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Original article

# The Potential Role of Vortioxetine and Dapagliflozin in Experimental Induced Ulcerative Colitis in Rats via Alleviation of Oxidative stress, Inflammation and Apoptosis

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**Abstract:**

**Background:** Inflammatory bowel disease is one of the most serious health problems. Vortioxetine (VRT) is Selective serotonin reuptake inhibitor (SSRIs) and Serotonin norepinephrine reuptake inhibitors (SNRIs) as it has multimodal profile. Dapagliflozin (Dapa), is Sodium-glucose co-transporter 2 SGLT2 inhibitor which might suppress the expression of inflammatory cytokine. **Aim of the study:** This work was designed to assess the potential prophylactic effect of VRT and Dapa alone and in combination in acetic acid induced UC in rats. **Materials and Methods:** This study was conducted on 36 adult rats, divided into 6 groups; (I) normal rats, (II) Non treated UC group, (III) sulfa treated UC group received sulfa (100 mg /kg/ day, orally), (IV) VRT treated UC group received VRT (10 mg/kg/day, orally), (V) Dapa treated UC group received Dapa (5mg/kg/day, orally) and (VI) VRT and dapa treated group received combination of VRT (10 mg/kg/day, oral) and dapa (5mg/kg/day, orally).**Results:** Treated groups showed significant decrease in colon weight, CMI , colon weight / length ratio, increase in colon length, improved in body weight , decrease in DAI, serum iNOS , CRP, colonic TNF-α , increase of colonic IL10, GSH decrease in colonic MDA, macroscopic examination and down regulation of Caspase-3 and TGFB-1 immuno expression compared with UC non treated rats. **Conclusion:** Current findings confirmed ameliorative impact of sulfa, VRT and dapa on UC. rats received combined therapy showed the best results as standard group (sulfa treated group) but rats received mono therapy either VRT or dapa had the lowest prophylactic effect.

**Keywords:** ulcerative colitis, sulfasalazine, vortioxetine and dapagliflozin.

## Introduction

Ulcerative colitis (UC) is one of the chronic idiopathic inflammatory disorders of colonic mucosa that influences the rectum besides other parts of the colon, with the greatest reported incidence in mainland Europe and Scandinavia of 9.2 to 20.3 per 100,000 people, totaling approximately 2.2 million sufferers in Europe alone[(1)], In Egypt, the clinical study of **Esmat et al., (2014 )** [(2)] revealed that the characteristics of IBD in the Egyptian population were more similar to Asian and African IBD patterns , The ratio of patients diagnosed with UC to those diagnosed with CD was approximately 6:1 .This is a far distinction from international ratio which was around 1:1.18 [(3)].UC resulting in a series of symptoms of abdominal pain, rectal urgency, bloody diarrhea , anemia and weight loss [(4)] .Additionally, the prevalence and the risk of depression and anxiety are reported to be high among patients with UC, which in turn exacerbate gastrointestinal inflammation in this group of patients [(5)].UC is characterized by diffuse, continuous inflammation without skip lesions, restricted to the rectal and colonic mucosa. The bowel is characteristically filled with blood-stained dark fluid mixed with mucus. At the onset of the disease, the mucosa shows diffuse granularity, oedema, and erythema justifying the term 'red velvety' appearance. With the progression of the disease, the mucosa becomes friable with the appearance of punctate ulcers [(6)]. Apoptosis of intestinal epithelial cells (IECs) has been considered an early event during the onset of UC and plays a crucial role in disease development. Thus, effectively inhibiting apoptosis of IECs is of critical significance for the clinical management of UC [(7)]. The anti-inflammatory cytokines (IL-10 and IL-37) play a marked role in downregulation of UC. IL-10 is a pleiotropic immunoregulatory cytokine that plays a key role in the anti-inflammatory effect associated with tissue recovery [(8)].

Sulfasalazine (sulfa), the oldest anti-inflammatory medication used in treatment of UC, is converted to the sulfapyridine and 5 Aminosalicylic acid (5-ASA) moieties by colonic bacteria. The 5-ASA moiety is thought to be active compound for treatment of UC, while sulfapyridine is thought to contribute to adverse effects. The exact mechanism of sulfa is not fully understood, but the most accepted mechanism is inhibition of prostaglandins, resulting in local anti-inflammatory effects in the colon [(9)].

Vortioxetine (VRT) differs from other antidepressants as selective serotonin reuptake inhibitors (SSRIs) and serotonin norepinephrine reuptake inhibitors (SNRIs) as it has particular multimodal profile, combining serotonin (5-HT) reuptake inhibition with modulations of other key pre- and post-synaptic 5-HT receptors These additional targets can be responsible for its further beneficial effects on generalized anxiety disorder and cognitive functions and on improved tolerability [(10)].

Dapagliflozin (Dapa) is a sodium glucose co-transporter 2 inhibitor (SGLT2 inhibitor), has proven to be an effective hypoglycemic due to its role in inhibiting the reabsorption of 30–50% of the glucose filtered by the kidney, besides its role in improvement of insulin resistance [(11)].Some previous studies have also shown that inhibition of SGLT2 might suppress the expression of inflammatory cytokine and inflammasome activation, However, the underlying mechanisms of SGLT2 inhibitors remain unclear [(12)].

**Aim of the study:** This work was designed to assess the potential prophylactic effect of VRT and Dapa alone and in combination in acetic acid induced UC in rats.

## Materials and Methods

It is a pilot study conducted during the period from Augustus 2023 to september 2023.

***Chemical, kits and drugs:***

Tumor necrosis factor alpha (TNF-α), C reactive protein (CRP), interleukein10 (IL10), and Malondialdehyde (MDA) kits were from (My BioSource, Inc, California& San Diego;USA). Inducible nitric oxide synthase (iNOS) was from (CUSABIO, USA & HOUSTON, TEXAS). Reduced Glutathione (GSH) kits was from (ShangHai, BlueGene, Biotech CO.,LTD). and Acetic acid solution was from (Chema jet chemical company, Alexandria, Egypt). Immunostaining were from (Thermo Fisher Scientific, USA). Formalin solution was from (El Gomhoria Pharmaceutical Chemical Co., ARE). Urethane was from (Sigma Chemical Co., USA). Hematoxylin and eosin were from (E. Merk, Darmastadt. , Germany).All chemicals used were of molecular grade. Dapagliflozin (Dapa) was from (AstraZeneca pharmaceutical company, Cairo, Egypt), Vortioxetine (VRT) was from (H.lundbeck, ottiliavei,valby, Denmark) while Sulphasalazine (Sulfa) was from (Minapharm Co, cairo, Egypt). Ketamine powder was from ( Hameln,Germany), and Xylazine powder was from (Bimeda, USA ,Canada).

***Animals and Experimental Design:***

Thirty-six adult male local strain rats (8-week-old weighing 180–200 g) were used for the current study. Animals were housed by adjusting room temperature at the Laboratory research of Pharmacology Department at Benha university and were hand−led manually for seven days to become totally adapted. The ethical rules for laboratory animal research were followed during all animal-related procedures based on the approval offered by Benha Faculty of Medicine (M.S.30.11.2022). Rats were divided into six equal groups. Group I (normal group): rats were given drug vehicle (distilled water) for period of study to evaluate the normal basic parameters. Group II (ulcerative colitis non treated group): rats were received intrarectal injection of 2 ml of 3% acetic acid to induce uc,They will be given drug vehicle (distilled water) for period of study.Group III (sulfa treated ulcerative colitis group) rats were medicated with sulfa ( 100 mg /kg/ day, orally) [(13)] for 2 weeks before

induction and continuous 1week after induction. Group IV(VRT treated ulcerative colitis group) rats were medicated with VRT (10 mg/kg/day, orally) [14] starting 2week before induction of ulcerative colitis and continuous for 1 weeks after induction. Group V (Dapa treated ulcerative colitis group) rats were medicated with Dapa (5mg/kg/day, orally) [15] for 2 weeks before induction of ulcerative colitis and continuous for 1 week after induction. group (VI) (VRT and dapa treated group) rats were medicated with a combination of VRT(10 mg/kg/day, orally) and dapa (5mg/kg/day, orally) for 2 weeks before induction of UC and continuous for 1 week after induction.

***Experimental Induction of ulcerative colitis in rats and sampling:***

Rats were fasted overnight and allowed free access to water. After anesthesia with intraperitone ketamine (50 mg/kg)/xylazine (10 mg/kg), a soft 6F polypropylene catheter pediatric nutrition lubricated with K–Y jelly (New Jersey, USA) was inserted 8 cm transrectally into the colon. 2 ml of 3% acetic acid was slowly injected into the distal colon. Before the catheter was withdrawn, 2 ml of air was injected to spread to the entire colon. The catheter was then gently pulled to prevent physical trauma. Rats were kept in a supine Trendelenburg position for 30 second to prevent the solution from expulsion or escaping backward [15].

Scarification and biological samples collection at the end of experiment period , animals were fasted overnight before sacrificing .The experimental animals were anesthetized with urethane (1.3-1.5 g/kg in a ~1.5 g/5 ml solution) and blood samples were collected from heart and samples were obtained by centrifugation of blood at 4000 R.P.M for 10 min. Sera were separated and kept in clean tubes, and stored at −20 ◦C until use for measurment of serum iNOS, CRP. Colons were removed, excised from adherent adipose tissue, washed with normal saline. Later on,colon lengths and body weights were measured. Furthermore, colon weight/colon length ratio and colon mass index (CMI) were calculated. , and examined for macroscopic scoring. A longitudinal colon sections were used to make colon homogenate for determination of coloic IL-10, colonic TNF-α, GSH, and MDA.

***Assessment of the macroscopic damage index (MDI):***

Following scarification and postmortem laparotomy, around 6 cm of colon extending approximately 2 cm above the anal margin was harvested and slit lengthwise, and the macroscopic changes in the colonic mucosa were scaled using a scoring system ranging from 0 to 4 as described elsewhere [16].

As shown in Table (1), the macroscopic damage criteria were applied along the colon and the score was recorded individually for each animal.The scoring criteria for the intestinal macroscopic tissue damage were adapted from an arbitrary scale ranging from 0 to 4 [17].

***Assessment of the disease activity index (DAI):***

To evaluate the severity of the developed UC. The parameters of the percentage body weight loss, diarrhea and bloody stool were recorded and the scoring criteria are described as shown in Table (2) [18]. The DAI score was calculated as the sum of scores of the mentioned parameters.

***Body weight measurement:***

Body weight for each rat was measured every day. Percentage change in body weight was calculated according to the following equations: [19].

(FBW-IBW) /IBW 100%

FBW, final body weight; IBW, initial body weight

***Measurement of inflammatory mediators: Serum iNOS , serum CRP, colonic IL-10 and TNF-α :***

Serum iNOS levels were measured using the ELISA kit (CUSABIO, USA & HOUSTON, TEXAS) following the manufacturer's protocol. On the other hand, CRP serum, colon IL-10 and TNF-α were measured using ELISA kit (MyBioSource,Inc,California&San Diego;USA) according the manufacturer instructions.

***Determination of oxidant/antioxidant biomarkers (colonic MDA and GSH):***

Colonic MDA was measured using the ELISA kit (MyBioSource,Inc, California&San Diego; USA) and GSH was measured using the ELISA kit (ShangHai, BlueGene ,Biotech CO.,LTD) according the manufacturer instructions.

***Histological examination of rats colons:***

Another section was also immersed in 10% neutral buffered formalin (NBF) for the following steps of histopathological examination and immunohistochemical analysis .The fixed specimens were washed with tap water and then dehydrated by a series of ascending concentrations of ethyl alcohol solutions, cleared in xylene and embedded into paraffin wax. Tissue paraffin sections with a thickness of 5 μm were cut using a rotatory microtome. These sections were stained with hematoxylin and eosin stain according to [20]. For evaluation of the histopathological changes in the colon, these stained sections were examined using Nikon Eclipse E800 light microscopy and representative photos were captured with an Olympus digital camera.

***Immunohistochemical evaluation of caspase-3 and Transforming growth factor beta (TGF- β) in the examined colon sections:***

The expressions of caspase-3 and TGF-β in colon tissues were measured by immunostaining using the Avidin-Biotin Complex (ABC) method [21]. utilizing polyclonal antibodies .

For morphometric evaluation, the mean area percentage of caspase-3 and TGF-β expressions were quantified in five non-overlapping randomly selected fields in five selected tissue paraffin sections from each group. The slides were examined using a Nikon Eclipse E800 microscope fitted with a digital camera and the images were analyzed using ImageJ software

(ImageJ 1.54g, National Institutes of Health, USA). The area of positive immunoexpression was determined and compared to the overall area of the tissue section.

***Data Analysis***

The data was tabulated and evaluated using statistical package for social sciences (SPSS) program to analyze the results (version 25, IBM Analytics, New York, NY, USA). The data were expressed as means ± Standard deviation (SD). To find variations between normally distributed data, the one-way analysis of variance (ANOVA) test was utilized. Tukey Kramer post-hoc test was used to determine level of significance. $p$ <0.05 was deemed significant in this study, and that was the accepted levelof significance.

## Results

***Ameliorative impacts* of *Sulfasalazine, Vortioxetine and Dapagliflozin on colon length, colon weight, colon mass index(CMI) and colon weight / length ratio parameters:***

**In table (3),** There are significant elevation of colon weight, CMI and colon weight/length ratio with significantly decreased colon length in the non treated uc rats if compared with normal rats. While pretreatment with sulfa, VRT and Dapa showed significant reduction in the colon weight, CMI and weight/length ratio with significant increase in the colon length compared with UC non treated. The best results were seen in (VRT + Dapa) treated group.

***Impacts* of *Sulfasalazine, Vortioxetine and Dapagliflozin sulfa, VRT and Dapa on macroscopic examination.***

Figure (1) demonstrates a significant increase incidence of severe ulceration (66.7%) in uc non-treated rats, while rats which received prophylactic therapy with sulfa, VRT and Dapa for 2 weeks before and 1 week after induction of UC showed significant reduction in ulceration, edema, and tissue necrosis if compared with uc non treated rats. The best improvement was seen in the combined therapy (VRT + Dapa) as 50% showing no macroscopic pathology.

***Effects of Sulfasalazine, Vortioxetine and Dapagliflozin on weight change along period of the study and disease activity index( DAI) in rats:***

In table (4), There are a significant elevation in the DAI with a decrease in body weight in uc non treated rats if compared with normal rats, while rats received sulfa, VRT and Dapa showed significant reduction in DAI, a significant weight gain compared with UC non treated rats. The best significant improvement was seen in combination therapy treated group (VRT + Dapa).

***Effects of Sulfasalazine, Vortioxetine and Dapagliflozin on serum iNOS and CRP:***

Serum iNOS and CRP was increase in colon tissues of UC non treated rats figure (2) A, B respectively compared to normal rats,while pretreatment with sulfa, VRT and Dapa showed significant decrease of serum iNOS and CRP. The best results were seen

in combination therapy treated ulcerative rats (Fig 2) A, B.

**Impacts of Sulfasalazine, Vortioxetine and Dapagliflozin on colonic TNF-α and IL-10 in colon homogenates:**

Figure (3) demonstrates a significant elevation in colonic TNF-α levels, decrease of colonic IL-10 in colon tissues of UC non treated rats(A, B respectively), while rats which received prophylactic therapy with sulfa, VRT and Dapa showed significant reduction in colonic TNF-α levels, with significant increase of colonic IL-10 if compared with UC non treated rats. The best significant improvement was seen in combined therapy (VRT + Dapa) treated ulcerative rats .

**Effects of Sulfasalazine, Vortioxetine and Dapagliflozin on colonic MDA and colonic GSH in colon homogenates:**

Figure (4) demonstrates a significant increase in colonic MDA levels, decrease of colonic GSH in colon tissues of UC non treated rats (A, B respectively), but rats which received prophylactic therapy with sulfa, VRT and Dapa showed significant decrease in colonic MDA with significant increase of colonic GSH if compared with UC non treated rats. The best significant findings were seen in combined therapy.

**Histopathological Examination:**

The experimental groups' colon histology was investigated in Figure 5. The normal group's all the examined colon sections of rats revealed typical histoarchitecture of the mucosa, submucosa, muscularis and serosa. (Figure 5A), while the rats in ulcerative non treated group demonstrated substantial colon damage with markedly distorted colon histoarchitecture. A typical microscopic picture of ulcerative colitis was prevalent in the most examined colon sections. Mucosal disruption was evident, widespread necrosis and sloughing of the mucosal epithelium with ruptured crypts, There was also mononuclear infiltration of the underlying tissues (Figure 5B). On the other hand, Groups with pretreatment using sulfa, VRT and Dapa showed improvement in colon histological structure with the best improvement was seen in combined therapy (VRT + Dapa) treated ulcerative rats.(Figure 5C,D,E,F).

**Immunohistochemical analysis of colonic expression of caspase-3:**

The experimental groups' colon immunohistochemical analysis was investigated in Figure 6. The normal group's all the examined colon sections of rats revealed mild immunoexpression.(Figure6A), while the rats in ulcerative non treated group demonstrated strong immunoexpression in the lamina propria and the degenerated crypts. (Figure 5B). On the other hand, Groups with pretreatment using sulfa, VRT and Dapa showed improvement in caspase-3 immunoexpression with the best improvement was seen in combined therapy. (Figure 5C,D,E,F).

**Immunohistochemical analysis of colonic expression of TGF-β:**

The experimental groups' colon Immunohistochemical analysis of TGF-β expression was investigated in Figure 7. The normal group's all the examined colon sections of rats revealed minimal TGF-β immunoexpression in the mucosa and submucosa.(Figure7A), while the rats in ulcerative non treated group demonstrated showing intensive TGF-β immunoexpression in the mucosa. (Figure 7B). On the other hand, Groups with pretreatment using sulfa, VRT and Dapa showed improvement in TGF-β immunoexpression with the best improvement was seen in combined therapy (VRT + Dapa) treated ulcerative rats. (Figure 7C, D,E,F).

**Table (1): Macroscopic damage criteria scoring system**

| Macroscopic features | Score |
|---|---|
| No macroscopic changes | 0 |
| Mucosal erythema only | 1 |
| Mild mucosal edema, slight bleeding or small erosions | 2 |
| Moderate oedema, slight bleeding ulcers or erosions | 3 |
| Severe ulceration, oedema and tissue necrosis | 4 |

**Table (2): Disease activity index (DAI) scoring system**

| Parameter | Evaluation criteria | Score |
|---|---|---|
| Percentage body Weight loss | None | 0 |
| | 1–5% | 1 |
| | 6–10% | 2 |
| | 11–20% | 3 |
| | > 20% | 4 |
| Diarrhea | Normal | 0 |
| | Loose stools | 1–2 |
| | Watery diarrhea | 3–4 |
| Bloody stool | Normal | 0 |
| | Slight bleeding | 1–2 |
| | Gross bleeding | 3–4 |

**Table 3.** Prophylactic effect of Sulfasalazine at dose (100 mg /kg/ day, oral) , Vortioxetine (10 mg/kg/day, oral) and Dapagliflozin (5mg/kg/day, oral) for 2 weeks before and 1 week after induction of UC by single intra rectal injection of 2ml of 3% acetic acid for each rate on colon length, colon weight, CMI and colon weight / length ratio in rats (N=6)(Mean ± SD):

| Studied groups Parameters | Normal | Non treated UC | Sulfa treated UC | VRT treated UC | Dapa treated UC | VRT and dapa treated UC |
|---|---|---|---|---|---|---|
| **Colon length (cm)** | 12.75±1.01 | $7.80^{a}$±0.49 | $12.47^{b}$±0.66 | $10.22^{a,b,c}$±0.75 | $8.72^{a,b,c,d}$±0.50 | $12.47^{b,d,e}$±0.92 |
| **Colon weight (g)** | 2.19 ± 0.12 | $3.19^{a}$±0.12 | $2.52^{a,b}$±0.09 | $2.65^{a,b,c}$±0.07 | $2.88^{a,b,c,d}$±0.10 | $2.23^{b,c,d,e}$±0.07 |
| **Colon mass index** | 0.85 ± 0.07 | $1.18^{a}$±0.07 | $0.94^{a,b}$±0.06 | $1.09^{a,b,c}$ ± 0.02 | $1.16^{a,c,d}$± 0.06 | $0.93^{a,b,d,e}$±0.04 |
| **Colon weight length ratio** | 0.14 ± 0.01 | $0.30^{a}$±0.02 | 0.15$b^{b}$±0.01 | $0.22^{a,b,c}$ ± 0.02 | $0.26^{a,b,c,d}$±0.01 | $0.15^{b,d,e}$ ± 0.01 |

a, Comparison between each group versus normal group;

b, Comparison between each group versus non treated group;

c, Comparison between each group versus sulfa treated group;

d, Comparison between each group versus VRT treated group;

e, Comparison between each group versus dapa treated group.

Values are means ±SD for 6 different rats per treatment. Values are statistically different at $p < 0.05$.

**Table 4.** Prophylactic effect of Sulfasalazine at dose (100 mg /kg/ day, oral) , Vortioxetine (10 mg/kg/day, oral) and Dapagliflozin (5mg/kg/day, oral) for 2 weeks before and 1 week after induction of UC by single intra rectal injection of 2ml of 3% acetic acid for each rate on weight change along period of the study and DAI

| Studied groups ParameterS | Normal | Non treated UC | Sulfa treated UC | VRT treated UC | Dapa treated UC | VRT and dapa treated UC |
|---|---|---|---|---|---|---|
| **Body weight change %** | 7.02±0.89 | $0.93^{a}$±0.39 | $2.24^{a,b}$±0.71 | $1.02^{a,b}$±1.34 | $1.65^{a,b}$±0.52 | $3.91^{a,b,c,d,e}$±0.81 |
| **Disease activity index (DAI) score** | 2.00±0.00 | $7.00^{a}$±1.10 | $2.83^{a,b}$±0.75 | $6.00^{a,c}$±1.79 | $6.67^{a,c}$±1.51 | 2.33 $^{b,d,e}$± 0.52 |

a, Comparison between each group versus normal group;

b, Comparison between each group versus non treated group;

c, Comparison between each group versus sulfa treated group;

d, Comparison between each group versus VRT treated group;

e, Comparison between each group versus dapa treated group.

Values are means ±SD for 6 different rats per treatment. Values are statistically different at $p < 0.05$.

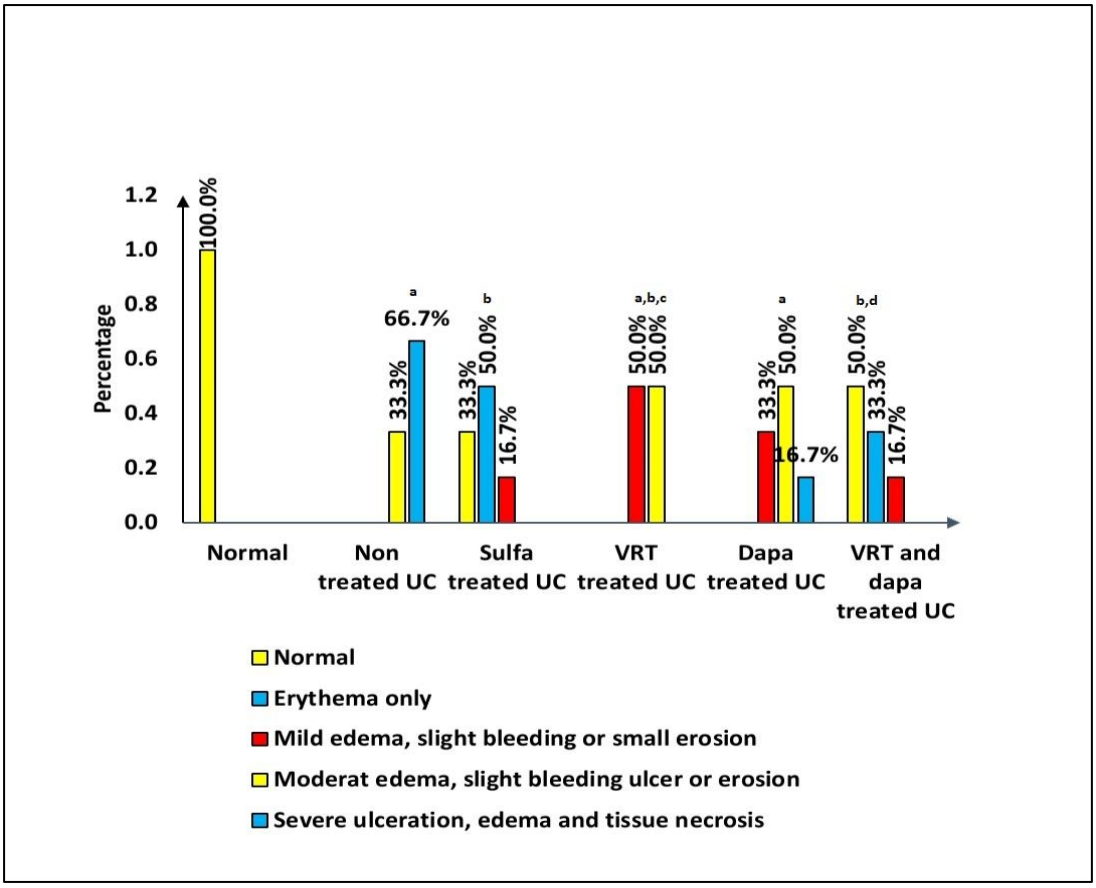



**Fig ( 1):** Effect of Prophylactic therapy of Sulfa at dose (100 mg /kg/ day, oral) , VRT (10 mg/kg/day, oral) and Dapa (5mg/kg/day, oral) for 2 weeks before and 1 week after induction of UC by single intra rectal injection of 2ml of 3% acetic acid on macroscopic examination in rats. Values are statistically different at $p < 0.05$.

a, Comparison between each group versus normal group;

b, Comparison between each group versus non treated group;

c, Comparison between each group versus sulfa treated group;

d, Comparison between each group versus VRT treated group;

e, Comparison between each group versus dapa treated group.

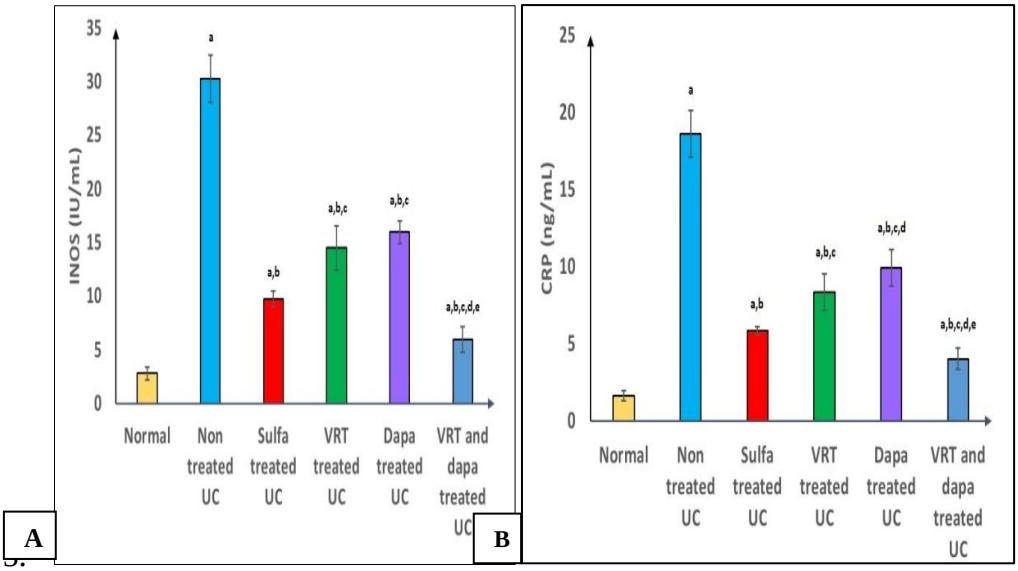



**Fig (2):** Effect of prophylactic therapy with of Sulfa at dose (100 mg /kg/ day, oral) , VRT (10 mg/kg/day, oral) and Dapa (5mg/kg/day, oral) for 2 weeks before and 1 week after induction of UC by single intra rectal injection of 2ml of 3% acetic acid on serum iNOS (A) and serum CRP (B) ) in rats.

a, Comparison between each group versus normal group;

b, Comparison between each group versus non treated group;

c, Comparison between each group versus sulfa treated group;

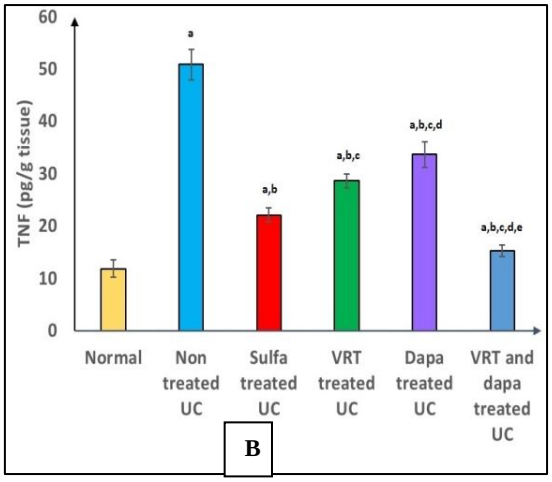
d, Comparison between each group versus VRT treated group;

e, Comparison between each group versus dapa treated group.

Values are means ±SD for 6 different rats per treatment. Values are statistically different at $p < 0.05$.

A

7.

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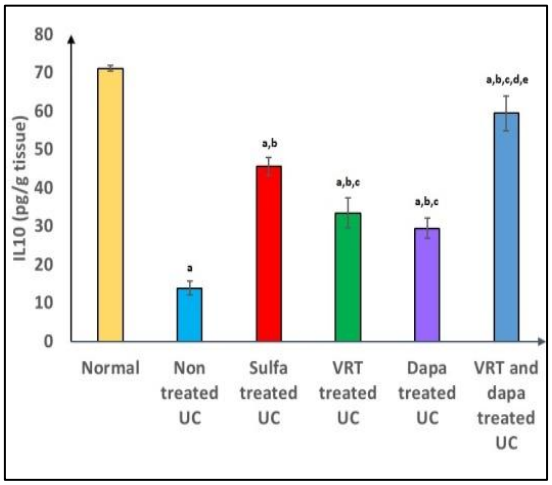



**Fig (3):** Prophylactic effect of Sulfa at dose (100 mg /kg/ day, oral) , VRT (10 mg/kg/day, oral) and Dapa (5mg/kg/day, oral) for 2 weeks before and 1 week after induction of UC by single intra rectal injection of 2ml of 3% acetic acid on colonic TNF-α (A) and colonic IL10(B) in rats.

a, Comparison between each group versus normal group;

b, Comparison between each group versus non treated group;

c, Comparison between each group versus sulfa treated group;

d, Comparison between each group versus VRT treated group;

e, Comparison between each group versus dapa treated group.

Values are means ±SD for 6 different rats per treatment. Values are statistically different at $p < 0.05$.

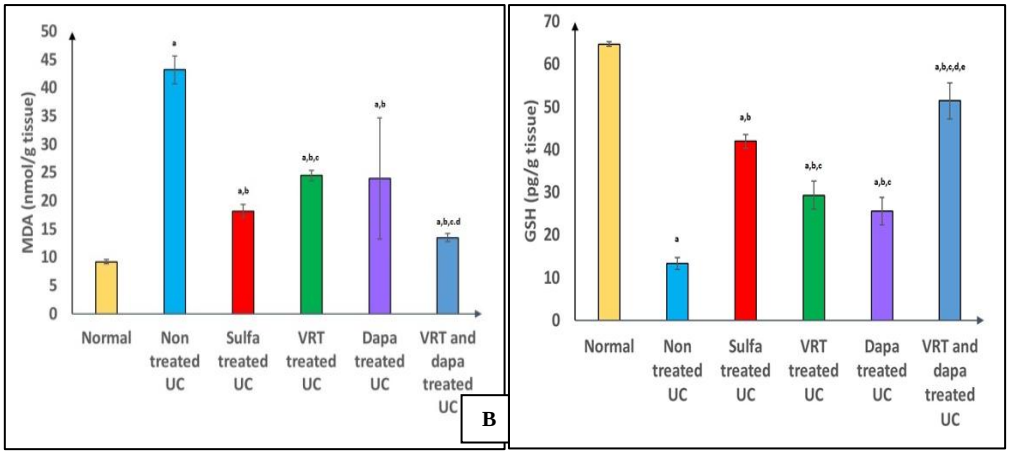



**Fig (4):** Effect of Prophylactic therapy of Sulfa at dose (100 mg /kg/ day, oral) , VRT (10 mg/kg/day, oral) and Dapa (5mg/kg/day, oral) for 2 weeks before and 1 week after induction of UC by single intra rectal injection of 2ml of 3% acetic acid on colonic MDA (A) and colonic GSH(B) in rats.

a, Comparison between each group versus normal group;

b, Comparison between each group versus non treated group;

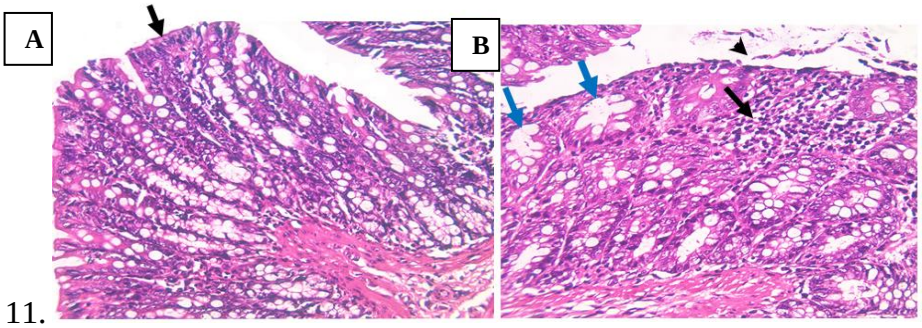
c, Comparison between each group versus sulfa treated group;

d, Comparison between each group versus VRT treated group;

e, Comparison between each group versus dapa treated group.

Values are means ±SD for 6 different rats per treatment. Values are statistically different at $p < 0.05$.

11.

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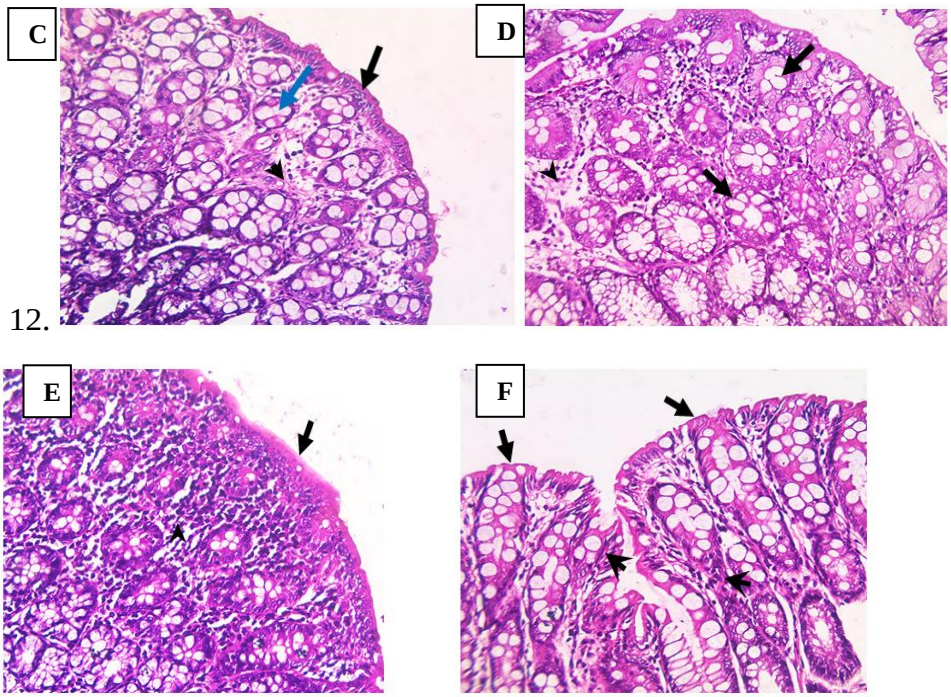


**Figure 5**. Impacts of prophylactic therapy with Sulfasalazine at dose (100 mg /kg/ day, oral) , Vortioxetine (10 mg/kg/day, oral) and Dapagliflozin (5mg/kg/day, oral) for 2 weeks before and 1 week after induction of UC by single intra rectal injection of 2ml of 3% acetic acid for each rate. (A): Normal group, Almost all the examined colon sections of rats revealed typical histoarchitecture of the mucosa, submucosa, muscularis and serosa. The mucosa was intact, folded and lined by simple columnar epithelial cells with many goblet cells(black arrows). (B): ulcerative non treated group showed showing extensive necrosis and sloughing of the mucosal epithelium with , loss of the superficial layer (black arrow heads) with crypt distortion (blue arrow) and mononuclear infiltration of the mucosa (black arrow). (C): sulfasalazine treated ulcerative group showed showing mild mucosal edema (black arrow head) and intact mucosal surface (black arrow) ,crypt irregularity(blue arrow). (D): Vortioxetine treated ulcerative group showed minimal mucosal edema (black arrow head )with crypt disruption (black arrow). (E): Dapagliflozin treated ulcerative group showed intact folded mucosa ( black arrow ) and many inflammatory cell infiltration of the colonic mucosa ( black arrow head).(F): Vortioxetine and dapagliflozine treated ulcerative group showed well-organized mucosa( black arrow ) and minimal inflammatory cell infiltration of the colonic mucosa( black arrow head) (H&E x200).

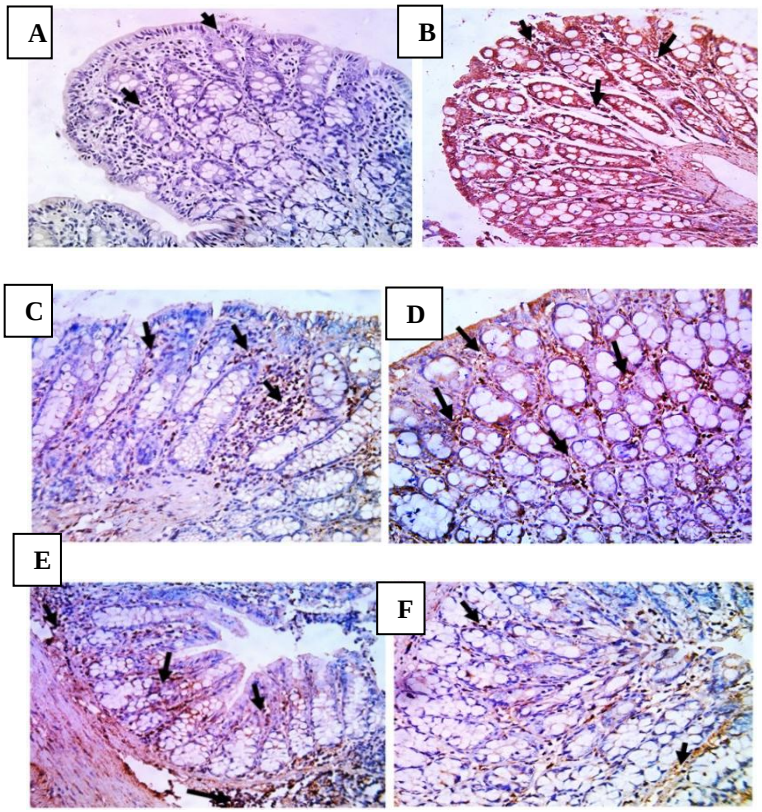


**Figure 6.** Prophylactic Effect of Sulfa at dose (100 mg /kg/ day, oral) , VRT (10 mg/kg/day, oral) and Dapa (5mg/kg/day, oral) for 2 weeks before and 1 week after induction of UC by single intra rectal injection of 2ml of 3% acetic acid on colon on immune histochemical changes of caspase3 protein expression in colonic tissue in rats (A):normal group showing mild immunoexpression. (B): non-treated group (UC group) showing strong immunoexpression in the lamina propria and the degenerated crypts.(C):sulfa pretreat group showing mild expression primarily in a few covering epithelium and lamina propria.(D):VRT pretreated group showing moderate expression in the covering epithelium, a few intestinal crypt cells, and interstitial tissues .(E): Dapa pretreated group showing moderate expression in some epithelial cells of the mucosa and crypts as well as within the interstitial tissue.(F): (VRT + dapa) pretreated group showing minimal expression in lamina propria and a few epithelial cells lining the crypts and mucosa. (black arrow indicate the positive expression) (IHC x200).

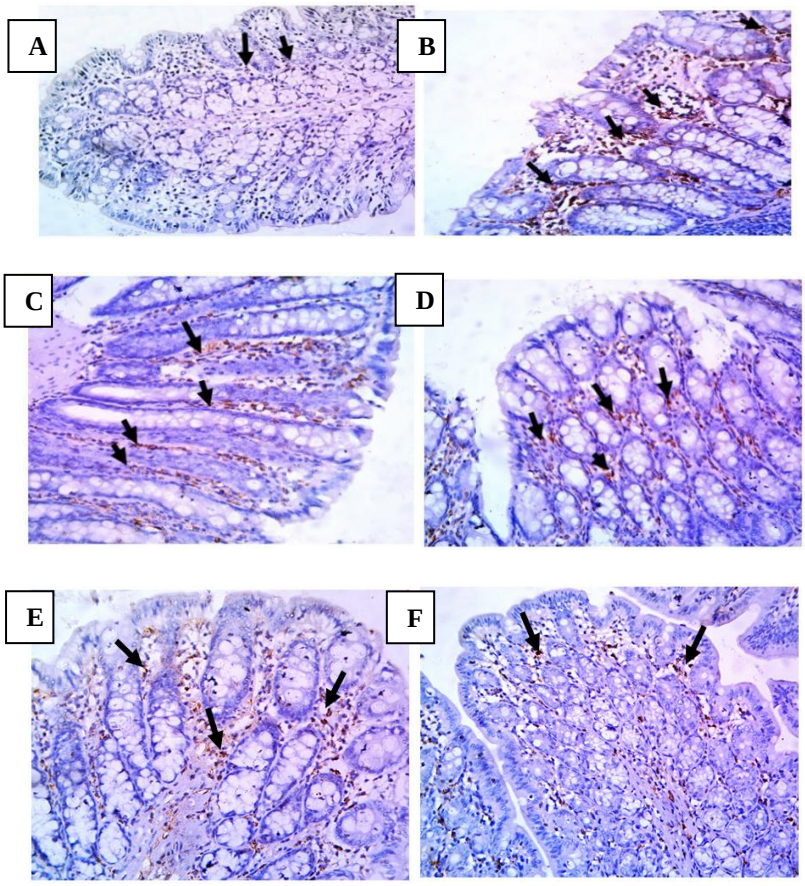


**Figure 7.** Prophylactic Effect of Sulfa at dose (100 mg /kg/ day, oral) , VRT (10 mg/kg/day, oral) and Dapa (5mg/kg/day, oral) for 2 weeks before and 1 week after induction of UC by single intra rectal injection of 2ml of 3% acetic acid on colon on immune histochemical changes of TGF-β protein expression in colonic tissue in rats (A):normal group showing minimal TGF-β immunoexpression in the mucosa and submucosa. (B): non-treated group (UC group) showing intensive TGF-β immunoexpression in the mucosa.(C):sulfa pretreat group showing weak TGF-β expression, between the crypts.(D):VRT pretreated group showing moderate TGF-β expression in interstitial tissues.(E): Dapa pretreated group showing moderate TGF-β expression in the mucosa and submucosa.(F): (VRT + dapa) pretreated group showing low TGF-β expression in colonic mucosa. (black arrow indicate the positive expression) (IHC x200).

## Discussion:

UC can be experimentally- induced by intra-rectal administration of low concentration of acetic acid. This a well-known model for the study of IBD [(22)]. The acetic acid colitis model has been found efficient for experimental colitis in the rat [(23)]. The model is reproducible and shows a high similarity to human colitis.

The experimentally induced UC (non treated rats) showed a significant increase in colon weight, colon mass index (CMI) and colon weight/length ratio, these finding was in consistent with Khodir et al. [(24)] and ElMahdy et al. [(16).]Also, these UC untreated rats also showed significantly decreased colon length if compared with normal rats. The daily oral pre-treatment of UC rats with Sulfa, VRT and Dapa alone and in combination for 2 weeks before and 1 week after induction of

UC resulted in significant decrease in the colon weight, CMI and weight/length ratio along with significant increase in the colon length compared with UC non treated rats. The best results were seen in (VRT + Dapa) treated group.

This is in agreement with Arab et al. [25] who found that Dapa as monotherapy significantly decreased the colon weight/length ratio, CMI compared to the UC non treated rats. To the best of our knowledge, our study is the first to evaluate the effect of VRT on UC on colon length, colon weight, CMI and weight/length ratio. These findings are parallel to those of Firouzabadi et al. [26] who mentioned that there was a significant decrease in colon weight/length ratio in rats treated with escitalopram (a selective serotonin reuptake inhibitor) compared to the UC non-treated group.

An explanation of this is supported by El-Rous et al.[15]who found that Dapa prevented colon shortening and caused a decline in the disease activity through targeting Nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB), AMP-activated protein kinase (AMPK), Nucleotide-binding domain-like receptor protein 3 (NLRP3) axis.

In our work, the intrarectal injection of acetic acid significantly increased the incidence of macroscopic damage index (MDI) namely severe ulceration, edema, and tissue necrosis when compared with normal rats [27],while pre-treatment of UC rats with Sulfa, VRT and Dapa alone and in combination, for 2 weeks before and 1 week after induction of UC, resulted in significant reduction in MDI if compared with UC non treated rats.

The same observation was noted by El-Mahdy et al. [16] who found that the MDI was significantly reduced in rats treated with Dapa.

Our results are also in agreement with Firouzabadi et al. [26] and Khazraei and Shamsdin. [28] who found that there was a significant decrease in MDI in escitalopram treated rats.

In the current study,acetic acid rectal administration exhibited a significant increase in the disease activity index (DAI) in non-treated UC rats [15,27]**,** as well as significant weight loss if compared with normal rats [29,30]. On other hand, the pre-treatment of UC rats with Sulfa, VRT and Dapa alone and in combination, orally daily for 2 weeks before and 1 week after induction of UC, resulted in a significant decrease in DAI and a significant weight gain compared with UC non treated rats. Noteworthy, the best improvement was seen in the combination therapy treated rats (VRT + Dapa).

Our finding is in line with a previous study by Arab et al. [25] who reported that Dapa attenuated the pathological symptoms of colitis in rats, as manifested by lowering the DAI. Also,VRT treated UC rats showed a decrease in DAI similarly as reported by Firouzabadi et al.[26] who found that there was a significant decrease in the DAI in escitalopram treated rats compared to the UC non-treated group.

Significant weight loss in UC non treated rats can be explained by

nutrient deficiency resulting from decreased appetite, malabsorption, and fast loss of body fluids from colorectal bleeding. Taken into account, TNF-α and IL-6, both play an important role in body-weight loss induced by the secretion of neuropeptides, suppressing the appetite in colitis [31] , while Dapa explaination of improved clinical evaluation (DAI) , macroscopic scoring, prevented colon shortening and suppressed the disease activity through targeting the NF-κB/AMPK/NLRP3 axis El-Rous et al.[15].

It seems that the inflammation associated with UC contributed to the presence of oxidative stress in the colon with the production of reactive oxygen and nitrogen species (ROS, RNS) [32].

In the present study, UC non treated rats showed significant elevation of serum inducible nitric oxide Synthase (iNOS) [32,33], as well as serum C-Reactive protein (CRP) [16,24] if compared with normal control rats, but pre-treatment of UC rats with Sulfa, VRT and Dapa alone and in combination orally daily for 2 weeks before and 1 week after induction of UC resulted in significant decrease in serum iNOS as well as serum CRP if compared with UC non treated rats.

It was detected that treatment with Dapa shows decrease in serum iNOS compared to UC non treated group. Also, treatment with Dapa shows decrease in serum CRP compared to UC non treated group in concordance with Makaro et al. [34] 2024 and Yosef et al. [35].

VRT treated UC group shows decrease in serum iNOS similarly as reported by Caruso et al. [36] who demonstrated that both fluoxetine and VRT reduced the expression of iNOS mRNA in a rat model of oxidative stress induced by amyloid-beta oligomers.

The decline in serum CRP was observed in VRT treated group is agreeing with Kavakbasi et al. [37] who studied the anti-inflammatory effects of VRT combined with celecoxib.

In our study, UC untreated group showed significant elevation of colonic tumor necrosis factor alpha (TNF-α) if compared with normal rats [27,32]. with significant decrease of colonic interleukin10 (IL10) if compared with normal rats [38], while The pre-treatment of UC rats with Sulfa, VRT and Dapa alone and in combination resulted in significant decrease in colonic TNF-α and significant increase of colonic IL10 if compared with UC non treated rats.

Our results are in harmony with Arab et al. [25], El-Rous et al. [15] who found that Dapa monotherapy significantly decreased the levels of TNF-α, significant increase in the levels of colonic IL-10 respectively compared to those of untreated UC rats. Also, VRT treated UC group shows decrease in TNF-α similarly as reported by Shafiek et al. [39] who demonstrated that VRT suppressed phospho serine 536 nuclear factor kappa B (pS536 NF-κB p65) activity and reduced TNF-α production in experimental autoimmune encephalomyelitis model of multiple sclerosis in mice .

Dapa provided anti-ulcerogenic and colo-protective effects against experimentally induced UC in rats, primarily mediated via down regulation of of Monocyte Chemoattractant Protein 1 (MCP1), IL-18 signaling, and NF-κB expression [(16)].

Medications with SSRI activity like escitalopram are used in managing chronic and inflammatory pain. Since there is a bidirectional path between the inflammation caused in the brain and the gut, it is found that escitalopram directly suppresses the inflammation caused in UC by increasing the level of serotonin in the brain [(29)].

GSH is regarded as a free radical scavenger or a cellular oxidation inhibitor, and depletion of the GSH content is a marker of oxidative stress [(40)]. Accordingly, the GSH drop directly resulted in elevation of the MDA level, an end product of lipid peroxidation, which lead to polyunsaturated lipid degradation [(41)].

In the current study UC untreated rats showed significant increase of colonic MDA [(24)] as well as significant decrease of colonic GSH [(24,32)] if compared with normal rats, but pre-treatment of UC rats with Sulfa, VRT and Dapa alone and in combination orally daily for 2 weeks before and 1 week after induction of UC resulted in significant decrease in colonic MDA with significant increase of colonic GSH, if compared with UC non treated rats.

This is in agreement with Doğan and Uzun.[(42)], Bastawy et al.[(43)] who found that Dapa lowered MDA levels, increase in the levels of colonic GSH, compared to untreated groups respectively.Also, VRT treated UC group shows decrease in MDA similarly as reported by Fotache et al.[(44)] who demonstrated that VRT treatment resulted in a significant decrease in serum MDA levels in rats subjected to physical stress, indicating a reduction in oxidative stress, and in agreement with Cim et al.[(45)] who found that there was a significant decrease in MDA levels and significant increase in GSH levels in VRT treated rats model of stress-induced brain injury which indicate that VRT is a neuroprotective antidepressant with higher antioxidant activity .

Our results can be explained by that this reduction was linked to decreased expression of NADPH oxidase and other oxidative stress markers, suggesting a protective effect against oxidative damage, which could correlate with increased GSH levels in treated rats [(46)] **,**while VRT explaination is that VRT is considered an inhibitor of Cytochrome P 450 (CYP 450), one of the major sources of ROS production, thus inhibition of CYP450 by VRT may substantially contribute to decline in oxidative stress observed in UC [(47)].

The data of this work revealed that experimental induction of UC resulted in colon damage with markedly distorted colon histoarchitecture, Mucosal disruption, widespread necrosis and sloughing of the mucosal epithelium with ruptured crypts and inflammatory cells infiltration .This is in line with Salama et al.[(27)] and El-

Rous et al.[15] who reported that UC untreated rats revealed massive ulcerative hemorrhagic lesions associated with massive confluent necrosis along the mucosa, indicating a significant increase in the histological score compared to the control group, While pre-treatment of UC rats with Sulfa, VRT and Dapa alone and in combination resulted in a significant decrease in the microscopic and histological parameters.

This is in harmony with previous results by Arab et al.[25] who found that histopathologic examination of the control and dapagliflozin groups demonstrated an intact structure of mucosa with normal intestinal crypts, submucosa, musculosa, and serosa layers.

Furthermore, Apoptosis of intestinal epithelial cells has been considered an early event during the onset of UC and plays a crucial role in disease development [48].

In the current study, UC non treated rats showed significant upregulation of Caspase 3 immuno-expression if compared with normal rats [30] , but pre-treatment of UC rats with Sulfa, VRT and Dapa alone and in combination resulted in significant downregulation in Caspase 3 immuno-expression compared with UC non treated rats. The best Caspase 3 results was observed in in the combination therapy treated rats (VRT + Dapa).

In agreement with us, Arab et al. [25] revealed that treatment with Dapa evolved a significant decrease in Caspase-3 expression. Also our results are in agreement with Ozmen et al.[49] who found that VRT treatment was associated with reductions in caspase-3 and NF-κB levels, indicating its potential protective role against apoptosis and inflammation in cardiac tissues of a rat model of Cardiac Responses to Chronic Unpredictable Mild Stress .

An explanation of this protective effect of Dapa is supported and explained by Cheng et al.[50] study who reported that empagliflozin prevented beta-cell death by reducing glucotoxicity induced oxidative stress.

TGFβ1 serves as the key mediator of tissue fibrosis as it induces secretion of fibrillary collagens and promotes cell death and undifferentiation [51].

In our study, UC non treated rats showed significant upregulation of TGFβ immuno-expression if compared with normal rats [52,53]**.** The pre-treatment of UC rats with Sulfa, VRT and Dopa alone and in combination resulted in significant downregulation in TGFβ immuno expression compared with UC non treated rats. The best TGFβ improvement was observed in in the combination therapy treated rats (VRT + Dapa). To the best of our knowledge, this is the first study to evaluate the effect of Dapa and VRT on UC as regards TGF-β1 immuno-expression. This can be supported by Liashev et al. [54] study, where Sulfa decreases the expression levels of TGF-β. Also Chen et al.[55]study,that proved Dapa could further inhibit the expression of TGF-β1 compared with that of perindopril,Dapa exerted an inhibitory effect on the TGF-β1-Smad signaling pathway, showing a better

cardioprotective effect than that of perindopril.Our results are also in agreement with Torrisi et al.[56] who found that treatment with Fluoxetine and VRT completely rescued hippocampal TGF-β1 levels in Aβ-injected mice as well as synaptophysin and PSD-95 levels.

**summary of results and conclusion:**

Treatment with Sulfasalazine, vortioxetine and dapagliflozin in ulcerative rats resulted in significant decrease in colon weight, colon mass index and colon weight / length ratio and significant increase in colon length. significant decrease in macroscopic examination, significant improvement in body weight and decreased DAI,significant decrease in serum iNOS as well as serum CRP, colonic TNF-α,significant increase of colonic IL10, colonic GSH and significant decrease in colonic MDA,improvement in the microscopic and histological parameters, significant downregulation of caspase-3 and TGF-β1 immune-expression.

Current findings confirmed ameliorative impact of dapagliflozin and vortioxetine on UC induced by acetic acid. rats received combined therapy showed the best results as standard group (sulfa treated group) but rats received mono therapy either VRT or dapa had the lowest prophylactic effect. UC altered colon length, colon weight, colon mass index, colon weight / length ratio, macroscopic examination, body weight,DAI, serum and colonic biomarkers, increased colonic inflammatory markers, colon lipid peroxidation in colon homogenate with altered different immun histochemical protein expression in colon tissue. The pre-administration of dapagliflozin and vortioxetine retrieved all altered markers at biochemical colon level, downregulated apoptosis and fibrosis. These results supported the potential use of dapagliflozin and vortioxetineto protect colon against UC.

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