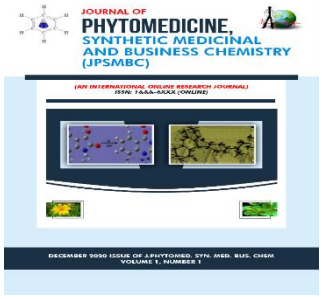
J. Phytomed. Syn. Med. Bus. Chem. 1(1) (2021) 1-16



Journal of Phytomedicine, Synthetic Medicinal and Business Chemistry
(*An International Online Research Journal*)
journal homepage: www.craigobafoundation.com

Research Article

Cite this: **J. Phytomed. Syn. Med. Bus. Chem. 1(1) (2021) 1-16**
Publication Date: December, 2021
Document heading doi:

Evaluation of anti-inflammatory, antioxidant and anti-ulcer effects of *Musa paradisiac* peel on inflammatory experimental models in rats

Mary O. Ologe[1], Mayowa Olaobaju[2], Adebola B. Alabi[3], Ezekiel O. Iwalewa[2*]

[1]Department of Pharmacology and Therapeutics, Faculty of Basic Medical Sciences, College of Health Sciences, University of Ilorin, Ilorin, Nigeria.

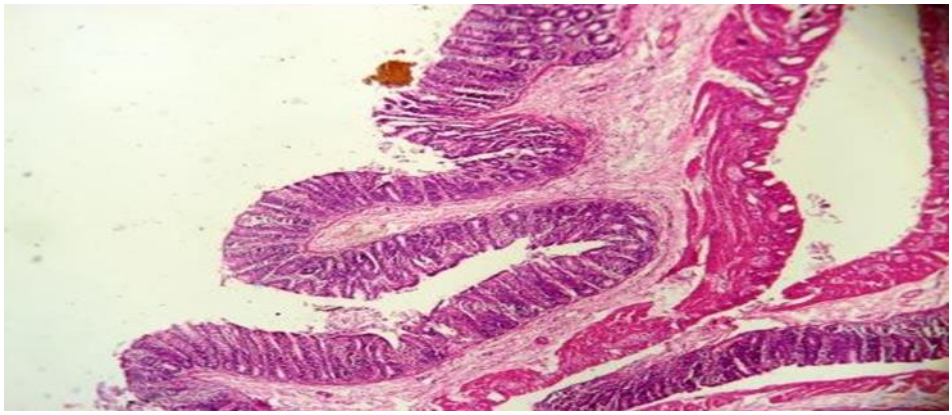
[2]Ethnopharmacology and Inflammation Unit, Department of Pharmacology and Therapeutics, Faculty of Basic Medical Sciences, College of Medicine, University of Ibadan, Ibadan, Nigeria

[3]Department of Pharmacology and Therapeutics, Faculty of Basic Clinical Sciences, College of Medicine, Bowen University, Nigeria.

Corresponding author mailing address and telephone number: Department of Pharmacology & Therapeutics, Faculty of Basic Medical Science, University of Ibadan, Ibadan, Nigeria. eoiwalewa@yahoo.com

Article history:
Received 15 July 2020
Received in revised form
14 September 2020
Accepted 21 September 2021
Available online December, 2021

Graphical Abstract



Abstract

Background- The use of *Musa paradisiac* (MP) as food and phytomedicine has been well documented both in Africa and South America as remedies in traditional medicine

Purpose- This study evaluated the anti-inflammatory role of MP in the acute and chronic experimental model of inflammation in rats.

Materials and Methods- Twenty-five male Wistar rats were assigned to five groups (n = 5) for two experimental models (carrageenan-induced paw oedema and 10% formaldehyde induced paw oedema): control, 5 mg/kg indomethacin, 250 mg/kg, 500 mg/kg and 1000 mg/kg MP. One hour after treatment, the right hind paw of each rat was determined before induction of acute inflammation with sub-plantar injection of 0.1ml of 1% carrageenan. The increase in paw volume and percentage inhibition of inflammatory oedema were calculated. In model 2, after one hour treatment, the initial right hind paw size of each rat were determined before induction of acute inflammation using Ugo Basile Plethysmometer which was followed by sub-plantar injection of 0.1ml of 10% Formaldehyde. The increase in paw volume was measured over the period of 1 hour, 2 hours, 3 hours and 4 hours using Ugo Basile Plethysmometer. The inflammatory fluid exudates were determined using the granuloma air pouch model of chronic inflammation. Effect of MP on the levels of GSH, SOD, MDA and nitrite in inflammatory fluid exudates were also assessed. The histology of stomach tissue was also assessed for inflammation and ulcer.

Results-MP (250 and 500 mg/kg, p.o) produced a significant inhibition of: inflammatory oedema induced by carrageenan, inflammatory oedema induced by 10% formaldehyde along with indomethacine. All doses of MP significantly increased the GSH and SOD level,

decreased MDA and nitrite level in inflammatory fluid exudates. MP (250 and 500 mg/kg, p.o) protect the stomach tissue against inflammation and ulcer.

Conclusion- MP exhibited in-vivo anti-inflammatory and antioxidant effects in both acute and chronic animal models of inflammation in rats.
Keywords: *Musa paradisica*, inflammation, oxidative stress, indomethacin, ulcer, oedema

Introduction

Inflammation is a response that involves the vascular, tissue and immune cells. The main aim of inflammation is to checkmate the cause of cell damage/injury, remove dead cells and tissues damaged from the site and promotes tissue repair. Inflammation is initiated by different factors such as viruses, bacteria, fungi, parasites, and antibody-antigen interaction, mechanical, organic and inorganic invaders [1]. Inflammation is a sequence of a well-coordinated event that relies on serial arrival of inflammatory leukocyte to the site of inflammation, where first neutrophils migrate to the tissue in response to noxious stimuli. It is assumed that the neutrophils infiltration or its related event might be pivotal for subsequent macrophage infiltrations [2].

The pro-inflammatory mediators are liberated from injured cells of the damaged tissues. The initiation of complement chain reactions from complement proteins is the source of chemotactic substances for neutrophils invasion of injured site [2]. Anaphylatoxin (C3a, C5a) released, incite degranulation of histamine releasing mast cells thereby causing release of histamine, blood vessel dilation and contraction of smooth muscle cells [3]. Fever, redness, pain and swelling are major symptoms of inflammation along with loss of function [4].

Although indomethacin, p-chlorophenylalanine, and cyproheptadine are anti-inflammatory drugs that can inhibit the production of 5-hydoxytryptamine, and histamine, these drugs can only reduce infection mildly. They are use is limited to suppressive and long term treatment, with no suppressive effect in curative measures against inflammation associated with malaria infection. In addition, a major adverse effect associated with the use of most anti-inflammatory drugs is immunosuppression, and the use of non-steroidal class of anti-inflammatory drugs is associated with severe toxic effect like gastric mucosa erosion that can cause ulcer, bleeding and gastrointestinal perforation. Due to the complications reported in the use of conventional anti-inflammatory drugs, many studies were designed to assess the role of natural food with high antioxidants, in the treatment of inflammation. This form the basis of evaluating the anti-

inflammatory effect of *Musa paradisiac* in animal model, which is predictive of human acute and chronic inflammation.

Materials and Methods

Experimental animals

Male Wistar rats with the weight range of 120-200 g were used for this study. They were purchased from the Central Animal House University of Ibadan, and kept under standard environmental conditions with free access to commercial food pellets and water on daily basis. Animal use and handling for this study complied with the World Medical Association Declaration of Helsinki regarding ethical conduct of research involving the Care and Use of Laboratory Animals.

Drugs and chemicals

Musa paradisica peel (Oje market), indomethacin (Sigma), Carrageenin (Sigma), 5,5'-dithio-bis (2-nitrobenzoic acid), DTNB (Sigma), trichloroacetic acid (Sigma), thiobarbituric acid (Sigma), sodium carbonate (BDH), potassium carbonate (BDH), sodium chloride (BDH) were used in this study.

Plant material and preparation of extract

The unripe *Musa paradisica* was gotten from Oje market in Ibadan and was identified at the Department of Pharmacognosy. The peel of the fruit was removed and air-dried. The dried peel was later pulverized. 200 g of the pulverized peel was then soaked in 70% methanol and left for 48 hrs. After 48 hrs., it was filtered on absorbent on what-man 3mm paper. The volume of the filterate was concentrated using rotary evaporator at 40 °C., and the paste of dark-brown colour was obtained when dried to a constant state in a desiccator before it was kept in a sterilized glass vial for use.

Experimental Procedure

Effect of *Musa paradisica* on carrageenan-induced paw oedem

Effect of *Musa paradisica* (MP) peel on carrageenan-induced acute inflammation was evaluated according to the previous method described by Winter et. al., [5]. The rats were split into five treatment groups (n = 5 per group). The first 3 groups were given MP (250, 500 or

1000 mg/kg) orally, the fourth and the fifth groups received indomethacin (5 mg/kg) and distilled water (10 mL/kg) respectively. One hour after treatment, the right hind paw of each rat was determined before inducing inflammation with sub-plantar injection of 0.1 ml of 1% carrageenin. The increased paw volume was measured at 3 hr. using Ugo Basile plethysmometer. The paw volume and percentage area of inhibition of inflammatory oedema were estimated.

Effect of *Musa paradisica* peel on 10% formaldehyde induced paw oedema.

As described above, the animals were divided into five groups (5 rats per group). The first 3 groups were treated orally with 250 mg/kg, 500 mg/kg and 1000 mg/kg of the MP, and 5 mg/kg of indomethacine to serve as positive control group and the negative control group were given distil water per body weight. One hour after treatment, the initial right hind paw size of each rat was determined before induction of acute inflammation using Ugo Basile Plethysmometer which was followed by sub-plantar injection of 0.1ml of 10% Formaldehyde. The increase in paw volume was measured over the period of 1 hour, 2 hours, 3 hours and 4 hours using Ugo Basile Plethysmometer.

Effect of *Musa paradisica* on carrageenan-induced granuloma air pouch

The fluid exudates from inflammatory site was determined using the granuloma air pouch model of chronic inflammation according to the technique of Selye, [6]. Twenty millimeters of air, followed by 2 mL of 100 mg/kg of carrageenan in 1.0 mL of groundnut oil was administered through subcutaneous route into the shaved dorsal skin surface of the animals. The animals (5 rats per group) were treated daily with MP (250, 500 or 1000 mg/kg), indomethacin (5 mg/kg) or saline (10 mL/kg) orally for five consecutive days, beginning on day 1 prior to the administration of carrageenan suspension. On the 5th day, the animals were sacrificed and the inflammatory exudates (mL) were collected using syringes.

Biochemical assays

GSH level was evaluated using the method described by Beutler et al, [7] and MDA level in the fluid exudates determined using the method of Olszewska et al, [8]. SOD level was estimated by measuring the inhibition of adrenaline auto-inhibition using the method of Mistra and Fridovich [9] with slight modification.

Histological Examination

Histological examination as described by Alabi et al, [10] of the pouch tissue lining was carried out to further reveal the protective role of *Musa paradisica* against granulomatous inflammation induced by carrageenan in rats.

Statistical analysis

Data were expressed as the mean ± SEM. Data were statistically analyzed using a one-way analysis of variance (ANOVA), followed by Neuman keul multiple comparison tests. Statistical significance was determined at a level of $*p < 0.05$.

Results

Musa paradisica reduced inflammatory oedema induced by carrageenan in rat

The administration of carrageenan increased paw oedema volume significantly. In comparison with the control rats, as shown in Table 1, MP (250 and 500 mg/kg, p.o) significantly ($*p <0.05$) reduced inflammatory oedema initiated by carrageenan. There was similar effect in rats treated with indomethacin (10 mg/kg p.o), the positive control drug.

Table 1: Anti-inflammatory effect of *Musa paradisica* on carrageenan induced paw oedema in rats

Samples	**Dosage (mg/kg)**	**Mean ± SEM**	**%inhibition of oedema**
Musa paradisica	1000 mg/kg	0.970 ± 0.022	6 %
Musa paraddisica	500 mg/ kg	0.850 ± 0.043	17 %
Musa paradisica	250 mg/kg	0.855 ± 0.855	17 %
Indomethacin	5 mg/kg	0.835 ± 0.018	18 %
Control	10 mL	1.028 ± 0.103	-

Each value represents the mean ± SEM for 5 rats in each group, $*p<0.05$ value differ significantly when compared with control group (ANOVA and Newman keul multiple comparison test).

***Musa paradisica* reduced inflammatory oedema induced by 10% formaldehyde in rat**

10% formaldehyde produced a significant increase in paw oedema volume. When compared with the control, as this was shown in Table 2, *Musa paradisiac* (250 and 500 mg/kg p.o) produced a significant (*p<0.05) inhibition of inflammatory oedema induced by 10% formaldehyde in rats. Indomethacin also inhibit formaldehyde-induced inflammatory oedema significantly (5 mg/kg p.o).

Table 2: Anti-inflammatory effects of *Musa paradisica* on 10% formaldehyde induced oedema

Samples	**Dosage (mg/kg)**	**Mean ± SEM**	**%inhibition of oedema**
Musa. paradisica	1000 mg/kg	0.88 ± 0.075	7
M.usa paradisica	500 mg/ kg	0.88 ± 0.065	16
Musa paradisica	250 mg/kg	1.02 ± 0.014	19
Indomethacin	5 mg/kg	0.91 ± 0.061	19
Control	10 mL	0.88 ± 0.075	-

Each value represents the mean ±SEM for animals in each group, *p<0.05 value differ significantly when compared with control group (ANOVA and Newman keul multiple comparison test)

***Musa paradisica* reduced the concentration of malondialdehyde (MDA) in inflammatory exudates in rats**

The significant increase in MDA level of the inflammatory fluid was inhibited by *MP* (250, 500 and 1000 mg/kg) significantly, (Figure 1). Indomethacin (5mg/kg) also produce a significant decrease in the concentration of MDA in the inflammatory exudates in comparison with the control.

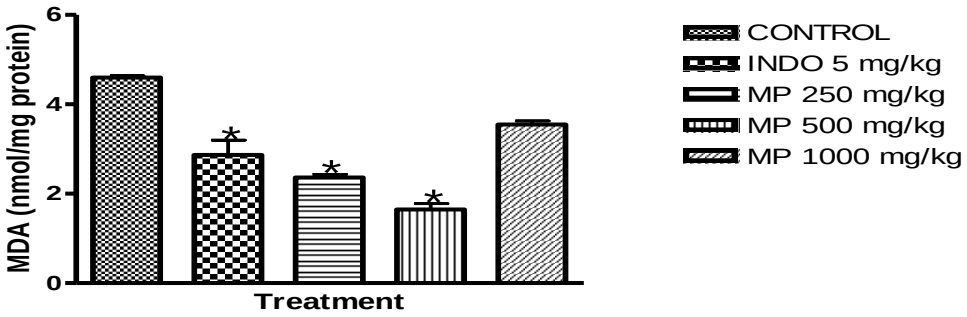


Figure 1: Effect of *MP* and indomethacin on malondialdehyde (MDA) production in granuloma air pouch model of chronic inflammation. Each column represents mean ± SEM from 5 animals. *p<0.05 value differ significantly when compared with control group (ANOVA and Newman keul multiple comparison test)

The effect of *Musa paradisica* on Gluthathione (GSH) level

Figure 2 revealed the effect of *MP* on the concentration of GSH in inflammatory exudates induced by carrabeenan in the granuloma air pouch model of inflammation in rats. *MP* (250, and 500 mg/kg) shows significant (*p<0.05) elevation in the concentrations of GSH in the inflammatory exudates in comparison with control suggesting free radical scavenging property. As shown in Figure 2, indomethacin (5 mg/kg) significantly increased the concentration of GSH in the inflammatory exudates.

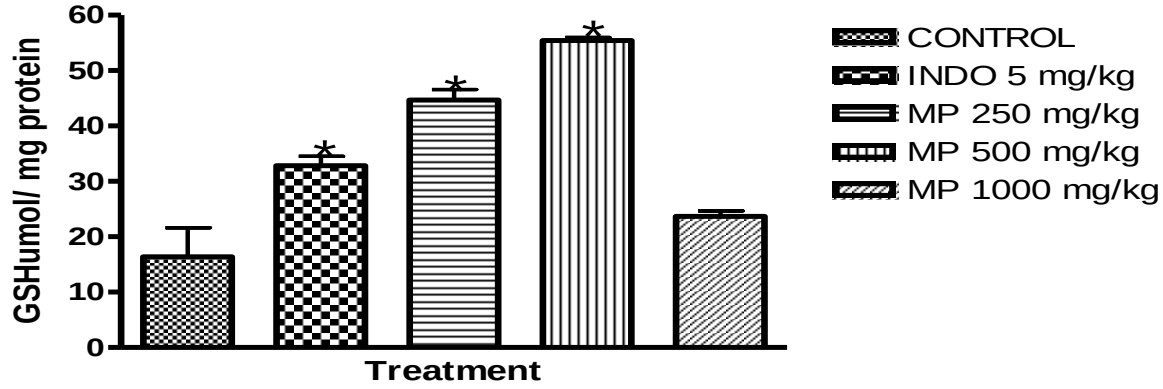


Figure 2: Effect of *MP* and indomethacin on Glutathione (GSH) production in granuloma air pouch model of chronic inflammation. Each column represents mean ± SEM for 5 rats. *p<0.05 value differ significantly when compared with control group (ANOVA and Newman keul multiple comparison test)

Musa paradisica decreased the concentration of Nitrite in inflammatory exudates in rat

Figure 3 showed the role of *MP* on inflammatory exudate level of nitrite induced by carrageenan in the granuloma air pouch model of chronic inflammation. The elevated nitrite level in the inflammatory fluid was significantly (*p<0.05) inhibited by *MP* (250 and 500 mg/kg). Indomethacin (5 mg/kg) also reduced the nitrite level in the inflammatory exudates in comparison with the control.

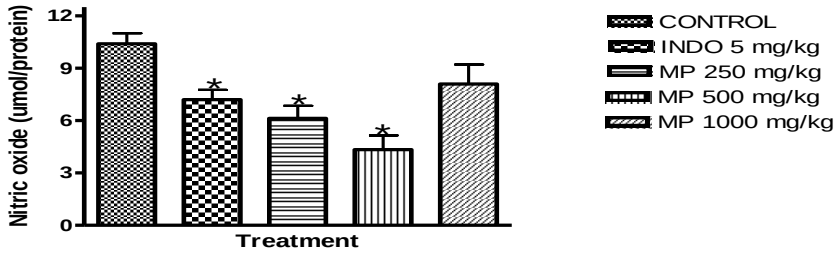


Figure 3: Effect of *MP* and indomethacin on Nitric oxide (NO) production in granuloma air pouch model of chronic inflammation. Each column represents mean ± SEM from 5 rats. *p<0.05 value differ significantly when compared with control group (ANOVA and Newman keul multiple comparison test)

Musa paradisica decreased the Superoxide Dismutase (SOD) level in inflammatory exudates

MP (250, and 500 mg/kg) shows significant (*p<0.05) elevation in the concentrations of SOD in the inflammatory exudates in comparison with control. As shown in Figure 4, indomethacin (5 mg/kg) significantly enhanced the SOD in the inflammatory exudates.

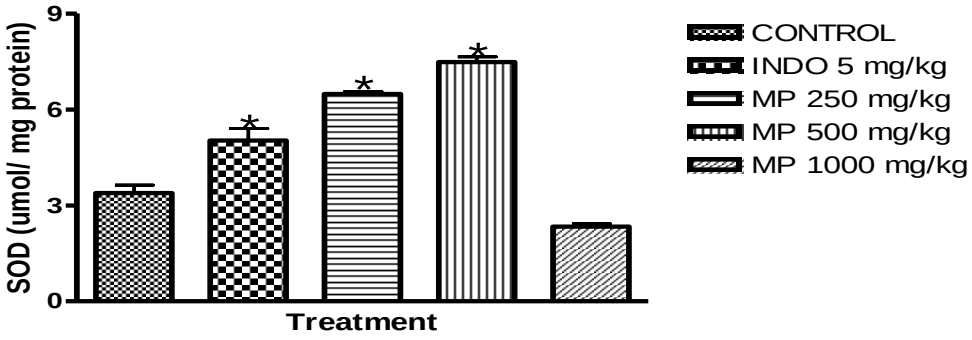


Figure 4: Effect of *MP* and indomethacin on Superoxide Dismutase (SOD) production in granuloma air pouch model of chronic inflammation. Each column represents mean ± SEM from 5 animals. *p<0.05 value differ significantly when compared with control group (ANOVA and Newman keul multiple comparison test).

Musa paradisica prevented destruction of stomach tissue

Histological examination of the stomach tissue reveals that *MP* offered a significant protection. When compared with the indomethacin (5 mg/kg), *MP* (250 and 500 mg/kg) revealed a significant protection as shown in the Figure 5.

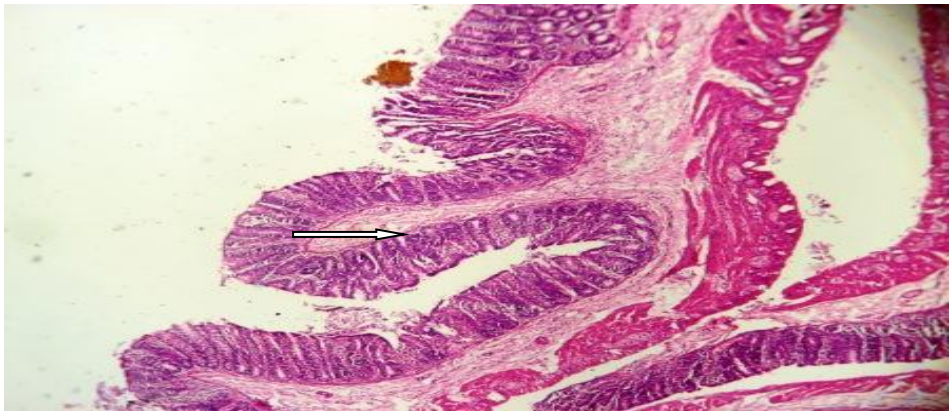

X 100

Figure 5: Photomicrograph effect of 250 mg/kg of *MP* on the stomach section stained by haematoxylin and Eosin showing mild papillary infolding, the mucosa surface epithelial layer is moderately preserved (white arrow), no mucosa ulcer seen, there is moderate infiltration of lamina propria by inflammatory cells (slender arrow) and the circular muscle layer appears normal (red arrow)

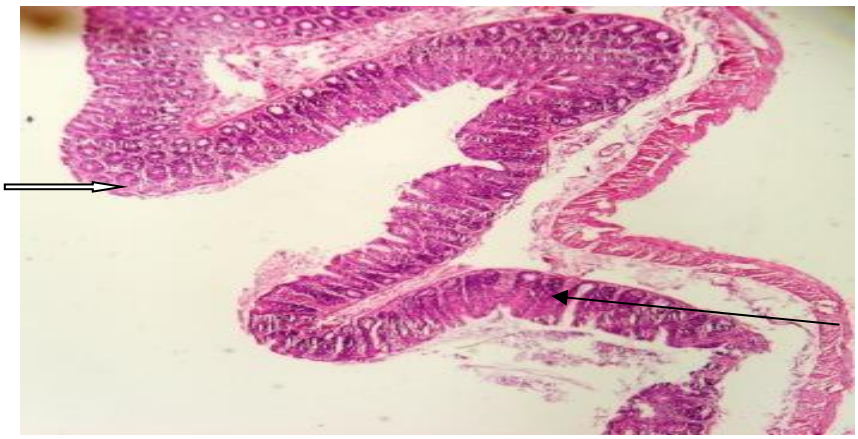

X100

Figure 6: Photomicrograph of the effect of 500 mg/kg of *MP* on stomach section stained by haematoxylin and Eosin showing normal mucosa surface epithelial layer which is moderately preserved (white arrow), no mucosa ulcer seen, there is moderate infiltration of lamina propria by inflammatory cells (slender arrow). The submucosal layer is mildly infiltrated by inflammatory cells consisting of polymophonuclear cells.

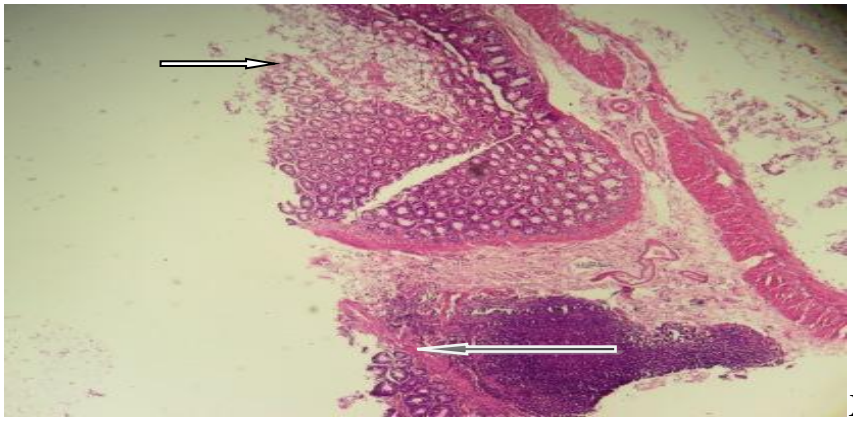

X100

Figure 7: Photomicrograph of effect of *MP* (1000 mg/kg) on stomach section stained by haematoxylin and Eosin showing mild papillary infolding, there is mild denudation of mucosa surface epithelial layer and focal area of mucosal ulceration (White arrow).

Discussion

The results obtained from the present study reveals that *Musa paradisica* is an inhibitor of acute inflammation, as it significantly reduced oedema paw volume induced by carrageenan in rats. Carragenan-induced acute inflammation is known to be mediated through a gradual release of chemical mediators like histamine, bradykinin and serotonin initially and prostaglandins later [11]. These mediators are known to induce vasodilation and enhance vascular permeability that trigger accumulation of fluid in the interstitial tissue [11]. Interstitial tissue oedema account for the inflammatory oedema that characterized the sub-plantar injection of carrageenan in rats. However, prostaglandins are known to be weak in producing inflammation, but are better at potentiating the effects of other chemical mediators. Moreover, histamine, serotonin and bradykinin are also known to stimulate the release of prostaglandin. Thus, inhibition of prostaglandin serves as a major target for discovery and development of drugs with anti-inflammatory property. Indeed, non-steroidal anti-inflammatory drugs (NSAIDs) owe their clinical efficacy in the treatment of inflammatory conditions to inhibition of prostaglandins synthesis [12, 13]. In a similar ways, acute inflammation induced by formaldehyde in rat have also been known to involve the release of some chemical mediators of inflammation which include histamine, serotonin, lysosomal enzymes, prostaglandins, leukotriene, activated oxygen species, nitric oxide, cytokines and most especially substance P which is a marker for nociceptive sensory neurons, these are the major culprit in acute inflammation. The findings that *Musa paradisica* reduced paw oedema size induced by carrageenan and by formaldehyde in rats suggest the presence of phytochemical(s) with anti-inflammatory property.

The role *Musa paradisica* against inflammation was further evaluated using granuloma air pouch model of chronic inflammation, based on the volume of inflammatory fluid formation,

number of leucocytes, free radical activity and pouch tissue histology in the present study. In the carrageenan- induced granuloma air pouch. *Musa paradisica* was found to produce a significant inhibition of exudative fluid formation in rats. It further reduced the number of leucocytes and also the concentration of malondialdehyde (MDA) in the inflammatory exudates.

In addition, *MP* significantly enhanced the gluthathione level in the inflammatory exudates. Histological examination of the pouch tissue revealed that *MP* protect the tissue against damage induced by carrageenan in the granuloma air pouch model of chronic inflammation in rats. Granuloma air pouch model of chronic inflammation can be used to mimic the pathology of rheumatoid arthritis (RA), as it has similar morphological features to the disease, including tissue destructions patterns, infiltration of cells and the disease progression [14, 15].

Although rheumatoid arthritis pathophysiology is complex, inflammatory cells are the main activator of this disease, because they respond to the deposits of crystal in the joint of bones [16]. Similarly, the inflammatory cells are sensitized by the deposit of carrageenan in the granuloma air pouch model of chronic inflammation and during the process of phargocytosis, mediators of inflammation like as cytokines, prostaglandins, and leukotrienes are released [12, 14]. These mediators in turns produced inflammation and further promotes the infiltration leucocytes to the site of inflammation [17]. The activity of leucocytes is also known to cause the release of reactive species of oxygen, which will further progress tissue and bone destruction that characterized granulomatous inflammation and rheumatoid arthritis respectively [18]. Thus, effect therapy for the treatment of the disease should be directed at inhibition of leucocytes migration and leucocyte-mediated release of free radicals and other cytotoxic substances. The finding that *Musa paradisica* significantly modify the components of granuloma air pouch model of chronic inflammation assessed in this study suggest that it plays a role in the management of chronic inflammatory disorders like rheumatoid arthritis.

By using experimental models of severe acute pancreatitis, a known inflammatory bowel disease, several studies revealed that antioxidant attenuate nuclear factor kappa B (NF-kB) activation and cytokine generation [19]. In this study, the effect of *MP* on the concentration of gluthathone(GSH) in inflammatory exudates induced by carrageenan in the granuloma air pouch model of chronic inflammation in rats demonstrated significant increase in the level of GSH which shows antioxidant properties . The use of total leucocytes in exudates and exudates volume as an indicator of anti-inflammatory effect of *MP* is further used to explain the anti-inflammatory potency of *MP* which causes significant change in the number of leucocytes in

exudates and exudates volume when compared with water group. The increase activity of reactive oxygen species in the inflammatory fluid was inhibited by *MP* as evidenced by a significant reduction in the concentration of MDA and elevation of the levels of GSH in the fluid. GSH plays a vital role in protecting the cells from oxidative damage. It is well known that GSH in blood maintains cellular levels of the active forms of vitamin-C and vitamin-E by neutralizing the free radicals. GSH status is a highly sensitive indicator of cell functionality and viability. Form the results obtained in the present study, inflammation suppressed GSH and the rats treated with *MP* showed enhanced level of GSH, suggesting the antioxidant role of MP. Also, *MP* was able to enhance enzymatic antioxidant defense systems and served as natural protective barriers against lipid peroxidation.

Inactivation of COX-1 by NSAIDs caused a decrease in the tissue production of prostaglandins resulting in the development of gastric damage and renal toxicity [20]. NSAIDs with mechanism of action such as indomethacin inhibits COX-2 non-selectively, decreasing inflammation-associated prostaglandins but causing severe injury to the GIT. However, the use of NSAIDs is associated with severe gastrointestinal event such as gastric mucosa erosion, ulceration, bleeding and perforation [21]. The aforementioned side effect was obviously noticed in this study as the administration of indomethacin produced gross mucosa damage histologically, compared with the control.

Therefore, it is considered a consistent biomarker of leucocytes infiltration in the stomach. Thus, based on the understanding of the mechanism of gastrointestinal damage of NSAIDs. The effect of MP on the GIT was carried out in this study, which further show its strong anti-inflammatory properties as well as its gastroprotective and cytoprotective ability.

Conclusion

The results of this present studies show that *MP* has in vivo anti-inflammatory effects both in acute and chronic animal models of inflammation in rats. The inhibitory effect of *Musa paradisica* on granulomatous inflammation induced by carrageenan may also be related to its antioxidant property, suggesting the ability to reduce the progression of chronic inflammatory disease.

Funding

The authors receive no direct funding for this research

Competing Interests

The authors declare no competing interests that could influence objective data presentation, analysis and interpretation.

References

1. C. Romay, N. Ledon, R. Gonzalenz, Further studies on anti-inflammatory activity of phycocyanin in some animal models of inflammation. 1998, Inflamm. Res. 47, 334-338. doi:10.1007/s000110050338.
2. C. D. Funk, G. A. FitzGerald. COX-2 inhibitors and cardiovascular risk. 2007, J. Cardiovasc. Pharmacol. 50, 470–479. doi: 10.1097/FJC.0b013e318157f72d.
3. S. D. Anderson, J. Brannan, J. Spring, N. Spalding, L. T. Rodwell, K. Chan, I. Gonda, A. Walsh, A. R. Clark, A new method for bronchial-provocation testing in asthmatic subjects using a dry powder of mannitol. 1997, Am. J. Respir. Crit. Care Med. 156, 758-765. doi: 10.1164/ajrccm.156.3.9701113.
4. Inflammation and Healing, In: Harsh Mohan textbook of pathology. 7th ed. Jaypee Brothers Medical Publishers (P) Ltd., New Delhi, 2005, pp 114-121.
5. C. A. Winter, E. A. Risley, G. W. Nuss, Carrageenin-induced edema in hind paw of the rat as an assay for antiiflammatory drugs. 1962, Proc. Soc. Exp. Biol. Med. 111, 544-547. doi: 10.3181/00379727-111-27849.
6. H. Selye. On the mechanism through which hydrocortisone affects the resistance of tissues to injury; an experimental study with the granuloma pouch technique. 1953, J. Am. Med. Assoc. 152, 1207–1213. doi:10.1001/jama.1953.63690130001006.
7. E. Beutler, O. Duron, B.M. Kelly. Improved method for the determination of blood glutathione. 1963, J. Lab. Clin. Med. 61, 882– 888.
8. D. M. Olszewska-Słonina, D. Mątewski, R. Czajkowski, K. J. Olszewski, A. Woźniak, G. Odrowąż-Sypniewska, K. Lis, D. Musiałkiewicz, B. Kowaliszyn, The concentration of thiobarbituric acid reactive substances (TBARS) and paraoxonase activity in blood of patients with osteoarthrosis after endoprosthesis implantation. 2011, Med. Sci. Monit.17, CR498–504. doi: 10.12659/msm.881936.

9. H. P. Misra, I. Fridovich. The role of superoxide anion in the autoxidation of epinephrine and a simple assay for superoxide dismutase. 1972, J. Biol. Chem. 217, 3170–3175.
10. B. A. Alabi, T. O. Omobowale, A. Oyagbemi, I-O. B. Emmanuel, A. A. Adedapo, O. Fagbemi, E. O. Iwalewa. *Corchorus olitorius* extract attenuate isoproterenol-induced cardiac injury via inhibition of oxidative stress, arrhythmia and pro-apoptotic protein Bax expression. 2020, J. Complement. Altern. Med. Res. 10, 17-28. doi: 10.9734/jocamr/2020/v10i230159
11. M. P. Holsapple, M. Schnur, G. K. Yim, Pharmacological modulation of edema mediated by prostaglandin, serotonin and histamine. 1980, Agents Actions. 10, 368-373. doi: 10.1007/BF01971442.
12. R. B. Zurier, Prostaglandins and inflammation. In: P. B. Curtis-Prior (ed.). Prostaglandins. Biology and Chemistry of Prostaglandins and Related Eicosanoids. Churchill Livingstone, Oxford, United Kingdom, 1988, pp. 595-615.
13. J. R. Vane. Inhibition of prostaglandin synthesis as a mechanism of action for aspirin-like drugs. 1971, Nat. New Biol. 231:232–235. doi: 10.1038/newbio231232a0.
14. K. F. Benitz, and L.M Hall. The carrageenan-induced abscess, a new test for anti-inflammatory activity of steroids and non-steroids. 1963, Arch. Int. Pharmacodyn. Ther. 144, 185-195.
15. V. R. Winrow, P. G. Winyard, C. J. Morris, D. R. Blake. Free radicals in inflammation: second messengers and mediators of tissue destruction. 1993, Br. Med. Bull. 49 506-522. doi: 10.1093/oxfordjournals.bmb.a072627.
16. K. Yuhki, A. Ueno, H. Naraba, F. Kojima, F. Ushikubi, S. Narumiya, S. Oh-ishi. Prostaglandin receptors EP2, EP3, and IP mediate exudate formation in carrageenin-induced mouse pleurisy. 2004, J. Pharmacol. Exp. Ther. 311, 1218–1224. doi: 10.1124/jpet.104.071548.
17. G. Hasçelik, B. Sener, Z. Hasçelik. Effect of some anti-inflammatory drugs on human neutrophil chemotaxis. 1994, J. Int. Med. Res. 22, 100-106. doi: 10.1177/030006059402200206.
18. D. J. Pattison, A. J. Salman, N. J. Goodson, M. Lunt, D. Bunn, R. Luben, A. Welch, S. Bingham, K-T Khaw, N. Day, D. P. M. Symmons, Vitamin C and the risk of developing inflammatory polyarthritis: prospective case-control study. 2004, Ann. Rheum. Dis. 63, 843-847. doi: 10.1136/ard.2003.016097.

19. E. M. Boyle. Jr., T. H. Pohlman, M. C. Johnson, E. D. Verrier. Endothelial cell injury in cardiovascular surgery: the systemic inflammatory response. 1997, Ann. Thorac. Surg. 63, 277-284. doi: 10.1016/s0003-4975(96)01061-2.
20. C Yuan, R. S. Sidhu, D. V. Kuklev, Y. Kado, M. Wada, I. Song, W. L. Smith. Cyclooxygenase Allosterism, Fatty Acid-mediated Cross-talk between Monomers of Cyclooxygenase Homodimers. 2009, J. Biol. Chem. 284, 10046–10055. doi: 10.1074/jbc.M808634200.
21. D. L. Simmons, R. M. Botting, T. Hla. Cyclooxygenase isoenzyme: the biology of prostaglandin synthesis and inhibition. 2004, Pharmacol. Rev. 56; 387-437. doi.org/10.1124/pr.56.3.3