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Research Article

Safety, anti-inflammatory and analgesic assessments of methanolic extract of *Musa paradisiaca* peel in Sprague Dawley rats

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Background: *Musa paradisiaca* peel is used in folklore for the treatment of inflammation and pains without any scientific evidence.

Objective: The present study, therefore, evaluated the safety, anti-inflammatory and analgesic effects of the methanolic extract of *M. paradisiaca* peel.

Methods: The methanolic extract of *M. paradisiaca* was administered orally in three different doses; 100, 200 and 400 mg/kg to Sprague Dawley rats. The anti-inflammatory effect of *M. paradisiaca* peel was tested in egg albumin-induced paw edema and compared to ibuprofen (25 mg/kg). The analgesic effect was evaluated using formalin-induced paw licking and acetic acid-induced writhing and compared to indomethacin (10 mg/kg). Also, after 21 days of extract administration rats were sacrificed serum was extracted from blood and evaluated for liver, renal function indices and lipid profile. Kidney and liver were excised and weighed.

Results: The methanolic extract of *M. paradisiaca* produced analgesia and decreased inflammation significantly ($p<0.05$) and in a dose dependent manner. The anti-inflammatory and analgesic effects were significant ($p<0.05$) at 400 mg/kg of *M. paradisiaca* when compared to ibuprofen (25mg/kg) and indomethacin (10mg/kg) respectively. Furthermore, *M. paradisiaca* did not produce significant ($p>0.05$) effects on organ weight, serum alkaline phosphatase, aminotransferases, conjugated bilirubin, total bilirubin, total cholesterol, triglyceride, low density lipoprotein, high density lipoprotein, glucose, creatinine, urea, uric acid, total protein, albumin, and serum electrolytes when compared to control.

Conclusion: This study observed that the methanolic extract of *M. paradisiaca* peel has anti-inflammatory and analgesic effects and may be safe with use.

Key words: *Musa paradisiaca,* anti-inflammatory, analgesic, toxicity, rats

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1. Introduction

Medicinal plants are a rich source of phytochemicals which can be used for drug development and synthesis. They play a critical role in the development of human cultures and in the treatment of diseases in the world (Fallah-Hosein et al, 2006). Recently, World Health Organization (WHO) formulated strategy for the development and promotion of traditional medicine (Naseri, 2004). Medicinal plants materials include leaves, flowers, fruit, seeds, stems, wood bark, roots, rhizomes or other plant parts, which may be entirely

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fragmented or powdered. In some countries, these materials may be processed by various local procedures (WHO, 2004). *Musa paradisiaca* is a medicinal plant that has its male and female reproductive organs on different flowers of the same individual plant. It belongs to the natural order; plantaginaceae which contains more than 200 species (Swathi et al*,* 2011). It grows 10-40 feet in height and has unusual broad green leaves which grow through hollow stem that bears flowers and fruit. It grows in all tropical areas (Phungo et al*,* 2012). *Musa paradisiaca* has been cited for the treatment of many disorders, although many of the claims have not been scientifically proven. The main documented pharmacological effects of this plant are anti-ulcer, wound healing, antioxidant, antidote for snake bite, hypoglycemic, atherogenic, and relaxation of skeletal muscles (Swathi et al*,* 2011). Flavonoids, tannins, phlobatannins, alkaloids, glycosides and terpenoids are compounds present in the ripe and unripe peels of *M. paradisiaca* (Ighodaro, 2012).

Inflammatory response is a complex process that includes the activation of white blood cells, the release of immune system chemicals such as complements and cytokines, and the release of inflammatory mediators (Ben et al*,* 2016). Inflammation may be acute or chronic depending on the disease course. Acute inflammation is characterized by heat, erythema, pain, swelling and loss of function (Tracy, 2006). Chronic inflammation on the other hand, results in a progressive shift in inflammatory cells characterized by simultaneous destruction and healing of the injured tissue (Tracy, 2006).

Biochemical mediators released during inflammation intensify and propagate the inflammatory response. These mediators are the target of anti-inflammatory agents (Ben et al*,* 2016). The cyclooxygenase enzymes (COX1 and COX2) play major roles in inflammation. Although COX-2 is the dominant cyclooxygenase in inflammation, there is suggestion that both isoforms of the human enzyme may contribute to acute inflammatory response. This is the mainstay for the use of non- steroidal anti-inflammatory drugs in the management of inflammation (Satyanarayana et al, 2004; Nkeh-Chungag et al*,* 2009).

Pain is a common and distressing feature of many diseases and analgesics relieve pain by acting on the central nervous system or on peripheral pain mechanisms (Satyanarayana et al*,* 2004). Several modern drugs are effectively used for the management of inflammation and algesia. Despite the progress in the discovery of anti-inflammatory and analgesic drugs, the chronic use of these drugs is hampered by their adverse effects such as hepatotoxicity, nephrotoxicity, gastric lesions or tolerance (Nkeh-Chungag et al*,* 2009).

It is therefore important to search for potent analgesic and anti-inflammatory drugs with less adverse effects from plant source. Therefore, the present study evaluated the anti-inflammatory and analgesic effects of the methanolic extract of *Musa paradisiaca* peel in Sprague Dawley rat. Also, its safety profile was evaluated on the liver and kidney function and lipid parameters.

2. Methods

2.1 Drugs and Plants

Indomethacin and Ibuprofen used for this study were obtained from a registered pharmacy in Port Harcourt, Rivers State. Ibuprofen (Ranbaxy Laboratories India) and indomethacin (Sun Pharmaceuticals Industries India) were used for this study. The ibuprofen and indomethacin were dissolved in physiological normal saline. Unripe plantain peels were collected in January, 2015 from Uratta, Owerri North, Imo state Nigeria. It was botanically identified at the Department of Pharmacognosy, Madonna University, Elele.

2.2 Preparation of plant extract

The fresh peels of unripe *M. paradisiaca* were air-dried for 21 days, after which the peels were chopped and powdered. 500g of the powder was macerated with methanol (1700ml) for 72hours with constant stirring by keeping the mixture on a mechanical shaker. The extract was filtered and concentrated using a rotary evaporator. The yield of the extract was found to be 47.5g. A specific amount was taken out for phytochemical analysis and the remainder was stored in the refrigerator for further use.

2.3 Animals

Seventy five Sprague Dawley female rats (150-170g) were used for this study. They were kept in the Animal House of the Department of Pharmacology and Toxicology, Madonna University, Elele Rivers State. They were allowed to acclimatize to laboratory conditions for 1 week prior to the experiment during which they were introduced to growers' mash. They animals were housed in clean gauze cages, having free access to feed and water and maintained under standard conditions.

2.4 Formalin -induced paw licking

The procedure was performed as described by Correa and Calixto (1993). Twenty (25) rats were used for this study. They were grouped into 5 groups of 5 rats each. Group I (control) received 0.3ml of water p.o., group II (standard drug) received 10mg/kg of indomethacin p.o., group III, IV and V received extract, which was triturated with distilled water and administered to rats at doses; 100mg/kg, 200mg/kg and 400mg/kg p.o. respectively, 30minutes before the induction of pain. Pain was induced by injecting 0.2ml of formalin into the hind paw of each rat. Their reaction to pain was noted, by counting the number of times they licked the site of formalin injection between 5-15 minutes.

2.5 Acetic acid -induced writhing

This was carried out according to the procedure described by Sawadogo et al, (2006).Twenty five 25 rats were divided in to 5 groups of 5 each. Group 1 (control) received 0.3ml of water p.o, group II (standard drug) received 10mg/kg of indomethacin p.o., and group III, IV and V received extract, which was triturated with distilled water (100 mg/kg, 200 and 300 mg/kg) p.o respectively. Thirty minutes later, 0.1 ml of 1% acetic acid was injected intraperitoneally, and the number of

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writhing movements was observed for 15 minutes beginning from 5 minutes after the injection of acetic acid. The percentage inhibition of writhing movement was calculated.

2.6 Egg albumin-induced inflammation

Inflammation was induced as reported by Akah and Nwanbie, 1994. Twenty five (25) rats were used. The rats were grouped into 5 groups of 5 rats each. Group I (control) received 0.3ml of water p.o., group II (standard drug) received 25 mg/kg of ibuprofen p.o, groups III, IV and V received the extract, which was triturated with distilled water and administered to rats at doses 100mg/kg, 200mg/kg and 400mg/kg p.o. respectively 30minutes before the induction of inflammation. Inflammation was induced by injecting 0.2ml of egg albumin into the hind paw of each rat. The hind paws of these animals were measured at 0 minutes i.e. before induction of inflammation and at 1 hour interval for 4 hours after inflammation was induced.

2.7 Toxicity evaluation

At the end of anti-inflammatory and analgesia evaluation of the extract, the oral administration of 100, 200 and 400mg/kg of the extract was continued for 21 days.

2.8 Collection of sample

At the end of 21 days of drug administration rats were sacrificed under inhalational diethyl ether. The liver and kidney were excised and weighed. Blood samples were collected via cardiac puncture, centrifuged at 250 rmp for 20 minutes and serum extracted and evaluated for liver and renal function parameters and lipid profile.

2.9 Evaluation of liver and renal function parameters and serum lipid profile

Serum creatinine, urea, albumin, total protein, aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase (ALP), total bilirubin (TB), conjugated bilirubin (CB), total cholesterol (TC), triglyceride (TG), high density lipoprotein cholesterol (HDL-C) and bicarbonate (HCO_3^-) were evaluated using standard laboratory test kits. Serum glucose (G) was evaluated using glucometer while low density lipoprotein cholesterol (LDL-C) was determined using Friedwald equation. Potassium (K^+) and sodium (Na^+) were determined using flame photometric methods while chloride (Cl^-) was determined using titrimetric method.

2.10 Statistical analysis

The graph pad prism, version 5.0 was used for the analysis of data. All the data presented are expressed as mean ± standard deviation. The statistical significance/comparative analysis between control and treated groups were analyzed using ANOVA.

3. Results and Discussion

Medicinal plants have formed the basis of health care since the earliest times of humanity and are still being widely used (Deka et al, 2011). The clinical, pharmaceutical and economic values of medicinal plants continue to grow, at different rates, relative to ethnicity (Maheshwari et al, 2013). Chemodiversity in plants has proven to be important in pharmacological research and drug development, not only for the isolation of bio-active compounds used directly as therapeutic agents, but as leads for the synthesis of drugs or as models for pharmacologically active compounds (Maheshwari et al, 2013). The rapid identification of bio-active compounds, however, is critical if this tool of drug discovery is to compete with developments in technology. The medicinal capability of a plant is dependent on its phytochemical constituents (Abbas et al, 2015). The phytochemical screening of *M. paradisiaca peel* shows the presence of flavonoids, tannins, glycosides, reducing sugars, carbohydrates, proteins, alkaloids and saponins. This observation is consistent with similar findings (Gupta et al, 2011).

Acetic acid-induced writhing test is a non-specific, but sensitive method widely used for analgesic screening (Le Bars et al, 2001). The oral administration of 100, 200 and 400 mg/kg of *M. paradisiaca* significantly ($p<0.05$) inhibited acetic acid-induced writhing in a dose dependent manner when compared to control (**Table 1**). Acetic acid has been found to cause an increase in peritoneal fluid levels of prostaglandins (PGE2 and PGF2), hence causing inflammatory pain by inducing capillary permeability (Amico-Roxas et al, 1984). The observed effects in the present study suggest that *M. paradisiaca* had an inhibitory effect on prostaglandins synthesis.

Formalin test has been described as a convenient method for producing and quantifying pain in rats (Tjolsen et al, 1992). The test employs an adequate painful stimulus to which the animals show a spontaneous response and it is sensitive to commonly used analgesics (Ghannadi et al, 2005). Intraplantar injection of 0.2ml of formalin evoked a characteristic licking response in the albino rats. However, the oral administration of 100, 200 and 400 mg/kg of *M. paradisiaca* significantly decreased ($p<0.05$) formalin-induced paw licking in a dose dependent fashion when compared to control (**Table 2**). The observed decrease in paw licking in rats administered with 400mg/kg of the extract was significant ($p<0.05$) when compared to 10mg/kg of indomethacin.

Egg albumin-induced inflammation model is a significant test for the evaluation of the anti-inflammatory effect of a putative drug. It has been reported that egg-albumen induced inflammation is similar to that produced by carrageenin (Akah et al, 1993). Significant ($p<0.05$) inflammatory reaction was observed in rats administered with 0.2ml of egg albumin into the hind paw when compared to control. On the other hand, egg albumin-induced paw inflammation was significantly ($p<0.05$) decreased in a dose dependent manner in rats administered with the extract of *M. paradisiaca* when compared to control. The observed decrease at 400mg/kg of the extract differ significantly at $p<0.05$ from the group treated with 25 mg/kg of ibuprofen (**Table 3**). Egg albumin is a potent edematous agent which produces inflammation through the release of some mediators of inflammation and increases vascular permeability thus bringing about fluid accumulation in tissues leading to edema (Ibegbu

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et al, 2012). The early phase of oedema, beginning from 1 h after the administration of the irritant, may be due to the release of histamine and serotonine, while the later phase, occurring from 3 to 5h after the administration of the irritant could be induced by bradykinin, protease, prostaglandin and lysosome (Harriot et al, 2004).

Table 1: Effect of methanolic extract of *M. paradisiaca peel* on acetic acid-induced writhing in rats

Treatment	Number of wriths/15 min	% inhibition
Control	40.5±5.07[a]	
100mg/kg MP	30.3 ±3.11[b]	25.2
200mg/kg MP	21.5 ±3.46[c]	46.9
400mg/kg MP	12.9 ±2.24[d]	68.2
10 mg/kg IM	10.5 ±2.13[d]	74.1

IM= Indomethacin. MP= *M. paradisiaca.* Results are presented as mean ± SD.
Values with different superscript down the column differ significantly at p<0.05 ANOVA.

Table 2: Effect of methanolic extract of *M. paradisiaca peel* on formalin-induced paw licking in rats

Treatment	Licking time	Licking frequency/10min
Control	28.5±5.07[a]	40.5± 6.35[a]
100mg/kg MP	20.5 ±3.11[b]	31.3 ± 1.37[b]
200mg/kg MP	14.5 ±3.46[c]	22.4 ± 1.54[c]
400mg/kg MP	8.9 ±2.24[d]	10.7 ± 1.46[d]
10 mg/kg IM	12.5 ±2.13[c]	15.4 ± 1.25[e]

IM= Indomethacin. MP= *M. paradisiaca.* Results are presented as mean ± SD.
Values with different superscript down the column differ significantly at p<0.05 ANOVA.

Table 3: Effect of methanolic extract of unripe peel of *M. paradisiaca* on egg-albumin induced inflammation in rats.

Treatment	0 hour	1 hour	2 hours	3 hours	4 hours
Control	2.17±0.06 [a]	3.35 ±0.03 [a]	3.73 ± 0.04 [a]	4.98 ± 0.02 [a]	5.23 ± 0.05 [a]
100mg/kg MP	2.13±0.05 [a]	2.75 ± 0.04[b]	2.6 0± 0.07 [b]	2.00 ± 0.03[b]	1.52 ± 0.02 [b]
200mg/kg MP	2.08±0.03 [a]	2.00 ± 0.09[c]	2.10± 0.04 [c]	1.45 ± 0.07[c]	1.10 ± 0.01[c]
400mg/kg MP	2.00±0.07 [a]	1. 40 ±0.02 [d]	1.00 ± 0.03 [d]	0.90 ± 0.03[d]	0.50 ± 0.05[d]
25 mg/kg 1B	2.00 ±0.01 [a]	2.10 ±0.02 [c]	1.5 0± 0.01 [e]	1.40 ± 0.06[c]	1.00 ± 0.07 [c]

IB= Ibuprofen. MP= *M. paradisiaca* .Results are presented as mean ± SD.
Values with different superscript down the column differ significantly at p<0.05 ANOVA.

Table 4: Effect of methanolic extract of *M. paradisiaca peel* on body and organ weights of rats

Dose (mg/kg)	Final body weight (g)	Absolute kidney weight (g)	Relative kidney weight (%)	Absolute liver weight (g)	Relative liver weight (%)
Control	200±10.2	0.75±0.03	0.38 ±0.06	6.61± 0.27	3.31± 0.17
100	170±11.7	0.70±0.01	0.42 ± 0.01	6.20 ± 0.31	3.65±0.19
200	175±10.6	0.71±0.04	0.41 ± 0.08	6.11 ± 0.18	3.50±0.13
400	200±7.54	0.78±0.02	0.39 ± 0.03	6.51± 0.33	3.26±0.03

Results are presented as mean ± SD

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The significant reductions in inflammation within the first hour by the administration of 200mg/kg and 400mg/kg indicate that *M. paradisiaca* extract contains some active constituents which block the release of histamine and serotonin from mast cells and also, inhibit the activity of other inflammatory mediators. Some of the phytochemicals present in the extract of *M. paradisiaca* include alkaloids, which are known to have multiplicity of host-mediated biological activities which include anti-inflammatory effect (Ameyaw and Eshun, 2009). Flavonoids are a group of polyphenolic compounds with diverse characteristics and chemical structures. The therapeutic potential of flavonoids has been determined and is known to have a number of pharmacological properties which inlude anti-inflammatory activity against cyclo-oxygenase and lipoxygenase enzymes (Cook and Samman, 1996).

Furthermore, having established the anti-inflammatory and analgesic effects of *M. paradisiaca* against, this study further evaluated its safety on the liver, kidney and serum lipids. Organ weight analysis is an important endpoint for the identification of potentially harmful effects of test compounds in toxicological studies (Bailey et al, 2004). In the present study, rats administered with methanolic peel extract of *M. paradisiaca* did not show significant ($p>0.05$) changes in the body, liver, and kidney weights when compared to control (**Table 4**). Kidney performs many excretory and regulatory functions necessary to sustain life. Kidney maintains the constancy of the extracellular environment by excretion of the waste products of metabolism and the adjustment of urinary water and electrolyte excretion. Studies have shown that with the advent of kidney damage a variety of diverse biological markers which include serum creatinine, urea, uric acid, total protein, albumin and electrolytes are employed to monitor the physiologic status of the kidney (Smith, 1951). In the present study, treatment with 100, 200 and 400 mg/kg of *M. paradisiaca extract* did not produce significant ($p>0.05$) effects on the above serum renal markers when compared to control (**Table 5** and **Table 6**).

The liver is responsible for a spectrum of functions including the uptake, metabolism, conjugation, and excretion of various endogenous and foreign substances. The liver also provides immunological function in phagocytosis, and clearance of microorganisms and endotoxins from portal blood. Studies have shown that the functions of the liver could be impaired due to its role in xenobiotic biotransformation (Schindl et al, 2006). Alkaline phosphatase, alanine aminotransferase, aspartate aminotransferase conjugated bilirubin and total bilirubin are markers used for the clinical assessment of liver function. The present study observed that the oral administration of 100, 200 and 400 mg/kg of *M. paradisiaca* extract did not produce significant ($p>0.05$) effects on the above serum liver markers when compared to control (**Table 7**). These observations showed that the use of *M. paradisiaca* may not be detrimental to liver and renal function. Furthermore, cardiovascular disease is one of the commonest causes of death. Recent investigations in both animals and humans have shown that consumption of some plant materials can perturb G, TC, TG, HDL-C and LDL-C levels causing cardiovascular damage (Angelis-Pereira et al, 2013). The present study observed no significant ($p>0.05$) effect on the above serum parameters in *M. paradisiaca* treated rats (**Table 8**). This shows that the use of *M. paradisiaca* may not be associated with cardiovascular adverse effect.

Table 5: Effect of methanolic extract of *M. paradisiaca peel* on serum renal function parameters of rats

Dose (mg/kg)	Creatinine (mg/dL)	Urea (mg/dL)	Uric acid (mg/dL)	Albumin (g/dL)	Total protein (g/dL)
Control	1.02±0.02	23.3±2.27	1.04±0.06	3.25±0.28	6.43±0.71
100	1.07±0.01	22.7±1.00	1.07±0.01	3.24±0.23	6.48±0.21
200	1.17±0.04	24.9±1.06	1.10±0.04	3.26±0.11	6.40±0.32
400	1.25±0.03	26.5±2.00	1.15±0.05	3.21±0.37	6.38±0.46

Results are presented as mean ± SD

Table 6: Effect of methanolic extract of *M. paradisiaca peel* on serum electrolytes of rats

Dose	Na^+ (mmol/l)	K^+ (mmol/l)	Cl^- (mmol/l)	Ca^{2+} (mg/dl)	HCO_3^- (mmol/l)
Control	123.0±5.10	2.50±0.14	110.6±5.22	9.10±0.21	15.2±1.34
100	120.2±7.12	2.57±0.31	115.0±4.51	9.14±0.34	17.0±2.62
200	121.0±4.00	2.54±0.26	108.2±6.42	9.00±0.32	13.7±2.21
400	124.1±6.42	2.49±0.62	114.7±7.00	9.05±0.41	16.1±1.46

Results are presented as mean ± SD

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Table 7: Effect of methanolic extract of *M. paradisiaca peel* on serum liver function parameters of rats

Dose (mg/kg)	ALT (U/L)	AST (U/L)	ALP (U/L)	CB (µmol/L)	TB (µmol/L)
Control	44.0±2.99	40.6±2.00	47.2±4.31	4.61±0.25	8.52±0.71
100	47.5±3.00	42.4±3.10	47.3±3.00	4.76±0.29	8.60±0.55
200	48.0±3.12	44.8±3.73	49.0±4.17	4.85±0.16	8.89±0.32
400	50.3±4.01	45.2±3.15	51.4±4.22	5.00±0.33	8.95±0.14

Results are presented as mean ± SD

Table 8: Effect of methanolic extract of *M. paradisiaca peel* on serum lipid profile of rats

Dose (mg/kg)	G (mg/dL)	TC (mg/dL)	TG (mg/dL)	HDL-C (mg/dL)	LDL-C (mg/dL)
Control	90.0±7.22	79.5±8.51	105.1±10.3	26.4±1.20	32.1±2.52
100	88.7±5.71	75.1±5.62	100.6±9.19	28.3±1.21	26.9±2.00
200	91.0±6.32	77.9±5.11	103.8±8.32	27.0±1.62	30.1±1.61
400	88.3±6.42	78.2±6.43	107.4±9.24	28.6±1.22	26.2±2.24

Results are presented as mean ± SD

4.0 Conclusion

The findings in the present study showed that methanolic extract of *M. paradisiaca* peel has potent anti-inflammatory and analgesic activities and therefore justifies its use in traditional medicine, in the management of inflammatory and pains. Also, its uses could be safe due lack of toxicological effects on the liver, kidney and serum lipids. However, subsequent investigations could be carried out to elucidate the compounds responsible for the observed pharmacological effects.

Conflict of Interest declaration

The authors declare no conflict of interest.

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