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PHARMACOLOGICAL INVESTIGATION OF ASPARAGUS RACEMOSUS WHOLE PLANT EXTRACT ON TNBS INDUCED ULCERATIVE COLITIS IN RATS

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ABSTRACT

Background: Ulcerative colitis (UC) is a chronic inflammatory bowel disease characterized by mucosal inflammation and ulceration. Current pharmacological treatments often have significant side effects. Asparagus species are traditionally recognized for their anti-inflammatory and antioxidant properties, suggesting a potential therapeutic role in UC. This study aimed to investigate the pharmacological effects of a specified Asparagus plant extract (APE) on 2,4,6-trinitrobenzene sulfonic acid (TNBS)-induced ulcerative colitis in a rat model and to elucidate the underlying mechanisms. **Objective:** the purpose of this study was toinvestigate the effects of asparagus racemosus on TNBS-induced ulcerative colitis. **Methods**: rats were randomly divided into five groups: a normal control group, a disease control group (TNBS-induced colitis), a standard treatment group (e.g., sulfasalazine), and two APE treatment groups (low and high doses). Colitis was induced by intra-rectal instillation of TNBS dissolved in ethanol. APE was administered orally once daily for [7 -11] days. Colonic damage was assessed by evaluating the Disease Activity Index (DAI), macroscopic inflammation score, and colonic weight/length ratio. Biochemical analysis included measuring the levels of pro-inflammatory cytokines and oxidative stress markers while quantifying antioxidant enzymes. Histopathological examination of colon tissue was performed to assess mucosal integrity and

inflammatory cell infiltration. **Result**: the study results revealed that treatment of rats with AR significantly decreases DAI scores, colon weight etc.

KEYWORDS: asparagus racemosus, ulcerative colitis, TNBS, asparagus plant extract, free radical.

INTRODUCTION

The aetiology, pathogenesis, and development of inflammatory bowel disorders (IBD) have baffled numerous gastroenterologists and immunologists throughout the world. IBD is a collection of composite intestinal illnesses that affect the colon and small intestine. IBD is an illness that has an enigmatic aetiology and primarily refers to ulcerative colitis and Chron's disease, both of which include severe GI tract inflammation. Although evidence suggests that the extended inflammation is a result of the immune system ambushing the harmless microorganisms that cause inflammation, IBD is frequently thought of as an autoimmune condition.

The condition known as ulcerative colitis causes the large intestine to become inflamed. which affects the colonic mucosa and causes ulceration that extends proximally and affects the entire length of the colon. The colon and rectum are most commonly affected by ulcerative colitis, which may result from an overactive immune system. Bloody diarrhoea, nausea, loss of appetite, loose and frequent bowel motions, stomach pain, weight loss, and nausea are just a few of the symptoms that might occur. There may be a number of less obvious causes for ulcerative colitis. Although the cause of ulcerative colitis is unknown, a growing body of research suggests that "a variety of immunogenic, genetic, and environmental factors contribute to the initiation and progression of the colitis."

The most common areas of the Gl tract affected by Chron's disease are the small intestine and colon, although it can affect any part of the GI tract, from the mouth to the anus, and it can affect the full thickness of the bowel wall. "Over time, the Chron's severity scale might range from mild to profound. The most typical symptoms include "diarrhoea, abdominal cramps, blood in stools, fever, fatigue, loss of appetite, weight loss," and they depend on where the disease is located.

Although the exact cause of ulcerative colitis is still unknown, research indicates that it is caused by improperly controlled intestinal immune responses that are controlled by complex

interactions between the host genome and intra luminal bacteria. Lymphocytes, macrophages, and other immune system cells are present in the lamina propia.

It can be difficult to treat ulcerative colitis because of its complicated aetiology. IBD patients are more likely than the general population to acquire colorectal cancer. "Ulcerative colitis is currently treated with pharmacotherapy, which includes immunosuppressive and anti-inflammatory drugs like corticosteroids, salicylates (sulfasalazine, 5-aminosalicylic acid), and in recent years, biologics like infliximab [IFX] and adalimumab.". The symptomatic alleviation after prolonged treatment is frequently disappointing, despite the fact that these therapeutic drugs could block the inflammatory response by down regulating the inflammatory mediators.

The plant used in this study is Asparagus racemosus belonging to family Lilliacea. Some of the important properties are Anti-inflammatory, Nerve tonic, Anti-cough, Anti-oxidant, Anti-diabetic, Anti-ulcer.

Hence this study was designed to study the molecular mechanism action of Asparagus racemosus on TNBS induce Ulcerative colitis in animal model.

Rats are given TNBS and ethanol intrarectally, with the ethanol disrupting the function of the intestinal barrier. When TNBS and ethanol are introduced, a cell-mediated response occurs that reflects a Thi inflammatory response and causes the release of several pro-inflammatory cytokines.

MATERIALS AND METHODS

1. Data source :- from insilico approaches and animal experimental studies.
2. Instruments :- Rotary apparatus, soxhlets, centrifuge, uv spectrophotometer, tissue homogeniser, weighing balance.
3. Chemical and reagents:-TNBS, sulfasalazine, methanol.
4. Software used :- Autodock 4.2, Discovery studio visualizer 2019, Marvin sketch, Cytoscape 3.7.2, Graph pad prism 9.

IN- SILICO METHODS

Network pharmacology

Methodology Identification of phytocompounds and their target identification With the aid of a thorough literature review and the mining of public databases like Dr. Duke's DB and

PCIDB (Phyto-Chemical Interactions DB), a dataset of phytochemicals found in Asparagus racemosus was created. BindingDB estimated the probable targets of each phytocompound with a probability score of 0.5. "To identify the gene IDs of protein targets, UniProt was used.".

Retrieving of DM targets and dexamethasone modulated proteins in ulcerative colitis.
By employing the keywords "ulcerative colitis" and the species "homo species," conventional medications that target therapeutic targets implicated in the pathophysiology were chosen from the literature and the Therapeutic Target Database" (TTD). Further research was conducted on "protein targets modulated by dexamethasone to induce ulcerative colitis and dexamethasone-induced ulcerative colitis and were selected."

Pathway enrichment and network construction

The set of target proteins affected by TNBS and phytoconstituents were entered into STRING 10.5 and the pathways affected by dexamethasone and phytocompounds were found using the "Kyoto Encyclopaedia of Genes and Genomes pathway" ("KEGG Pathway") database. "Finally main signalling enriched pathways associated with the pathogenesis of DM was identified, and dexamethasone and active ingredients with their respective interacting targets were created and submitted to cytoscape" 3.7.2 software to construct, visualise, and analyse "target-pathway" and "compound-target-pathway" interaction networks.

Compound -target network

In order to identify corresponding protein targets modulated by the phytoconstituents of Asparagus racemosus, the data of active ingredients and their interacting targets were created and submitted to Cytoscape 3.7.2 software to construct, “visualise and analyse the network”. “To explore the relationship between phytocompounds and protein targets of DM compound”- target network was constructed, visually analysed and screened by using Cytoscape 3.7.2.

Extraction procedure

The leaves of Asparagus racemosus Where collected and washed carefully with distilled water, kept for sun dry covered with cotton cloth for 7 days, leaves were crushed and used for further extraction process. Soxhlets apparatus is used for extraction, thimble of crushed leaves were prepared for which 99% methanol is used. Collected marc is evaporated with

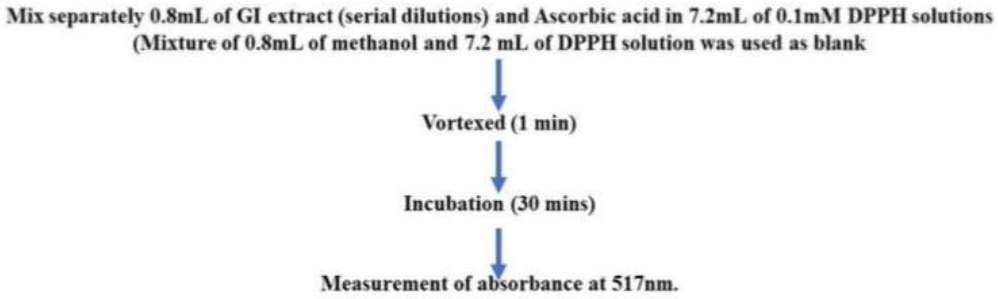
rotary evaporator at 400c, the sticky extract was poured in petri plates to remove excess moisture with the help of water bath and the extract is used for further animal studies.

Antioxidant activity

1. DPPH assay

- Preparation of Stock solutions: "Dissolve 10mg of GI extract in of 10 ml water and 10mg of Ascorbic acid in ml of methanol".
- From above stock solutions, prepare different concentrations (serial dilutions) 50, 100, 200, 400 and 800µg/ mL of GI extract and ascorbic acid".
- Solvent: Distilled water
- Preparation of 0.1mM DPPH solution: 11.7 mg of DPPH in 300ml of methanol.

Procedure



% Inhibition was calculated by following formula:

$$\textbf{\% inhibition} = \frac{\text{Abs (Control)} - \text{Abs (test)}}{\text{Abs (Control)}} \times 100$$

Ulcerative Colitis induction:- Animal after Acclimatization of 7 days were grouped and induction of ulcerative colitis is done as per the method of Tomasello et al. with certain modification.

Procedure: each animal is kept for 24 hour of fasting prior to induction. Animal were anaesthetized by sodium thiopentone IP, a dose of 50mg/kg TNBS dissolved in 50% of ethanol is instilled in colon with the help of rubber catheter. Catheter is inserted 8cm adjacent to anus so it can reach colon part easily. after the dose of TNBS rats were held upside down

with tail for 60 second to avoid leaking out of TNBS animal were transferred to their cages and had free access to food and water, treatment is started after induction of ulcer for a period of 21 days.

Ulcer index (UI):- Utilizing the method described by Dengizet al., a colon sample is cleansed, pinned to a whitesurface, the ulcer area is measured, and a formula is employed to calculate the ulcer index. UI is calculated using the formula, UI [Ulcerated area / Colon area] x 100

PARAMETER TO EVALUATE

PHYSICAL PARAMETERS

Body weight (70):- Body weight of individual rats were measured before the start of treatment, followed by change in body weight for every 7 days till the period of 21 days. Percentage body weight is calculated by using below formula. RBW=ABT (g) / IB (g) ×100 RBW-relative body weight ABT (absolute body weight)-weight before start of treatment IB (initial body weight)-weight at the start of treatment.

Stool consistency (71):Stool consistency is measured with the help of scale in which grade is given from 0 to 3 0- Normal stool, rigid as normal 1- Loose stool, pellet with moisture, in shape 2- Loose stool, with much moisture, shapeless 3- Watery or diarrhoea with blood.

Food intake:-The food intake was taken for every 24 hours for a period of 21 days.

Bleeding in faeces:-For measurement of faecal bleeding, grade of 0 to 2 is given. 0-no bleeding 1-occult bleeding 2-gross bleeding (naked)

Ulcer index:- Ulcer index is calculated by using the procedure as per Dengizet al, ulcerative colitis sample is washed and pinned on white surface background, ulcer area is determined and formula is used to determine the ulcer index UI = [Ulcerated area / Total area of colon] x100

BIOCHEMICAL PARAMETERS

Estimation of biochemical parameters: Colonic samples were homogenized using ice cold 0.1 M phosphate buffered saline. Aftercentrifugation the supernatant was used for various antioxidant assays. MPO activity wascarried out according to. et al. CAT. & GSH. levels were estimated using ELISA plate reader. SOD and MDA level (marker of lipid

peroxidation). were estimated spectrophotometrically. NO production was also accessed as given by green et al. method. using ELISA plate reader. ALP level was estimated on clinical chemical analyser (name of analyzer) and results were expressed in IU/L.

Reagents

- Tris-HCL Buffer mixture: (1.5137 g of Tris HCL+0.093g of EDTA in 500 ml distilled water) adjust the pH 8.5
- Pyrogallol: 50 mg pyrogallol +10 ml distilled water.

Sr. No	Reagents	Blank solution	Control solution	Test solution
1	Tris – HCI buffer	5.8 ml	5.8 ml	5.8 ml
2	Pyrogallol solution		0.2 ml	0.2 ml
3	Liver homogenate	--	--	20 µl

After completion of procedure measure the absorbance of solution at 420nm. Absorbance was measured at 2 different intervals 60 mins and 120 mins.

RESULTS

Mining of phytoconstituents and their related target prediction

Total, 104 phytoconstituents from Asparagus racemosus were identified through extensive Dr/ Dukes online server, IMPPAT database and literature review. Canonical smiles of each phytoconstituents were retrieved from PubChem database. After eliminating ovelaps, 9-phytocompounds of Asparagus racemosus predicted to modulate 164 protein targets out of which 12 targets are found to be highly associated 6-pathway of ulcerative colitis.

Phytoconstituents	Molecular weight	NHBA	NHBD	Mol LogP	Drug likeness score
Stigmasterol	412.37	1	1	7.74	0.62
Tretinoin	300.21	2	1	6.25	0.71
Beta-sitosterol	414.39	1	1	8.45	0.78
Donepezil	329.21	4	0	4.73	1.76
Calycosin	284.26	5	4	-0.39	0.55
Quercetin	302.23	7	5	1.19	0.52
quercetin-3-rhamnoside	610.5	16	10	-1.99	0.78
Gallic acid	170.12	5	4	0.78	-0.22
Cardol	320.5	2	2	8.51	-1.04

Mining of TNBS modulated protein molecules in Ulcerative colitis - Totally 12 target were highly modulated by TNBS that are potentially responsible for the development of ulcerative colitis were retrieved from gene card database and literature review.

Enrichment analysis of phytoconstituents protein targets - The molecular mechanism pathway enrichment analysis of targets of phytoconstituents was found to involve in 112 molecular pathways. Among 112 pathways, 7 were associated with ulcerative colitis.

KEGG Pathway	Description pathway	Count in gene set	False discovery rate	Gene codes
hsa04668	TNF signaling pathway	112	5.75E-27	MAPK1, NFKB1, NOS2, OPRD1, RAF1, KRAS, MAPK3,ESR1,EGFR,AR,SRC
hsa04010	VEGF signaling pathway	288	4.96E-15	MAPK1, MAPK14, KDR, TP53, EGFR, CASP3,IL2
hsa04217	HMG signaling pathway	149	3.54E-17	TNFSF10, IL1A, STAT3, TNFRSF10B, GLUD1 , AIFM1
hsa04151	P13-Akt signaling pathway.	350	5.12E-05	MAPK1, EGFR, TP53, EGFR, AKT1, SYK
hsa04660	P13K-Akt signaling pathway	101	2.97E-18	MAPK1, NFKBIA, NFKB1, IL2, IFNG, MAPK14, IL4
hsa04066	Pathways in cancer	106	2.48E-04	MAPK1, EGFR, NOS2, AKT1, VEGFA, PRKCA
hsa04657	IL-17 signaling pathway	92	3.64E-18	MAPK1, NFKBIA, CSF3, CCL2, NFKB1, IFNG
hsa04659	Th17 cell differentiation	101	2.24E-17	MAPK1, IL2RB, NFKBIA, TGFB1, NFKB1, IL2
hsa04370	HIF1 signaling pathway	57	5.81E-14	MAPK1, NFKBIA, CSF3, EGFR,AR , IFNG
hsa04657	IL-17 signaling pathway	92	2.65E-05	MAPK1, MAPK14, CASP3, PTGS2, TNF, ESR1,EGFR,
hsa04621	IG1FR signaling pathway.	174	0.0006	MAPK14, MAPK1, TNF, NFKBIA

Gene enrichment analysis of the proteins modulated by phytoconstituents

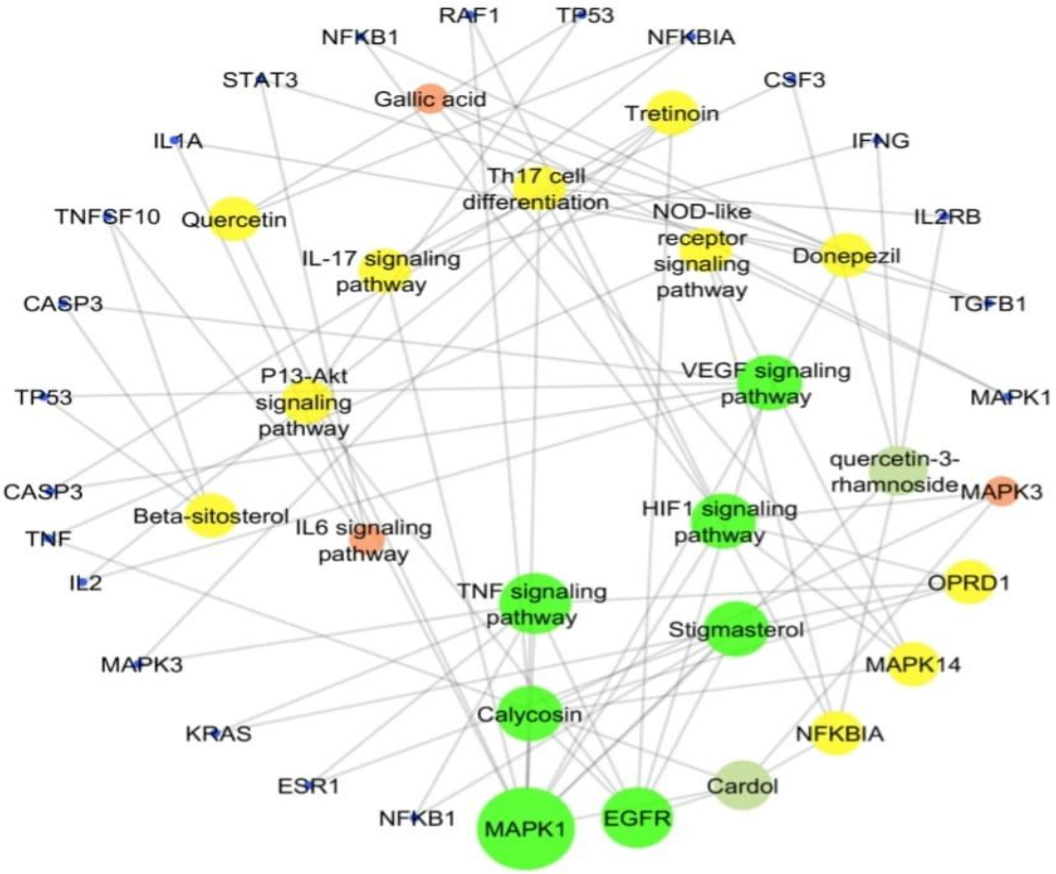


Fig no: Network interaction between common pathways and common modulated targets of TNBS and phytoconstituents of Tridax Procumbens involved in the pathogenesis Ulcerative colitis.

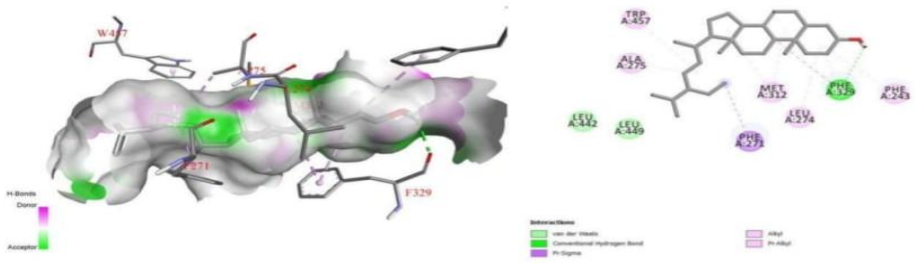
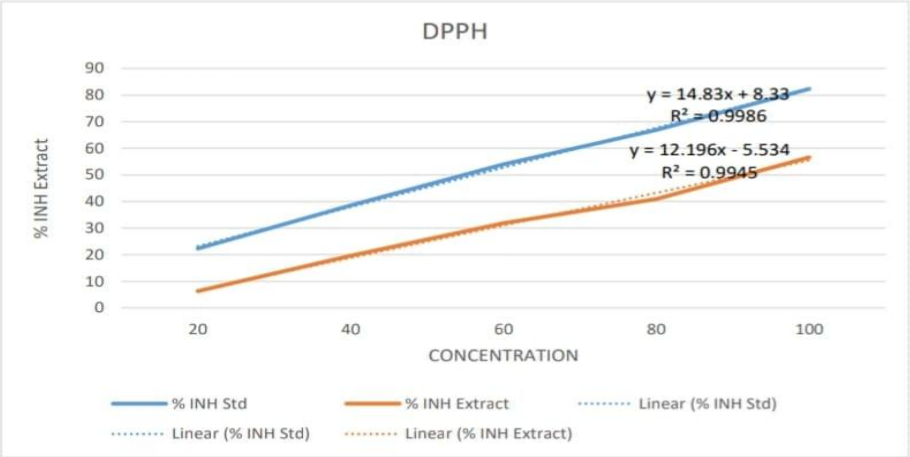


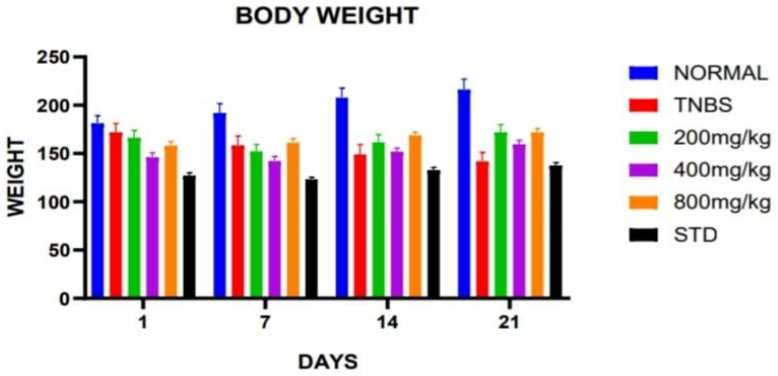
Figure No. : 3D and 2D image of highly modulated Calycosin with MAPK protein. green bond indicates H-bond interaction(s) whereas rest of the other bonds indicates hydrophobicinteractions.

DPPH scavenging assay of ascorbic acid and AR extract.

Sl. No	Conc	% INH STD	% INH LA EXTRACT
1	20	22.3±0.455	6.27±0.17
2	40	38.6±0.22	19.6±0.27
3	60	54.0±0.26	31.9±0.48
4	80	66.9±0.87	40.9±0.51
5	100	82.3±0.46	56.6±0.21



EFFECT OF ASPARAGUS RACEMOSUS EXTRACT ON BODY WEIGHT IN TNBS INDUCE ULCERATIVE COLITIS RATS



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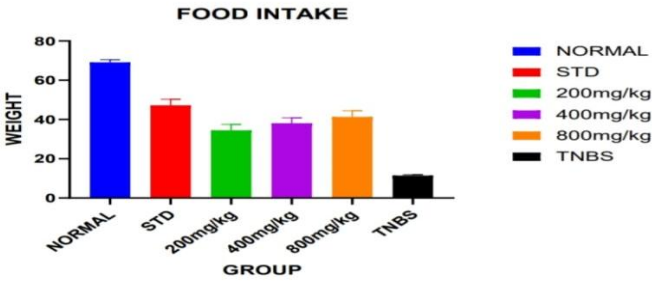
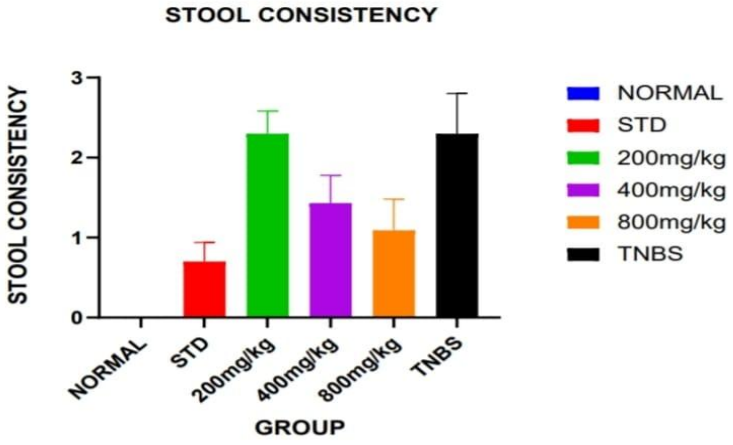
Data are analysed by two way ANOVA, followed by Bonferronis multiple comparison test and is expressed in Mean±SEM. * P< 0.001 vs normal group.

EFFECT OF ASPARAGUS RACEMOSUS EXTRACT ON FOOD INTAKE IN TNBS INDUCE ULCERATIVE COLITIS RATS



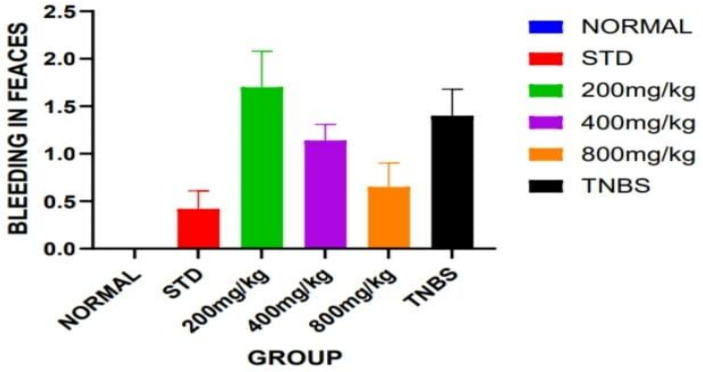
Data are analysed by two way ANOVA, followed by Bonferronis multiple comparison test and is expressed in Mean±SEM. * P< 0.001 vs normal group.

EFFECT OF ASPARAGUS RACEMOSUS EXTRACT ON STOOL CONSISTENCY IN TNBS INDUCE ULCERATIVE COLITIS RATS



are analysed by two way ANOVA, followed by Tukeys multiple comparison test and is expressed in Mean±SEM. * P< 0.001 vs normal group.

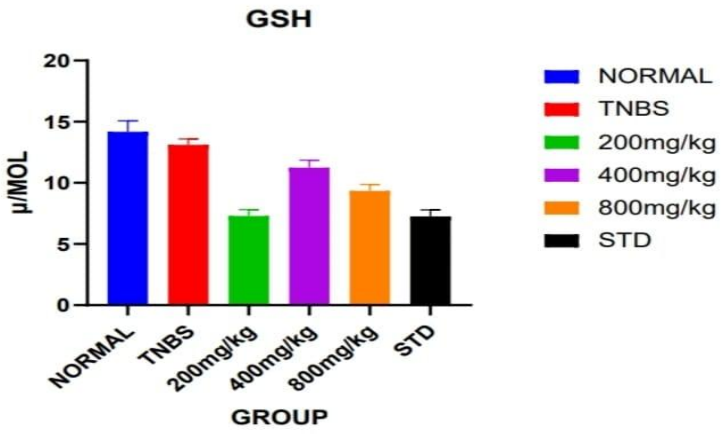
EFFECT OF ASPARAGUS RACEMOSUS EXTRACT ON BLEEDING IN FAECES IN TNBS INDUCE ULCERATIVE COLITIS RATS



Data are analysed by two way ANOVA, followed by Tukeys multiple comparison test and is expressed in Mean±SEM.

* P< 0.001 vs normal group

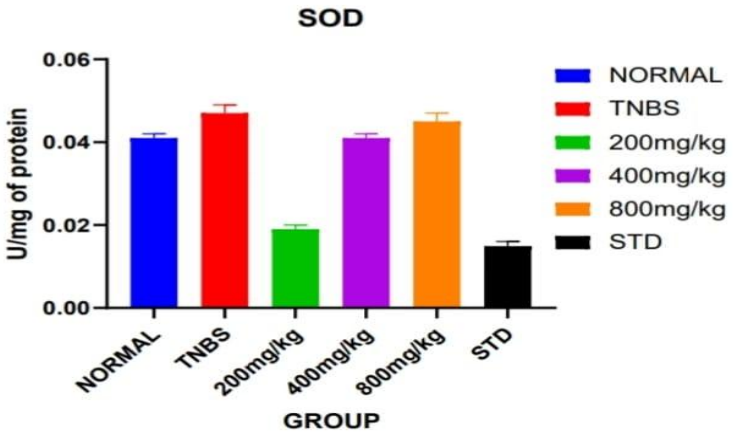
EFFECT OF ASPARAGUS RACEMOSUS EXTRACT ON GSH IN TNBS INDUCE ULCERATIVE COLITIS RATS



Data are analysed by one-way ANOVA, followed by Bonferronis multiple comparison test and is expressed in Mean±SEM.

- P< 0.001 vs normal control group
- @@@ p< 0.05 vs sulfasalazine
- %%% p<0.05 vs 400mg/kg
- $$$ p<0.05 vs 200mg/kg
- # p<0.001 vs TNBS group

EFFECT OF ASPARAGUS RACEMOSUS EXTRACT ON SOD IN TNBS INDUCE ULCERATIVE COLITIS RATS



Data are analysed by one way ANOVA, followed by Bonferronis multiple comparison test and is expressed in Mean±SEM.

- *P< 0.001 vs normal group
- # p< 0.001vs TBNS group
- %%% p< 0.001 vs 400mg/kg
- @ p<0.001 vs sulfasalazine

DISCUSSION

For ulcerative colitis conventional drugs include Amino salicylates, Corticosteroids, Antibiotics, Immuno modulators, Anti-tumour necrosis factor –Alpha, Calcineurine inhibitors. Selection of these drugs manly depends on severity of ulcerative colitis. (mild, moderate, severe) extend (proctitis, distal colitis, left sided colitis, pancolitis) and stage (active/remission) of the disease. such as mucosal lesions, loss of vascular pattern and friable mucosa. Remission is identified by resolution of symptoms and disappearance of active ulcerations The main aim of this study is to treat the UC, to achieve mucosal healing with reduction of clinical symptoms by Asparagus racemosus.

Stressful lifestyle and fast food consumption are the main reason for the development of UC, especially in younger adults. impairment of cell-mediated immune responses to new antigens occur hence impairment of age-related immunity of gut mucosa. This may be the reason for second peak onset of disease in old age. Immune system is affected by nervous at both systemic and gut mucosal levels. It is suggesting that stress induced changes in gastrointestinal inflammation may be mediated through hypothalamic-pituitaryadrenal (HPA) axis, alterations in bacterial-mucosal interactions and via mucosal mast cells and mediators such as corticotrophin releasing factor (CRF). In Ayurveda, Asparagus racemosus also known as queen of herb because of its strong rejuvenating, nurturing and stabilizing effect on excessive air, gas, dryness and agitation in body and mind.

Asparagus racemosus used for increasing the secretion of milk and improving appetite in lactating women. Ripe fruits of Asparagus racemosus cause abortion, tuberous roots with honey are given in dysuria, diabetes, and dysentery.

To know potential molecular mechanism Asparagus racemosus on ulcerative colitis, insilico approaches and wet lab experimentation were utilized. Networks including compound target-pathway network were constructed by utilizing Cytoscape version 3.7.2. The construction of

the network was based on the binding of active compounds to the correlative targets and the signaling pathways.

The study helps in finding of the therapeutic targets of bioactive compounds with help of swiss target prediction and Binding DB the probable values were fixed for above zero targets. Further, therapeutic target Database were used to retrieved target for disease of ulcerative coilitis. Venny 2.1 online server was used to find out common targets between phytoconstituents of plant and UC targets. For gene enrichment analysis selected genes were inserted in String database.

EGFR protein was found to be highly modulating followed by MAPK3,TNF and IL-2 with bioactive compound Calycosin fallowed by Stigmasterol, Donepepil bioactive with highest edge count through TNF signaling pathway.

There is growing evidence that activation of the TNF pathway is involved in the pathogenesis, progression, and oncogenic behaviour of human ulcerative colitis & colorectal cancer..[72]

Activation of the TNF signaling pathway leads to increased NF-kB activity, resulting in the expression of pro-inflammatory cytokines like TNF-α and IL-1β. These cytokines cause imbalanced secretion, leading to inflammatory responses and mucosal damage, contributing to ulcerative colitis (UC) development.

Evaluation of in-vitro antioxidant activity of Asparagus racemosus extract through DPPH assays, demonstrating its potential scavenge of free radicals.

Further wet lab experiment shows number of different parameter were evaluated such as physical and bio chemical parameter. In physical parameter, food intake, body weight, stool consistency, bleeding in faeces, ulcer index were recorded. When compared to control group all other group shown positive result for treatment, but in control group severity of diseases is maintained. Food intake was calculated on daily basis but for other parameter weekly data is maintained and ulcer index was calculated at day of dissection.

In bio chemical parameter SOD, GSH, MPO, catalase is evaluated. TNBS treated group exhibited significantly decrease in GSH and SOD level related to normal control group, when treatment with 400mg/kg and 800mg/kg it showed a good antioxidant capacity in comparison

with 200mg/kg Asparagus racemosus extract group. Significantly decrease in MPO level had been observed in TNBS treated group compare to normal control group with the dose dependent increase in MPO level has been seen in 200mg/kg, 400mg/kg, 800mg/kg BL extract treated groups compare to sulfasalazine treated group with ($p<0.001$). the result of catalase was recorded as same as SOD result.

CONCLUSIONS

This study demonstrates prophylactic treatment of Asparagus racemosus extract on TNBS induced UC. Due to its free radical scavenging property its capable to show prophylactic treatment when compared to treatment group through a reduction of UL biomarkers.

ACKNOWLEDGMENT

Working on research on PHARMACOLOGICAL INVESTIGATION OF ASPARAGUS RACEMOSUS WHOLE PLANT EXTRACT ON TNBS INDUCED ULCERATIVE COLITIS IN RATS was a source of immense knowledge to me, I would like to express my sincere gratitude to MR. SUNIL GANDE SIR for the guidance and valuable support throughout the course of the research work.

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