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Comparative study of nano-selenium with dexamethasone against experimental ulcerative colitis in rats

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Abstract
The present study aimed to evaluate the anti-colitis actions of SeNP and Dexamethasone in acetic acid induced colitis model in rats. Group 1 was kept as normal control throughout the experimental period. Remaining 3 groups were induced colitis by intra- colonic injection of acetic acid @ 4% (2 ml). Treatment protocols were initiated from day 2 and were continued for next 14 days.
Group 1: Non Colitis control,
Group 2: Acetic acid induced colitis control (UC) (4% concentration @ 2ml, single dose intra colonic),
Group 3: UC + SeNP (0.5 mg/kg, p/o) treatment for 14 days, Group 4: UC + Dexamethasone (2 mg/kg B. wt., p/o) treatment for 14 days. Average body weights were recorded at weekly intervals and colon lengths and weights were recorded after sacrifice. On the 14th day the colitis group induced by acetic acid in Cytokines *viz*. IL-10 and TNF-α, showed alterations in the colitis group (group 2). Histopathology of colon tissue revealed neutrophilic infiltration, disruption of epithelium and glands. Semi thin section revealed eroded villi and increase in thickness of epithelium. The control group did not show any changes in serum, tissue biomarkers and histology of the colon. Treatment with Dexamethasone showed significant amelioration as evident by rise in the antioxidant profiles and decrease in the Proinflammatory markers such as TNFα.

Keywords: ulcerative colitis, IBD, crohn's disease, nano selenium, SeNP, dexamethasone

1. Introduction
Ulcerative colitis (UC) and Crohn's disease (CD) (collectively termed as inflammatory bowel disease (IBD). Ulcerative colitis (UC) is a chronic disease with a remitting and relapsing course that can progress from asymptomatic mild inflammation to extensive inflammation of the colon, resulting in frequent bloody stools, colonic motility dysfunction, potentially permanent fibrosis and tissue damage (Ryan Unago *et al*., 2019). Ulcerative colitis (UC) mainly presents in the rectal and colonic mucosa and is accompanied by weight loss, diarrhea, abdominal pain, and rectal bleeding. This kind of uncontrolled gut inflammation affects millions of individuals in the world (Fumery *et al*., 2018) [2]. In population based studies, it also indicated that UC patients will have proximal disease extension within 10years. (Qui *et al*., 2019).
Ulcerative colitis induced oxidative stress causes molecular damage to lipids, DNA and proteins, and can contribute to a range of pathologies (Rodriguez *et al*., 2010). Enzymatic markers of colonic damage like ALP, and MPO are also elevated in colitis condition (Nieto *et al*., 2000) [9]. Tumor necrosis factor- alpha (TNF-α) and interleukin-10 (IL-10) are pleiotropic cytokines that play a very important role in the initiation and maintenance of inflammatory and immune responses (Wan Yue *et al*., 2011) [3].
SeNP are envisaged widely in biomedicine due to their high bioavailability and diverse biological activities (Bhattacharjee *et al*., 2017) [4] Selenium in Nano form has been reported to possess biological activities like down regulation of m-RNA expression of pro-inflammatory cytokines, including inducible- NO-synthase, Interleukin - I and TNF-alpha, thus reducing inflammation (Zhang *et al*., 2008) [6]. Nano- Selenium anti-inflammatory activity was reported in, carrageenan induced inflammation (El-Ghazaly *et al*., 2016) [7].
Dexamethasone is a synthetic glucocorticoid, which is a steroid, but unlike the "anabolic" steroids, it is a "catabolic" steroid (Haribabu *et al*., 2012). Exogenous glucocorticoids are widely used as anti-inflammatory therapy in ulcerative colitis and are the first line of therapy in both severe and moderate cases (Dubois-Camacho*et al*., 2017) [8].

Table 1: The treatment was given daily per orally.

Group	Treatments
I	Non-colitis control
II	Acetic acid induced colitis control (UC) (4% concentration @ 2ml, single dose intra colonic)
III	UC + SeNP (0.5 mg/kg, p/o) treatment for 14 days
IV	UC + Dexamethasone (2 mg/kg B. wt., p/o) treatment for 14 days

Inflammatory therapy in ulcerative colitis and are the first line of therapy in both severe and moderate cases (Dubois-Camacho*et al*., 2017) [8].

2. Review of Literature

Ulcerative colitis is a chronic inflammatory disease of the colon with an increasing incidence worldwide (Fumery *et al*., 2018) [2]. The medical management of this disease continues to expand as drugs to induce and maintain remission are sought to avoid the need for colectomy. Ulcerative colitis (UC) is a chronic disease with a remitting and relapsing course that can progress from asymptomatic mild inflammation extensive inflammation of the colon, resulting in frequent bloody stools, colonic motility dysfunction, potentially permanent fibrosis and tissue damage (Ungaro *et al*., 2019) [1]. As the etiopathologies of UC are unclear, current therapeutic strategies are aimed to ameliorate inflammatory response and prevent further relapses (Luca pastorelli *et al*., 2009) [6]. The molecular etiology of UC development is complex and involves genetic, microbial, environmental, and other unknown factors (Molodecky NA *et al*., 2012).

4. Material and Method

4.2 Experimental animals

Twenty four adult male Wistar rats were randomly divided into four groups with six rats in each group. The details of the experimental groups and their treatment are summarized in
All the animals were housed in clean steel cages in acclimatized room of laboratory animal house as per the specifications of Committee for the Purpose of Control and Supervision of Experiment on Animals (CPCSEA) and given ad-libitum feed and water throughout the experimental period. Acclimatization period of two weeks was observed before the start of the experiment. The experimental protocol was conducted with the approval from the Institutional Animal Ethics Committee.

4.3 Experimental design

Experimental groups and their treatments (n=6).

4.4 Body weight

Body weight was recorded before induction of toxicity and once weekly on 7th and 14th day.

4.5 Cytokine profile of TNF alpha Protein and IL- 10 in the colon homogenate: TNF-α concentrations were determined in colon tissue homogenate using enzyme linked immune adsorbent assay (ELISA, Krishgen Biologicals, USA). The measurement was carried out according to the manufacturer's instructions.

5. Results

The results are of various investigations to assess the efficacy of SeNP and also to compare the efficacy of SeNP and Dexamethasone in Acetic acid induced Ulcerative colitis in male Wistar rats. The investigations included synthesis and characterization of SeNP, performance, biochemical parameters, tissue antioxidants, cytokines, and histopathological changes during experimental period.

5.1 Weekly body weight

The body weights (g) in the control group 1 were significantly ($p<0.05$) higher (ranged from 278.8 ±2.1 to 285.6 ± 2.3) as compared to the other groups at respective time intervels throughout the experiment. The body weight in control group 2 (colitis-induced) was significantly ($p<0.05$) lower (244.2 ± 3.6) as compared to group 1 on 14th day. The weights in groups 3 and 4 were significantly ($p<0.05$) lower (266 ± 3.1 and229.9 ± 5.1 respectively) as compared to group 1 at the end of 7th day (281.4± 1.9). The groups 3 showed significant ($p<0.05$) increase in the body weights compared to group 2 at the end of 14th day (262.3 ± 4.4), while group 4 showed a significant ($p<0.05$) decrease in the body weight compared to remaining groups at the end of 14th day (197.4 ± 4.3)

Cytokine Profile

5.2 Interleukin-10

The concentration of interleukin-10 (pg/mg tissue) in colon revealed a significant ($p<0.05$) reduction in group 2 (0.87 ± 0.04) as compared to group 1 (2.94± 0.1). Groups 3 and 4 showed a significant ($p<0.05$) increase in IL-10 concentration (2.54± 0.1 and 1.36 ± 0.1 respectively) as compared to group 2, but significantly ($p<0.05$) decreased as compared to group1.

5.3 Tumor Necrosis Factor (TNFα)

The concentration of TNF-α (pg/mg tissue) in colon revealed a significant ($p<0.05$) rise in group 2(187.24 ± 4.6) as compared to group 1 (84.14 ± 1.5). Groups 3 and 4 showed a significant ($p<0.05$) decrease in TNF-α concentration (134.31 ± 3.7 and 162.84 ± 2.8 respectively) as compared to group 2, but significantly ($p<0.05$) increased as compared to group 1

6. Summary

Anti-colitis actions of SeNP and Dexamethasone were evaluated in acetic acid induced colitis model in rats. Group 1 was kept as normal control throughout the experimental period. Remaining 3 groups were induced colitis by intra-colonic injection of acetic acid @ 4% (2 ml). Treatment protocols were initiated from day 2 and were continued for next 14 days.

The results of the study are summarized as follows:

1. The body weights (g) in the control group 1 were significantly ($p<0.05$) higher as compared to the other groups at respective time intervals throughout the experiment. The body weight in control group 2 (colitis-induced) was significantly ($p<0.05$) lower as compared to group 1 on 14th day. The weights in groups 3 and 4 were significantly ($p<0.05$) lower as compared to group 1 at the end of 7th day. The groups 3 showed significant ($p<0.05$) increase in the body weights compared to group 2 at the end of 14th day, while group 4 showed a significant ($p<0.05$) decrease in the body weight compared to remaining groups at the end of 14th day (197.4 ± 4.3)
2. The concentration of interleukin-10 (pg/mg tissue) in colon revealed a significant ($p<0.05$) reduction in group 2 as compared to group 1. Groups 3 and 4 showed a significant ($p<0.05$) increase in IL-10 concentration as

compared to group 2, but significantly ($p<0.05$) decreased as compared to group 1.

3. The concentration of TNF-α (pg/mg tissue) in colon revealed a significant ($p<0.05$) rise in group 2 as compared to group 1. Groups 3 and 4 showed a significant ($p<0.05$) decrease in TNF-α concentration as compared to group 2, but significantly ($p<0.05$) increased as compared to group 1.

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