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Neuroprotective effect of *Chenopodium pallidicaule* flour (cañihuaco) suspension against ethanol toxicity in mice

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ABSTRACT

Introduction: Food plays an important role in preventing various neurodegenerative diseases. *Chenopodium pallidicaule* flour (cañihuaco) is characterized by its phytonutrients content, among them polyphenols which have the potential to exert neuroprotective properties.

Objective: To evaluate the effect of the administration of cañihuaco suspension against ethanol toxicity in mice.

Materials and methods: Experimental design. 35 male mice were used, receiving the following treatments, for five days: groups I-II water 10mL/kg, groups III-V received cañihuaco at doses of 200mg/kg, 400mg/kg and 800mg/kg respectively. On the fifth day, 99% ethanol was administered subcutaneously, 5g/kg, except for group I. After four hours mice were sacrificed by decapitation. The brain and cerebellum were extracted, weighed, and stored for histological analysis. Biochemical indicators were determined in the right hemisphere.

Results: Group III and IV showed higher tissue protein levels ($p<0.05$). Groups III-V showed higher levels of protein sulfhydryl groups, with a significant increase observed in group V. There was no difference in GSH levels in any treatment group with respect to group II. At the histological level, group V showed preservation of nervous tissue.

Conclusion: The administration of *Chenopodium pallidicaule* (cañihuaco) flour suspension at doses of 200, 400, and 800 mg/kg exhibits a dose-response trend reduction of histological damage in the brain and cerebellum. Additionally, it enhances the levels of protein SH groups.

KEY WORDS

Medicinal plant; neurodegeneration; glutathione; Chenopodium; mice.

INTRODUCTION

Aging is considered a risk factor for various neurodegenerative because it promotes neuronal dysfunction. This places a greater burden on the health care system and a greater financial impact on the country, consequently, therapies aimed at delaying or preventing the onset of neurodegenerative diseases should be taken into consideration[1].

It has been seen that there is a close relationship between people's diet and cognitive impairment, in fact, it is known that a diet rich in antioxidants with a high consumption of fruits, vegetables and whole grains could reduce the prevalence of neurodegenerative diseases. It is for this reason that dietary patterns such as the Mediterranean diet have been shown to delay the progression of these diseases[2].

Neuronal cell death in neurodegenerative diseases is related to protein misfolding and aggregation, mitochondrial dysfunction, generation of reactive oxygen species and neuroinflammation. This is why research for the treatment of these pathologies has been pointing to the regulation of these pathways using a therapeutic approach[3].

In this sense, Peruvian Andean grains such as cañihua contains interesting bioactive metabolites, developed in extreme climates, enabling efficient antioxidant defense systems to survive in these environments, consequently they could be

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used to delay or prevent neurodegenerative diseases in the population at higher risk[4].

The aim of the study was to evaluate the neuroprotective effect of the administration of *Chenopodium pallidicaule* (cañihuaco) flour suspension against ethanol toxicity in mice.

MATERIALS AND METHODS

Study design: The study is pure experimental with a post-test and control group, designed with an explanatory scope. (Hernández Sampieri 2018)[5].

Sample size calculation: The sample size was calculated to get a 24.7% difference in GSH levels comparing control and intervention groups, according to previous literature addressing similar functional foods using the KISS method[6], an increase in 15% in sample was considered because previous research used non-parametric inferential tests and present skewed data[7].

Acquisition of the flour and preparation of the suspension: The flour of *Chenopodium pallidicaule* (cañihuaco) was acquired in a local supermarket in Lima - Peru, this product presented the sanitary registration number E4656217N DAPOAD - DIGESA, lot 06 ABR HA. The flour was dissolved in boiling water (100ºC) at a concentration of 8% and then allowed to stand for 30 minutes.

Evaluation of neuroprotection: male *Mus musculus* mice of the BALB/c strain with weights between 30.7 ± 1.9 g of three months of age were used in the study, these mice were obtained from the National Institute of Health (INS). The animals were acclimatized in the biotherium of the Faculty of Medicine of San Fernando, fed a balanced diet provided by the National Agrarian University of La Molina (UNALM) and had ad libitum water consumption for seven days, respecting the photoperiods.

The experimental animals were randomly distributed into five groups (n=7) which received the treatment via orogastric for five days after fasting.

- Group I: (Negative Control), Water 10 mL/kg
- Group II: (Positive Control), Water 10 mL/kg
- Group III (Experimental 1): Dose 200 mg/kg, *Chenopodium pallidicaule* (cañihuaco) flour suspension.
- Group IV (Experimental 2): Dose 400 mg/kg, *Chenopodium pallidicaule* (cañihuaco) flour suspension.
- Group V (Experimental 3): Dose 800 mg/kg, *Chenopodium pallidicaule* (cañihuaco) flour suspension.

On the final day (5th day), immediately after the last treatment, ethanol at a concentration of 5 g/kg was administered subcutaneously Tahir Ali (6) to groups II-VI, and after four hours the animals were sacrificed by decapitation, and then the brain was removed, washed with NaCl 0.9% and weighed on an analytical balance. The left hemisphere was preserved in 10% buffered formalin (phosphate buffer 0.075 mol/L pH 7.4) for the corresponding histological analysis, and the right hemisphere was used for biochemical tests.

Histological description

For the histological study, the tissues were fixed in kerosene by a medical technology professional and then stained with hematoxylin-eosin. The slides were read by a pathologist of the Institute of Legal Medicine and Forensic Science. The analysis took into account the state of the cerebral and cerebellar cortex, level of edema in glial cells, pyramidal cells and in the perivascular zone, distribution of Purkinje cells per field with or without edema, as well as the presence and degree of eosinophilia in nervous tissue[7].

Determination of Biochemical Indicators

Preparation of the homogenate: The previously weighed right hemisphere was homogenized with phosphate buffer 0.01 mol/L pH 7.4 in a ratio of 1:10, then centrifuged at 3000 rpm for 5 minutes to obtain the supernatant of the homogenate, which was used for biochemical evaluation.

Determination of GSH: The method of Lindsay and Sedlak (1968) with Béjar (2016) modifications was performed[8], a deproteinized sample was prepared with 950 µL of supernatant and 50 µL of 100% TCA, then centrifuged at 13 000 rpm for 5 minutes. From the supernatant obtained, 300 µL were mixed with 1.5 mL of phosphate buffer pH 6.8 0.5 mol/L. Ascorbic acid and glyoxylic acid were used in a 2:1 ratio for the detection of total GSH, these samples were placed in a water bath at 67°C for 5 minutes, then allowed to cool and 0.3 mL of DTNB (5,5'-Dithiobis 2-nitrobenzoic acid) in 0.5 mol/L phosphate buffer was added at a concentration of 1.5 mg/mL. Readings were taken at 412 nm[9].

Determination of protein levels and protein sulfhydryl groups: The amount of protein was quantified following Lowry's technique (1951)[9]. The method of Lindsay and Sedlak (1968) was used to measure the total sulfhydryl groups (SH)[10] with modifications from Suarez (2014)[11], for this purpose 0.1 mL of the homogenate supernatant was diluted and combined with 900 µL of buffer pH 7.4 mol/L and placed in a water bath at 37°C for 5 minutes, subsequently DNTB was added continuing with the steps outlined in the GSH protocol, these samples were read at 412 nm. To get the protein sulfhydryl groups the total SH groups were subtracted with the non-protein sulfhydryl groups (GSH).

Statistical Analysis

To evaluate the distribution of the results, the evaluation was based on histograms, the Skewness test, kurtosis and the

Shapiro-Wilk normality test (n<50), followed by an ANOVA test to determine if there was a difference between the means of the groups, Levene's test for homogeneity of variances and Dunnet's post hoc test for those variables that showed symmetry. For asymmetric variables, the Kruskal-Wallis test and Mann Whitney U test with Holm's correction for multiple comparisons were used. A p value < 0.05 was considered. The data were entered in Microsoft Excel 2019 and then exported to the R Studio program.

Ethical Considerations

This protocol was approved by the Ethics and Research Committee of the Nutrition Department of the Universidad Nacional Mayor de San Marcos (RD N°000392-2024-D-FM/UNMSM). The reduction and refinement of the 3Rs of Rusell and Burch (1959) were taken into account[12]. To minimize the number of animals used in control groups, our research was conducted concurrently with another project of our research group using the same ethanol-induced damage methodology[13]. In addition, the Peruvian animal protection and safety law 30407 of 2016 was also considered[14].

RESULTS

Protein levels in brain tissue in the groups III and IV (received cañihuaco) were higher compared to group II (p<0.01) **(Table 1)**. The protein sulfhydryl levels in the groups receiving various doses of cañihuaco exhibited a gradual increase; in group V, this increase was significant compared to group II (p=0.01) **(Table 1)**.

With respect to GSH levels, all the groups treated with cañihuaco (III-V) showed a tendency to increase GSH and the GSH/GSSG ratio; however, no significant differences were observed compared to group II **(Table 2)**.

Table 1. Levels of proteins and protein sulfhydryl groups in brain tissue according to treatment group

Treatment groups	Protein* (mg/g tissue) Mean ± SD	Protein SH** (µmol/mg protein) Median (IQR)
Group I: Water + NaCl	60.4 ± 4.30	2.69 (2.11-3.40)
Group II: Water + ethanol	55.7 ± 5.68	3.00 (2.70-3.21)
Group III: Cañihuaco 200 mg/kg + ethanol	72.0 ± 6.56 (a)	2.60 (2.51-2.78)
Group IV: Cañihuaco 400 mg/kg + ethanol	67.1 ± 4.32 (b)	2.98 (2.54-3.35)
Group V: Cañihuaco 800 mg/kg + ethanol	60.9 ± 4.56	4.25 (3.90-4.48) (b)

* Skewness=0.36, Levene (p>0.05), ANOVA (p<0.01), Post hoc Dunnet.
** Skewness=0.51, Levene (p>0.05) Kruskal-Wallis (p=0.01), U de Mann-Whitney with Holm-Bonferroni correction.
(a) p < 0.01 compared to group II.
(b) p =0.01 compared to group II.

Table 2. GSH, total GSH and GSH/GSSG levels according to treatment group

Treatment groups	GSH (nmol/mg prot)** Median (IQR)	GSH total (nmol/ mg prot)* Mean ± SD	GSH/GSSG** Median (IQR)
Group I: Water + NaCl	83.6 (76.2-109)	278 ± 64.5	0.64 (0.47- 0.79) (b)
Group II: Water + ethanol	68.9 (60.5-80.0)	303 ± 33.5	0.31 (0.25-0.33)
Group III: Cañihuaco 200 mg/kg + ethanol	33.9 (30.1-35.4) (a)	197 ± 21.3 (a)	0.20 (0.19-0.20)
Group IV: Cañihuaco 400 mg/kg + ethanol	41.0 (35.8-53.6)	224 ± 32.4	0.23 (0.20-0.27)
Group V: Cañihuaco 800 mg/kg + ethanol	61.0 (59.9-78.7)	260 ± 16.6	0.31 (0.30-0.41)

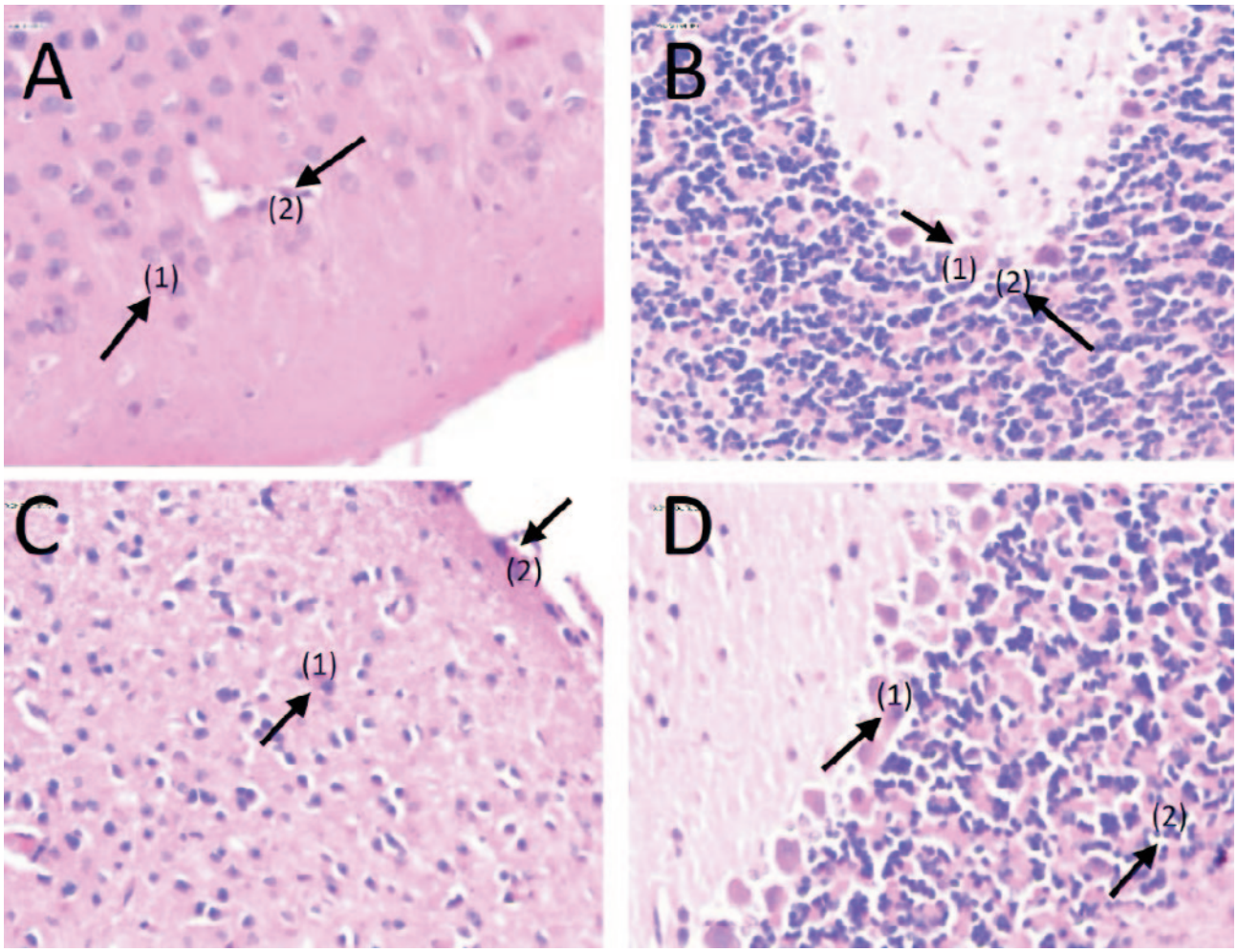
* Skewness=0.24, Levene (p>0.05), ANOVA (p<0.01), Post hoc Dunnet.
** Skewness=1.4 – Kruskal Wallis (p<0.05), Mann-Whitney U test with Holm-Bonferroni correction.
(a) p < 0.01 compared to group II.
(b) p < 0.05 compared to group II.

In the histological section, in group I (received water + NaCl) there was no alteration neither in the brain nor in cerebellum tissue. In group II (received ethanol) there was mononuclear inflammation in the perivascular zone, an increase of glial cells, edema in neuronal cells, eosinophilia, nuclear pyknosis and disruption of the cytoplasm around the nucleus. In the cerebellum, cytoplasmic retraction was observed in the molecular layer and eosinophilia in the Purkinje layer.

In the brain tissue of group III, congestive vessels, hypercellularity, cytoplasmic eosinophilia and few glia were observed. Regarding the cerebellum, slightly congestive blood vessels, scarce lymphocytes, and eosinophilia in some Purkinje cells, with double and triple row distribution were observed. Finally, there was marked hypercellularity in the granular layer.

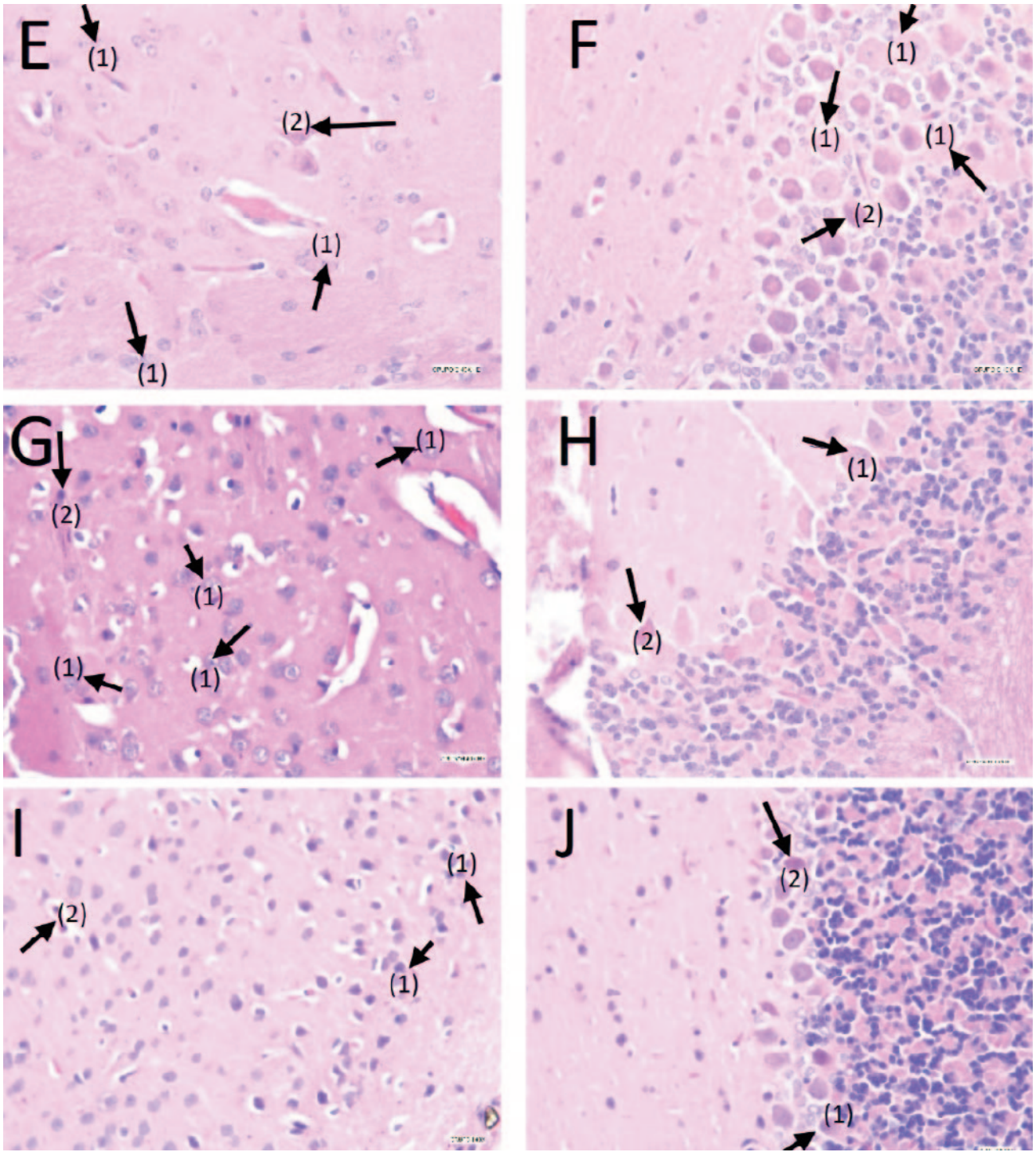
Group IV showed in the brain tissue lymphocytes distributed at the level of the ventricular and perivascular space, some cells with back-to-back distribution with hypercellularity and eosinophilia. The cerebellum showed vascular congestion in the subarachnoid space and diffuse cellular changes in several layers, as well as eosinophilia in the Purkinje layer and scarce cellularity in the medullary layer.

In group V brain, the subarachnoid space showed well distributed vessels and little eosinophilia. The medullary layer



In brain tissue of group I **(A)** cellularity was adequately distributed **(1)** and there was no visible alteration of blood brain barrier **(2)**, in cerebellum tissue Of group I **(B)** Purkinje cells **(1)** and molecular layer **(2)** without alteration. In brain tissue of group II **(C)** there was notable eosinophilia of neuronal cells **(1)** and vascular congestion in the subarachnoid space **(2)**. The cerebellum tissue of group II **(D)** showed cytoplasm with eosinophilia in Purkinje cells **(1)** and cellular edema **(2)**.

Figure 1. Hematoxylin-eosin **(HE)** 40X staining of brain **(A, C)** and cerebellum tissue **(B, D)** in control groups



In brain tissue of group III **(E)** hypercellularity **(1)** and eosinophilia of the neuronal cell **(2)** is appreciated. In cerebellum tissue of group III **(B)** there is an of Purkinje cells per field **(1)** eosinophilia in 50% in Purkinje cells **(2)**. In brain tissue of group IV *back-to-back* organization of cells **(1)** and cytoplasmic eosinophilia of neuronal cells **(2)** is shown. In cerebellum of group IV (H) 90% of hypercellularity is observed **(1)** and eosinophilia in Purkinje cells **(2)**. In brain tissue of group V, hypercellularity and scarce diffuse eosinophilia **(1)** is observed as well as slight vascular congestion of the blood-brain barrier **(2)**. In cerebellum, Purkinje cells organized in bilayer rows **(1)** with slight eosinophilia in few Purkinje cells **(2)**.

Figure 2. Hematoxylin-eosin (HE) 40X staining of brain (G, I) and cerebellum tissue (H, J) in treatment groups

had uniform thickness and slightly congestive vessels in all layers. In the cerebellum, the molecular layer presented hypocellularity, the Purkinje layer presented bilayer cells, with scarce eosinophilic cells and the medullary layer showed variable thickness with slightly congestive capillaries.

DISCUSSION

Our findings showed that cañihuaco administration exerted brain and cerebellum tissue protection against ethanol-induced damage. The various bioactive compounds present in cañihuaco could be related to the observed results. It has been shown that quercetin, in synergy with other nutraceutical substances such as kaempferol, induces crucial pathways to counteract oxidative stress, one of them is the Nrf2-ARE pathway as it prevents its ubiquitination and promotes its binding to DNA improving Nrf2 transcription, this pathway causes the expression of gamma glutamyl cysteine synthetase generating GSH available to prevent cell damage[15]. The observed phenomena may be linked to the elevated levels of glutathione (GSH) and the dose-response ratio of GSH to oxidized glutathione (GSSG) in the groups subjected to cañihuaco (III-V), with the highest dosage group exhibiting a more pronounced increase.

The escalating levels of protein sulfhydryl (SH) groups in cañihuaco-treated groups (III-V), correlating with increasing doses, can be attributed to the presence of quercetin in cañihua. Quercetin induces the expression of glutaredoxin, an enzyme essential for the glutathionylation process. This process involves the utilization of glutathione (GSH) to reduce oxidized protein SH groups, yielding oxidized glutathione and rejuvenated protein SH groups. The observed dose-response trend augmentation in protein SH groups suggests a direct relationship with the quercetin content, emphasizing the role of quercetin-induced glutaredoxin in enhancing the reduction of oxidized protein SH groups.

The observed reduction in tissue protein levels with increasing doses in the experimental groups (III-V) is likely attributable to the neuroprotective influence of quercetin. This effect is linked to the heightened expression of AMP-activated protein kinase (AMPK) at the neuronal level[17], AMPK, in turn, exerts a multifaceted impact by diminishing the generation of reactive oxygen species (ROS) through the inhibition of NADPH oxidase, nitric oxide synthase, and xanthine oxidase[18], Additionally, AMPK promotes the inactivation of TORC1 and directly phosphorylates ULK1 (Unc-51-like autophagy-activating kinase), thereby activating autophagy[19].

The preservation of nervous tissue in the cañihuaco-treated groups (III-V) may be attributed to the presence of ferulic acid in cañihua. Ferulic acid has demonstrated the ability to reduce microglial activation, as evidenced by decreased levels of IL-1β, IL-6, and TNF-α, thereby mitigating the inflammatory cascade associated with NF-κB signaling[20]. Another compound implicated in the neuroprotective effects is kaempferol, which inhibits the activation of toll-like receptor 4 (TLR4), NF-κB, and p38MAPK (p38 mitogen-activated protein kinases), consequently suppressing the activation of microglial cells involved in neuroinflammation[21].

Furthermore, other compounds present in cañihua, such as vanillic acid, likely play a role in the regulation of neuroinflammation by inhibiting the expression of JNK (c-Jun N-terminal kinases), a pathway known to activate NF-κB. Consequently, vanillic acid suppresses inflammatory mediators, including TNF-α, IL-1β, and NOS-2 (nitric oxide synthase 2) in the cortex and hippocampus[22]. Additionally, cañihua contains linolenic acid, which may contribute to the preservation of nervous tissue in the treated groups (IV-VI). Linolenic acid is known to favor the expression of Bcl-xL proteins, a part of the Bcl-2 protein family responsible for preventing apoptosis by inhibiting the expression of caspase 3[23]. This dual action on inflammatory pathways and anti-apoptotic mechanisms could explain the observed low inflammatory component and the preservation of nervous tissue in the cañihuaco-treated groups.

Within the encountered limitations, it's important to acknowledge that the orogastric route may not represent a typical form of consumption when extrapolated to a more natural setting. Furthermore, the omission of other pertinent biochemical indicators of ethanol metabolism, such as catalase (CAT), limits our ability to fully elucidate the underlying mechanisms involved. Additionally, the study's design restricts its extrapolation to humans. Nevertheless, despite these constraints, the present study lays the groundwork for future research in this domain, offering valuable insights that can inform and guide subsequent investigations.

CONCLUSION

In the face of ethanol-induced aggression, the administration of *Chenopodium pallidicaule* (cañihuaco) flour suspension at doses of 200, 400, and 800 mg/kg exhibits a dose-response trend reduction in histological damage in the brain and cerebellum. Additionally, it enhances the levels of protein SH groups, suggesting a potential neuroprotective effects.

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REFERENCES

1. Thelen M, Brown-Borg HM. Does Diet Have a Role in the Treatment of Alzheimer's Disease? Front Aging Neurosci [Internet]. 2020 [cited 2021 Aug 30];12:473. Available from: https://www.frontiersin.org/article/10.3389/fnagi.2020.617071

2. Milošević M, Arsić A, Cvetković Z, Vučić V. Memorable Food: Fighting Age-Related Neurodegeneration by Precision Nutrition. Front Nutr [Internet]. 2021 [cited 2021 Aug 30];8:507. Available from: https://www.frontiersin.org/article/10.3389/fnut.2021.688086

3. Karvandi MS, Sheikhzadeh Hesari F, Aref AR, Mahdavi M. The neuroprotective effects of targeting key factors of neuronal cell death in neurodegenerative diseases: The role of ER stress, oxidative stress, and neuroinflammation. Front Cell Neurosci. 2023 Mar 6;17:1105247.

4. Peñarrieta JM, Alvarado JA, Åkesson B, Bergenståhl B. Total antioxidant capacity and content of flavonoids and other phenolic compounds in canihua (Chenopodium pallidicaule): An Andean pseudocereal. Mol Nutr Food Res. 2008;52(6):708–17.

5. Hernández-Sampieri, R. & Mendoza, C (2018). Metodología de la investigación. Las rutas cuantitativa, cualitativa y mixta | RUDICS [Internet]. [cited 2023 Dec 15]. Available from: https://virtual.cuautitlan.unam.mx/rudics/?p=2612

6. Festing MF. On determining sample size in experiments involving laboratory animals. Lab Anim [Internet]. 2018 Aug 1 [cited 2024 Jan 13];52(4):341–50. Available from: https://doi.org/10.1177/0023677217738268

7. Palomino Sierra LA. Efecto neuroprotector del cocimiento de hojuelas de Chenopodium quinoa (quinua) variedad negra en ratones sometidos a daño por etanol [Internet]. Universidad Nacional Mayor de San Marcos; 2019. (Universidad Nacional Mayor de San Marcos). Available from: https://cybertesis.unmsm.edu.pe/handle/20.500.12672/10735

8. Béjar Camarena E. Efecto antioxidante del extracto hidroalcohólico de hojas de Jungia paniculata (dc.) A. Gray "matico serrano" en un modelo de daño gástrico en ratas inducido por etanol 70%. 2016.

9. Ellman GL. Tissue sulfhydryl groups. Arch Biochem Biophys. 1959 May;82(1):70–7.

10. Sedlak J, Lindsay RH. Estimation of total, protein-bound, and nonprotein sulfhydryl groups in tissue with Ellman's reagent. Anal Biochem. 1968 Oct 24;25(1):192–205.

11. Suárez Cunza S. Actividad captadora de radicales libres y efecto antioxidante de metabolitos secundarios del extracto acuoso del Allium sativum var. Huaralino (ajo) en modelos in vitro. 2014.

12. Reemplazo, reducción y refinamiento - PubMed. Available from: https://pubmed.ncbi.nlm.nih.gov/12098013/

13. Ruelas MG, Huamán-Gutierrez OG. Effect of Coturnix japonica (quail) egg yolk in ethanol damage-induced mice. Nutr Clínica Dietética Hosp [Internet]. 2023 Oct 2 [cited 2024 Mar 25];43(4). Available from: https://revista.nutricion.org/index.php/ncdh/article/view/441

14. El Peruano - Ley de protección y bienestar animal - LEY - N° 30407 - PODER LEGISLATIVO - CONGRESO DE LA REPUBLICA. Available from: https://busquedas.elperuano.pe/normaslegales/ley-de-proteccion-y-bienestar-animal-ley-n-30407-1331474-1/

15. Grewal AK, Singh TG, Sharma D, Sharma V, Singh M, Rahman MdH, et al. Mechanistic insights and perspectives involved in neuroprotective action of quercetin. Biomed Pharmacother [Internet]. 2021 Aug 1 [cited 2021 Aug 27];140:111729. Available from: https://www.sciencedirect.com/science/article/pii/S0753332221005114

16. Allen EMG, Mieyal JJ. Protein-Thiol Oxidation and Cell Death: Regulatory Role of Glutaredoxins. Antioxid Redox Signal [Internet]. 2012 Dec 15 [cited 2024 Jan 13];17(12):1748–63. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3474186/

17. Khan A, Ali T, Rehman SU, Khan MS, Alam SI, Ikram M, et al. Neuroprotective Effect of Quercetin Against the Detrimental Effects of LPS in the Adult Mouse Brain. Front Pharmacol [Internet]. 2018 Dec 11 [cited 2021 Jun 28];9:1383. Available from: https://www.frontiersin.org/article/10.3389/fphar.2018.01383/full

18. Islam MdS, Quispe C, Hossain R, Islam MT, Al-Harrasi A, Al-Rawahi A, et al. Neuropharmacological Effects of Quercetin: A Literature-Based Review. Front Pharmacol [Internet]. 2021 [cited 2021 Aug 21];12:1533. Available from: https://www.frontiersin.org/article/10.3389/fphar.2021.665031

19. Hardie DG. AMPK and autophagy get connected. EMBO J [Internet]. 2011 Feb 16 [cited 2021 Aug 21];30(4):634–5. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3041958/

20. Ojha S, Javed H, Azimullah S, Khair SBA, Haque ME. Neuroprotective potential of ferulic acid in the rotenone model of Parkinson’s disease. Drug Des Devel Ther [Internet]. 2015 Oct 7 [cited 2021 Aug 28];9:5499–510. Available from: https://www.dovepress.com/neuroprotective-potential-of-ferulic-acid-in-the-rotenone-model-of-par-peer-reviewed-fulltext-article-DDDT

21. Silva dos Santos J, Gonçalves Cirino JP, de Oliveira Carvalho P, Ortega MM. The Pharmacological Action of Kaempferol in Central Nervous System Diseases: A Review. Front Pharmacol [Internet]. 2021 [cited 2021 Aug 28];11:2143. Available from: https://www.frontiersin.org/article/10.3389/fphar.2020.565700

22. Ullah R, Ikram M, Park TJ, Ahmad R, Saeed K, Alam SI, et al. Vanillic Acid, a Bioactive Phenolic Compound, Counteracts LPS-Induced Neurotoxicity by Regulating c-Jun N-Terminal Kinase in Mouse Brain. Int J Mol Sci [Internet]. 2020 Dec 31 [cited 2021 Aug 29];22(1):361. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7795830/

23. Park HA, Broman K, Stumpf A, Kazyak S, Jonas EA. Nutritional Regulators of Bcl-xL in the Brain. Molecules [Internet]. 2018 Nov 19 [cited 2021 Aug 29];23(11):3019. Available from: https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6278276/