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Original Research Article

Modulatory Effect of Dietary *Pentadiplandra brazzeana* Baill Root Supplemented Feed in Oedematous and Polyarthritic Rat

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ABSTRACT

Musculoskeletal disorders including osteoarthritis, rheumatoid arthritis and rheumatism are chronic inflammations linked with intense joint pain. *Pentadiplandra brazzeana* Baill root (Joy perfume tree) root is a dietary food used in traditional care to manage inflammatory disorders. Anti-inflammatory, antioxidant, and immunomodulatory effects of *P. brazzeana* root-supplemented feed (PBRF) against acute oedema and chronic polyarthritis were studied in Wistar rats. *Zingiber officinale* served as the standard. Plasma alanine aminotransferase (ALT), aspartate aminotransferase (AST), oxidative stress markers were investigated using standard methods. Nuclear factor kappa B (NF-κB), cyclooxygenase-2 (COX-2), and tumour necrosis factor-alpha (TNF-α) were determined using ELISA assays. Neutrophils, monocytes, basophils, eosinophils, procalcitonin, white blood cells, platelets, haemoglobin, red-blood cells, and lymphocytes, counts were assayed using autoanalyzer. The PBRF significantly ($p < 0.05$) suppressed rat paw thickness in carrageenan, complete Freund's adjuvant (CFA) and formaldehyde models. The activities of AST and ALT in formaldehyde-induced oedema model were significantly reduced by PBRF. Furthermore, PBRF significantly decreased COX-2 activity, TNF-α, NF-κB, and malondialdehyde concentrations, while reduced glutathione level, catalase, superoxide dismutase, and glutathione peroxidase activities, were significantly increased in the CFA-induced polyarthritis model. The PBRF-treated groups had low lymphocytes, basophils, white blood cells, monocytes, neutrophils, eosinophils, and procalcitonin counts, compared to the negative control diet group. The PBRF exhibited considerable anti-inflammatory, antioxidant and immunomodulatory curative effects against acute oedema and chronic polyarthritis in rats. The mechanistic action could be through, COX-2, TNF-α and NF-κB signaling pathways inhibition, boosting of the antioxidant defense system and modulation of immunological parameters.

***Keywords*:** antioxidant, immunomodulation, inflammation, oedema, *Pentadiplandra brazzeana*, polyarthritis, root supplement

Introduction

Polyarthritis is a chronic, symmetric, polyarticular, inflammatory arthritic disease, affecting five or more joints.[1] Individuals having little to no visible inflammation may experience certain symptoms attributed to immunological pathways linked with pain and disruptions in the joint microenvironment.[2] Chronic inflammation is the leading cause of non-communicable diseases including rheumatoid and osteoarthritis.[3-5] Arthritis and joint diseases affect nearly 350 million people globally and about 43 million people in the United States which is approximately 20% of the population.[6-7] In Nigeria, amongst the elderly that attended pilgrimage in Elele, a rheumatoid arthritis prevalence of 4% was seen among women (65-80 years) and 1% among men (61-70 years).[8] Synovitis and bone marrow oedema, are characteristics of rheumatoid arthritis at the early stage,[9-10] with suppressed immunity, cell and organ damage as symptoms at the advanced stage.[4-5]

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The presence or lack of antibodies is normally used for the classification of rheumatoid arthritis into a seropositive or seronegative condition. The inflammatory nature of rheumatoid arthritis often leads to permanent disability with approximately 60% of the affected individuals being unproductive at least, 10 years after the onset of the disease.[6] Osteoarthritis on the other hand is associated with cartilage breakdown, synovial membrane inflammation and restructuring of the hip and knee. It also affects the joints of the extremities and spine and manifest occasionally with stroke.[11] Therefore, understanding the pathogenic mechanism of the onset of polyarthritis will give insight into its management.

The mechanism underlying oedema and polyarthritis involves transduction and reactions that modulate the expression of TNF-α, NF-κB,[3,12] cyclooxygenases,[13-14] pancreatic enzymes that upregulate subcutaneous fat necrosis and arthritis[1] and hepatocytes immune effector cells and cytokines.[15] Studies reveal polyarthritis disease was observed in some patients after inoculation with mRNA vaccine against severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2).[16-18] Complications and mortality arising from oedema and polyarthritis have increased the reliance on the use of corticosteroids, analgesics, non-steroidal anti-inflammatory drugs (NSAIDs), and disease-modifying antirheumatic drugs in their treatment. Unfortunately, the therapeutic approaches of these treatment options, are often not achieved in clinical practice due to reduced levels of effective treatment compared with clinical trial results.[19] Additionally, these therapeutic approaches do not stop or reduce the progress of structural damage and are often associated with gastrointestinal and digestive disturbances. This has increased the need for the search of alternative management and treatment outcomes from dietary plant supplements.[11,13,20]

Plant foods are sources of essential nutrients and phytochemicals.[21-22] They confer functional properties on them, and are used to reduce risk of nutrition-related human inflammatory diseases.[23,24] Bioactive compounds in complex dietary supplements have been demonstrated to be responsible for ameliorating pain, enhancing movement and promoting life quality in osteoarthritic patients.[11] Several food spices reportedly possess immunomodulatory, anti-inflammatory potentials for their phytochemicals including polyphenols in them.[25] Supplements obtained from spices and herbal products including *Z. officinale* (ginger), were suspected to confer protective effect on the immune system[26-27] by regulating gene expression[28] and oxidative stress.[29,13]
Pentadiplandra brazzeana is an ethnomedicinal plant commonly called joy perfume tree. It is known as J´oublie in French and "osumada" in South-South, Nigeria. The roots of *P. brazzeana* are predominantly used in Nigeria, Equatorial Guinea, Democratic Republic of the Congo, Northern Angola, Cameroon, Central African Republic, and Gabon.[30,21] *P. brazzeana* roots have been earlier reported to be used in the management of pain, rheumatism, and arthritis. N-Benzyl-N¹-(4-methoxybenzyl) urea, N, N¹-di-(4-methoxybenzyl) urea, N, N¹-dibenzyl urea and p-methoxythiobenzaldehyde have been previously isolated.[31] Three of the synthesized urea-based compounds were demonstrated to have potent soluble epoxide hydrolase (sEH) inhibitory activity. In animal studies, the substance 1, 3-bis (4-methoxybenzyl) urea has been demonstrated to significantly reduce inflammation-related pain.[32] Additionally, essential oil from *P. brazzeana* roots has been found to contain benzyl isothiocyanate and benzyl cyanide.[33] Studies revealed that the essential oil from *P. brazzeana* roots was more effective than *Aframomum sulcatum* and *Polyalthia suaveolens* plants in inhibiting the growth and germination of *Bacillus cereus, B. substilis, B. stearothermophilus* and *B. megaterium*. As a result, it could be employed to mitigate food poisoning.[34] Furthermore, locals in Kisangani-Zaire, Democratic Republic of the Congo, are said to use the ethanol extract of fresh *P. brazzeana* roots (Arredoul Jaune), as an antidiarrheal medication.[30,21,32,33] In spite of the existing literature, there is a dearth of scientific evidence supporting the use of *P. brazzena* roots as functional anti-inflammatory food. The possible mechanisms of action have also not been elucidated. This research investigated the anti-inflammatory, antioxidant and immunomodulatory effects of *P. brazzeana* root-supplemented feed (PBRF) against acute oedema and chronic polyarthritis in Wistar rats

Materials and Methods

Chemicals and reagents
Sodium hydroxide (NaOH), sodium carbonate, sodium chloride, reduced glutathione (GSH), formaldehyde (37%), diethyl ether, and hydrogen peroxide, were purchased from Loba Chemie Pvt. Ltd., Mumbai, India; boric acid, selenium dioxide and 98% pyrogallol were obtained from Aldrich Chemical Co. Ltd; AST, ALT and biuret reagent kit were sourced from Randox Laboratories Ltd, Antrim, United Kingdom while carrageenan, COX-2, NF-κB and TNF-α, CFA were purchased from BioTuva Life Sciences, London, United Kingdom, and used for the study.

Plant material
Samples of *P. brazzeana* roots were collected on December 14th, 2020, from local Ika farms in Agbor (6° 15' 50.7312" N and 6° 12' 6.7788" E), Delta State, Nigeria. The plant and its root were identified and verified at the Obafemi Awolowo University Herbarium, and a voucher specimen number Ife-17935 was assigned. Sample of *Z. officinale* was sourced from local markets in Mowe, Ogun State, Nigeria.

Feed preparation
Fresh root samples of *P. brazzeana* were washed with water to remove dirt and sand. The piliferous layer was scraped off to obtain the soft fibrous layers and subsequently oven-dried at 40°C. The dried samples were pulverized and preserved at 4°C for further study. The supplemented feeds were prepared by blending pulverized *P. brazzeana* roots with standard commercial rat pellet and re-pelletizing - ND (0 g supplement/Kg feed), NCD (0 g supplement/Kg feed), PCD (200 g *Z. officinale* supplement/Kg feed), TDI (100 g *P. brazzeana* supplement/Kg feed), TDII (200 g *P. brazzeana* supplement/Kg feed) and TDIII (400 g *P. brazzeana* supplement/Kg feed) respectively. Supplemented re-pelletized rat feed was then oven dried at 50°C and used for the study.[35]

Animals
Ninety, healthy, young, male albino Wistar rats (130 – 180 g), were used for the research. Prior to the study, animals were kept in well-aerated polypropylene cages under standard laboratory conditions to acclimatize for two weeks with free access to water and commercially available rat chow pellet diets from Ladokun Feeds Limited, Ibadan.

Animal grouping
Three models Carrageenan-induced oedema (CIO), Formaldehyde-induced oedema (FIO), and Complete Freund's adjuvant-induce polyarthritis (CFAIP) were used. For each of the models, 30 rats were randomly distributed into six groups, each having five animals. Group 1 was the normal (commercial) diet (ND) group; Group 2 was the untreated negative control diet (NCD) group; Group 3 was the positive control diet (PCD) group; Group 4 was the test diet I (TDI) group; Group 5, the test diet II (TDII); and Group 6 was the test diet III (TDIII) group.

Animal inflammation models
Effect of *P. brazzeana* roots supplemented feed was evaluated using the models described below:

Carrageenan-induced paw oedema (CIO)
The (CIO) in rats was induced using the modified method of Winter *et al*.[36] Rats had no access to food all night except water before the experiment started. A micrometer screw gauge was used to measure each rat's initial paw size. Animals in different groups were fed their respective diets (as previously described). After one hour of commenced feeding with the respective diets, oedema was induced with 0.1 mL of 1% carrageenan solution via direct injection into the left hind paw of rats (under the plantar of aponeurosis) to induce oedema. Increased left paw oedema was measured hourly for six hours post-diet feeding. The mean scores from the hind limbs were acquired, and the change in mean paw size values was expressed as an increase in paw volume in milliliters. The increased total change in mean paw size was calculated hourly as shown:

$$Change\ in\ Mean\ Paw\ Size\ = \frac{\sum (X2 - X1)}{N}$$

Where; X1= Initial paw size; X2= Final paw size; N = Sample number

Formaldehyde-induced oedema (FIO)
The FIO was induced in rats using a modified method of Arzi and coworkers.[37] Rats were fasted overnight but were given water ad libidum prior to the start of experiment. Rats' left hind paws were injected with 0.1 mL of 2.0% v/v formaldehyde under the plantar of aponeurosis on the first and third days of therapy to induce oedema. This was done one hour after feeding with test diet. Feeding with test diet was done for eight days. Paw thickness and oedema were measured using a micrometer screw gauge 30 minutes before the induction of oedema and every 24 hours for eight days. The mean scores for the hind limbs were acquired, and the change in mean paw size was calculated as a milliliter increase in paw volume by deducting the initial value from the increasing paw volumes measured at each interval. The change in mean paw size was calculated daily as shown:

$$Change\ in\ Mean\ Paw\ Size\ = \frac{\sum (X2 - X1)}{N}$$

Where; X1= Initial paw size; X2= Final paw size; N = Sample number.

Animals were sacrificed on the ninth day, blood collected was used for AST, ALT and FBC analysis.

Complete Freund's adjuvant-induced polyarthritis (CFA)
Polyarthritis was induced in rats following a modified method described by Anyasor *et al*.[38] Polyarthritis was induced in rats using 0.1 mL of

complete Freund's adjuvant emulsion injection into rats' left hind paw sub-plantar region and observed for 21 days. At day "0," test foods were given to the animals an hour before CFA injections were injected into rats' left hind paws. Animals were given treatment diets once daily until the 21st day. Paw sizes and oedema were measured from the inflamed paws at days 0, 1, 7, 14 and 21. The mean scores were obtained from the hind limbs to obtain the change in mean paw size values, paw swelling was expressed as milliliter increase in paw volume, obtained by deducting the baseline value from the increased paw volumes.
The change in mean paw size was calculated daily as shown:

$$Change\ in\ Mean\ Paw\ Size\ = \frac{\sum (X2 - X1)}{N}$$

Where; X1= Initial paw size; X2= Final paw size; N = Sample number

Blood sample collection
Rats in the FIO and CFAIP models were fasted overnight, euthanized using diethylether and blood was collected via cardiac puncture. The blood was collected into EDTA and heparinized bottles, as well as into plain tubes to obtain serum. Blood in EDTA bottle was used to analyse full blood count (FBC) using biochemical analyzer (XN-L series; XN-550/XN-450/XN-350), from Sysmex Corporation, Kobe, Japan. The FBC analysis was conducted to measure the lymphocytes, RBC, WBC, procalcitonin, haematocrit, haemoglobin, neutrophils, basophils, eosinophils, and monocytes counts. The blood dispensed into heparinized bottles was used for the analysis of ALT and AST. Serum obtained from whole blood centrifuged at 3000 rpm for 5 minutes, was used to carry out inflammatory assays using ELISA technique.

In vivo anti-inflammatory and antioxidant assays
The ALT and AST were determined using commercial Randox kits from Randox Laboratories Ltd, Antrim, United Kingdom.[39] Serum COX-2, NF-kB and TNF-α of CFAIP rats were assayed using ELISA technique, following the instruction manual of BioTuva Life Sciences, Greater London, WC2H 9JQ, United Kingdom. Antioxidant enzymes in the serum of CFAIP rats were assayed using spectrophotometric method: SOD,[40] catalase,[41] MDA,[42] GSH[43] and glutathione peroxidase (GPx).[44] The protein concentration was assayed using the biuret method.

Statistical analysis
Statistical Package for Social Sciences (SPSS) version 23 software was adopted to determine the differences in the mean of data by using one-way analysis of variance (ANOVA). Post-hoc analysis followed using Duncan Multiple Range Test. Data was expressed as Mean ± Standard Error of Mean (SEM) and represented in graphs and bar charts using Microsoft Excel Package. The level of significance was taken at $p < 0.05$.

Ethical approval
Babcock University Health Research Ethics Committee (BUHREC) approved the research proposal for this study with approval number BUHREC565/20. Complete adherence to the BUHREC directives and ethical principles as documented by National Institutes of Health guidelines for the care and use of laboratory animals in biomedical research were strictly followed.[45]

Results and Discussion

Change in mean paw sizes in carrageenan-induced oedema (CIO), formaldehyde-induced oedema (FIO) and CFA-induce polyarthritis (CFAIP) models
Polyarthritis is a musculoskeletal disorder including osteoarthritis, rheumatoid arthritis and rheumatism linked with intense joint pain and poor life quality. NSAIDs, commonly used in the treatment of arthritis, present several limitations including side effects of toxicity and variation in clinical efficacy.[1,6] This has necessitated the use of various dietary supplements[11] and natural plant products in the management of inflammation and arthritis through phytotherapy for various medical and therapeutic benefits.[46,5]

Figure 1 showed that within the PBRF groups, there was no significant difference ($p > 0.05$) at 1 hour, although there was a substantial increase ($p < 0.05$) in paw sizes in the NCD group compared to the ND diet group. Comparing the PCD group to the TDII and TDIII groups, there was a significant decline. At 2 hours, a significant reduction was observed in the TDI compared with the NCD group. Paw sizes in the PBRF groups significantly decreased compared to NCD group at the 3rd and 4th hours, but there was no difference in the PBRF and PCD groups.
Figure 2 showed at Day 1, there was no significant change ($p > 0.05$) between, the NCD and PBRF groups, compared to the PCD group. However, there was significant rise in TDIII group but none in the TDI and TDII groups compared to the PCD group. On Day 2, there was no difference ($p > 0.05$) between the PBRF groups and the PCD group. On day 3, there was a significant increase ($p < 0.05$) in the NCD group compared to the TDI and TDIII groups, and in the TDII group compared to the PCD group. On Days 4, 5, 6, 7 and 8, paw sizes increased significantly ($p < 0.05$) in the NCD group compared to PCD and PBRF groups. There was no difference ($p > 0.05$) in PBRF groups for days 6, 7 and 8 compared to the PCD group.
In addition, Figure 3 revealed on Day 1, a significant paw size increase ($p < 0.05$) in the NCD group in contrast to the ND group, TDI and TDIII groups. There was no substantial distinction ($p > 0.05$) between the PCD and PBRF groups. Data on Day 7 showed a significant increase ($p < 0.05$) in the NCD group compared to the PBRF groups. Days 14 and 21 data showed significant increase in NCD group in contrast to the TDI and TDIII groups. There was no statistical difference ($p > 0.05$) between the PBRF and PCD groups all through the experiment. Results from CIO, FIO and CFAIP models of this research revealed that PBRF suppressed paw oedema by reducing the mean paw sizes across the treatment groups. This is in accordance with previous reports of other anti-inflammatory, arthritic agents,[38,37] which showed that PBRF was able to reduce mean paw oedema and polyarthritis score. This indicates decreased disease progression, as an increase in mean paw oedema and polyarthritis score has a direct association with synovial inflammation and hyperplasia.[9,47,5] The present study revealed that PBRF has anti-inflammatory property in line with previous *in vivo* inflammatory pain models research that showed the analgesic benefits of isothiocyanate and dibenzylurea-based active soluble epoxide hydrolase (sEH) inhibitors from *P. brazzeana*.[32,48,33]
Aspartate and alanine aminotransferase activities in formaldehyde-induced oedema model

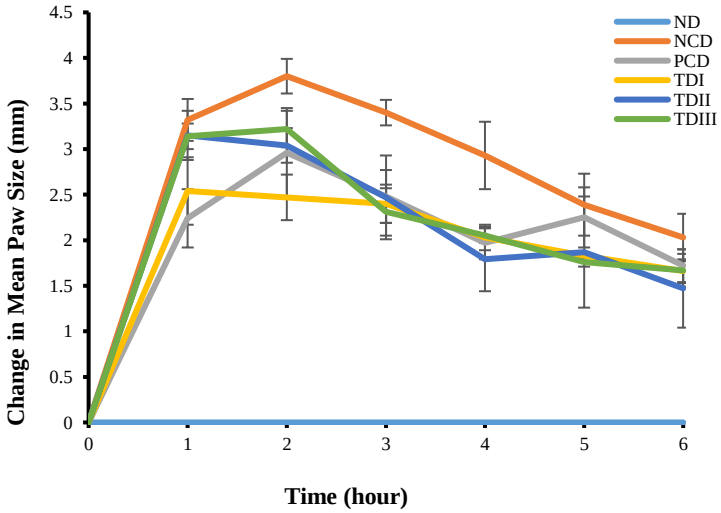

Figure 1: Effects of *Pentadiplandra brazzeana* baill root supplemented feed on change in mean paw size in rats induced with carrageenan for six hours.
ND (0 g supplement/Kg feed), NCD (0 g supplement/Kg feed), PCD (200 g *Z. officinale* supplement/Kg feed), TDI (100 g *P. brazzeana* supplement/Kg feed), TDII (200 g *P. brazzeana* supplement/Kg feed) and TDIII (400 g *P. brazzeana* supplement/Kg feed).

Figure 4 showed a significant elevation ($p < 0.05$) in AST activity in NCD group in contrast to the PBRF groups. AST activity in the TDI group increased significantly ($p < 0.05$) compared to TDII and TDIII groups. There was no substantial difference ($p > 0.05$) between the PCD and PBRF groups. Figure 5 depicted a statistical elevation ($p < 0.05$) in ALT activity in the NCD group in contrast to the PBRF groups. There was a significant decrease ($p < 0.05$) in ALT activity in the TDII group in comparison with the TDI, TDIII and PCD groups. Data in this study showed elevated ALT and AST activities in the NCD FIO rats compared with the PBRF-treated rats, thus corroborating earlier reports that increase in ALT and AST activities indicated toxin-induced hepatotoxicity.[49]Additionally, glucosinolates exert their effects on cytochrome p450 isoforms in various cells and lessen the bioactivation of environmental carcinogens in the liver. This study, therefore, suggests that indole-type glucosinolates earlier isolated and identified in the roots of *P. brazzeana*,[50] could have exerted hepatoprotective effects on cytochrome p450 isoforms in various cells and potentially reduced the hepatic bioactivation of formaldehyde in the experimental rats.[51]

Effect of PBRF on full blood count in formaldehyde-induced oedema and CFA-induced polyarthritis model

Table 1 (formaldehyde-induced oedema) showed a statistical increase ($p < 0.05$) of WBC in the NCD group in comparison with a decrease observed in TDII and TDIII groups, but no difference ($p > 0.05$) compared to the ND, PCD and TDI groups. There was no significant change ($p > 0.05$) within the treatment groups, but a significant decrease ($p < 0.05$) was noted in the TDII and TDIII groups compared with the PCD group. A significant increase ($p < 0.05$) in neutrophils count was observed in the NCD group compared with PCD and PBRF groups, with no significant difference ($p > 0.05$) within the treatment groups. For the MID (combined cells and percentage value of white blood cells not classified as lymphocytes or granulocytes) counts, there was a significant increase in the NCD group in contrast with the PBRF groups. There was no significant change in the NCD lymphocytes counts compared with the ND and all treatment groups, but a significant decrease in platelets count in the NCD group compared with the PCD, TDI and TDIII groups. A significant decrease ($p < 0.05$) in haematocrit count in the NCD group was observed when compared to the PCD, TDI and TDII groups. Haemoglobin counts in the NCD group decreased compared with the ND, PCD, TDI, and TDII groups. RBC count was reduced ($p < 0.05$) in the NCD group when compared with the TDI and TDIII groups.

Data in Table 2 (CFA-induced polyarthritis) revealed that WBC count in NCD group was significantly higher ($p < 0.05$) than the PCD group, TDII and TDIII groups. WBC in PCD group compared favorably with TDI, TDII and ND groups. WBC in TDIII was significantly lower than all treated groups. Neutrophils count was significantly higher in NCD group compared to ND, TDII and TDIII groups but non-significantly higher in TDI and PCD. Eosinophils' count in NCD group significantly increased compared to all treated groups. TDIII was significantly higher than all treated groups and compared favorably with the ND group. Monocytes count in NCD group was significantly higher compared to the TDIII group but non-significantly higher with respect to other experimental groups. Basophiles count in NCD group was significantly higher compared to the TDII and TDIII groups and non-significantly higher than the PCD and TDI groups. There was no significant difference in the PCD, TDII and TDIII groups compared to the ND group. Lymphocytes counts in the NCD group increased compared to the TDIII group while a non-significant increase was observed in NCD compared to all other treated groups. Platelets in the NCD group was low compared to the ND and TDI group, with a non-significant difference in all other treated groups. Furthermore, there was a significant increase in procalcitonin in the NCD group compared to the TDI group and a non-significant increase compared to other treated groups. A significant decrease occurred in the NCD group compared to the TDI group. Haemoglobin levels in PCD group, compared favorably with other treated groups. RBC counts decreased in NCD group compared to the PCD and TDI groups.

Previous research reports that neutrophils, monocytes and procalcitonin counts are elevated in acute or chronic inflammation.[52-53]

Haematological parameters of FIO and CFAIP rats showed that PBRF-treated groups had decreased lymphocytes, eosinophils, WBC, basophils, monocytes, neutrophils, and procalcitonin counts compared to the NCD group. Increase in lymphocytes, basophils, WBC, neutrophils, monocytes, eosinophils, and procalcitonin counts and simultaneous decrease in platelets, haemoglobin and red blood cells in the NCD group indicated a higher level of inflammatory response of control group rats induced with oedema and polyarthritis. This implies that PBRF could have modulated immune response by inhibiting prolonged infiltration of cells at the sites of tissue injury and further signaling of leukocytes against cytokines including TNF-α, NF-κB and COX-2 that promote tissue damage.[29,54,55,6,13]

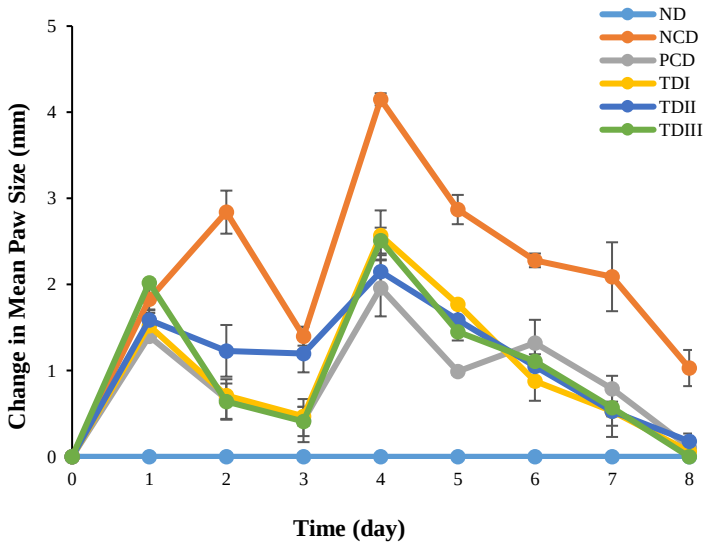

Figure 2: Effects of *Pentadiplandra brazzeana* baill root feed supplement on change in mean paw oedema in rats induced with formaldehyde for eight days.
ND (0 g supplement/Kg feed), NCD (0 g supplement/Kg feed), PCD (200 g *Z. officinale* supplement/Kg feed), TDI (100 g *P. brazzeana* supplement/Kg feed), TDII (200 g *P. brazzeana* supplement/Kg feed) and TDIII (400 g *P. brazzeana* supplement/Kg feed).

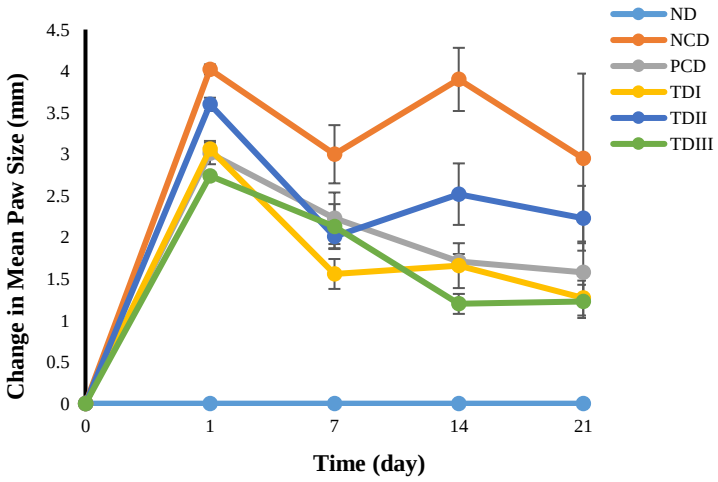

Figure 3: Effects of *Pentadiplandra brazzeana* baill root feed supplement on change in mean paw size in complete Freund's adjuvant-induced polyarthritis in rats.
ND (0 g supplement/Kg feed), NCD (0 g supplement/Kg feed), PCD (200 g *Z. officinale* supplement/Kg feed), TDI (100 g *P. brazzeana* supplement/Kg feed), TDII (200 g *P. brazzeana* supplement/Kg feed) and TDIII (400 g *P. brazzeana* supplement/Kg feed).

Table 1: Effect of *P. brazzeana* baill root supplemented feed on full blood count in formaldehyde-induced oedema

Parameter	ND	NCD	PCD	TDI	TDII	TDIII
WBC (x 10 $^{-3}$/µL)	8633.33 ± 1178.04 ^{b}	1058.33± 1091.76 ^{b}	9933.33 ± 166.67 ^{b}	7466.67 ± 1251.42 $^{a, b}$	4900.00 ± 600.00 ^{a}	5300.00 ± 750.56 ^{a}
NEUT (%)	23.33 ± 1.67 ^{a}	39.67 ± 2.03 ^{b}	22.67 ± 2.73 ^{a}	25.33 ± 4.67 ^{a}	25.33 ± 4.70 ^{a}	21.67 ± 1.45 ^{a}
MID (%)	6.33 ± 0.67^{b}	8.33 ± 0.88^{b}	6.33 ± 0.88^{b}	3.33 ± 1.33^{a}	3.33 ± 0.33^{a}	5.67 ± 0.88^{a}
LYMPH (%)	63.67 ± 2.60 ^{a}	60.67 ± 4.26 ^{a}	61.00 ± 3.51 ^{a}	57.00 ± 2.89 ^{a}	57.67 ± 4.91 ^{a}	64.17 ± 4.11 ^{a}
PLT (x 10 ^{9}/L)	617.67 ± 22.93 ^{b}	495.00 ± 14.18 ^{a}	655.33 ± 51.82 ^{b}	621.33 ± 12.84 ^{b}	570.67 ± 17.84 $^{a, b}$	657.00 ± 13.58 ^{b}
HCT (%)	39.40 ± 1.30 $^{a, c}$	32.90 ± 2.01 ^{a}	43.80 ± 1.83 $^{c, d}$	48.70 ± 0.89 ^{e}	45.13 ± 1.43 $^{d, e}$	36.71 ± 0.70 $^{a, b}$
HGB (g/L)	13.13 ± 0.43 $^{b, c}$	11.03 ± 0.73 ^{a}	13.93 ± 0.13 $^{c, d}$	16.50 ± 0.21 ^{e}	15.17 ± 0.59 $^{c, d, e}$	12.23 ± 0.23 $^{a, b}$
RBC (x 10 ^{12}/L)	8.52 ± 0.07 $^{a, b}$	8.06 ± 0.23 ^{a}	9.02 ± 0.00 $^{b, c}$	9.62 ± 0.19 ^{c}	8.38 ± 0.38 $^{a, b}$	8.85 ± 0.12 ^{b}

Different alphabet on each bar, indicate significant difference at $p < 0.05$. ND (0 g supplement/Kg feed), NCD (0 g supplement/Kg feed), PCD (200 g *Z. officinale* supplement/Kg feed), TDI (100 g *P. brazzeana* supplement/Kg feed), TDII (200 g *P. brazzeana* supplement/Kg feed) and TDIII (400 g *P. brazzeana* supplement/Kg feed). WBC- White blood cells; NEUT- Neutrophil; LYMP- Lymphocytes; PLT-Platelets; HCT- Heamatocrit; HGB- Haemoglobin; RBC- Red blood cells.

Table 2: Effect of *P. brazzeana* baill root feed supplement on full blood count in complete Freund's adjuvant-induced polyarthritis in rats

Parameter	ND (0 g)	NCD (0 g)	PCD (200 g)	TDI (100 g)	TDII (200 g)	TDIII (400 g)
WBC (x 10 ^{9}/L)	5.56 ± 0.50 ^{b}	8.57 ± 0.15 ^{c}	5.04 ± 1.38 ^{b}	6.34 ± 1.03 $^{b, c}$	5.27 ± 0.10 ^{b}	2.26 ± 0.53 ^{a}
NEUT (x 10 ^{9}/L)	0.25 ± 0.09 ^{a}	1.01 ± 0.32 ^{b}	0.64 ± 0.09 $^{a, b}$	0.57 ± 0.09 $^{a, b}$	0.38 ± 0.09 ^{a}	0.38 ± 0.10 ^{a}
EOSIN (x 10 ^{9}/L)	0.03 ± 0.00 ^{a}	0.25 ± 0.02 ^{c}	0.12 ± 0.05 ^{b}	0.13 ± 0.01 ^{b}	0.13 ± 0.03 ^{b}	0.03 ± 0.01 ^{a}
MONO (x 10 ^{9}/L)	0.26 ± 0.04 $^{a, b}$	0.53 ± 0.01 $^{b, c}$	0.49 ± 0.08 $^{b, c}$	0.74 ± 0.18 ^{c}	0.24 ± 0.09 $^{a, b}$	0.15 ± 0.03 ^{a}
BASO (x 10 ^{9}/L)	0.16 ± 0.01$^{a, b}$	0.41 ± 0.11 ^{d}	0.32 ± 0.01 $^{b, c, d}$	0.36 ± 0.05 $^{c, d}$	0.18 ± 0.03 $^{a, b, c}$	0.12 ± 0.03 ^{a}
LYMPH (x10 ^{9}/L)	3.99 ± 0.80 $^{a, b}$	4.97 ± 0.93 ^{b}	3.38 ± 0.99 $^{a, b}$	4.17 ± 0.87 $^{a, b}$	3.00 ± 0.63 $^{a, b}$	1.68 ± 0.44 ^{a}
PLT (x 10 ^{12}/L)	1023.00 ± 82.00 ^{b}	688.00 ± 14.00 ^{a}	834.00 ± 20.00 $^{a, b}$	969.00 ± 166.00 ^{b}	905.00 ± 3.00 $^{a, b}$	660.50 ± 20.50 ^{a}
PCT (%)	0.16 ± 0.16^{a}	0.70 ± 0.03 ^{b}	0.67 ± 0.05 ^{b}	0.18 ± 0.18 ^{a}	0.60 ± 0.02 ^{b}	0.42 ± 0.08 $^{a, b}$
HGB (g/L)	13.40 ± 0.42 $^{a, b}$	13.17 ± 0.37 $^{a, b}$	14.17 ± 0.23 $^{b, c}$	14.73 ± 0.53 ^{c}	13.77 ± 0.55 $^{a, b, c}$	12.57 ± 0.09 ^{a}
RBC (x 10 ^{12}/L)	7.11 ± 0.56 ^{a}	7.40 ± 0.14 $^{a, b}$	8.60 ± 0.21 ^{c}	8.59 ± 0.56 ^{c}	8.43 ± 0.12 $^{b, c}$	7.79 ± 0.18 $^{a, b, c}$

Different superscript across the group, indicate significant difference at $p < 0.05$. ND (0 g supplement/Kg feed), NCD (0 g supplement/Kg feed), PCD (200 g *Z. officinale* supplement/Kg feed), TDI (100 g *P. brazzeana* supplement/Kg feed), TDII (200 g *P. brazzeana* supplement/Kg feed) and TDIII (400 g *P. brazzeana* supplement/Kg feed). NEUT- Neutrophils; EOSIN- Eosinophils; Mono- Monocytes; LYMP- Lymphocytes; PLT- Platelets; PCT- Procalcitonin; WBC- White blood cells; HGB- Hemoglobin; RBC- Red blood cells. BASO- Basophils

It can further be inferred that PBRF may have restored immune organ and improved blood level parameters across the various treatment groups in the FIO and CFAIP models. This study therefore, supports previous reports that some medicinal food plants possessing immunomodulatory properties inhibit pro-inflammatory signals by reducing the production of reactive oxidative burst and inflammatory markers [38,6] including cyclooxygenases, leukotrienes, prostaglandins and platelet-stimulating factors triggered by phospholipase A2.[56,14]

Effect of PBRF on COX-2, NF-κB, TNF-α inflammatory markers and CAT, SOD, GPx and GSH antioxidant markers in CFA-induced polyarthritis model

Table 3 revealed a distinct decrease ($p < 0.05$) in COX-2 activity in the PBRF groups compared with the NCD group, but no difference in the TDI and TDII groups compared with the PCD group. A significant decline ($p < 0.05$) was observed in NF-κB levels of PCD and PBRF groups compared with the NCD group. TDI and TDIII groups compared favorably with PCD group but a significant decline occurred in TDII group. A significant decline in TNF-α concentration occurred in the PBRF groups compared with the NCD group, while all treated groups were not altered.

The effect of PBRF was determined on antioxidant status. SOD activity in PCD and PBRF groups increased significantly with respect to the NCD group.

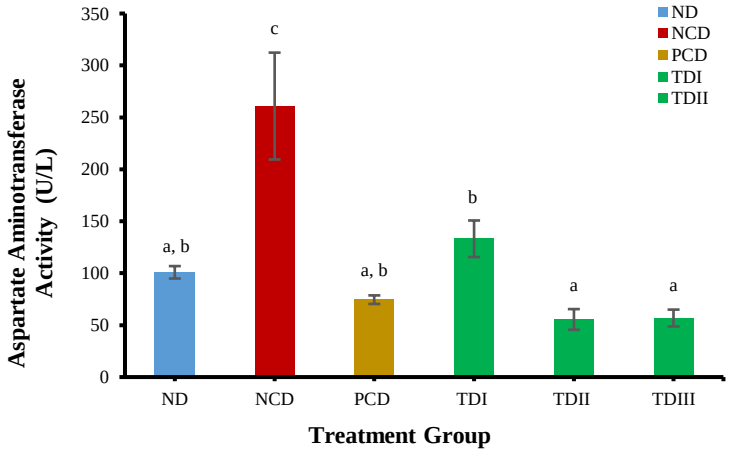

Figure 4: Effects of *Pentadiplandra brazzeana* baill root feed supplement on aspartate aminotransferase activity on rats induced with oedema using formaldehyde for eight days.
Different alphabet on each bar, indicate significant difference at $p < 0.05$. ND (0 g supplement/Kg feed), NCD (0 g supplement/Kg feed), PCD (200 g *Z. officinale* supplement/Kg feed), TDI (100 g *P. brazzeana* supplement/Kg feed), TDII (200 g *P. brazzeana* supplement/Kg feed) and TDIII (400 g *P. brazzeana* supplement/Kg feed).

Also, there was a significant elevation in SOD activity in TDI group compared with the TDIII and PCD groups. CAT activity was significantly upregulated in PCD, TDI and TDIII groups compared with the NCD group. CAT activity in TDI and TDIII groups compared favorably with the PCD group but a significant decrease comparable with the normal group existed in TDII group. MDA concentration in TDI, TDII and TDIII groups decreased statistically when compared with the NCD group. MDA levels in TDI and TDIII groups remained unchanged compared with the PCD group but a significant decline was observed in TDII group compared with all treatment groups. A significant increase in GPx activity was observed in the TDI, TDIII and ND groups compared to the NCD group. GPx activity increased in TDI and TDIII groups compared to the PCD and TDII groups but no change in the TDII group compared to PCD group. In addition, a significant increase in GSH concentration in the TDI and TDIII groups was observed compared to the NCD group. All other treated groups remained unaltered.

Literature reports that induced oxidative stress elevates the levels of cytokines and NF-κB growth factor, which collectively signals the transcription of pro-inflammatory cytokines and COX-2. Anti-inflammatory agents elicit down-regulation of COX-2 expression and restoration of tumor suppressor p53 level, by increasing the activation of Nrf2 and upregulation of TGF-β.[57-59,5] The findings from this study is in congruent with previous reports, showing decreased COX-2 activity and NFκB concentration in PBRF treated rats compared to untreated rats. Agents rich in polyphenols elicit an inhibitory inflammatory response of NF-κB, and upregulate anti-inflammatory gene transcription factors.[60] Anti-inflammatory and anti-polyarthritis activities in Wistar rats could possibly be attributed to synergistic bioactive actions of the phytochemicals previously identified in *P. brazzeana* roots[21] and their interferences with pro-inflammatory cytokines signaling as well as the inhibition of prostaglandins and leukotriene biosynthesis. Inhibition of NF-κB translocation could have contributed to the protective effect of PBRF against oedema and inflammatory polyarthritis in the experimental rats. Polyphenols in PBRF in line with existing data could have also modulated gene expression regulated by NF-κB at multiple levels by restraining NF-κB activation in Hodgkin's lymphoma cells and Jurkat T cells. This interactions with NF-κB proteins, could prevent NF-κB from binding to DNAκB sites, thereby regulating the expression of numerous genes encoding proteins involved in immune stimuli and inflammatory activities.[61,28] This suggests a suppressive effect of *P. brazzeana* root on NF-κB's translocation and the biosynthesis of prostaglandins, leukotriene and COX-2 in the PBRF-treated rats.

The data from this research in consonance with the report of Zahra et al.,[56] also revealed that untreated CFAIP rats, had increased levels of TNF-α compared to PBRF-treated rats. This, indicates severe inflammatory disease conditions in the untreated rats. Immunomodulatory action of anti-inflammatory agents through the suppression of plasma leucocytes and inhibition of the release of inflammatory mediators[55,23] could have contributed to the reduced TNF-α levels observed in the PBRF-treated rats. Furthermore, previous proximate analysis of *P. brazzeana* roots revealed appreciable amounts of crude fiber, minerals, and vitamins C, A and E. Some micronutrients, and both soluble and insoluble fiber are associated with lowering levels of interleukin 6 and TNF-α.[62] These components could have accounted for the inclusive reduction in TNF-α levels observed in the various PBRF groups. Therefore, our study suggests that *P. brazzeana* root inhibits TNF-α expression in polyarthritis rats by downregulating pathological changes generally mediated by TNF-α.

This study further demonstrated that rats fed with PBRF, exhibited elevated activities of GPx, SOD, CAT and GSH concentration and reduced MDA levels compared to the untreated NCD polyarthritis rats. The increase in SOD activity resulting from exposure to CFA and phagocytosis of CFA could have led to increased SOD activity in macrophages. The increased SOD activity and lymphocytes production, which in turn stimulated the production of H_2O_2 required for CAT activity are in line with earlier reports. Consistent with previous findings,[63] increased SOD, CAT, GPx, activities and GSH concentration observed in PBRF treated rats, with reduced MDA levels, could be attributed to the flavonoids, saponins, alkaloids, tannins, and phenolic compounds previously reported in *P. brazzeana* roots.[21] *P. brazzeana* roots polyphenolic phytochemicals could have conferred improved antioxidant status on the PBRF treated rats due to the radical scavenging ability of their hydroxyl groups. This ability allows for the conversion of radical products to more resonance-stabilized, non-reactive products, thereby regulating the expression of pro-inflammatory cytokine genes.[54,28,27] Hence, the observed reduction in the risk of inflammation and oxidative stress amongst the PBRF treated rats, a property enhanced by adequate intake of dietary polyphenol-rich PBRF,[13,51] also improved heamatological and immunological status, as demonstrated by Necdem et al.[64]

Additionally, the glucosinolates that were previously found in the roots of *P. brazzeana* produce a variety of hydrolysis-derived compounds, such as isothiocyanates (ITCs), oxazolidine-2-thiones, nitriles, and epithionitriles. Isothiocyanates' bioactivities earlier reported include antioxidant, antiproliferative, bactericidal and antimutagenic potentials. Arylalkyl isothiocyanates, thioureas and thiocarbamates, have also been previously isolated from *P. brazzeana* roots. The isolated arylalkyl isothiocyanates were 4-methoxybenzyl isothiocyanates, benzyl isothiocyanates and 2-(4-methoxyphenyl)-2,2-dimethylethyl isothiocyanates, suggesting the presence of benzyl-, 4-methoxybenzyl-, and 2-(4-methoxyphenyl)-2,2-dimethylethyl glucosinolates, respectively, in *P. brazzeana* roots. These bioactive substances have been linked to the anti-inflammatory effects of the essential oil previously found in the roots of *P. brazzeana*.[33] The antioxidant and anti-inflammatory activities of PBRF observed in the PBRF-treated rats in this study support the claims that, indole-type glucosinolates identified in *P. brazzeana* roots, could have provided protection to the cytochrome p450 isoforms in different cells and decreased hepatic bioactivation of formaldehyde and CFA in the PBRF-treated rats.

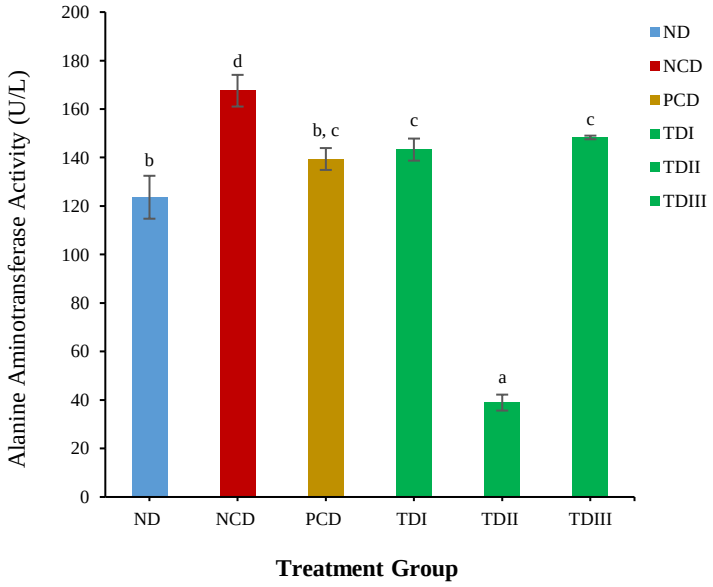

Figure 5: Effects of *Pentadiplandra brazzeana* baill root feed supplement on alanine aminotransferase activity in rats induced with oedema using formaldehyde for eight days.

Different alphabet on each bar, indicate significant difference at $p < 0.05$. ND (0 g supplement/Kg feed), NCD (0 g supplement/Kg feed), PCD (200 g *Z. officinale* supplement/Kg feed), TDI (100 g *P. brazzeana* supplement/Kg feed), TDII (200 g *P. brazzeana* supplement/Kg feed) and TDIII (400 g *P. brazzeana* supplement/Kg feed).

Table 3: Effect of *P. brazzeana* baill root supplemented feed on inflammatory and antioxidant markers in CFA-induced polyarthritis model

Parameter	ND	NCD	PCD	TD 1	TDII	TDIII
COX-2	147.07 ± 5.86 [c]	222.76 ± 2.27 [d]	67.38 ± 0.96 [a]	65.93 ± 0.36 [a]	74.66 ± 8.03 [a]	125.60 ± 6.40 [b]
NF-κB (ng/L)	9349.92 ± 94.45 [b, c]	11731.29 ± 11.69 [d]	9241.98 ± 40.48 [b]	9208.25 ± 6.75 [b]	1133.17 ± 13.49 [a]	9444.36 ± 91.26 [b, c]
TNF-α (ng/L)	430.19 ± 39.12 [b, c]	571.90 ± 43.10 [c]	302.10 ± 53.28 [a, b]	260.20 ± 59.96 [a]	260.20 ± 59.96 [a]	375.68 ± 7.38 [a, b]
SOD (Unit/mg protein)	95.14 ± 2.24 [a, b]	85.18 ± 3.63 [a]	105.30 ± 5.57 [b]	188.44 ± 6.86 [c]	108.09 ± 5.03 [b]	110.31 ± 5.25 [b]
CAT (Unit/mg protein)	0.70 ± 0.01 [a]	0.71 ± 0.03 [a]	0.86 ± 0.04 [b]	0.91 ± 0.03 [b, c]	0.73 ± 0.03 [a]	1.01 ± 0.05 [c]
MDA (nmol/mL)	32.71 ± 2.37 [d, e]	40.07 ± 1.60 [e]	24.14 ± 2.51 [b, c]	27.46 ± 4.01 [c, d]	9.42 ± 1.68 [a]	17.68 ± 1.26 [b]
GPX (Unit/mg protein)	58.50 ± 1.21[c]	48.00 ± 0.56 [a]	49.10 ± 0.49 [a]	56.27 ± 4.20 [b, c]	51.22 ± 1.88 [a, b]	58.58 ± 2.48 [c]
GSH (µmol/mL)	1.36 ± 0.10 [a, b]	1.22 ± 0.04 [a]	1.35 ± 0.02 [a, b]	1.39 ± 0.05 [b]	1.35 ± 0.02 [a, b]	1.39 ± 0.02 [b]

Different superscript across the groups, indicate a significant difference at $p < 0.05$. ND (0 g supplement/Kg feed), NCD (0 g supplement/Kg feed), PCD (200 g *Z. officinale* supplement/Kg feed), TDI (100 g *P. brazzeana* supplement/Kg feed), TDII (200 g *P. brazzeana* supplement/Kg feed) and TDIII (400 g *P. brazzeana* supplement/Kg feed). GPx-Glutathione peroxidase; TNF-α- Tumor necrosis factor α.; CAT- Catalase; GSH- Reduced glutathione; COX-2- Cyclooxygenase 2; SOD-Superoxide dismutase; NF-κB- Nuclear factor kappa B

Conclusion

The PBRF suppressed paw oedema in both CIO and FIO rats showed hepatoprotection by inhibiting the elevation of plasma AST and ALT activities, and modulated immunological and haematological parameters. PBRF also suppressed inflammation in CFAIP rats, inhibited COX-2 activity, and reduced TNF-α and NF-κB concentrations. PBRF improved the antioxidant status of CFAIP rats by increasing SOD, CAT, and GPx activities as well as enhancing GSH concentrations. It also modulated immunological and haematological parameters in the rats. Findings from this research suggest that *P. brazzeana* root could be a potential food plant for the development of functional foods to manage oedema and polyarthritis. However, further studies are required to explore and maximize the dietary and medicinal potentials of *P. brazzeana* roots.

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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