The Potential Efficacy of Antidepressants and *Moringa oleifera* in Experimentally Induced Ulcerative Colitis in Rats

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Abstract: Ulcerative colitis (UC) is a recurrent bowel disease resulting from uncontrolled inflammation that ultimately leads to mucosal disruption and ulceration. Medicinal plants have played a key role in world health in spite of great advances observed in conventional medicine in recent decades, herbal medicine still makes an important contribution to health care. Also Psychological disorders such as depression have more prevalence in inflammatory bowel disease patients and can exacerbate the clinical course of the disease, so anti-depressant therapy may have a potential to positively impact the disease course. On the other hand several antidepressant drugs have shown anti-inflammatory and immunomodulatory properties. Therefore, an attempt was made to investigate the possible prophylactic and therapeutic effects of *Moringa oleifera* and fluoxetine on dextran induced colitis in male wistar rats in comparison with the reference drug Sulfasalazine using the following biomarkers including (MPO, MDA, NO, GSH and TNFα).The results showed that both *Moringa oleifera*and fluoxetine have significant therapeutic activity against experimental colitis in rats, as indicated by biochemical evaluations. Fluoxetineseems to be the most effective as Curative therapy.
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Key words: Ulcerative colitis, *Moringa oleifera*, fluoxetine**,** dextran

1.Introduction

Ulcerative colitis (UC) is a recurrent bowel disease resulting from uncontrolled inflammation that ultimately leads tomucosal disruption and ulceration (**Boussennaetal., 2016**). It affects1.4 million individuals in North America and 2.2millionsin Europe, and is increasing in Africa everyday (**El-Salhy and Umezawa, 2016**). Although the etiology of Ulcerative colitis (UC) remains unclear, There is evidence that it involves environmental factors including air pollution, medication and certain diets (**Molodecky and Kaplan, 2010**). Immune and genetic factors are in turn related to the in itiation and progression of colitis.

The growing prevalence of this disease increases both economic and healthcare burden. Several medications are used to treat patients with active UC. However, these are associated with side effects that add to the disease-related complications especially considering the chronic and relapsing nature of this condition (**Abdel-Azizetal., 2013**) Thus, better and more affordable treatment and eventually acure is greatly needed (**Triantafyllidi et al., 2015, Lowetal., 2013 and Tomassoni et al.,2 010**).

Medicinal plants have play edakey role in world health in spite of great advances observed in conventional medicine in recent decades, herbal medicine still makes an important contribution to healthcare (**Payyappallimana, 2010**). World Health Organization estimated that 80% of the developing countries depend on herbal medicine to meet their healthcare needs (**WHO 2015**). Due to the increase dose of herbal medicine. Thus, there is an urgent need for the appropriate systems of quality control int hepractice as well as in the production and use of the herbal medicines.

Moringa oleifera is the sole genus in the flowering plant family Moringaceae. The species that is more common and popular, called *Moringa oleifera (M.oleifera*).*M. oleifera* also known as the horseradish tree, drumstick tree (**Karagiorgou et al., 2016**, **Elangovanet al., 2014**).*M. oleifera* is important for its nutritional and medicinal properties. Various parts of this plant such as the leaves, seeds, bark, fruits, roots and flowers act as cardiac and circulatory stimulants,

possess antitumor and antipyretic activities are routinely used in folk medicine for the treatment of different ailments in several countries **(Gopalakrishnan et al.,2016, Farooq et al.,2012)**.

Aim of the work:

The aim of the present work is to study the following:-

1) Investigate the possible therapeutic effects of the Antidepressant (fluoxetine) on the extent and severity of colitis induced in rats.

2) Evaluate the effect of *Moringa oleifera* in experimentally induced colitis in rats.

3) Compare efficacy of both Antidepressant (fluoxetine) and *Moringa oleifera* separately or in combination in ulcerative colitis.

2. Materials and Methods:

Experimental design:

Thirty-six adult male albino rats weighing **(200-250g)** were used throughout this work. Rats were Kept in plastic cages in the animal house and kept on a standard diet and water ad libitum. The rats will be randomly divided into the following groups:

- **Group (1)**: This group consisted of 6 rats that served as the untreated normal control group and received normal saline for 15 days.
- **Group (2):** This group consisted of 6 rats that received dextran for 5 days then fluoxetine for 10 days.
- **Group (3):** This group consisted of 6 rats that received dextran for 5 days then *Moringa oleifera*f or 10 days.
- **Group (4):** This group consisted of 6 rats that received dextran for 5 days Then Fluoxetine + *Moringa oleifera* for 10 days.
- **Group (5):** This group consisted of 6 rats that received dextran for 5 days Then Sulfasalazine for 10 days.
- **Group (6):** This group consisted of 6 rats that served as the toxicant control group and received dextran 5% for 5 days.

Drugs were dissolved in distilled water and administered by oral gavage once daily throughout the experimental period (15 days) respectively.

3. Results

Statistical analysis

Data were collected, tabulated, statistically analyzed using a personal computer with Statistical Package of Social Science (SPSS) version 20, where the following statistics were applied.

Two types of statistics were done:

a) Descriptive statistics e.g mean ($\bar{X}$) and standard deviation (SD).

- 1) Arithmetic mean (x): was used as a measure of central tendency.
- 2) Standard deviation (SD): was used as a measure of dispersion.

b) Analytic statistics:

1-One way Anova test: for comparison between more than two groups having quantitative variables and with independent parametric data

2-Post hoc test: is used after one a way ANOVA (F test) to show any significant difference between the individual groups.

p value at 0.05 was used to determine significance regarding:

- P-value > 0.05 to be statistically insignificant.
- P-value ≤ 0.05 to be statistically significant.
- P-value ≤ 0.001 to be highly statistically significant.

1- Myeloperoxidase (MPO)

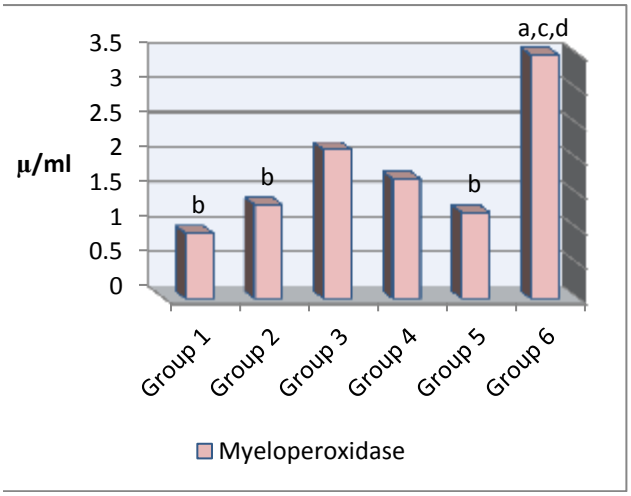

Figure (1): Efffect of dextran, Moringa, Fluoxetine, Fluoxetine + Moringa, S.salazine on Myeloperoxidase (MPO) in dextran-induced ulcerative colitis in rats.

- Group (1) : Normal control group
- Group (2) :treated group with Fluoxetine
- Group (3) :treated group with moringa
- Group (4) :treated group with Fluoxetine + moringa
- Group (5) :treated group with standard drug (s.salazine)
- Group (6) :dextran induced colitis group

- **[a]Significant change compared to normal group at p<0.05**
- **[b] Significant change compared to dextran group at p<0.05**
- **[C] Significant change compared to Fluoxetine group at p<0.05**
- **[d] Significant change compared to S. salazine group at p<0.05**

2- Malonaldehyde (MDA)

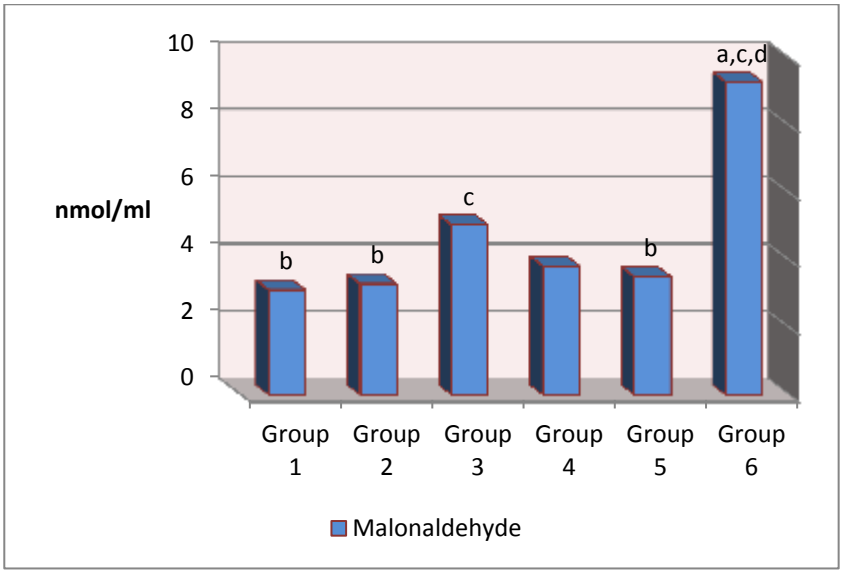

Figure (2): Efffect of dextran, Moringa, Fluoxetine, Fluoxetine + Moringa, S. salazine on Malonaldehyde (MDA) in dextran-induced ulcerative colitis in rats.

- Group (1) : Normal control group
- Group (2) :treated group with Fluoxetine
- Group (3) :treated group with moringa
- Group (4) :treated group with Fluoxetine + moringa
- Group (5) :treated group with standard drug (s.salazine)
- Group (6) :dextran induced colitis group

- **[a]Significant change compared to normal group at p<0.05**
- **[b] Significant change compared to dextran group at p<0.05**
- **[C] Significant change compared to Fluoxetine group at p<0.05**
- **[d] Significant change compared to S.salazine group at p<0.05**

3- Nitric oxide(NO)

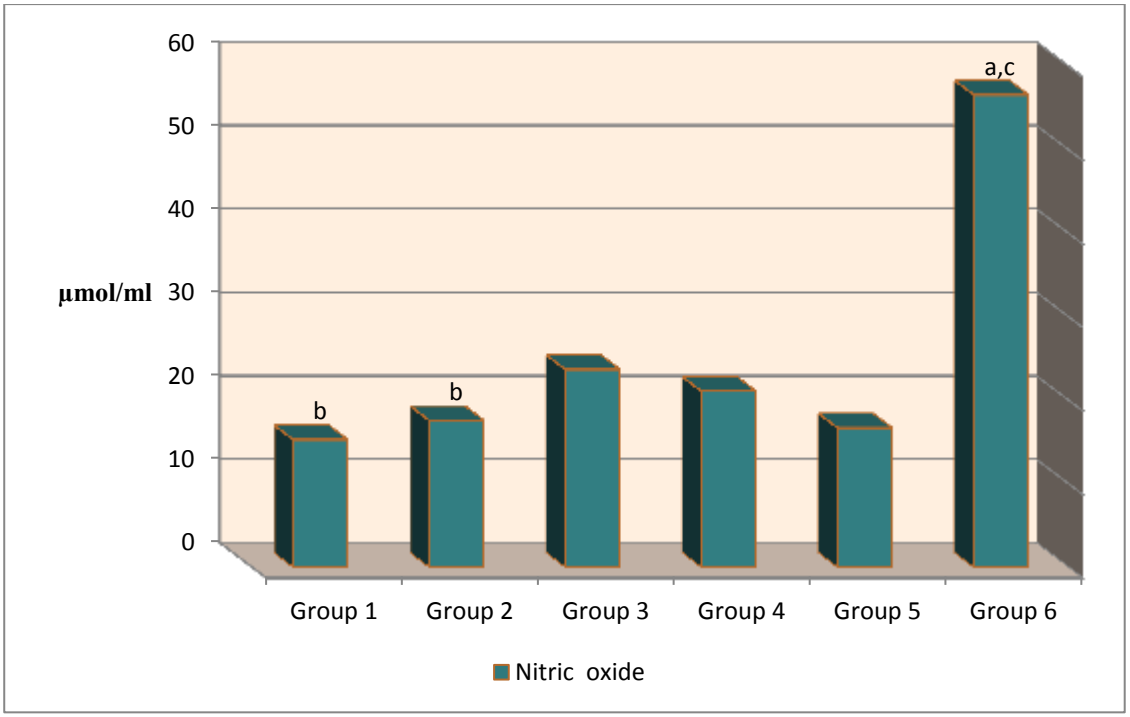

Figure (3):Efffect of dextran, Moringa, Fluoxetine, Fluoxetine + Moringa, S.salazine on Nitric oxide (NO) in dextran-induced ulcerative colitis in rats.

- Group (1) : Normal control group
- Group (2) :treated group with Fluoxetine
- Group (3) :treated group with moringa
- Group (4) :treated group with Fluoxetine + moringa
- Group (5) :treated group with standard drug (s.salazine)
- Group (6) :dextran induced colitis group

[a]Significant change compared to normal group at p<0.05

[b]Significant change compared to dextran group at p<0.05

[C] Significant change compared to Fluoxetine group at p<0.05

4- Glutathione (GSH)

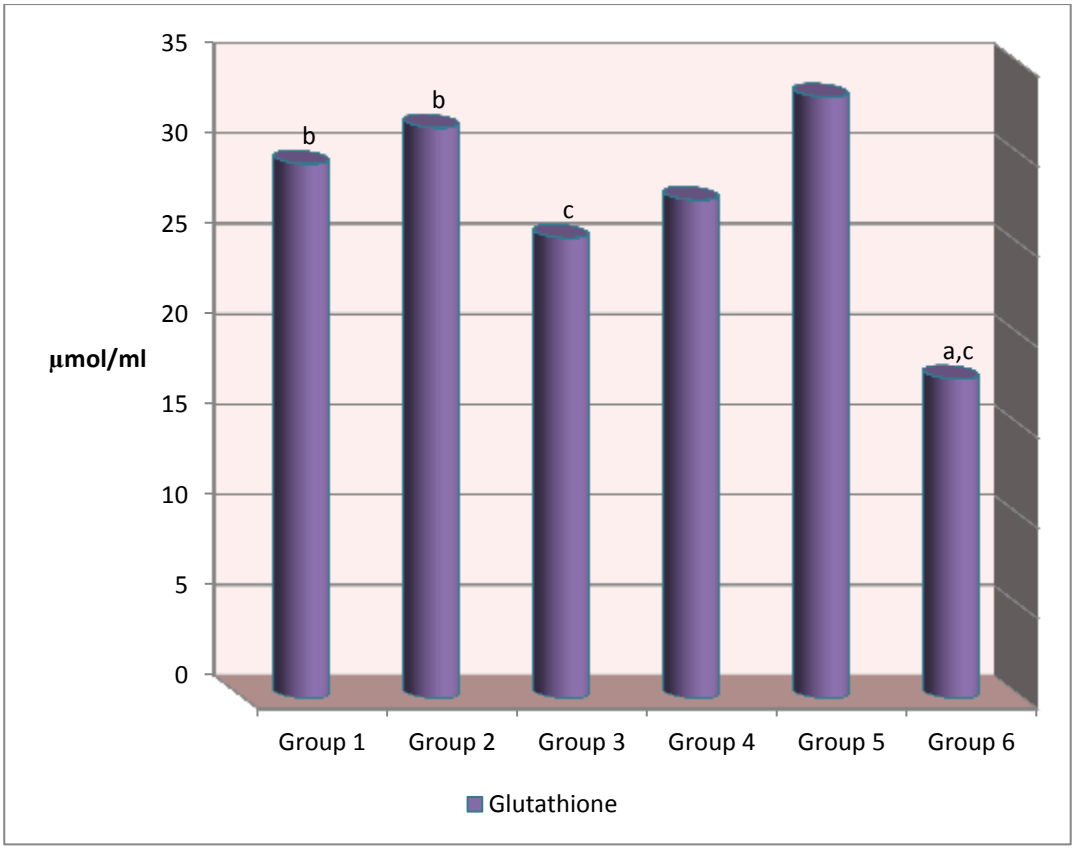

Figure (4):Efffect of dextran, Moringa, Fluoxetine, Fluoxetine + Moringa, S.salazine on Glutathione (GSH)in dextran-induced ulcerative colitis in rats.

- Group (1) : Normal control group
- Group (2) :treated group with Fluoxetine
- Group (3) :treated group with moringa
- Group (4) :treated group with Fluoxetine + moringa
- Group (5) :treated group with standard drug (s.salazine)
- Group (6) :dextran induced colitis group

[a]Significant change compared to normal group at p<0.05

[b]Significant change compared to dextran group at p<0.05

[C] Significant change compared to Fluoxetine group at p<0.05

5- Tumor Necrosis Factor- alpha(TNF)

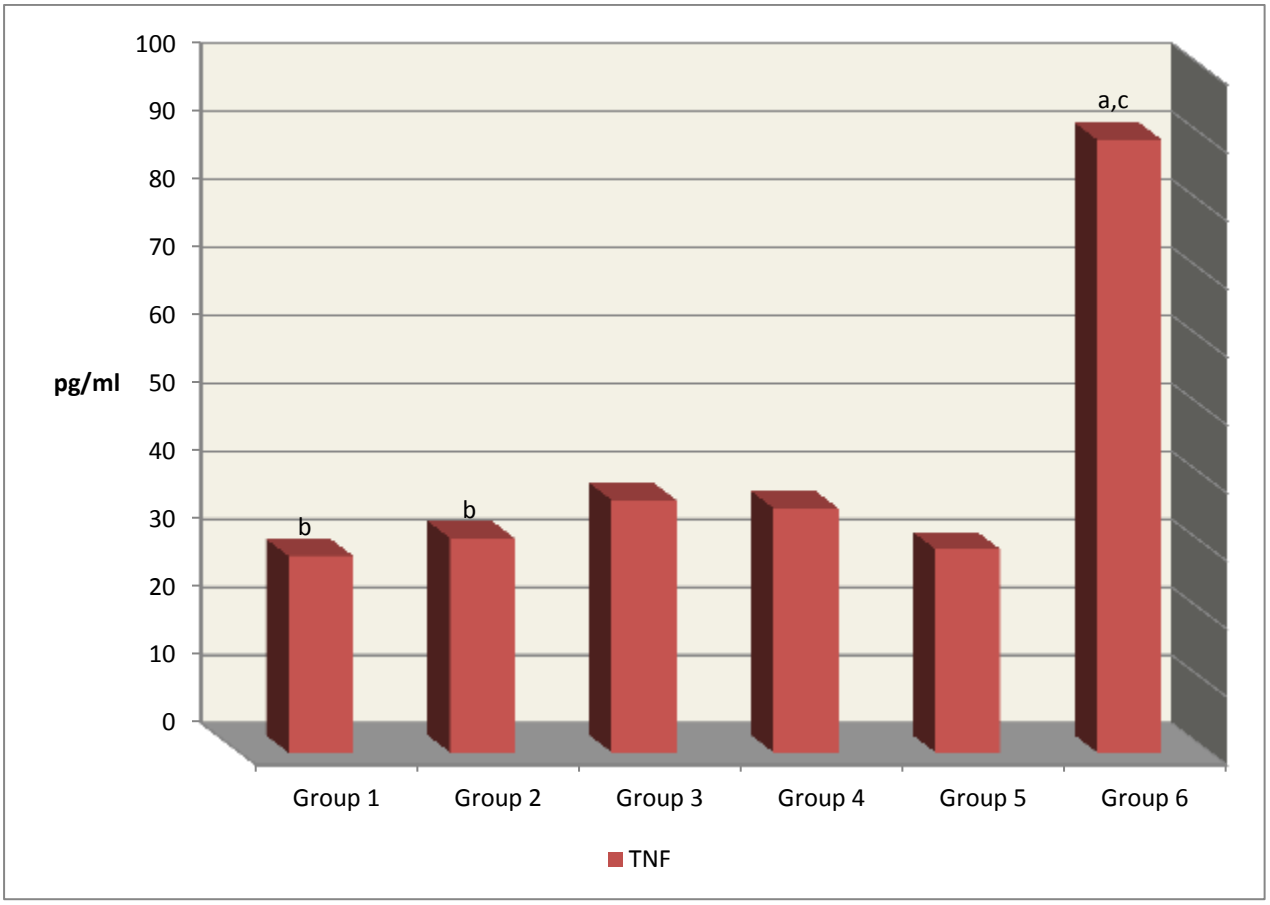

Figure (5): Efffect of dextran, Moringa, Fluoxetine, Fluoxetine + Moringa, S.salazine on Tumor Necrosis Factor- alpha(TNF-α) in dextran-induced ulcerative colitis in rats.

- Group (1) : Normal control group
- Group (2) :treated group with Fluoxetine
- Group (3) :treated group with moringa
- Group (4) :treated group with Fluoxetine + moringa
- Group (5) :treated group with standard drug (s.salazine)

Group (6) :dextran induced colitis group[a]**Significant change compared to normal group at p<0.05**

[b]**Significant change compared to dextran group at p<0.05**

[C] **Significant change compared to Fluoxetine group at p<0.05**

Table (1) showing: Efffect of Moringa, Fluoxetine, Fluoxetine + Moringa, S.salazine on Myeloperoxidase (MPO),Malonaldehyde MDA, Nitric oxideNO ,GlutathioneGSH and Tumor necrosis factor – alpha TNF-α in dextran-induced ulcerative colitis in rats.

Variables	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6	**Anova test**	P value
Myeloperoxidase **Mean ±SD**	0.94±0.48	1.35±0.27	2.14±0.27	1.72±0.41	1.24±0.25	3.5±0.08	41.9	<0.001 HS
Sig.bet. groups	P1=<0.05 p2=>0.05 P3=<0.001							
Malonaldehyde **Mean ±SD**	3.12±0.71	3.3±0.58	5.05±0.52	3.83±0.51	3.51±0.44	9.3±0.83	73.6	<0.001 HS
Sig.bet. groups	P4=<0.05 P5=>0.05 P3=<0.001							
Nitric oxide **Mean ±SD**	15.3± 3.2	17.6±3.6	23.7±2.1	21.09±3.5	16.7±4.6	56.6±5.6	90.4	<0.001 HS
Sig.bet. groups	P4=<0.05 P5=>0.05 P3=<0.001							
Glutathione **Mean ±SD**	29.6±6.4	31.6±5.2	25.5±4.8	27.6±3.2	33.3±.3	17.7±6.1	5.4	0.002 S
Sig.bet. groups	P6=<0.05 P7= >0.05 P3=<0.001							
TNF-α **Mean ±SD**	28.9±3.8	31.5±2.8	37.1±5.05	35.9±4.9	29.9±6.2	90.1±5.02	101.7	<0.001 HS
Sig.bet. groups	P4=<0.05 P5= >0.05 P3=<0.001							

Number of rate in each group=6
P1=compare between group1 and group 2, 3.4 and 6
P2= compare between group 1 and group 5
P3=compare between group 6 and group 1,2,3,4 and 5
P4=compare between group 1 and group 3 and 6
P5=compare between group 1 and 2 ,4 and 5
P6=compare between group 1 and group 6
P7=compare between group 1 and group 2,3,4 and 5

P =<0.05 consider significant
P = >0.05 consider insignificant
P = <0.001 consider high significant

- Group (1) : Normal control group
- Group (2) :treated group with Fluoxetine
- Group (3) :treated group with moringa

- Group (4) :treated group with Fluoxetine + moringa
- Group (5) :treated group with standard drug (s.salazine)
- Group (6) :dextran induced colitis group

4. Discussion

Dextran induced colitis model is similar to human ulcerative colitis in terms of histological features. It affects the distal colon portion and induces non-transmural inflammation, massive necrosis of mucosal and submucosal layers, mucosal oedema, neutrophil infiltration of the mucosa and submucosal ulceration. Inflammation is the pathogenesis of IBD, and several pathways are associated with inflammatory response in IBD due to mucosal intestinal flora **(Nakhai*et al.*, 2007).**

The results showed that bothMoringaoleifera and Fluoxetine have got a significant protective activity against experimental colitis in rats, as indicated by biochemical evaluations with priority to Fluoxetine.

Oxidative stress is believed to play a key role in the pathogenesis of IBD-related intestinal damage (**Grisham *et al.*, 1988**). Intestinal mucosal damage in the IBD is related to both increased free radical production and a low concentration of endogenous antioxidant defence (**Koutroubakis *et al.*, 2004**).

Psychological disorders such as depression have more prevalence in inflammatory bowel disease patients and can exacerbate the clinical course of the disease, so anti-depressant therapy may have a potential to positively impact the disease course. On the other hand several antidepressant drugs have shown anti-inflammatory and immunomodulatory properties **(Abdel-Salam *et al., 2004*)**.

There is a bidirectional interaction between the gut and the brain through the autonomic nervous system and the circumventricular organs in physiological and pathological conditions called brain-gut axis (**Bonaz *et al., 2013***). Environmental signals, such as stress or depressive symptoms, are perceived initially by the central nervous system (CNS). Signals are transmitted through this innervated plexus to the gut, and become involved in the initiation and relapse of experimental colitis (***Prins A., 2011***).

Mast cells of the intestinal mucosa serve as end effectors of the brain-gut axis and release several pro-inflammatory mediators following stress and other psychological disorders that can profoundly affect GI physiology by inducing intestinal hyper permeability and activation of mucosal immune function Thus treatment of these psychological disorders by anti-depressant Fluoxetine can modulate the function of these inflammatory cells and reduce intestinal inflammation. Furthermore, experimental evidence is accumulating that various types of antidepressants (particularly SSRI e.gFluoxetine) exert anti-inflammatory and analgesic effects., it is deduced from our results that some beneficial effect of Fluoxetine in experimental colitis might be, in part, due to its anti-inflammatory and anti-nociceptive effects.

Biochemical examination revealed that both Fluoxetine and *Moringaolifera* decreased ulcer scores in variable ratios. Biochemical analysis of Fluoxetine pre-treated tissues demonstrated reductions in tumor necrosis factor (TNF)-α and myeloperoxidase (MPO) levels and concomitant increases in nitric oxide (NO) and reduced glutathione (GSH) contents. The results here indicated fluoxetine exhibited better gastroprotective effects and this could be due to anti-oxidant and anti-inflammatory effects of the drug.

Conclusions

It is deduced from our results that some beneficial effect of Fluoxetine in experimental colitis might be, in part, due to its anti-inflammatory and anti-oxidant effects. Biochemical examination revealed that both Fluoxetine and *Moringaolifera* decreased ulcer scores in variable ratios. The results of this investigation showed anti-inflammatory effect of the anti-depressant, Fluoxetine in dextran-induced colitis. Our results confirmed that a coherent communication exist between depression and the course of IBD probably through the brain-gut axis. The issue which has historical background when IBD was considered as a psychosomatic disease. Further studies are suggested to evaluate other anti-depressant drugs with similar pharmacological properties in the treatment of ulcerative colitis.

The results of this investigation showed anti-inflammatory effect of the anti-depressant, Fluoxetine in acetic acid-induced colitis. Our results confirmed that a coherent communication exist between depression and the course of IBD probably through the brain-gut axis. This correlation was previously approved in irritable bowel syndrome, the issue which has historical background when IBD was considered as a psychosomatic disease. Further studies are suggested to evaluate other anti-depressant drugs with similar pharmacological properties in the treatment of ulcerative colitis.

References

1. Abdel-Aziz H., Wadie W., Abdallah D.M., Lentzen G. and Khayyal M.T., (2013): Novel effects of ectoine, a bacteria-derived natural tetra - hydropyrimidine, in experimental colitis. Phytomedicine; 20(7): 585-91.
2. Abdel-Salam OM, Baiuomy AR, Arbid MS. (2004): Studies on the anti-inflammatory effect of fluoxetine in the rat. Pharmacol Res.;49:119–131.
3. Bonaz BL, Bernstein CN. (2013): Brain-Gut Interactions in inflammatory bowel disease. Gastroenterology.;144:36–49. [PubMed].
4. Boussenna A, Cholet J, Goncalves-Mendes N, Joubert-Zakeyh J, Fraisse D, Vasson M, Texiera O and Felginesa C, (2016):Polyphenol-rich grape pomace extracts protect against dextran sulfate sodium-induced colitis in rats.J Sci Food Agric.
5. D Zama, Z Meraihi, S Tebibel, W Benayssa, F Benayache, S Benayache et al. (2007): Chlorpyrifos-induced oxidative stress and tissue damage in the liver, kidney, brain and fetus in pregnant rats: The protective role of the butanolic extract of Paronychia argentea L. Indian J Pharmacol; 39(3):145-150.
6. Elangovan, M., Dhanarajan. M.S., Rajalakshmi, Jayachitra, A., Mathi, P., Bhogireddy N., (2014): Analysis of Phytochemicals, Antibacterial and Antioxidant activities of *Moringaoleifera* Lam. Leaf extract- an in vitro study. Int. J. Drug Dev. & Res., 6 (4): 173-180.
7. El-Salhy M and Umezawa K (2016):Anti-inflammatory effects of novel AP-1 and NF-κB inhibitors in dextran-sulfate-sodium-induced colitis in ratsInternational Journal of Molecular Medicine;1457-1464.
8. Farooq F, Rai M, Tiwari A, Khan AA, Farooq S., (2012): Medicinal properties of *Moringaoleifera*: An overview of promising healer. J Med Plants Res.;6(27):4368-4374.
9. Gopalakrishnan, L., Doriya, K., Kumara, D. S., (2016): *Moringaoleifera*: A review on nutritive importance and its medicinal application. Food Sci. Human Wellness, 5: 49–56.
10. Grisham MB, Granger DN. (1988): Neutrophil-mediated mucosal injury: Role of reactive oxygen metabolites. Dig Dis Sci;33:6S-15S.
11. Joshi S V, Vyas B A, Shah P D, Shah D R, Shah S A, Gandhi T R. (2011): Protective effect of aqueous extract of Oroxylumindicum Linn. (root bark) against DNBS-induced colitis in rats. Indian J Pharmacol; 43(6):656-61.
12. Karagiorgou I, Grigorakis S, Lalas S, Makris D, (2016): Polyphenolic burden and in vitro antioxidant properties of *Moringaoleifera* extracts J HerbMedPharmacol.; 5(1): 33-38.
13. Koutroubakis IE, Malliaraki N, Dimoulios PD, Karmiris K, Castanas E, Kouroumalis EA (2004):. Decreased total and corrected antioxidant capacity in patients with inflammatory bowel disease. Dig Dis Sci;49:1433-7.
14. Low D., Nguyen D. D. and Mizoguchi E., (2013): Animal models of ulcerative colitis and their application in drug research. Drug Des DevelTher.; 7, 1341–1357.
15. Minaiyan M., Hajhashemi V., Rabbani M., Fattahian E. and Mahzouni P. (2014): Beneficial Effects of Maprotiline in a Murine Model of Colitis in Normal and Reserpinised Depressed Rats. International Scholarly Research Notices; 2014: 359841.
16. Molodecky NA and Kaplan GG.,(2010): Environmental risk factors for inflammatory bowel disease, GastroenterolHepatol (N Y);6:339-46.
17. Nakhai LA, Mohammadirad A, Yasa N, Minaie B, Nikfar S, Ghazanfari G., (2007) Benefits of ZatariamultifloraBoiss in experimental model of mouse inflammatory bowel disease. Evid Based Complement Alternat Med;4:43-50.
18. Payyappallimana U. (2010): Role of Traditional Medicine in Primary Health Care: An Overview of Perspectives and Challenging.
19. Prins A. (2011): The brain-gut interaction: the conversation and the implications. S Afr J Clin Nutr.;24:S8–S14.
20. Roberto W, Thellung S, Bajetto A, Mazzanti M, Florio T, Barbieri F (2016): Drug-repositioning opportunities for cancer therapy: novel molecular targets for known compounds, Volume 21, Issue 1, Pages 190–199.
21. Tomassoni D, Gabrielli MG, Mattioli L, Titomanlio F, Polzonetti V, Accili D and Perfumi M.,(2010): Inflammatory bowel disease induced by intracolon instillation of acetic acid: screening study of the effects of different natural drugs. Ital. J. Anat. Embryol 115: 167-176.
22. Triantafyllidi A, Xanthos T, Papalois A, Triantafillidis JK., (2015): Herbal and plant therapy in patients with inflammatory bowel disease. Ann Gastroenterol; 28:210-20.
23. WHO (2015): National policy on traditional medicine and regulation of herbal medicines: Report of a WHO global survey.
24. Yang HT, JU JH, Wong YT, Shmulevich (2016):Literature-based discovery of new candidates for drug repurposing,oxford univ press ISSN 1467-5463.

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