, Faculty of Pharmacy; 2021.



Table 1. Effect of Cisplatin, Grape juice, and Honey on tail-flick test in cisplatin-induced neuropathy in mice

Groups	Latencytime (Second) on different days				
	0	7	15	22	29
Control	21.38 ± 0.2	21.8 ± 0.4	21.02 ± 0.3	18.99 ± 1.3	19.57 ± 0.3
Cisplatin	21.76 ± 0.2	20.05 ± 0.2	12.1 ± 0.3 <sup>a</sup>	9.7 ± 0.4 <sup>a</sup>	8.5 ± 1.4 <sup>a</sup>
Grape Juice	21.9 ± 0.4	21.8 ± 0.5	16.53 ± 0.36 <sup>a, c</sup>	16.54 ± 0.36 <sup>c</sup>	17.3 ± 0.4 <sup>c</sup>
Honey	21.02 ± 0.4	20.5 ± 0.3	13.5 ± 0.5 <sup>a, e</sup>	15.23 ± 0.4 <sup>b, c</sup>	16.3 ± 0.34 <sup>c</sup>
Grape Juice + Honey	20.66 ± 0.4	21.28 ± 0.3	11.5 ± 0.38 <sup>a, f, h</sup>	13.6 ± 0.5 <sup>a, d, g</sup>	16.6 ± 0.4 <sup>c</sup>

Values are mean ± S.E.M. (n = 8).

<sup>a</sup> P < 0.001 and <sup>b</sup> P < 0.01 vs. Control group (normal saline). <sup>c</sup> P < 0.001 and <sup>d</sup> P < 0.01 vs. Cisplatin group. <sup>e</sup> P < 0.001, <sup>f</sup> P < 0.01, and <sup>g</sup> P < 0.05 vs. Grape juice group. <sup>h</sup> P < 0.005 vs. Honey group.

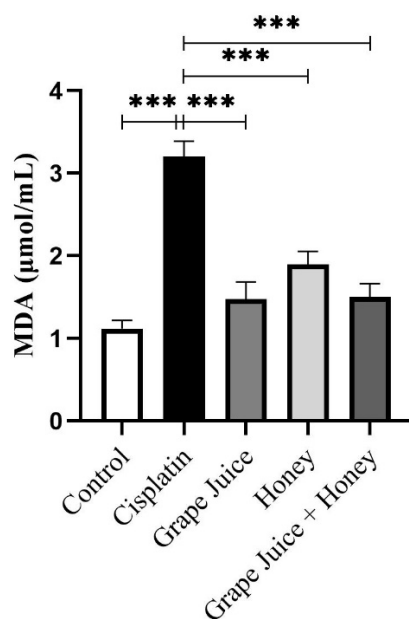


Fig. 1. Effect of Grape Juice and Honey on MDA in cisplatin-induced neuropathy in mice. Values are presented as mean ± S.E.M (n=8). \*\*\*p<0.001.

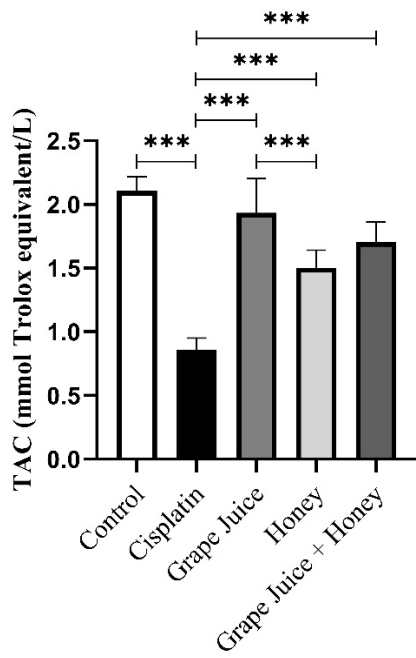


Fig. 2. Effect of Grape Juice and Honey on TAC in cisplatin-induced neuropathy in mice. Values are presented as mean  $\pm$  S.E.M (n=8). \*\*\*p<0.001.