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Trigonella Foenum-Graecum Seeds as a Potential Alternative Neuroprotect Agent against Morphine Dependence in Rat

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ABSTRACT

Morphine is known as a pain reliever which frequently prescribed globally. However, genuine result such as, dependence, pain relieving resilience, immunosuppression, gastrointestinal (GI) manifestations limit their utilization (12). The word Opium comes from the ancient Greek OPOS which means means vegetable juice. It is also refer to the Opium Poppy (Papver somniferum) (1). In order to overcome tolerance, a higher dosage of morphine is commonly used, although this technique leads patients to a greater risk of having serious side effects, such as morphine reward and withdrawal symptoms (4).

INTRODUCTION

Morphine is known as a pain reliever which frequently prescribed globally. However, genuine result such as, dependence, pain relieving resilience, immunosuppression, gastrointestinal (GI) manifestations limit their utilization (12). The word Opium comes from the ancient Greek OPOS which means means vegetable juice. It is also refer to the Opium Poppy (*Papver somniferum*) (1). In order to overcome tolerance, a higher dosage of morphine is commonly used, although this technique leads patients to a greater risk of having serious side effects, such as morphine reward and withdrawal symptoms (4)

Morphine addiction is a major crisis that happened in the society nowadays. Brain areas, such as the ventral tegmental area (VTA), nucleus accumbens (NAc), and hippocampus (Hipp), have been revealed to involved in morphine addiction (5). The formation of addiction is conditioned by several factors. With specific attention to the mesolimbic dopamine system, which is an integral element of the reward system, the dopaminergic system has been shown to be the main element, thus, changes in this framework can be associated with drug use disorder and dependency (11). The dynamic interaction of genetic, epigenetic, and environmental factors are causes by dependence and these are the outcome of the repetitive exposure and behavioral changes to addictive chemicals (7).

Stimulation of morphine triggers opioid G-protein-coupled receptors and then causes significant molecular changes inside the cell, such as adenylate cyclase activity inhibition and potassium channel activation (14). Bawor et al in 2015 (2) stated that leading to its presence in the reward-dependence process, the dopamine receptor D2 (DRD2) gene plays a significant role in opioid use disorders. The DRD2 gene is located on chromosome 11q23 and is responsible for the synthesis of dopamine D2 receptors that are involved in many addiction-based signaling and neurotransmission processes, including motivation, enjoyment, and reward. A drop in dopamine receptor signaling has been related to the syndrome of reward deficiency, whereby persistent use of opioids serves to compensate for this suppressed release of dopamine or the condition of 'low reward'.

A number of studies has shown that oxidative stress is associated in the development of many addictive drug addictions, one of it is morphine when taken excessively which will result in regeneration of free radicals, such as reactive oxygen species (ROS) and reactive nitrogen species (RNS) that leads to decreasing in antioxidant activities in targeted cells (11). Abdel-Zaher et al (2013) (1) leant from their research that the level of glutamate and lipid peroxide malondialdehyde (MDA) increasing progressively in the morphine-treated rats, while simultaneously decrease in level of glutathione (GSH) and glutathione peroxidase (GSH-Px) activities. An oxidant and antioxidant imbalance will contribute to excessive use of morphine and later will result in symptoms of dependency and withdrawal. When these actions take place over a longer period of time, the progression of chronic and degenerative diseases can occur (15).

In current days, natural substances are frequently use as a substitution to the chemical drugs to prevent the dependence of drug addiction. One of the natural substance that has a huge potential as an alternative medicine is the seeds of *Trigonella foenum-gracum* or also knows as Fenugreek. This herb is an annual, short-lived plant belonging to the family *Fabaceae* which use as condiments or spices and as indigenous medicine in many parts of Asia, Africa and Europe (13). The seeds possess important medicinal effects, including antidiabetic, antihyperlipidemic, antiobesity, antioxidant and immunomodulatory properties (5).

The existence of different groups of secondary metabolites such as saponins, steroids, alkaloids, flavonoids, terpenes, phenolic acid derivatives, amino acids and fatty acids has been discovered by phytochemical analysis of fenugreek, and their derivatives illustrate the structural diversity of fenugreek isolated compounds (9). Trigonelline is a derivative of pyridine alkaloid and nicotinic acid betaine and it is chemically a compound of quarternary ammonium with the properties of ionic zwitter. Biologically, because of its capacity to stimulate estrogen receptors, trigonelline is often graded as phytoestrogen in addition to being hypoglycemic and neuroprotective (13).

Fenugreek contains a variety of beneficial flavonoids and polyphenol compounds which are the antioxidants that promote to reduce neurodegenerative diseases (7). It has been reported to contain a broad range of flavonoids in the alcoholic extracts of the entire plant, namely quercetin, luteolin, vitexin and7, 4'-dimethoxy flavanones (13). Similar results for the existence of aglycones kaempferol, quercetin, tricin and naringenin have been published in several other classes (10 & 13). Furthermore, isolated polyphenol derivatives from fenugreek extract, such as zingerone, vanillin, gingerol and eugenol, and indicated anticancer activity of these compounds (9). Therefore, the purpose of this study is to discover and seek for greater understanding of the beneficial properties of *Trigonella foenum-gracum* as an anti-oxidative substance to reduce the oxidants level in morphine dependence rats.

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REFERENCES

[1] Abdel-Zaher, A. O., Mostafa, M. G., Farghly, H. M., Hamdy, M. M., Omran, G. A., and Al-Shaibani, N. K. (2013b). Inhibition of brain oxidative stress and inducible nitric oxide synthase expression by thymoquinone attenuates the development of morphine tolerance and dependence in mice. Eur. J. Pharmacol. 702 (1-3), 62–70. doi: 10.1016/j.ejphar. 2013.01.036

[2] Bawor, M., Dennis, B. B., Tan, C., Pare, G., Varenbut, M., Daiter, J., Plater, C., Worster, A., Marsh, D. C., Steiner, M., Anglin, R., & Desai, D. (2015). Contribution of BDNF and DRD2 genetic polymorphisms to continued opioid use in patients receiving methadone treatment for opioid use disorder : an observational study. Addiction Science & Clinical Practice, 1–9. https://doi.org/10.1186/s13722-015-0040-7

[3] Brook, K., Bennett, J., & Desai, S. P. (2017). Abbreviated Title : Elucidating the structure of morphine. *Journal of Anesthesia History*. https://doi.org/10.1016/j.janh.2017.02.001

[4] Dong, A., Kim, H., Kim, N. J., Zhao, R. J., Kim, H., Yang, C. H., Kim, H. Y., Gwak, Y. S., Jang, E. Y., Kim, J. S., Lee, Y. K., & Lee, H. J. (2017). Effects of acupuncture on the anxiety-like behavior induced by withdrawal from chronic morphine use. *Neuroscience Letters*. https://doi.org/10.1016/j.neulet.2017.11.008

[5] Jiang, W., Si, L., Li, P., Bai, B., Qu, J., Hou, B., Zou, H., & Fan, X. (2018). *Serum metabonomics study on antidiabetic e ff ects of fenugreek fl avonoids in streptozotocin-induced rats*. *1092*(June), 466–472. https://doi.org/10.1016/j.jchromb.2018.06.041

[6] Kim, J., Ham, S., Hong, H., Moon, C., and Im, H. I. (2016). Brain Reward Circuits in Morphine Addiction. Mol. Cells 39 (9), 645–653. doi: 10.14348/ molcells.2016.0137

[7] Moustafa, E. M., Dawood, M. A. O., Assar, D. H., Omar, A. A., Elbialy, Z. I., Farrag, F. A., Shukry, M., & Zayed, M. M. (2020). Modulatory effects of fenugreek seeds powder on the histopathology , oxidative status , and immune related gene expression in Nile tilapia (Oreochromis niloticus) infected with Aeromonas hydrophila. *Aquaculture*, *515*(August 2019), 734589. https://doi.org/10.1016/j.aquaculture.2019.734589

[8] Nogueira, D.D.S.; Merienne, K.; Befort, K. Neuroepigenetics and addictive behaviors: Where do we stand? Neurosci. Biobehav. Rev. 2019, 106, 58–72. doi:10.1016/j.neubiorev.2018.08.018.

[9] Pająk, P., Socha, R., Broniek, J., & Królikowska, K. (2018). Antioxidant properties , phenolic and mineral composition of germinated chia , golden flax , evening primrose , phacelia and fenugreek. *Food Chemistry*. https://doi.org/10.1016/j.foodchem.2018.09.081

Annals of R.S.C.B., ISSN:1583-6258, Vol. 25, Issue 6, 2021, Pages. 432 – 434
Received 25 April 2021; Accepted 08 May 2021.

[10] Rashid, F., Hussain, S., & Ahmed, Z. (2017). Extraction purification and characterization of galactomannan from fenugreek for industrial utilization Running title : Galactomannan from fenugreek for industrial utilization. *Carbohydrate Polymers*. https://doi.org/10.1016/j.carbpol.2017.10.025

[11] Skrabalova, J., Drastichova, Z., and Novotny, J. (2013). Morphine as a Potential Oxidative Stress-Causing Agent. Mini Rev. Org. Chem. 10 (4), 367–372. doi: 10.2174/1570193X113106660031

[12] Suchanecka, A., Chmielowiec, J., Chmielowiec, K., & Masiak, J. (n.d.). *Dopamine Receptor DRD2 Gene rs1076560 , Personality Traits and Anxiety in the Polysubstance Use Disorder*. *64*, 1–12. https://doi.org/10.3390/brainsci10050262

[13] Venkata, K. C. N., Swaroop, A., Bagchi, D., & Bishayee, A. (2017). *R EVIEW A small plant with big benefits : Fenugreek (Trigonella foenum-graecum Linn .) for disease prevention and*. *1600950*, 1–26. https://doi.org/10.1002/mnfr.201600950

[14] Wang, F., Meng, J., Zhang, L., Johnson, T., Chen, C., & Roy, S. (2018). Morphine induces changes in the gut microbiome and metabolome in a morphine dependence model. *Scientific Reports*, *August 2017*, 1–15. https://doi.org/10.1038/s41598-018-21915-8

[15] Zeng, X., Geng, W., Wang, Z., & Jia, J. (2020). *Morphine Addiction and Oxidative Stress : The Potential Effects of Thioredoxin-1*. *11*(February), 1–6. https://doi.org/10.3389/fphar.2020.00082