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Restoration of Intestinal MCP-1 and Protein Oxidation Products by *Spondias pinnata* Bark Extract in Etoposide Induced Rat Gut Mucositis

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KEYWORDS

AOPP,
COX-2,
MCP-1,
Mucositis,
Spondias pinnata

ABSTRACT:

Introduction Chemotherapeutic agents, despite their anticancer properties, can cause mucositis by damaging normal cells. Protecting these cells during therapy is crucial.

Objectives: Present study aims to assess the impact of Spondias pinnata (SP) bark extract on Monocyte chemoattractant protein-1, Cycloxygenase-2, Altered Oxidative protein products, and Superoxide Dismutase levels in an etoposide-induced mucositis rat model, comparing it with normal control and etoposide control groups. This evaluation is essential for understanding the protective effects of SP extract during chemotherapy.

Methods: 78 Albino Wister rats were categorized into 13 groups including normal control group, etoposide control, SP control, etoposide treated with SP bark extract groups, each of these groups were sub-divided based on daily treatment (24, 48, 72 & 96 hr). Mucositis was induced by single dose of intra-peritoneal injection of Etoposide (45mg/Kg body wt.). Time of injection of etoposide was considered as zero hr and the parameters were studied by sacrificing the animals on daily basis, until 96hr. SP dose of 200mg/Kg body wt. was given to SP control and treated group.

Results: SP bark extract led to moderate upregulation of Monocyte chemoattractant protein-1 ($p=0.019$) and Superoxide Dismutase ($p=0.0000542$) levels at 96 hr. Additionally, Altered Oxidative protein products ($p=0.0381$) and Cycloxygenase-2 levels decreased significantly.

Conclusions: These finding looks promising in alleviating the metabolic imbalance due to etoposide and SP bark extract can be used as an adjuvant during chemotherapy to protect the normal cells and could help them improve their quality of life.

1. Introduction

Mucositis is an unavoidable and commonest concern after chemotherapy. It is characterized by the painful inflammation of the mucosal lining of the GI tract, which confines even the basic activities of the patient like the routine food intake and also affects the therapeutic management. Almost all chemodrugs cause mucositis. Etoposide is one of the common chemotherapeutic agents used to treat cancer of lungs, prostrate, colon etc., via inhibition of topoisomerase II, by arresting the resealing of DNA breaks. As like any other chemotherapeutic regimen, etoposide also causes many ill-effects on normal tissue [1]. Sonis was the first to pathologically define mucositis and has classified it into 5 stages which hints us about the various molecular mechanisms that could be involved during mucositis [2, 3]. During the initiation and signal transduction phase of mucositis, different types of reactive oxygen species (ROS) are generated and are the major causative of the vulnerability. These further can initiate amplification of the stages involved in mucositis including infiltration of gut microbiota [4]. In addition to the altered immunological responses, various proteins and transcriptional factors at gene level can trigger the severity of mucositis [5].

Monocyte chemoattractant protein-1(MCP-1), otherwise called as C-C motif chemokine ligand-2 (CCL-2) is a protein belonging to the class of CC chemokines,

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which follows CC motif like structure. Studies have revealed that it leads the migration of monocytes, macrophages, and other chemokines to the site of inflammation, thus helping in bringing about immune responses [6]. Moreover MCP-1 or CCL-2 is expressed in various cells like endothelial cells, smooth muscle cells, epithelial cells, astrocytes, T cells, tumor cells etc., [7]. Further, studies in mice have deduced that MCP-1 can influence the gut microbiome in bringing about age-related inflammatory response [8].

ROS generated due to various mechanisms during mucositis, augment inflammation. One of the conventional forms of the free radical produced during chemotherapy induced mucositis is the superoxide radical (O2 -1). In this regard, superoxide dismutase (SOD) is one of the antioxidant enzymes, which actively converts superoxide radical to hydrogen peroxide and is subsequently reduced to water [9]. SOD provides substantial antioxidant effect during the chemotherapeutic drug metabolism, which functions as gatekeeper for the maintenance of cellular redox environment. SOD mimetics have been used for modifying the chemotherapeutic toxicities which are now a newer approach in oncology [10, 11]. SOD levels tend to modify whenever there is noticeable enhancement of cellular toxicity, DNA breakage, protein carbonylation, membrane lipid peroxidation and advanced oxidative protein products [12].

Advanced oxidation protein products (AOPP) belong to the family of oxidated protein compounds, are the modified proteins due to oxidative stress. They have been linked to various clinical conditions including metabolic syndrome, liver failure, chronic kidney disease, cancer etc., and have said to mediate through bcl-2/ Bax apoptosis pathway and are NADPH oxidase dependent [13, 14]. In one of the studies on intestinal bowel disease (IBD), high levels of AOPP in colon has been observed which demonstrates a strong correlation with the condition and this could be attributed to the intestinal dysbiosis [15]. However, the significance of the association of AOPP in mucositis is yet to be determined.

Cyclooxygenase-2 also known as prostaglandin synthase is an inducible enzyme and a well-known mediator of inflammation [16]. High levels of COX-2 are implicated in various malignancies [17]. COX-2 inhibitors are widely used in combination with chemotherapeutic agents to reduce the pain and inflammation [18]. However, the effect of chemotherapeutic agents alone on COX-2 activity during mucositis is the point of interest and is a part of this study.

Study on mucositis is on the limelight, as chemotherapy is marked by diarrhoea /constipation, ulceration, inflammation, and recurrent infections of the GIT, which imposes a greater impact on even the basic needs of the patients like food intake, management of the condition and socio-economic status, that urges supplementary or palliative care [19]. Hence, it needs a remedy which is more economical, efficient, and promising to reduce the physiological, psychological, and socio-economic burden of the patients.

Spondias pinnata is a deciduous tree found along the coastal area and western ghat sections Of Bharath (India). The fruit either tender or ripen is used as a local vegetable and the bark is rich with medicinal properties. It is known to have antimicrobial, anti-inflammatory, anti-analgesic, and anti-pyretic activity [20]. Thus, in this regard, the present study is an attempt to evaluate the effect of Spondias pinnata bark extract (SP) on normal cells in Etoposide induced mucositis followed by treatment in albino Wistar rats.

2. Objectives

Objectives of this research work was to study

1. The preventive/ protective effects of *Spondias pinnata* bark extract on MCP-1 levels , AOPP levels, SOD activity and COX activity in the intestinal tissue of Etoposide induced mucositis rat model.

2. to study the effect of SP on oesophageal cells in etoposide induced mucositis rat model.

3. Methods

This experimental study was conducted after obtaining institutional animal ethical clearance (No: KMC/MNG/IAEC/05-2018) Albino wistar rats (n=78) with average 200-220 g of bodyweight were the study subjects. They were maintained in temperature and humidity-controlled environment, fed with standard rat food and water ad libitum , housed in Propylene cages with husk as bedding material was used which was changed on alternate days.

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Animals and the grouping:

- There were 13 groups with 6 animals in each group (n=6).
- Mucositis was induced by intraperitoneal administration of a single dose of Etoposide (65mg/Kg body weight) in mucositis (EP) and mucositis treated (EP+SP) groups. This was considered as 0 hr.
- SP was administered orally using orogastric gavage (daily dose of 200mg/kg body weight until 96 hr) to the SP control and mucositis treated (EP+SP) groups.
- The groups were sub-divided into Normal control, EP-24, EP-48, EP-72, EP-96, SP-24, SP-48, SP-72 , SP-96 EP+SP-24, EP+SP-48, EP+SP-72 & EP+SP-96 based on the time of sacrifice.

Histological Analysis:

Animals were sacrificed by cervical dislocation. Part of the oesophagus was dissected out, washed in ice cold PBS and was placed in 10% formalin for histological assessment. H&E-stained slides were used for the histological analysis.

Biochemical estimations:

Intestinal section was collected for the assessment of biochemical parameters. A 10% homogenate was prepared using PBS, centrifuged and the supernatant was preserved at -20°C until analysis.

1. Estimation of SOD:

The estimation of the superoxide dismutase enzyme was carried out by the pyrogallol autoxidation method of Marklund and Marklund based on the ability of superoxide dismutase to inhibit the autoxidation of pyrogallol in the presence of EDTA [21]. For the test sample, 0.1 mL of tissue homogenate was treated with 2.5 mL of Tris –HCl buffer of pH 8.2, 0.1 mL of 1mM EDTA (Ethylene Diamine Tetra acetic acid), 0.5 mL of 1mM DTPA (Diethylene Triamine Penta acetic acid) and 0.1 mL of 0.02mM pyrogallol, change in autoxidation of pyrogallol was observed for 3 min for each sample at 420 nm. Control sample was run in the same way, without taking tissue homogenate but taking 2.6 mL of Tris-HCl buffer.

2. Estimation of AOPP:

The levels of advanced oxidation protein products (AOPP) was estimated by the modified method of Witko et al. [22] using potassium iodide & glacial acetic acid and read against a reference blank at 340nm using a spectrophotometer.

3. Estimation of MCP-1 & COX-2 activity:

Enzyme-linked immunosorbent assay kit for Rat MCP-1& COX-2 was procured from ELab science, UK.

Statistical Analysis:

Data was analysed using EZR software version 1.54. Results were expressed as mean ± SD or median with interquartile range. Analysis of the obtained data was performed using Independent sample t test for the data showing normal distribution, data following non-normal distribution was analysed by Kruskal-Walli's rank sum test/Mann Whitney U test. p-value < 0.05 was considered statistically significant.

4. Results

SOD activity:

The present study result analysis shows a borderline decrease in the SOD activity (Figure 1), in the EP control (148.93 ± 25.64) group than that of the normal control (142.12 ± 8.26) during the study period. Enzyme activity was dropped down from 148.93 ± 25.64 (0hr) to 101.39 ± 47.82 (96hr) after the administration of EP, along the time with a maximum fall in the 96 hr group with a small increase in the activity at 24 hr. However, the decrease was statistically not significant, and the decrease could be probably due to the body mechanism to act against oxidative stress developed after the administration of EP. However, the SOD activity has been regained in the treated group (EP+SP) and is maintained either at normal level / above in all the study groups. In comparison with normal control and SP control group, the SOD activity was 131.76 ± 4.99 and 129.60 ± 5.79 in EP+SP the 72hr and 96hr group and was statistically significant with a p-value of 0.030 and 0.0161, respectively. The 48hr and 96hr SP treated group showed a significant increase in

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Table 1: Baseline values of the analysed parameters				
Groups	**SOD** (U/g Tissue) **(Mean ± SD)**	**MCP-1** (ng/ml) **[Median (Q1,Q3)]**	**AOPP** (µmol/L) **(Mean ± SD)**	**COX-2** (ng/ml) **[Median (Q1,Q3)]**
Normal	142.12 ± 8.26	0.134 (0.098,0.14)	0.15 (0.12,0.27)	0.365 (0.31, 0.47)
EP-24	148.93± 25.63	0.134 (0.10, 0.152)	0.09 (0.05, 0.12)	0.92 (0.699, 1.00)
EP-48	130.16± 14.32	0.07 (0.04, 0.11)	0.36 (0.28,0.91)	0.96 (0.9, 1.11)
EP-72	137.96 ± 3.66	0.101 (0.09, 0.31)	0.22 (0.08, 0.4)	1.05 (0.99, 1.10)
EP-96	101.39± 47.82	0.08 (0.06, 0.10)	0.13 (0.06, 0.14)	0.49 (0.4, 0.6)
SP-24	133.85 ± 6.67	0.13 (0.105,0.152)	0.17 (0.13, 0.5)	0.34 (0.215, 0.76)
SP-48	131.06 ± 9.95	0.14 (0.12, 0.15)	0.16 (0.03, 0.32)	0.179 (0.07,0.44)
SP-72	131.76 ± 4.99	0.146 (0.04, 0.22)	0. 08 (0.06, 0.33)	0.15 (0.12, 0.22)
SP-96	129.60 ± 5.79	0.109 (0.072, 0.13)	0.05 (0.05, 0.07)	0.13 (0.11, 0.25)
EP+SP-24	142.82± 32.96	0.134 (0.09, 0.145)	0.133(0.09, 0.16)	0.31 (0.18, 0.87)
EP+SP-48	167.65 ± 2.85	0.15 (0.07, 0.23)	0.09 (0.08,0.100)	0.62 (0.24, 0.71)
EP+SP-72	137.13± 37.08	0.13 (0.10,0.33)	0.07 (0.05, 0.27)	0.38 (0.381, 0.443)
EP+SP-96	159.94 ± 4.57	0.27 (0.21, 0.27)	0.03 (0.02, 0.05)	0.27 (0.15, 0.28)

Table 1: Data following normal distribution depicted as Mean ± SD, that which follows non-normal distribution given as Median (Q1, Q3)

Table 2: List showing the p- values for the comparison between 2 groups				
Groups	**SOD**	**MCP-1**	**AOPP**	**COX-2**
Normal vs EP-24	0.588	1	0.171	0.61
Normal vs EP-48	0.144	0.17	0.0823	0.329
Normal vs EP-72	0.333	0.93	0.662	0.24
Normal vs EP-96	0.094	0.11	0.42	0.537
Normal vs SP-24	0.15	**0.04***	0.53	0.937
Normal vs SP-48	0.079	0.32	0.93	0.31
Normal vs SP-72	0.031	0.818	0.93	**0.009***
Normal vs SP-96	0.016	0.58	**0.04***	**0.041***
Normal vs EP+SP-24	0.964	0.17	0.662	0.699
Normal vs EP+SP-48	**<0.001***	0.81	0.064	0.589
Normal vs EP+SP-72	0.77	0.63	0.699	0.748
Normal vs EP+SP-96	**<0.001***	**<0.05***	**0.038***	0.132
EP-24 vs EP+SP-24	0.77	0.28	0.41	0.76
EP-48 vs EP+SP-48	**<0.001***	0.17	**0.004***	0.2
EP-72 vs EP+SP-72	0.962	0.24	**0.004***	0.06
EP-96 vs EP+SP-96	**<0.05***	**0.01***	0.11	0.08
SP-24 vs EP+SP-24	0.614	0.42	0.31	1.0
SP-48 vs EP+SP-48	**<0.001***	1	1	0.24
SP-72 vs EP+SP-72	0.791	0.39	0.85	**0.01***
SP-96 vs EP+SP-96	**<0.001***	0.06	0.2	0.58
EP-24 vs SP-24	0.298	0.285	0.19	0.352
EP-48 vs SP-48	0.904	0.06	0.12	**0.04***
EP-72 vs SP-72	0.09	0.53	0.85	**0.04***
EP-96 vs SP-96	0.181	0.47	0.11	**0.017***

Table 2: Independent sample t-test done for analysis of SOD, Mann Whitney U test for MCP-1, AOPP and COX-2

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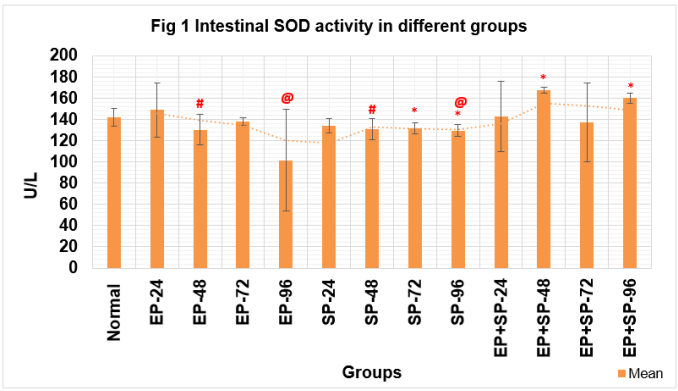

Fig. 1 depicting the intestinal SOD activity in different groups

* : significant p value (<0.05) in comparison with normal group
# : significant p value (<0.05) in comparison with EP+SP-48 group
@: significant p value (<0.05) in comparison with EP+SP-96 group

the SOD activity than the EP control with a value of 167.65 ± 2.85 and 159.94 ± 4.57, was statistically significant (p-value 0.0000542 and 0.00139, respectively) as from Fig 1.

MCP levels:

MCP-1 level in etoposide control showed a decrease than that of normal control 0.134 (0.098,0.14) though it was statistically not significant. In all the SP control groups, MCP-1 levels remained at the range of normal controls. In comparison with the normal control 0.134 (0.098, 0.14), the MCP-1 levels of SP treated mucositis EP+SP 96hr group, 0.270(0.21, 0.27) showed a moderate increase, however it remained statistically insignificant. (p value=0.07). The 96hr treated group (EP+SP) showed an increase in MCP-1 levels when compared with that of the 96hr EP control (Fig 2).

AOPP levels:

It is evident from Fig 3 that the levels of AOPP reached to maximum in EP control at 48hr. with a value of 0.36, (0.28,0.91). Further, treatment with SP showed a decrease in the AOPP 0.03 (0.02,0.05) at 96hr which was statistically significant (p= 0.038) compared to the normal control 0.15 (0.12,0.27). While comparing with corresponding EP controls, EP+SP,48hr group [0.09 (0.08,0.100)], as well as at 72 hr. [0.22 (0.08, 0.4)], a statistically significant (p=0.004) decrease in AOPP levels was observed.

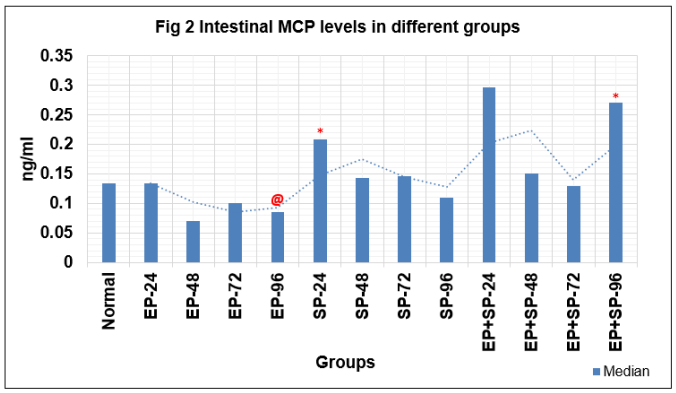

Fig. 2 depicting the intestinal MCP levels in different groups

* : significant p value (<0.05) in comparison with normal group
@: significant p value (<0.05) in comparison with EP+SP-96 group

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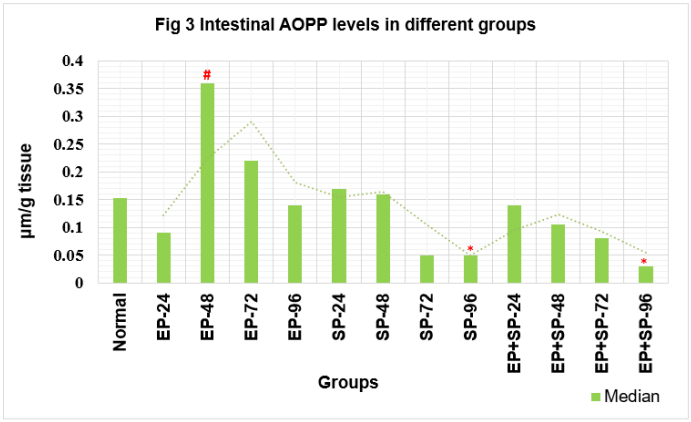

Fig. 3 depicting the intestinal AOPP levels in different groups
* : significant p value (<0.05) in comparison with normal group
# : significant p value (<0.05) in comparison with EP+SP-48 group

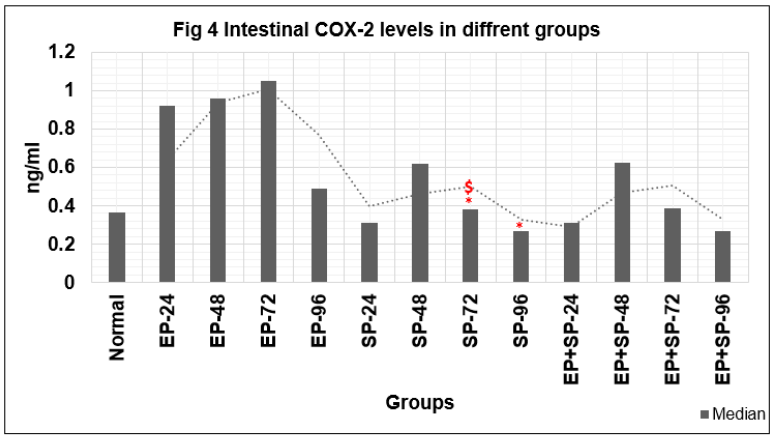

Fig.4 depicting the intestinal COX-2 levels in different groups
* : significant p value (<0.05) in comparison with normal group
$: significant p value (<0.05) in comparison with EP+SP-72 group

COX-2 activity:

COX-2 activity remained high in EP group vs all other groups and was reverted to normal in EP+SP (96hr). COX-2 levels though not significant, the trend observed is an interesting finding.

Histological analysis:

Histological evaluation showed that oesophagus was less vulnerable to EP exposure with minimal change in the cell architecture in all the groups except that of EP-96 group. At 96 hr post EP treatment, there was keratinization along with the degeneration of muscularis mucosa layer.

Discussion

Intestinal mucositis is a common dismay of any chemotherapy. Etoposide being an inhibitor of topoisomerase, acts rapidly on dividing cells of GI mucosa causing apoptosis by inhibiting DNA synthesis. Outcomes of our study agree with the findings mentioned

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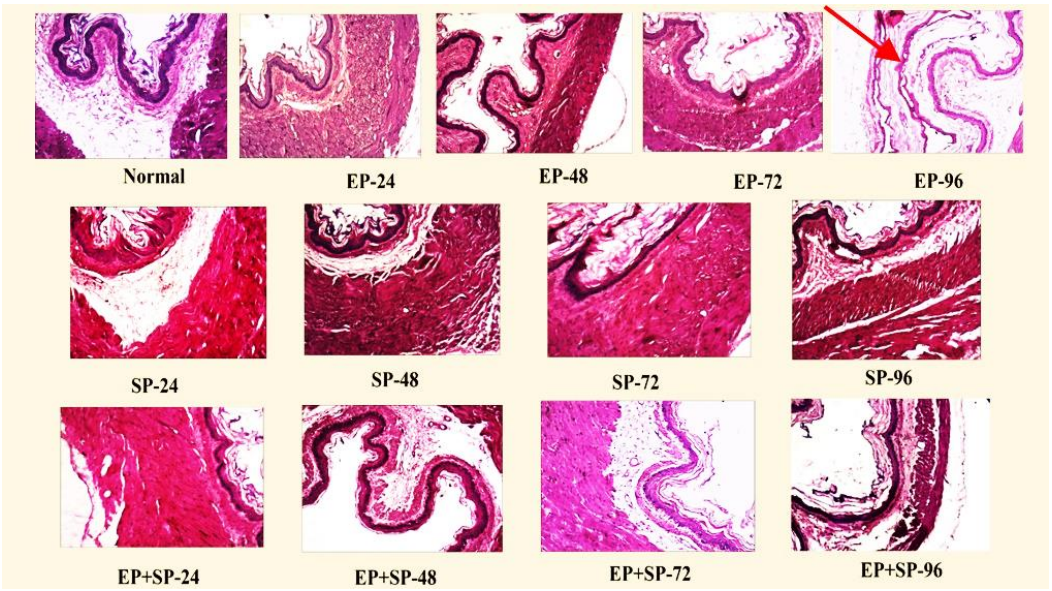

Fig.5 depicting the histology of the Esophagus in different groups
EP-96: Degeneration of muscularis mucosa seen (with red arrow)
EP+SP-96: Shows improved histological architecture.

in other studies with several other chemotherapeutic drugs on small intestine [23]. Histological observations during the study shows that oesophagus is less vulnerable to mucositis in comparison with other parts of GIT. During mucositis, because of the disruption of intestinal epithelial barrier, translocation of microbiota takes place and a shift from commensal to pathogenic observed by earlier studies. To some extent ROS is beneficial for the destruction of microbial pathogens through oxidative processes involving the activation of innate immune system via specialized immune cells, such as neutrophils or macrophages [24].

Effect of SP on MCP-1 levels:

Monocyte chemoattractant protein -1 or CCL2 is a crucial chemokine, that binds to the CCR2 receptor, can attract monocytes, macrophages, and lymphocytes. Along with other immunological activities it includes a subsidiary regulation of neutrophil relocation under infectious conditions [25,26]. One of the earlier study results indicate that endogenous MCP-1, protects rat intestine from bacterial toxicity which can occur during mucositis, as it was up-regulated [27]. We observed a decrease in MCP-1 levels in etoposide treated rats and an increased levels in EP+SP group. This result suggests the protective role of MCP-1 related to its ability to limit bacterial load. It has been stated that an enhanced bactericidal reaction to sepsis is linked to MCP-1 dependent recruitment of myeloid cells to the spleen and liver. In addition, one of the studies by Jia et al shows that MCP-1/CCL2 is key molecule in action during microbial invasion in different preclinical models of infection [28]. One of the earlier studies reported that recombinant MCP-1/CCL2 increasing bactericidal action via macrophages stimulation [29]. This could be the explanation for the observed enhancement in the MCP-1 activity after SP treatment and one of the protective effect of SP bark extract against mucositis, may be by reverting intestinal dysbiosis.

Effect of SP on COX-2 and SOD activities:

Activity of the COX-2, the inflammatory marker enzyme was decreased in the EP+SP group, and comparable to that of SP control group. Though insignificant, the pattern displays that the mucositis severity was reduced by the SP bark extract. This is in accordance with the many other studies [30]. and showing that SP bark extract is helpful in attenuating the severity of mucositis. Qualitative analysis of bark extract showed the presence of tannins, saponins, flavonoids, triterpenes and the beneficial effect of these components explains the anti-inflammatory properties is evident in the study. Another

study with Erythima speciosa leaves showed pronounced reduction in the COX-2 and PGE2 expressions which also lead to wound healing [31]. Similarly, Yagjin Shengjzi powder showed beneficial effect on oral ulcer healing because of the inhibition of COX-2 activity and inflammatory factors such as TNF-α, IL-6 etc.,[32]. A similar type of study by Ju Hasn Liu on 5-FU induced mucositis showed that Radix Aucklandiae herbal preparation also suppressed COX-2 activity and is one of the reasons for the improvement [33]. 5-FU induced mucositis study by Pepe G et al has been reported that the polyphenol content of the pomegranate juice is the reason for the observed recovery during the study [34]. Pronounced decrease in COX-2 activity was also evident in 5-FU induced mucositis was advocated by Saikosaponin-A [35]. Cysteine also reduced the oral mucositis induced by 5-FU by acting on the COX-2 activity [36]. All these prospects the beneficial effects of components of SP that would be useful in treating mucositis by targeting COX-2 activity.

The present study observations shows that SOD levels did not alter to large extent in the study group compared to that of controls and treated one. However, this could be due to the involvement/utilisation of superoxide radicals in invading bacterial since the variation in the SOD activity looks parallel to the changes in MCP-1.

Histological findings:

Histological changes in the esophagal tissue are only evident in mucositis group at 96 hr (EP-96). This shows that oesophageal cells remain less prone to the chemo-drug, which is an interesting finding and hints at dose dependent alteration of the tissues of the GIT.

Conclusion:

Present study shows a decrease in MCP-1 levels in etoposide induced mucositis group with a parallel increase in AOPP and COX-2 levels. Ingestion of SP bark extract helped to retain/regain the levels of these parameters to that of normal control in EP+SP group. Along with this a parallel decrease in AOPP and COX-2 levels in mucositis treated group (after SP bark extract treatment) is also seen, and the same remained elevated in etoposide control group.

This result advocates the protective role of Spondias pinnata bark extract by increasing MCP-1 to moderate levels, maintaining the SOD levels and by decreasing the oxidated protein products. All these observations also provide its ability to limit the events that upheaval during mucositis. This significant finding paves way for mechanistic analytics of the molecular mechanisms behind this effect.

Conflicts of interest:

The authors have no competing interests to declare that are relevant to the content of this article.

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