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Original Research Article

Unlocking the Therapeutic Potential: Ethanol Extract from *Musa paradisiaca* L. Var Sapientum Peel in the Modulation of CFA-Induced Rheumatoid Arthritis and Immunomodulatory Responses

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ABSTRACT

Immunomodulatory agents help maintain a balanced immune system by suppressing excessive immune response or by stimulating the immune system. This study aims to determine the antirheumatoid arthritis and immunomodulatory activities of ethanol extract of *Musa paradisiaca* L. Var Sapientum peel. Wistar rats were divided into five groups, and induced with rheumatoid arthritis by the intraplantar administration of Complete Freund's Adjuvant (CFA). On day 17 following CFA-induction, the rats were treated as follows; Group 1 (Negative control): sodium carboxymethyl cellulose (1%), Group II (Positive control): diclofenac sodium, Groups III, IV, and V: banana peel extract at doses of 100 mg/kg, 300 mg/kg, and 500 mg/kg, respectively. All treatments were administered orally once daily for 14 days. Paw volume was measured on day 1, 17, and 31. Percentage reduction in paw edema and arthritis index was also measured. Immunomodulatory test was done using delayed-type hypersensitivity which was induced by intraperitoneally and intraplantar administration of 10% sheep red blood cells (SRBC) on 3rd and 7th day. Banana peel extract (100 mg/kg, 300 mg/kg, and 500 mg/kg) was administered orally for 7 days. Paw volume was measured at 4 h (T4), 24 h (T24), and 48 h (T48). Results show that banana peel extract had antirheumatoid arthritis effect. The 100 mg/kg dose was the most effective, with 37.93% reduction in paw edema and an arthritis index of 0.83. In addition, the extract showed activity as immunomodulator at all doses. Therefore, banana peel extract has potential for use as anti-rheumatoid arthritis and immunomodulatory agent.

***Keywords*:** Antirhematoid, CFA-Induced, Immunomodulatory, Inflammation, *Musa paradisiaca L. Var Sapientum.*

Introduction

The immune system plays a vital role in defending the body against pathogens, including bacteria, viruses, parasites, and other pathogenic organisms or foreign matter. The immune response is determined by the ability of the immune system to identify a foreign substance (antigen) and initiate the proper response to eradicate the antigen.[1,2]

When the immune system is compromised, the body becomes vulnerable to attack by various disease causing organisms. Hence, it is important to maintain an optimal immune system in order to withstand attacks by foreign substances such as pathogenic microorganisms. One way to maintain an optimal immune system is by the use of immunomodulators. Immunomodulators are substances that help normalize the immune response in situations where there is a compromised immune system.[1]

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Immunomodulatory compounds normalize the immune response by stimulating the immune system, inhibiting excessive immune responses, increasing the production and activation of immune cells such as B cells, T cells, and NK cells, as well as increasing the activation of regulatory T cells (Treg) which are essential components in maintaining immunological tolerance and prevents excessive immune response.[2-4] Immunomodulators can also increase the ability of macrophages and neutrophils to carry out phagocytosis. They can influence the maturation and function of dendritic cells to ensure they effectively present antigens to T cells.

Complete Freund's Adjuvant (CFA) is a commonly used agent in immunological research to stimulate the immune response. The whole adjuvant induction by Freud causes inflammatory reactions.[5] CFA contains dead mycobacteria that can cause significant local inflammatory reactions at the injection site. This inflammation involves the release of various cytokines and pro-inflammatory chemokines that attract immune cells to the area, causing edema. It can also be used to induce arthritis in experimental animals, which is characterized by swelling of the joints and edema.[6,7]

Bananas *(Musa paradisiaca* L. VarSapientum), especially the peel, have many benefits, one of which is its use as medicine. It has the potential to be developed into useful functional food and nutraceuticals.[8,9] Banana peel waste has not been widely utilized despite its nutritional value as a rich source of proteins and carbohydrates. Banana peel also contains secondary metabolites like flavonoids, terpenoids, and tannins.[10,11] Flavonoids are well known for their antioxidant properties, and antioxidants can act as immune system boosters.[12] Based on the foregoing, the present study aims to investigate the effect of banana peel as an immunomodulator that could have a therapeutic role in the management of rheumatoid arthritis (RA).

Materials and Methods

Equipment and chemicals
Plethysmometer (panlab), analytical balance (ohaus), Complete Freund's Adjuvant (CFA), 70% ethanol, distilled water, 1% Na-CMC, Diclofenac Sodium.

Collection of plant sample
The peels of banana (*Musa Paradisiaca* L. VarSapientum) (Figure 1) were collected from Makassar City, South Sulawesi Province, Indonesia. The samples were cleaned using clean running water. The cleaned samples were cut into small pieces, air-dried, and then powdered.

a b

Figure 1: (a) Banana *(Musa paradisica*L. VarSapientum*),* **(b)** *Musa paradisica* L. Var Sapientum Peel

Preparation of banana peel extract
The powdered banana peels (500 g) were macerated with 70% ethanol at room temperature for 24 h while protected from direct sunlight. The extract was filtered, and the residue was remacerated in 70% ethanol under the same condition. The combined extract was concentrated to dryness using a rotary evaporator at reduced pressure.

Animals
Male Wistar rats were used for the study. The animals were acclimatized to the laboratory conditions in the Pharmacology Laboratory of the Faculty of Pharmacy at Universitas Muslim, Indonesia) for 7 days. They were fed with standard rodent pellets and allowed free access to drinking water. The study was approved by ethics committee with ethical approval number: UMI011803073.

Evaluation of anti-rheumatoid arthritis activity
The Wistar rats were divided into 5 groups (I – V), and were induced with CFA (0.1 mL) intraplantarly on the first day and left until the 16th day. From the 17th day to the 30th day (14 days), the groups of experimental animals were treated as follows; Group I (Negative control) was administered Na-CMC (1%), Group II (Positive control) was administered diclofenac sodium, Groups III, IV, and V were administered the banana peel extract at doses of 100 mg/kg, 300 mg/kg, and 500 mg/kg, respectively. All treatments were administered orally once a day. Paw volume of each rat was measured on the 1st day (before induction with CFA), the 17th day (before administration of the extract), and the 31st day (after administration of the extract).
Inhibition of paw edema wascalculated using the following formula:
Inhibition of edema (%) = $[(a-b)/a]$ x 100
Where; a = average rat paw volume before treatment, b = average rat paw volume after treatment.
Arthritis index was estimated based on the parameters in Table 1 below.[13, 14]
Each rat in the group was observed for the arthritis scoring index. Rats were declared to have rheumatoid arthritis if they have an arthritis scoring index of ≥ 1.

Test for delayed type hypersensitivity (DTH)
The test animals were divided into 5 groups (I – V). Rats in group I served as the control, they were not induced with sheep red blood cells (SRBC), and were not administered the extract. Group II rats were induced with 10% SRBC, and were without extract administration. Group III rats were induced with 10% SRBC and administered the extract at 100 mg/kg, group IV rats were induced with 10% SRBC and administered the extract at 300 mg/kg, while group V rats were induced with 10% SRBC and administered the extract at 500 mg/kg.
The banana peel extract was administered orally once daily for 7 days. On the 3rd day, rats in groups II, III, IV, and V were induced with 1 mL of 10% SRBC (antigen) intraperitoneally. On the 7th day, the animals in groups II, III, IV, and V were re-induced with 0.5 mL of 10% SRBC intraplantarily. The size of the edema was measured using a plethysmometer at 4 hours (Th4), 24 hours (Th24), and 48 hours (Th48) after intraplantar induction with 0.5 mL of 10% SRBC.[13, 14]

Statistical analysis
Data were subjected to descriptive analysis, paired samples T-test, followed by the One-Way Analysis of Variance (ANOVA), normality test using the Shapiro-Wilk test. Differences between means were analyzed using LSD post-hoc test, Kruskal-Wallis test, followed by Mann-Whitney test.

Table 1: Parameters of arthritis scoring index

No.	Symptoms of Arthritis	Score
1	One toe is swollen and red	0.25
2	At least two toes are swollen and red	0.50
3	Swelling of the feet's soles	0.75
4	Toes are swollen and red, as well as changes to the size of foot soles	1.00
5	Both toes and soles are swollen and red	1.25
6	Toes are swollen and red, as well as little swelling of the soles and ankles	1.50
7	The fingers and soles of the feet are swollen and red, as well as swelling in almost all the soles and ankles	1.75
8	Toes, soles, and ankles are swollen and red	2.00

Results and Discussion

The immune system serves as the body's defense mechanism against threats from a wide range of dangerous pathogens, including bacteria, viruses, and other disease causing germs. The immune system can be maintained by the use of immunomodulatory agents. This study examined the immunomodulatory properties of banana peel ethanol extract in CFA-induced rheumatoid arthritis in rats.
Anti-rheumatoid arthritis effect of banana peel extract
The mean paw volume of rheumatoid arthritis rats before and after treatment with banana peel extract are shown in Table 2. There was a decrease in paw volume on day 31 after treatment with the extract. At doses of 100 mg/kg and 300 mg/kg, banana peel extract resulted in a significant reduction in paw volume compared to the control. Results have shown that the banana peel extract caused 37.93%, and 32.81% reduction of paw volume after 14 days of treatment with 100 mg/kg, and 300 mg/kg, respectively, of banana peel ethanol extract (Table 3).

Effect of banana peel extract on arthritis index
The arthritis index is an observation parameter used to determine whether or not the rats have rheumatoid arthritis. This observation was done by giving a value in the form of a score on the feet of the rats. Table 4 shows the mean arthritis index (AI) before and after treatment with the extract, and the results showed an increase in AI after 14 days of treatment with the extract.
This study used CFA intraplantarly to cause arthritis in the test animals. CFA is widely used to induce arthritis in various laboratory animal model, including rats. CFA injection triggers tissue damage which causes increased vascularization, T-cell infiltration, and activates macrophages to produce inflammatory cytokines such as TNF-α.[15,16]

Tables 2, 3, and 4 show a decrease in paw volume (edema) and arthritis index in all treatment groups compared to the control (Na-CMC). Group I (negative control) showed a low paw volume of only 6.06% and an arthritis index of 1.33 ± 0.14. Despite the low AI value, it still indicated the occurrence of RA (arthritis index ≥1).

Table 2: Rats paw volume before and after treatment with banana peel extract

Group	Paw volume (mL)		
	Day 1	Day 17	Day 31
I: Control	1.09 ± 0.31	1.98 ± 0.35	1.86 ± 0.75
II: CFA + Na.Diclofenac	1.05 ± 0.08	1.94 ± 0.39	1.16 ± 0.24
III: CFA + extract 100 mg/kg	1.17 ± 0.07	2.03 ± 0.12	1.26 ± 0.06
IV: CFA + extract 300 mg/kg	0.87 ± 0.05	1.92 ± 0.10	1.29 ± 0.06
V: CFA + extract 500 mg/kg	1.15 ± 0.55	2.04 ± 0.27	1.76 ± 0.42

Values are Mean ± SD

Table 3: Percentage reduction in rat paw volume after treatment with banana peel extract

Group	Reduction in paw volume (%)
I	6.06
II	40.21
III	37.93
IV	32.81
V	13.73

In group II (diclofenac sodium), the paw volume reduction was up to 40.21%, indicating a very significant anti-rheumatoid arthritis effect in response to CFA-induced rheumatoid arthritis. It has been demonstrated that the non-steroidal anti-inflammatory drug (NSAID), diclofenac, sodium effectively reduces inflammation and arthritis symptoms.This corroborated the arthritis index result, which showed an arthritis index below 1, which is indicative of healing. Animals in this group experienced a **more significant** decrease in paw volume compared to the other groups. This is due to the fact that diclofenac sodium is a medication used in pharmacological therapy for rheumatoid arthritis.

Treatment Groups III, IV, and V received varying doses of the banana peel extract. Paw volume decreased by 37.93% in Group III (100 mg/kg), suggesting that the banana peel extract at a dose of 100 mg/kg may have anti-inflammatory properties.Group IV, administered banana peel extract at a dose of 300 mg/kg showed a decrease in paw volume of 32.81% indicating a lower anti-inflammatory effect compared to group III. At 500 mg/kg dose (Group V), the extract resulted in a 13.73% reduction in paw volume, and an arthritis index above 1. This indicates that at this dose the extract may be less effective in relieving arthritis symptoms compared to lower doses.

The existence of a non-linear dose response with therapeutic effects shows the complexity of the interaction between the active components in the extract and the biological response. There may be a saturation point or even opposite effects at higher doses. The findings from this study indicate that higher extract doses do not produce significant therapeutic effects compared to lower extract doses, which needs further investigation.

The secondary metabolites; flavonoids, terpenoids, and tannins found in banana peels are thought to be responsible for the anti-arthritis activity of the extract. These substances, particularly flavonoids act as antioxidants and are useful in shielding the body against various oxidative stressors. Antioxidants play a role in the prevention and management of several illnesses, including chronic degenerative conditions such as rheumatoid arthritis.[17,18] From the observations highlighted above, it could be explained that the ethanol extract of banana peels at a dose of 100 mg/kg successfully acted as an anti-rheumatoid arthritis agent.

Effect of banana peel extract on delayed type hypersensitivity (DTH)

The DTH method is simple, fast, and can easily detect changes in the immune system. DTH is an immunological reaction mediated by T-cells and usually takes 24-72 hours to develop after antigen exposure. The DTH method is often used in research for cellular immune responses to various antigens. The antigen used in this study was sheep red blood cells (SRBC). The SRBC is used because it is a polyvalent antigen, a protein with more significant determinant potential compared to monovalent antigens. SRBC antigens are easier to make and safer compared to bacteria antigens. The more foreign the antigen used, the more influential the immune response generated will be.

In this study, SRBC (10% v/v) was used as an immunogenic antigen - antigens originating from genes of other species.[19] SRBC antigen injection was administered twice. The first injection was intraperitoneal, which is the stage of recognizing the test animal's immune system against the antigen or the sensitization phase. The purpose of the first injection is to activate T-cells to produce a faster and more specific immune response. The second injection was administered intraplantarily or in the effector phase, namely - as re-exposure to the antigen. The second injection aims to find out if there is an immune response in the form of a local inflammatory reaction.

Table 5 displays the immunomodulatory effects of banana peel ethanol extract with respect to DTH. There were no changes in the paw edema in the normal control group because this group was not induced with antigen. In group II, which was induced with RBCS, but no extract treatment showed only a slight reduction in edema, but significantly different compared to the control. This indicates that the RBCS antigen successfully stimulated inflammation.

Groups III, IV, and V which were induced by RBCS (10% v/v) and treated with the banana peel extract at a doses of 100 mg/kg, 300 mg/kg, and 500 mg/kg, respectively showed significant alterations in the paw edema ($p < 0.05$). This proves that banana peel ethanol extract can modulate the immune system of experimental animals. Meanwhile, comparison between each extract group, the extract group at doses of 300 mg/kg BW and 500 mg/kg resulted in no significant changes in the edema ($P > 0.05$). However, at a dose of 100 mg/kg, the extract resulted in a significant increase in paw edema ($p < 0 .05$).

It is important to note that the extracts at different doses stimulated an immunological response, as seen by an increase in paw edema in the first 4 h (T4), followed by a decrease in the edema at 24 h (T24), and at 48 h (T48). The extract group with the greatest reduction in paw edema was the extract group given at a dose of 100 mg/kg. Therefore, a dose of 100 mg/kg was shown to be more effective in modulating the immune response.

The increase in edema at 4 h after antigen induction (T4), suggests that antigen can stimulate an immediate inflammatory immune responses such as TNf-α and IL-6. At T24 and T48, the extract stimulated immune responses such as the cytokines IL2 and Inf-ɣ. Increasing the dose of the extract was not accompanied by an increase in the immune response, perhaps because the T-lymphocyte receptors had been occupied by the active compounds in the extract.

Too large an extract dose allows many active compounds to be free and not bind to the receptor. This can potentially interfere with compounds bound to the receptor because the drug binding to the receptor is a weak

bond, and can easily be displaced. As a result, the resulting immune response was not optimal.

The ethanol extract of banana peels can improve the immune system, allegedly because they contain flavonoids. Flavonoids have been shown to act as **immunomodulators that** boost IL-2 activity and the proliferation of lymphocytes. Th-1 cells will then become activated due to CD4+ cells influencing lymphocyte proliferation. Activated Th-1 cells affect IFN-γ, which in turn activate macrophages, which are more effective at eliminating antigens and exhibit a quick phagocytic activity.[20]

Antirheumatoid arthritis and immunomodulator compounds

Rheumatoid arthritis (RA) is an autoimmune condition typified by joint inflammation that can harm the surrounding tissue as well as the joints themselves. In this condition, the immune system attacks joint tissue and causes chronic inflammation. Therefore, the management of RA often involves the use of various types of medications, including immunomodulatory compounds. Immunomodulatory compounds can improve RA symptoms such as pain, swelling/edema, and redness.[18,21] Immunomodulators work by balancing the immune system by suppressing excessive immune responses or by stimulating necessary immune responses. In RA, the goal is to suppress the activity of T-cells and pro-inflammatory cytokines that cause joint inflammation.

Table 4: Arthritis index of rats before and after treatment with banana peel extract

Group	Arthritis Index (mL)		
	Day 1	Day 17	Day 31
I	0.00 ± 0.00	1.42 ± 0.14	1.33 ± 0.14
II	0.00 ± 0.00	1.67 ± 0.14	0.92 ± 0.14
III	0.00 ± 0.00	1.17 ± 0.14	0.83 ± 0.29
IV	0.00 ± 0.00	1.33 ± 0.29	1.08 ± 0.29
V	0.00 ± 0.00	1.83 ± 0.14	1.58 ± 0.14

Values are Mean ± SD

Table 5: Rats paw edema after treatment with banana peel extract in DTH

Group	Paw edema (mL)			
	T0 (hour)	T4 (hour)	T24 (hour)	T48 (hour)
I: Normal control	0.99 ± 0.006	0.99 ± 0.006	0.99 ± 0.006	0.99 ± 0.006
II: SRBC 10%	1.05 ± 0.05	1.33 ± 0.01	1.32 ± 0.06	1.26 ± 0.06
III: SRBC 10% + extract 100 mg/kg	1.02 ± 0.02	1.55 ± 0.09	1.15 ± 0.04	1.03 ± 0.02
IV: SRBC 10% + extract 300 mg/kg	0.99 ± 0.006	1.25 ± 0.07	1.17 ± 0.02	1.02 ± 0.02
V: SRBC 10% + extract 500 mg/kg	0.98 ± 0.03	1.30 ± 0.06	1.18 ± 0.01	1.00 ± 0.02

Values are Mean ± SD, DTH = Delayed type hypersensitivity

Conclusion

The findings from this study have shown that ethanol extract of banana peels can modulate the immune system and reduce edema in rats with rheumatoid arthritis. Therefore, reducing inflammation can help maintain joint integrity and function.

Conflict of Interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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