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ORIGINAL ARTICLE

In-vivo pharmacological Investigation of traditionally used *Buchanania lanzan* Spreng for the treatment of Oral Mucositis

Bhushan Muley*[1], Pankaj Masih[1], Neeraj Sharma[1]
Patel College of Pharmacy, MPU, Bhopal
*Corresponding Author's E-mail: - muley.b@gmail.com

ABSTRACT
Oral hygiene is an integral part of general health of a person. Oral disease can significantly affect the general wellbeing of a person by causing considerable pain and discomfort, thus affecting quality of life. Naturally occurring compounds is attractive as they are generally perceived to have fewer side effects compare to synthetic medication. Oral Mucositis are an open sore of the skin or mucus membrane characterized by inflamed dead tissue. It is a lesion on the surface of mucus membrane by a superficial loss of tissue. The anti-oral mucositis activity can be possible and different extracts may supports the Ethno medicinal claim about the use of traditional Buchanania lanzan in the treatment of oral disorder like tooth ache, wound, ulcer,
Keywords: Buchanania lanzan, Oral hygiene, Mucositis

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INTRODUCTION

Oral Mucositis is a debilitating inflammatory disorder varies in population between 20% to 80% depending upon dose, type and duration of systemic chemo or radiation therapy. Oral Mucositis causes high degree mobility for the affected person in the form of pain, local and systemic infection, and difficulty in oral hygiene measure [1]. Naturally occurring compounds is attractive as they are generally perceived to have fewer side effects compare to synthetic medication. Oral Mucositis are an open sore of the skin or mucus membrane characterized by inflamed dead tissue. It is a lesion on the surface of mucus membrane by a superficial loss of tissue. Common causes of Oral Mucositis include nutritional deficiencies such as iron, vitamins, poor oral hygiene, infections, stress, indigestion, mechanical injury, food allergies, hormonal imbalances, skin disease etc. It is an inflammatory mucosal destruction as a result of chemotherapy and/or radiation therapy, which in severe cases can impair patients' quality of life [2]. Moreover, mucosal infection and/or systemic involvement due to compromised immunity lead to delay or discontinuation of the treatment. Oral Mucositis is also known as oral ulcer, buccal ulcer, mucosal ulcer and aphthous ulcer. It can be painful while eating, drinking or brushing teeth. Depending upon size of ulcer it is of three types. Minor ulcer (2-8 mm) and usually clear from 10 days to two week. Major ulcer is a bigger and dipper sore and require several weeks to heal. Herpetiform ulcer is a cluster of dozens of smaller sores about the size of pinheads[3].Mucositis affects all gastrointestinal tract and oral cavity inducing patient pain, inability to eat, weight loss and local infection. Conversely, patients affected by an aberrant epithelial proliferation, as psoriasis, exhibit a reduction in mucositis incidence. In general old age, female gender, high bodyweight, a reduced clearance of drugs and genetic susceptibility are mucositis related development risk factors [4]. The World Health Organization (WHO) scale for oral mucositis (OM) evaluation accounts for objective criteria, such as the presence of either erythema or ulceration. These are functional criteria based on the ability of the patient to eat. A quantitative scale that assesses ulceration dimension is used by the Oral Mucositis Assessment Scales (OMAS). The Eastern Cooperative Oncology Group (ECOG) mucositis scale is reported in the common toxicity criteria guide in which mucositis severity is differently classified based on the anatomic site of development. Similarly, the

National Cancer Institute (NCI) provides in the Common Terminology Criteria for Adverse Event (CTCAE) mucositis severity measure scale based on anatomic site of development and on the kind of treatment, either chemo or radiotherapy [5-6].Mucositis development consists of a cascade of events that can be divided in five stages occurring consecutively and mechanistically linked. The injury of mucosa membranes, named mucositis initiation phase, is caused by either radio- and/or chemotherapy [7-9]. Patients, based on the duration and the extent of neutropenia, can develop bacteremia or septicemia, mainly caused, in OM, by streptococci and staphylococci. Mucositis is an acute event that mostly self-resolves as the anticancer treatment ends. At this stage the healing process is activated, during which stimuli from the sub mucosa extracellular matrix and mesenchyme promote tissue reepithelialisation [10].Ulcerative oral mucositis is colonized by oral micro flora and is sometimes complicated by local infection such as herpes simplex virus (HSV) infection and candidiasis. In patients who are immunosuppressed due to chemotherapy, these ulcerative lesions can provide a route for systemic sepsis, which is potentially life threatening [11]. Diagnosis of oral mucositis is usually made clinically, based on clinical appearance and a history of cytotoxic cancer therapy within the expected timeframe. The most common clinically relevant secondary infections of oral mucositis lesions involve Candida species fungi and HSV. These are more likely to be seen in patients who are immunosuppressed due to chemotherapy or in patients with hypo salivation due to RT [12].Oral Mucositis causes high degree mobility for the affected person in the form of pain, local and systemic infection, and difficulty in oral hygiene measure. The basic object behind the current research work is to investigate pharmacognostic, phytochemical and pharmacological activity of *Buchanania lanzan* bark for the treatment of oral mucositis. The present research work of different extracts of selected parts of *Buchanania lanzan* Spreng may open newer corner for the treatment of oral mucositis. The different solvent extracts may be formulated in the semisolid gel dosage form for the treatment of oral mucositis.

Material and Methods:

Extraction process of plant: *Buchanania lanzan* Spreng stem bark plant drugs were extracted sequentially with petroleum ether, ethyl acetate and ethanol using continuous hot extraction method i.e. Soxhalate extraction. The aqueous extract obtained by maceration with water for 24h.

Pharmacological screening: Wistar albino rats (180-220g) of either sex were used for experimental study. The animals were housed in cages at 25 ± 2ºC, and relative humidity (50 ± 5%) with 12 h light, and 12 h dark cycle. All the animals were acclimatized to laboratory environment for a week before the experiment. They were provided with free access to food and water ad libitum. The animals were cared and used in accordance with the CPCSEA guidelines and experimental protocols approved by institutional animal ethics committee of Madhyanchal Professional University, Bhopal, M.P. (PCP/CPCSEA/2021/01 dated 30.10.2021).

Acute toxicity studies of *Buchanania lanzan Spreng as* per OECD guideline: Acute toxicity studies of extracts of *Buchanania lanzan* Spreng were performed in Albino rat dose levels of 50, 200 and 2000 mg/kg as per OECD guide lines. The treated animals did not demonstrate any significant changes in behavioral pattern and exhibited normal activity. Also there were no clinical signs of tremors, convulsions, exophthalmos, salivation, diarrhea and lethargy.

In Vivo oral Mucositis Screening

Preparation of Test Compound and Standard Drug Test Compound: The *Buchanania lanzan* bark extracts was dissolved in sufficient quantity of water and was administered orally to rats at a dose of 10 mL/kg. Standard Drug. Sufficient quantity of L-glutamine powder was mixed with 3% of tween 80, triturated, and administered orally.

Procedure for Induction of Oral Mucositis

Methotrexate Induced Oral Mucositis: Induction of mucositis was achieved by the procedure described previously with few modifications. In brief, methotrexate (purchased from United Biotech) 2.5 mg/kg was dissolved in phosphate-buffer saline (PBS) and injected subcutaneously each day for three consecutive days. Induction of mucositis along with formation of proinflammatory cytokines was validated previously by this model. *Buchanania lanzan* bark and leaves extracts (200 mg/kg) were administered once daily by oral route. Animals pretreated for 3 days with L-glutamine (1 g/kg p.o.) followed by mucositis induction with methotrexate (n=6) along with L-glutamine administration for 15 days in standard group. Animals pretreated for 3 days with extrct (100 mg/kg, p.o.) followed by induction of mucositis with busulfan and radiation (n=6) or with methotrexate (n=6) along with extract (100 mg/kg, p.o.) treatment for next 15 days in treated group.

EABB: Ethyl acetate extract of *Buchanania lanzan* bark (100-500µg/ml)
EOBB: Ethanol extract of *Buchanania lanzan* bark (100-500µg/ml)
AQBB: Aqueous extract of *Buchanania lanzan* bark (100-500µg/ml)

Group 1 (Normal control): received tween 80 (3% v/v) in water p.o.
Group II (Mucositis control): Mucositis induction by methotrexate received only vehicle tween 80 (3% v/v) in water p.o.
Group III (standard): L-glutamine (1 g/kg p.o.) followed by mucositis induction along with L-glutamine administration for 15 days.
Group IV (EABB): Ethyl acetate extract of *Buchanania lanzan* bark (100 mg/kg, p.o.) treated followed by mucositis induction
Group V (EOBB). Ethanol extract of *Buchanania lanzan* bark (200 mg/kg, p.o.) treated followed by mucositis induction
Group VI (AQBB): Aqueous extract of *Buchanania lanzan* bark (200 mg/kg, p.o.) treated followed by mucositis induction

Parameters Assessed during Study Period

Body Weight: Body weights were observed regularly in each group during 15 days of study. Initial body weights were recorded and after 15 days study body weight were recorded.
Food Intake: For determination of food intake, animals were housed individually and 15 g of food pellet was kept in each cage and after 24 h left-over food was measured.
Oral Mucositis Score. Different scoring system was used for scoring oral mucositis on dorsal surface of rat tongue mucosa. A previously described scoring system was used for methotrexate induced mucositis are 0 (Normal), 1.0 (Slight pink), 2.0 (Slight redness), 3.0 (Redness on tooth mucosa plus severe redness of tongue)
Mortality Rate. Mortality rate among the groups was determined during 15 days of study period and % mortality for each group was calculated accordingly.
Haematological Parameter. Blood count was measured on 7th and 12th day of study period in oral mucositis model. Methotrexate induced oral mucositis model blood count was determined on 7th day and 12th day of study period by veterinary blood cell counter (model PCE-210 VET from ERMA INC., Tokyo).
Histopathology. Rats of standard and normal group were sacrificed on 15th day from the initiation of treatment. Tongue specimens were collected and stored in 10% neutralized buffered formalin and processed for histopathological findings. Tongue specimen was also collected from mucositis control group if they died before 15th day and was processed similarly.
Statistical Analysis. All values were expressed as mean ± SEM (standard error of mean) for 6 animals in each group. Data were analyzed using one-way ANOVA followed by Turkey's multiple comparison tests using Prism 5.03 (Graph Pad Software). Score for oral mucositis was analyzed using Kruskal-Wallis test followed by Dunn's multiple comparison tests.

RESULT AND DISCUSSION

Acute Toxicity Study of *Buchanania lanzan* Sprengon rats were to assess the toxicological profile of the test drug when given orally once (single dose) to the test system (rats) and monitor the vital signs for 14 days. Acute toxicity studies of extracts of *Buchanania lanzan* Spreng were performed in Albino rat dose levels of 50, 200 and 2000 mg/kg as per OECD guide lines. The treated animals did not demonstrate any significant changes in behavioral pattern and exhibited normal activity. Also there were no clinical signs of tremors, convulsions, exophthalmos, salivation, diarrhea and lethargy. There was no significant difference in the mean body weights between treated groups and control group and the rats exhibited normal body weight gain during the study. No lethal effects or mortality was observed in animals throughout the test period following single oral administration at all selected dose levels of all extracts. The animals were examined for long term toxicity (14 days).
Oral mucosititis associated with inflammation and pain in mouth during eating. A number of drugs are available in market for relieving pain but they are accompanied with serious side effect. Still there was use of plant medicine in folk culture which is safer than these medicines. Tribal people of Jharkhand and Chhattisgarh are using *Buchanania lanzan* Spreng. for its anti-inflammatory and analgesic activities. In this study we made an effort to rationalize the use of *Buchanania lanzan* Spreng. as anti-inflammatory and analgesic agent. Ethanol extract of *Buchanania lanzan* Spreng bark showed potent anti-inflammatory and analgesic activities than *Buchanania lanzan* Spreng leaves. Findings of the study indicate that EOBB and EOBL exert significant analgesic activity along with significant anti-inflammatory activity.

In vivo Oral Mucositis activity

Toxicological Study: The limit test for acute toxicity study showed that ethyl acetate, ethanol and aqueous extract of *Buchanania lanzan* Spreng bark was tolerated at a dose of 2000 mg/kg p.o. without

any change in normal behaviour. No mortality was observed during 72 h and thereafter up to 14 days of observation

Methotrexate Induced Oral Mucositis

Body Weight: Increase in body weight of about 10 to 20% over a period of 15 days was observed in normal control group, whereas methotrexate treatment considerably reduced the body weight nearly 5 to 11 % in mucositis control during the study period. Treatment with standard and test compound showed progressive increase in body weight during the study period after methotrexate treatment.

Individual body weight gains were recorded before study imitation (Day 0), and weekly thereafter from the 1st week to the end of the study, a gradual increase in body weight was recorded in normal control group, whereas the rate of decrease in body weight oral mucositis control rat Animals treated with *Buchanania lanzan* bark extracts, the weight gradually increased compared to diseased control animals.

Food Intake. The average food intake of normal control group was found to be 12.98 ± 1.25 g during the study period. Mucositis control group showed progressive decline in food intake after methotrexate administration. Treatment with L glutamine and *Buchanania lanzan* bark extracts (200 mg/kg) showed significant (P< 0.05) increase in food intake compared to mucositis control. Ethanol extract of *Buchanania lanzan* bark showed 10.01 ± 0.38 g.

Oral Mucositis Score (OMS): Normal control exhibited a score of zero which indicates absence of oral mucositis. However, presence of severe redness of tongue mucosa was observed in mucositis control group indicated by the highest score of 3.0. Treatment with standard and test extract did not show significant (P< 0.05) difference of OMS compared to mucositis control whereas EOBB (200 mg/kg) showed significant (P< 0.05) reduction in OMS compared with mucositis control.

Mortality Rate. In normal control, all animals survived the entire study period and the mortality was 0%. In mucositis control, 50% mortality was observed on 7th day and on 14th day the mortality rate was 100%. No death was observed in standard group during the entire study period leading to 0% mortality. In EABB (200 mg/kg) the mortality rate was 33% on 8th day and it was constant till the end of study period. In EOBB (200 mg/kg) none of the animals died during the study period leading to 0% mortality.

Haematological Parameters. All blood components were within the normal range in normal control group. On day 7th in mucositis control, WBC and platelets count showed significant (P< 0.05) decrease compared to normal control. Treatment with standard and test compound showed progressive increase in WBC count compared to mucositis control; however, the improvement was insignificant. RBC count did not decrease significantly in any of the groups on 7th day In contrast, during 12th day of study period WBC count and platelets showed improvement in the treatment groups compared to mucositis control. However, a slight decrease in RBC count was observed among the treatment groups compared to normal.

Histopathology: Normal control showed intact epithelium, no lymphocytic infiltration, and normal number of blood vessels. However, in mucositis control, the thickness of epithelium layer was altered and lymphocytic infiltration was observed along with reduction in average number of blood vessels indicating presence of oral mucositis. Treatment with standard and extract protected the epithelial layer and showed normal number of blood vessels and absence of lymphocyte infiltration. Chemotherapy cause discomfort in the mucosal lining, as a result of which difficulty in drinking, eating, and swallowing can be observed. In the present study decrease in food intake and body weight was observed in methoteraxate models indicating inflammation of oral mucosa or difficulty in swallowing. However, improvement in body weight and food intake was observed in extract treatment group. Severity of oral mucositis is graded by oral mucositis score (OMS) and a decrease in OMS is considered as an improvement. Our results demonstrated a decrease in OMS among the treatment groups in methoteraxate induced mucositis confirming a protective effect. In methoteraxate induced mucositis model standard and ethanol extract of *Buchanania lanzan* Spreng bark indicated effectiveness in reducing the OMS endorsing a protective effect. However, during the 15 days of study period, 100% mortality was observed within 8th day in mucositis control group in methoteraxate induced mucositis. In contrast, 0% and 16.6% mortality was observed in standard and treatment groups, respectively, which demonstrated the protective effect of extract of *Buchanania lanzan* Spreng bark and leaves against toxicity of chemotherapy. Treatment with EOBB (200 mg/kg) proved effective for this model as the mortality rate was 0% within the study period which was at par with the standard. Extract and standard treated group show restoring effect on the blood parameters especially WBC and platelets in methoteraxate induced mucositis, on blood parameters, especially WBC and platelets were observed. Histology of tongue revealed the presence of oral mucositis, as the thickness of epithelial layer was altered and lymphocytic infiltration was observed along with reduction in number of blood vessels in methoteraxate induced mucositis. Treatment with extract improved the thickness and higher number of blood vessels was observed indicating the protective effect of EOBB in oral mucositis. EOBB was found more effective than other extract.

Summary and Conclusion: From the present study, we can conclude ethanol extract of *Buchanania lanzan* Spreng bark at 200 mg/kg could protect oral mucositis against methotrexate induced oral mucositis. Ethanol extract of *Buchanania lanzan* Spreng bark was found more effective than other extract. Ethyl acetate and aqueous extract of bark of *Buchanania lanzan* Spreng also protect oral mucositis in some extent. Haematological investigations could suggest that ethanol extract also improve haematological parameter such as WBC and platelet in some extent.Oral mucosititis associated with inflammation and pain in mouth during eating. A number of drugs are available in market for relieving pain but they are accompanied with serious side effect. Still there was use of plant medicine in folk culture which is safer than these medicines. Tribal people of Jharkhand and Chhattisgarh are using *Buchanania lanzan* Spreng. for its anti-inflammatory and analgesic activities. In this study we made an effort to rationalize the use of *Buchanania lanzan* Spreng. as anti-inflammatory and analgesic agent. Ethanol extract of *Buchanania lanzan* Spreng bark showed potent anti-inflammatory and analgesic activities. Findings of the study indicate that EOBB exerts significant analgesic activity along with significant anti-inflammatory activity. A variety of secondary metabolites including flavonoids, phenolics and other bioactive components which are present in *Buchanania lanzan* Spreng bark may be responsible for the protective effect. Furthermore isolation of the active components will be further studies to confirm better insight regarding the active constituents.

Table 1: Change in Body Weight of animal in methotrexate induced oral mucositis treated with *Buchanania lanzan* bark extract

Physical parameters	Normal Control	Mucosititis induced	Standard treated	EABB	EOBB	AQBB
Initial body weight	200.5±17.30	210.5±17.30	220.7±18.7	231.7±18.7	215 ±19.7	240 ± 09.11
Final body weight	240 ± 12.21	190.5 ± 12.21	254 ± 16.27	251.7± 16.27	249 ± 18.16	253± 16.09
Weight gain	40±10.06	-20±10.06	34±11.24	20±11.24	34±7.18	13±12.08

Table 2: Effect of *Buchanania lanzan* bark extract on average food intake in methotrexate induced oral mucositis.

S. No.	Extract	Average food intake
1	**Normal Control**	12.98 ± 1.25
2	**Mucosititis induced**	05.21 ± 0.38
3	**Standard treated**	09.58± 0.51
4	**EABB**	08.21 ± 0.42
5	**EOBB**	10.01± 0.38
6	**AQBB**	07.58± 0.16

Table 3: Oral mucositis score in methotrexate induced oral mucositis (*Buchanania lanzan* bark extract)

S. No.	Extract	Score
1	**Normal Control**	0
2	**Mucosititis induced**	3
3	**Standard treated**	1
4	**EABB**	1.2
5	**EOBB**	1
6	**AQBB**	1.4

Table 4: Change in haematological parameter on 7th day of study period in methotrexate induced oral mucositis (*Buchanania lanzan* bark extract)

Groups	WBC ($\times 10^3$ cells/mm^3)	RBC ($\times 10^6$ cells/mm^3)	PLT ($\times 10^3$ cells/mm^3)
Normal control	15.8 ± 0.52	7.76 ± 0.12	565.3 ± 11.67
Mucositis control	3.2 ± 1.24	5.86 ± 0.19	161.20 ± 27.01
L-Glutamine	14.52 ± 1.21	6.34 ± 0.28	267.21 ± 99.70
EABB (200 mg/kg)	11.12 ± 1.83	6.02 ± 0.47	201.25 ± 31.83
EOBB (200 mg/kg)	13.89 ± 2.23	6.94 ± 0.71	245.33 ± 67.17
AQBB (200 mg/kg)	10.23 ± 0.76	5.71 ± 0.61	189. 2 ± 16.43

Table 5: Change in haematological parameter on 12th day of study period in methotrexate induced oral mucositis (*Buchanania lanzan* bark extract)

Groups	WBC (×10³ cells/mm³)	RBC (×10⁶ cells/mm³)	PLT (×10³ cells/mm³)
Normal control	16.14 ± 0.52	7.94 ± 0.22	578.2 ± 16.43
Mucositis control	3.1 ± 1.20	7.10 ± 0.19	172.33 ± 30.02
L-Glutamine	14.85 ± 1.29	5.42 ± 0.28	510.21 ± 78.70
EABB (200 mg/kg)	12.12 ± 1.83	5.42 ± 0.47	381.25 ± 31.83
EOBB (200 mg/kg)	13.79 ± 2.36	5.51 ± 0.71	414.33 ± 67.17
AQBB (200 mg/kg)	11.56 ± 1.76	5.22 ± 0.35	397.25 ± 21.50

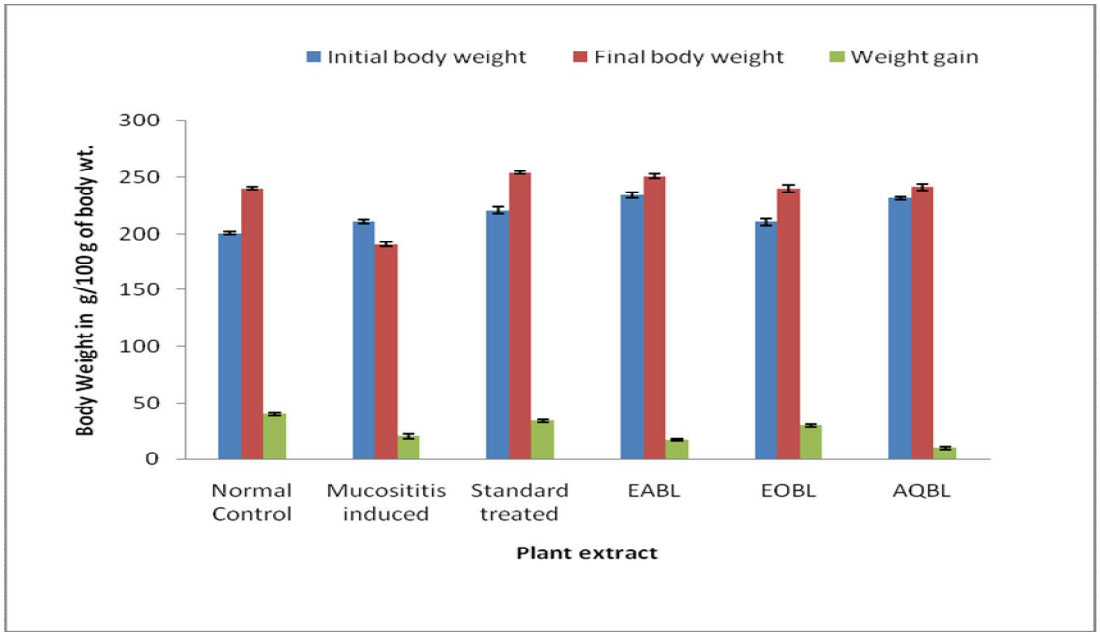

Figure 1: Change in Body Weight of animal in methotrexate induced oral mucositis treated with *Buchanania lanzan* bark extract

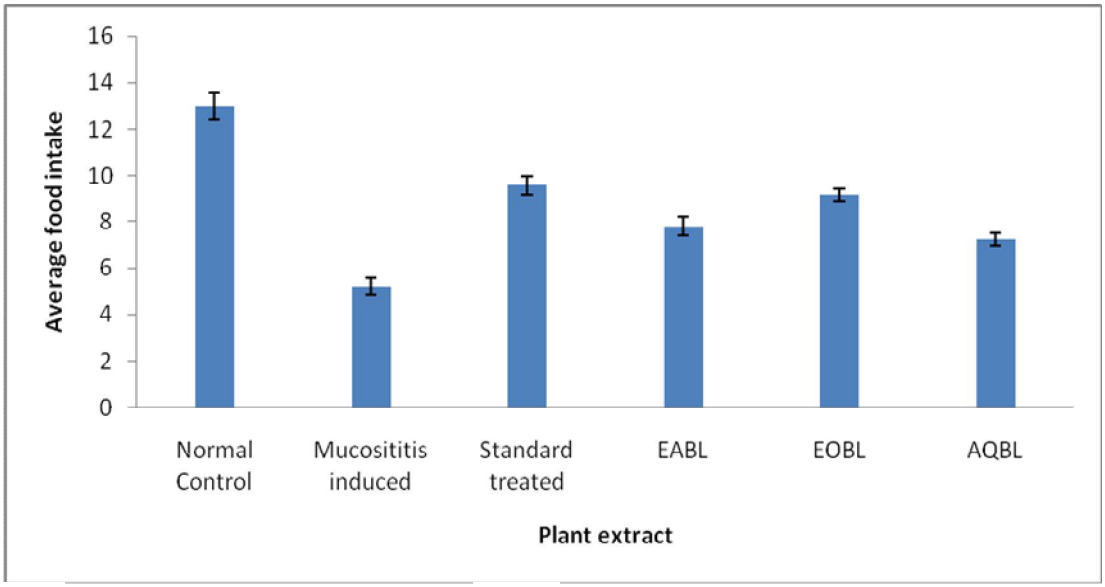

Figure 2: Effect of *Buchanania lanzan* bark extract on average food intake in methotrexate induced oral mucositis

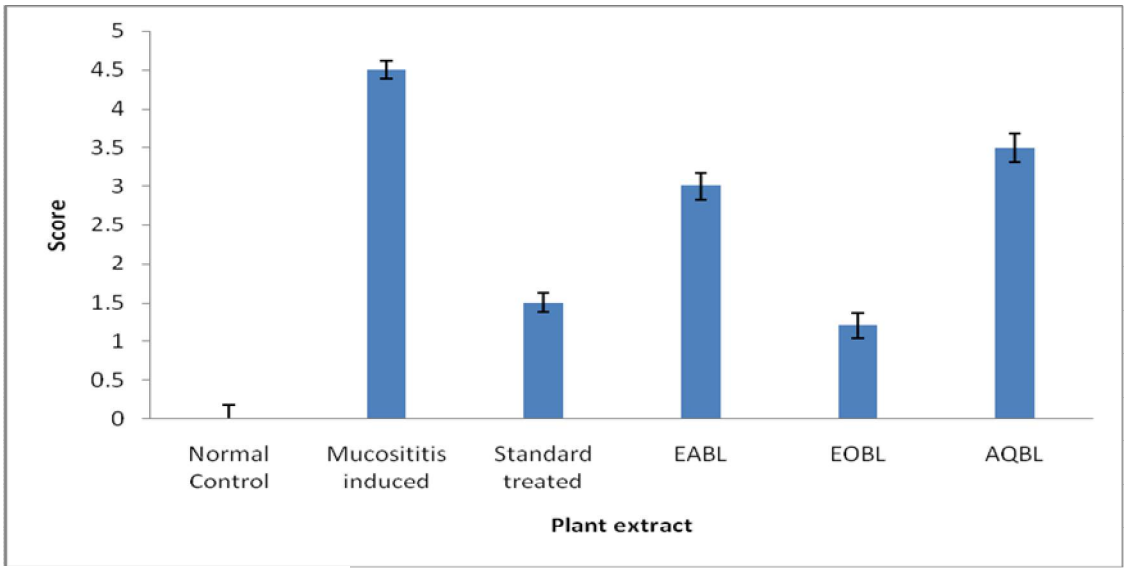

Figure 3: Oral mucositis score in methotrexate induced oral mucositis (*Buchanania lanzan* bark extract)

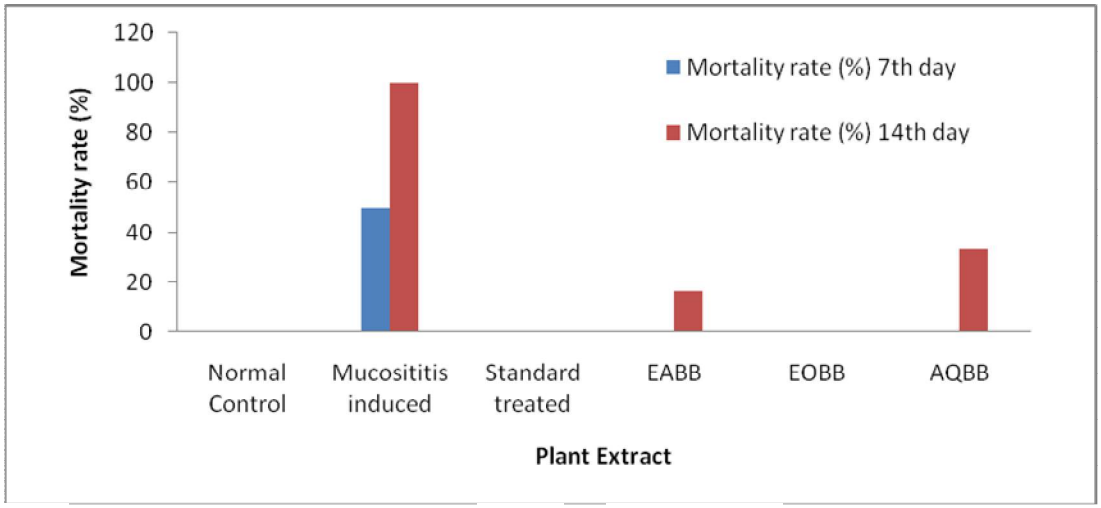

Figure 4: Effect of *Buchanania lanzan* bark extract on Mortality Rate in methotrexate induced oral mucositis

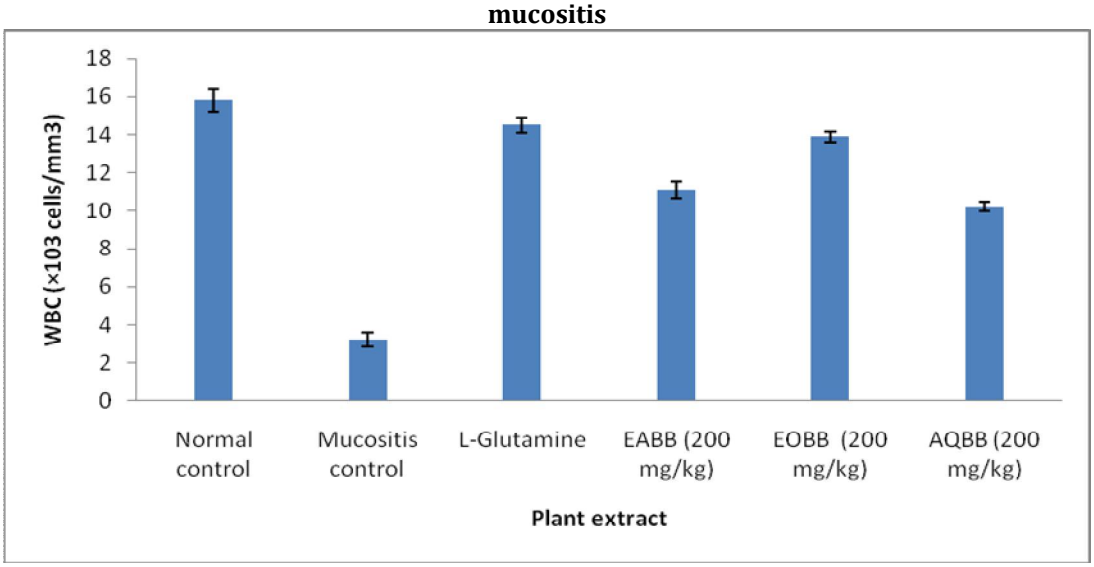

Figure 5: Effect on WBC on 7th day of study period in methotrexate induced oral mucositis (*Buchanania lanzan* bark extract)

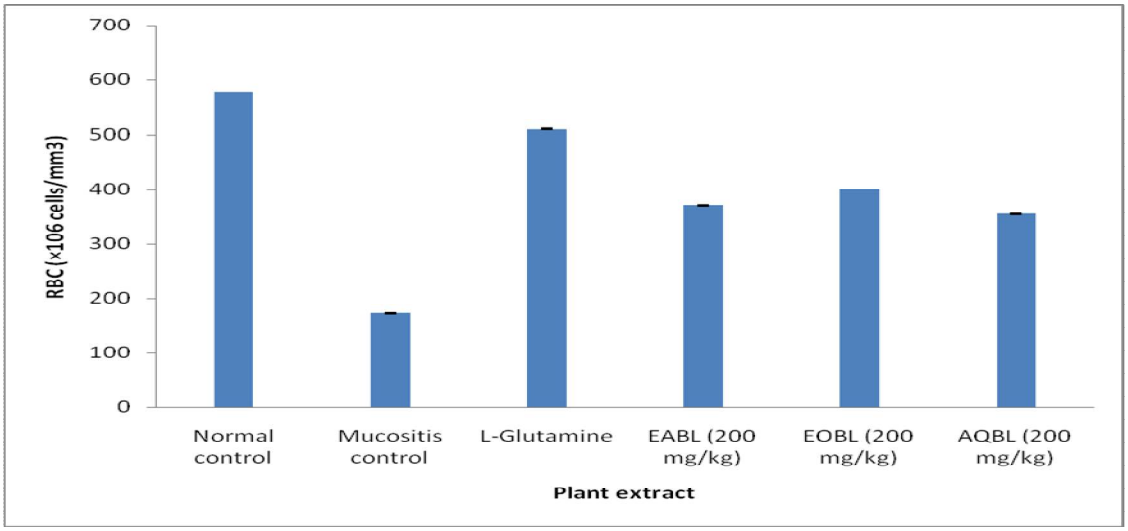

Figure 6: Effect on RBC on 7th day of study period in methotrexate induced oral mucositis (*Buchanania lanzan* barkextract)

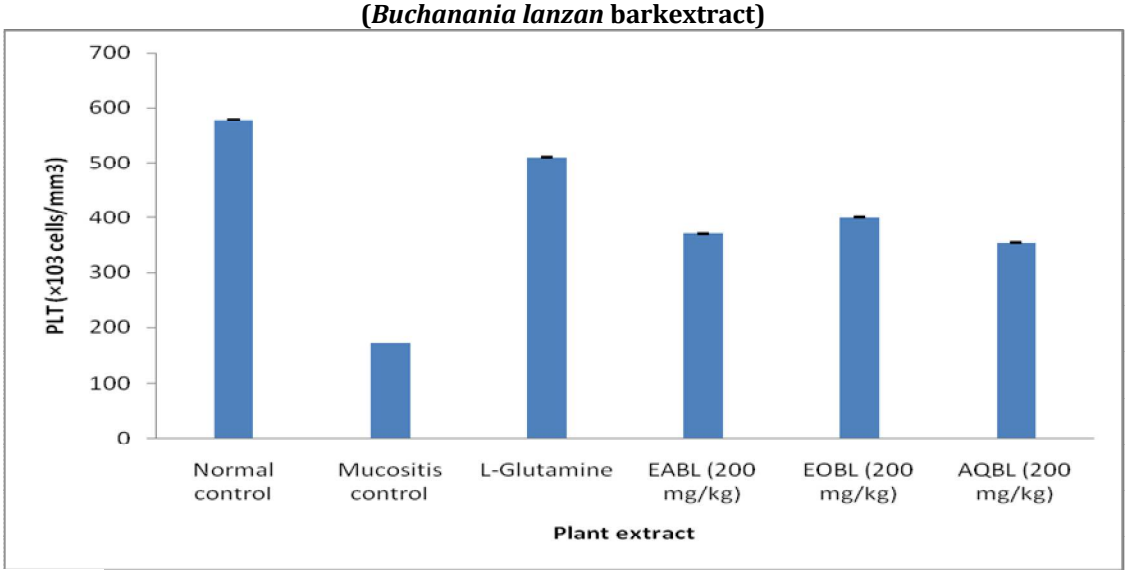

Figure 7: Effect on platelets on 7th day of study period in methotrexate induced oral mucositis (*Buchanania lanzan* bark extract)

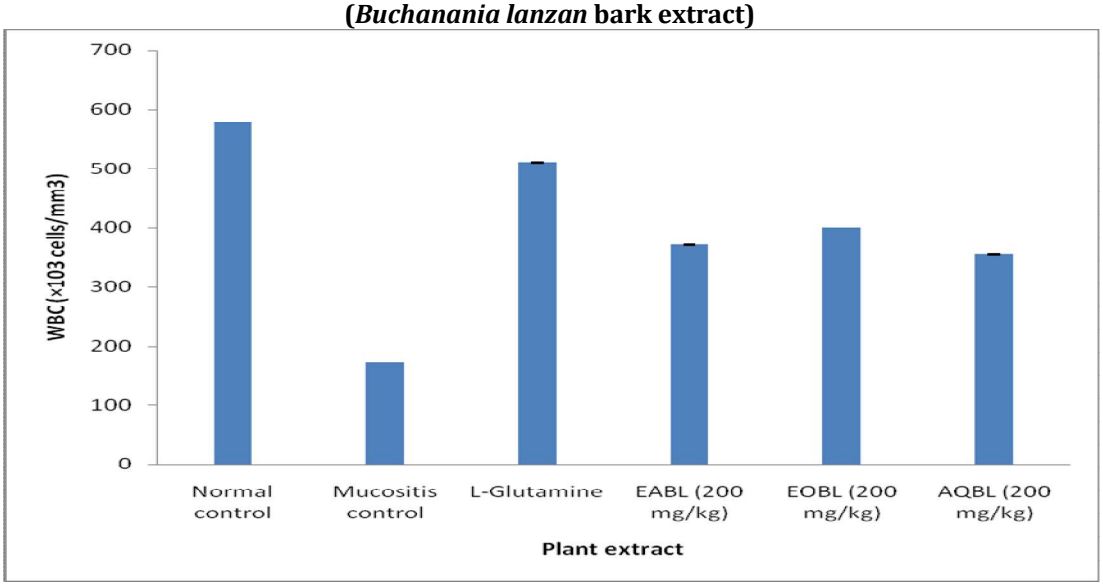

Figure 8: Effect on WBC count on 12th day of study period in methotrexate induced oral mucositis (*Buchanania lanzan* bark extract)

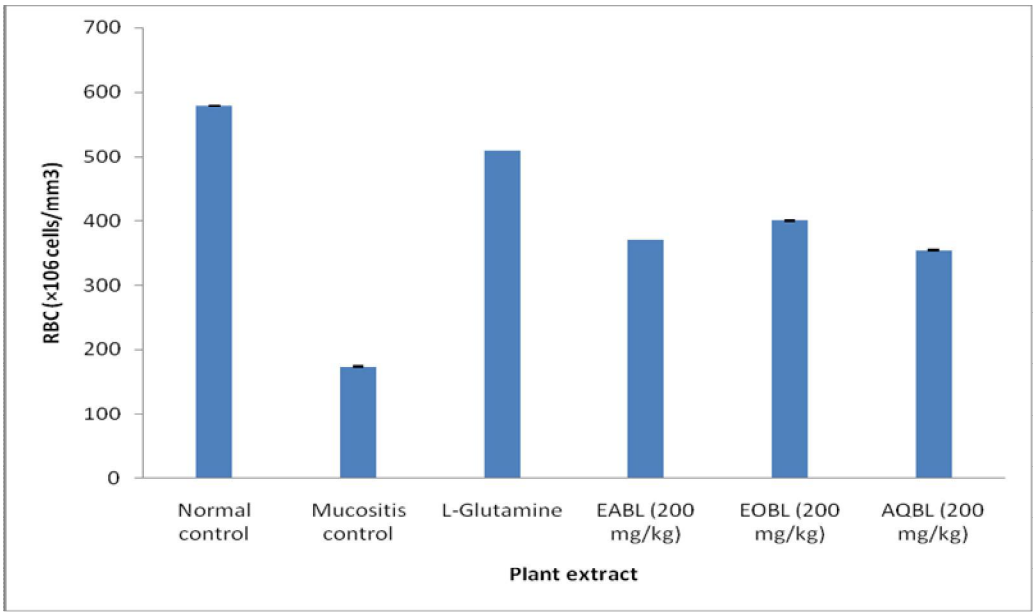

Figure 9: Effect on RBC count on 12th day of study period in methotrexate induced oral mucositis (*Buchanania lanzan* bark extract)

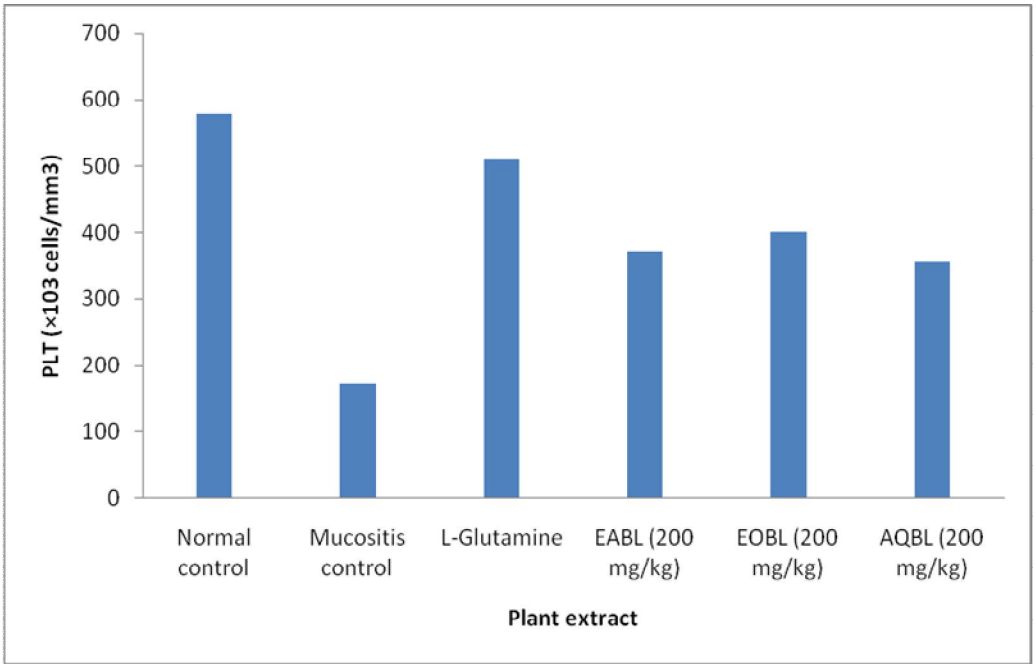

Figure 10: Effect on platelets count on 12th day of study period in methotrexate induced oral mucositis (*Buchanania lanzan* bark extract)

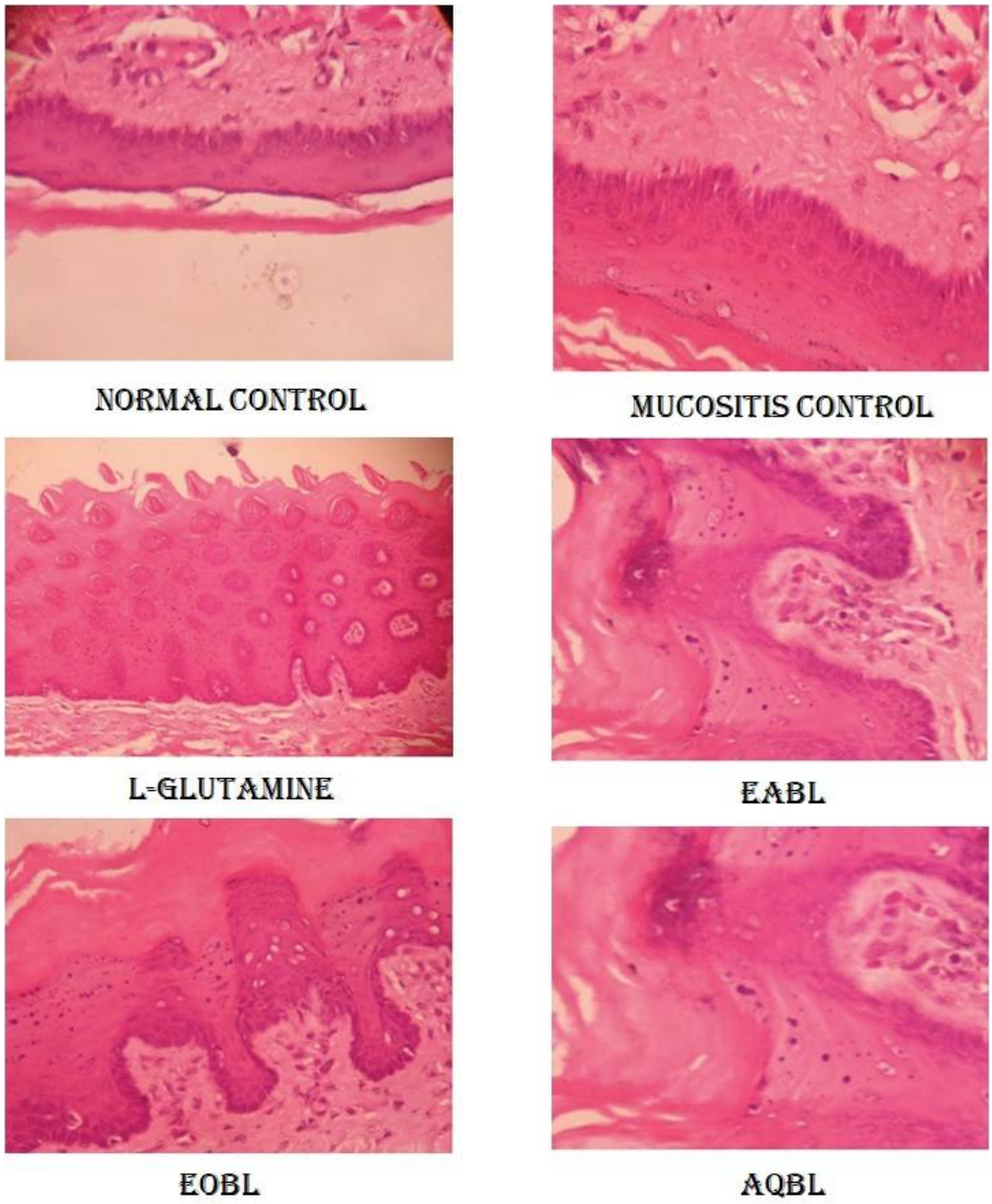

Figure 11: Histological Findings of various extract of *Buchanania lanzan* Spreng bark

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