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The effect of alpha-pinene on anxiety-like behaviors in acetic acid-induced ulcerative colitis in rats: The gut-brain axis

Kaveh Rahimi[1*]

[1] Assistant Professor, Department of Basic Sciences, Faculty of Veterinary Medicine, Shahid Chamran University of Ahvaz, Ahvaz, Iran

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Abstract

Ulcerative colitis is associated with various neurological complications including peripheral neuropathy, headache, depression, anxiety, and cognitive impairments. This study aimed to evaluate the anxiolytic and anti-inflammatory effects of alpha-pinene on anxiety-like behaviors in an acetic acid-induced colitis model in male Wistar rats. Twenty-four rats were randomly assigned into four groups (n=6): control, colitis with normal saline treatment, and two colitis groups treated with alpha-pinene at doses of 50 and 100 mg/kg. Following colitis induction, anxiety-like behaviors were assessed using the open field test and elevated plus maze. Additionally, TNF-α levels in brain tissue were measured. The results of the study showed that colitis significantly increased anxiety-like behaviors and elevated TNF-α levels in the brain. Treatment with alpha-pinene at both doses markedly reduced anxiety-like behaviors and brain TNF-α levels. These findings suggest that alpha-pinene exerts notable anti-inflammatory and anxiolytic effects in the acetic acid-induced colitis model and may serve as a potential therapeutic agent to alleviate neurological complications associated with colitis.

Key words: Alpha-pinene, Anxiety-like behaviors, Ulcerative colitis, TNF-a, Rats

[*] **Corresponding Author**: Kaveh Rahimi, Assistant Professor, Department of Basic Sciences, Faculty of Veterinary Medicine, Shahid Chamran University of Ahvaz, Ahvaz, Iran
E-mail: K.rahimi@scu.ac.ir

Refrences

Abautret-Daly, A., Dempsey, E., Riestra, S., de Francisco-Garcia, R., Parra-Blanco, A., Rodrigo, L., Medina, C., Connor, T. J., & Harkin, A. (2017). Association between psychological measures and inflammatory and disease-related markers of inflammatory bowel disease. *International Journal of Psychiatry in Clinical Practice, 21*(3), 221–230.

Allenspach, K. (2011). Clinical immunology and immunopathology of the canine and feline intestine. *Veterinary Clinics of North America: Small Animal Practice, 41*(2), 345–360.

Cerquetella, M., Spaterna, A., Laus, F., Tesei, B., Rossi, G., Antonelli, E., Villanacci, V., & Bassotti, G. (2010). Inflammatory bowel disease in the dog: Differences and similarities with humans. *World Journal of Gastroenterology, 16*(9), 1050–1056.

Choi, K., Chun, J., Han, K., Park, S., Soh, H., Kim, J., Lee, J., Lee, H. J., Im, J. P., & Kim, J. S. (2019). Risk of anxiety and depression in patients with inflammatory bowel disease: A nationwide, population-based study. *Journal of Clinical Medicine, 8*(5), 654.

Craig, C. F., Filippone, R. T., Stavely, R., Bornstein, J. C., Apostolopoulos, V., & Nurgali, K. (2022). Neuroinflammation as an etiological trigger for depression comorbid with inflammatory bowel disease. *Journal of Neuroinflammation, 19*(1), Article 4.

Dempsey, E., Abautret-Daly, A., Docherty, N. G., Medina, C., & Harkin, A. (2019). Persistent central inflammation and region-specific cellular activation accompany depression- and anxiety-like behaviours during the resolution phase of experimental colitis. *Brain, Behavior, and Immunity, 80*, 616–632.

Dowlati, Y., Herrmann, N., Swardfager, W., Liu, H., Sham, L., Reim, E. K., & Lanctôt, K. L. (2010). A meta-analysis of cytokines in major depression. *Biological Psychiatry, 67*(5), 446–457.

Frenkel, S., Bernstein, C. N., Sargent, M., Jiang, W., Kuang, Q., Xu, W., & Hu, P. (2020). Copy number variation–based gene set analysis reveals cytokine signalling pathways associated with psychiatric comorbidity in patients with inflammatory bowel disease. *Genomics, 112*(1), 683–693.

Haj-Mirzaian, A., Amiri, S., Amini-Khoei, H., Hosseini, M.-J., Haj-Mirzaian, A., Momeny, M., Rahimi-Balaei, M., & Dehpour, A. R. (2017). Anxiety- and depressive-like behaviors are associated with altered hippocampal energy and inflammatory status in a mouse model of Crohn's disease. *Neuroscience, 366*, 124–137.

Hugot, J.-P., Chamaillard, M., Zouali, H., Lesage, S., Cézard, J.-P., Belaiche, J., Almer, S., Tysk, C., O'Morain, C. A., & Gassull, M. (2001). Association of NOD2 leucine-rich repeat variants with susceptibility to Crohn's disease. *Nature, 411*(6837), 599–603.

Jang, S., Lim, S., Jeong, J., Jang, H., Lee, H., Han, M., & Kim, D. (2018). Gastrointestinal inflammation by gut microbiota disturbance induces memory impairment in mice. *Mucosal Immunology, 11*(2), 369–379.

Kim, D. S., Lee, H. J., Jeon, Y. D., Han, Y. H., Kee, J. Y., Kim, H. J., Shin, H. J., Kang, J., Lee, B. S., Kim, S. H., Kim, S. J., Park, S. H., Choi, B. M., Park, S. J., Um, J. Y., & Hong, S. H. (2015). Alpha-Pinene Exhibits Anti-Inflammatory Activity Through the Suppression of MAPKs and the NF-κB Pathway in Mouse Peritoneal Macrophages. *The American journal of Chinese medicine, 43*(4), 731–742.

Mawdsley, J. E., & Rampton, D. S. (2005). Psychological stress in IBD: New insights into pathogenic and therapeutic implications. *Gut, 54*(10), 1481–1491.

Mohammadi, M., Rahimi, K., Rezaie, A., & Tabandeh, M. R. (2025). The role of fecal microbiota transplantation on the NLRP3–caspase 1 pathway and anxiety-like behavior in a rat model of ulcerative colitis. *Scientific Reports, 15*(1), Article 14831.

Neuendorf, R., Harding, A., Stello, N., Hanes, D., & Wahbeh, H. (2016). Depression and anxiety in patients with inflammatory bowel disease: A systematic review. *Journal of Psychosomatic Research, 87*, 70–80.

Ogura, Y., Bonen, D. K., Inohara, N., Nicolae, D. L., Chen, F. F., Ramos, R., Britton, H., Moran, T., Karaliuskas, R., & Duerr, R. H. (2001). A frameshift mutation in NOD2 associated with susceptibility to Crohn's disease. *Nature, 411*(6837), 603–606.

Ostanin, D. V., Bao, J., Koboziev, I., Gray, L., Robinson-Jackson, S. A., Kosloski-Davidson, M., Price, V. H., & Grisham, M. B. (2009). T cell transfer model of chronic colitis: Concepts, considerations, and tricks of the trade. *American Journal of Physiology–Gastrointestinal and Liver Physiology, 296*(2), G135–G146.

Rahimi, K., Zalaghi, M., Shehnizad, E. G., Salari, G., Baghdezfoli, F., & Ebrahimifar, A. (2023). The effects of alpha-pinene on inflammatory responses and oxidative stress in the formalin test. *Brain Research Bulletin, 203*, 110774.

Riazi, K., Galic, M. A., Kuzmiski, J. B., Ho, W., Sharkey, K. A., & Pittman, Q. J. (2008). Microglial activation and TNF-α production mediate altered CNS excitability following peripheral inflammation. *Proceedings of the National Academy of Sciences, 105*(44), 17151–17156.

Shabani, M., Erfani, S., Abdolmaleki, A., Afzali, F. E., & Khoshnazar, S. M. (2023). Alpha-pinene modulates inflammatory response and protects against brain ischemia via inducible nitric oxide synthase–nuclear factor-kappa B–cyclooxygenase-2 pathway. *Molecular Biology Reports, 50*(8), 6505–6516.

Soltani, M., Ghotbeddin, Z., Rahimi, K., & Tabandeh, M. R. (2024). Effects of alpha-pinene on oxidative stress and inflammatory response in acute gastric ulcers in rats. *Iranian Veterinary Journal, 20*(3), 101–113.

Tarar, Z. I., Zafar, M. U., Farooq, U., Ghous, G., Aslam, A., Inayat, F., & Ghouri, Y. A. (2022). Burden of depression and anxiety among patients with inflammatory bowel disease: Results of a nationwide analysis. *International Journal of Colorectal Disease, 37*(2), 313–321.

Wang, K., Yuan, C.-P., Wang, W., Yang, Z.-Q., Cui, W., Mu, L.-Z., et al, (2010). Expression of interleukin-6 in brain and colon of rats with TNBS-induced colitis. *World Journal of Gastroenterology, 16*(18), 2252–2259.

Weston-Green, K., Clunas, H., & Jimenez Naranjo, C. (2021). A review of the potential use of pinene and linalool as terpene-based medicines for brain health: Discovering novel therapeutics in the flavours and fragrances of cannabis. *Frontiers in Psychiatry, 12*, 583211.

Zhang, C. K., Hewett, J., Hemming, J., Grant, T., Zhao, H., Abraham, C., Oikonomou, I., Kanakia, M., Cho, J. H., & Proctor, D. D. (2013). The influence of depression on quality of life in patients with inflammatory bowel disease. *Inflammatory Bowel Diseases, 19*(8), 1732–1739.

Zhou, F., Jiang, H., Kong, N., Lin, J., Zhang, F., Mai, T., Cao, Z., & Xu, M. (2022). Electroacupuncture attenuated anxiety- and depression-like behavior via inhibition of hippocampal inflammatory response and metabolic disorders in TNBS-induced IBD rats. *Oxidative Medicine and Cellular Longevity, 2022*, 8295580.

Zonis, S., Pechnick, R. N., Ljubimov, V. A., Mahgerefteh, M., Wawrowsky, K., Michelsen, K. S., & Chesnokova, V. (2015). Chronic intestinal inflammation alters hippocampal neurogenesis. *Journal of Neuroinflammation, 12*(1), Article 65.