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Exacerbation of Hypersensitivity Reactions in Wistar Rats Following Co-administration of Methanolic Leaf Extract of *Azadirachta indica* and Ampicloxacillin

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ABSTRACT

Azadirachta indica is one of the medicinal plants known for its antimicrobial and immunomodulatory properties.; however, its concurrent use with synthetic antibiotics raises concerns regarding potential herb–drug interactions. This study investigated the haematological and immunological effects of methanolic leaf extracts of A. indica, administered alone and in combination with Ampicloxacillin, in Wistar rats. Methanolic extract of A. indica leaves were prepared using a Soxhlet apparatus. Thirty-five adult Wistar rats (150–200 g) were randomly assigned into seven groups (n = 5), including normal and negative controls, a positive control (Ampicloxacillin, 50 mg/kg), extract-treated groups (200 and 400 mg/kg), and combination groups. Treatments were administered orally for 28 days, after which blood samples were collected for analysis. The results showed significant reductions in packed cell volume (PCV), haemoglobin (Hb), and platelet counts, particularly in the combination groups. In contrast, white blood cell count, eosinophils, and basophils were significantly elevated ($P < 0.05$), indicating enhanced immune activation. Immunological markers, including immunoglobulin E (IgE), histamine, and pro-inflammatory cytokines (IL-4, IL-6, and TNF-α), were also increased, while the anti-inflammatory cytokine IL-10 decreased. These findings suggest that concurrent use may increase the risk of hypersensitivity reactions, particularly in susceptible individuals. Further studies are required to clarify underlying mechanisms and establish safe therapeutic guidelines.

Keywords: *Azadirachta indica*; Ampicloxacillin; Herb–Drug Interaction; Haematological Parameters; Immunological Markers; Immunoglobulin E (IgE); Cytokines; Hypersensitivity; Inflammation; Wistar Rats; Medicinal Plants; Immunomodulation.

1. Introduction

Hypersensitivity reactions are exaggerated immune responses that may range from mild allergic manifestations to severe systemic inflammatory conditions [1,2]. These reactions occur when the immune system overreacts to harmless antigens, causing tissue damage and disease [2,3]. They are classified into four main types based on their underlying mechanisms: Type I, Type II, Type III, and Type IV hypersensitivity. Each type involves different immune components and leads to distinct clinical manifestations [4]. For instance, Type I hypersensitivity is mediated by immunoglobulin E (IgE) [5–7]. It occurs in response to allergens such as pollen, food, insect venom, or certain medications [8,9]. When an individual is exposed to an allergen, the immune system produces IgE antibodies, which bind to mast cells and basophils [10]. Upon subsequent exposure, these cells release histamine and other inflammatory mediators, leading to anaphylactic symptoms such as itching, swelling, and difficulty breathing [10,11].

Azadirachta indica, commonly called dogoyaro in Nigeria, is widely used in traditional medicine for its antimicrobial [12] and immunomodulatory properties [13], but some studies suggest it may also trigger immune hyperactivation [14,15]. The bioactive compounds in *A. indica* have been shown to interact with the immune system, potentially altering hypersensitivity responses. Studies have demonstrated that the plant extracts can modulate immune functions by enhancing the activity of macrophages and increasing the counts of CD4+ and CD8+ T cells. For instance, an aqueous extract of its leaves was found to elevate lymphocyte and monocyte counts

in mice [16]. Additionally, its oil has been reported to reduce the activity of interferon-gamma (IFN-γ) and increase phagocytic activity, indicating its role in modulating immune responses [17]. These immunomodulatory effects suggest that bioactive compounds in *A. indica* may influence hypersensitivity reactions. For instance, contact with *A. indica* oil containing high levels of azadirachtin has been found to cause allergic contact dermatitis, manifesting as skin redness, itching, and inflammation [18].

Ampicloxacillin is a combination antibiotic consisting of ampicillin and cloxacillin, which are broad-spectrum penicillin β-lactam antibiotics used in the treatment of bacterial infections [19]. It is known to cause drug-induced hypersensitivity reactions through IgE-mediated pathways [20,21]. Combining *A. indica* leaf extracts with antibiotics may influence immune responses, as previous studies suggest that herb–drug interactions can enhance inflammatory pathways [22–24]. Despite the increasing use of herbal remedies alongside conventional antibiotics, few studies have investigated their combined effects on hypersensitivity reactions. Hence, this study seeks to investigate the effects of methanolic leaf extracts of *A. indica* combined with Ampicloxacillin on Type I hypersensitivity reactions in Wistar rats to assess potential risks and interactions.

1.1. Study Objectives

The main objective of this study was to evaluate the effects of methanolic leaf extract of *Azadirachta indica*, administered alone and in combination with Ampicloxacillin, on haematological and immunological responses associated with Type I hypersensitivity in Wistar rats. The specific objectives were to:

1. Determine the effects of methanolic leaf extract of *Azadirachta indica*, administered alone and in combination with Ampicloxacillin, on selected haematological parameters (packed cell volume (PCV), haemoglobin (Hb), platelet count, total white blood cell (WBC) count, eosinophil count, and basophil count).
2. Evaluate the effects of the treatments on immunoglobulin E (IgE) and histamine levels as biomarkers of allergic response and mast cell activation.
3. Assess the influence of the treatments on pro-inflammatory cytokines (IL-4, IL-6, and TNF-α) and the anti-inflammatory cytokine (IL-10) to determine alterations in immune and inflammatory responses.
4. Investigate the potential herb–drug interaction between *Azadirachta indica* leaf extract and Ampicloxacillin by comparing the haematological and immunological responses of combination-treated rats with those receiving either treatment alone.

2. Materials and Methods

2.1. Collection and Preparation of Plant Extract

Fresh leaves of *A. indica* were collected from an abandoned farmland in Afam, Oyigbo Local Government Area of Rivers State, Nigeria, and authenticated by a botanist at the Federal University, Otuoke, Bayelsa State. The leaves were washed, air-dried, and finely ground into powder. The methanolic extraction was carried out using a Soxhlet apparatus, with 80% methanol as the solvent. After the extraction, the solvent was evaporated under reduced pressure, and the residue was dissolved in distilled water to achieve the required concentrations (200 and 400 mg/kg). The extract was stored at 4°C until use.

Figure 1. *A. indica* leaves

Source: https://www.feedipedia.org/node/182

2.2. Experimental Animals

Thirty-five (35) healthy adult Wistar rats, weighing 150–200 g, were used for this study. The animals were housed under standard laboratory conditions with a 12-hour light/dark cycle, controlled temperature (22 ± 2°C), and relative humidity of 50 ± 5%. They were provided with standard rodent chow and clean drinking water ad libitum. The study was conducted in accordance with institutional guidelines for the care and use of laboratory animals, and ethical approval was obtained from the Animal Ethics Committee of the Federal University, Otuoke, Bayelsa State, Nigeria.

2.3. Experimental Design and Administration of Treatment

This study employed a randomised controlled experimental design to evaluate the haematological and immunological effects of *A. indica* leaf extract and its interaction with Ampicloxacillin in Wistar rats. A total of thirty-five (35) adult Wistar rats were randomly assigned into seven (7) groups (n = 5 per group) as follows:

Group	Description	Treatment
G1	Normal environmental control	No treatment (standard feed and water only)
G2	Negative control	Vehicle (normal saline)
G3	Positive control	Ampicloxacillin (50 mg/kg/day)
G4	Experimental group I	*A. indica* extract (200 mg/kg/day)
G5	Experimental group II	*A. indica* extract (400 mg/kg/day)
G6	Experimental group III	*A. indica* (200 mg/kg/day) + Ampicloxacillin
G7	Experimental group IV	*A. indica* (400 mg/kg/day) + Ampicloxacillin

Treatments were administered once daily by oral gavage for 28 consecutive days.

2.4. Blood Collection

At the end of 28-day experiment, blood samples were collected via cardiac puncture under light anesthesia to minimize stress and ensure accurate measurements. The samples were drawn into EDTA-coated tubes (BD

Vacutainer, USA) for haematological analysis and serum separator tubes (Greiner Bio-One, Austria) for immunological assays. After collection, the samples were centrifuged at 3000 rpm for 10 minutes, and the separated plasma and serum were stored at -80°C until further analysis.

2.5. Measurement of Haematological and Immunological Parameters

2.5.1. Estimation of Haematological Parameters

Haematological parameters (PCV, Hb, platelet count, WBC count, eosinophil count, and basophil count) were determined using an automated haematology analyser (Sysmex KX-21N, Sysmex Corporation, Kobe, Japan) according to the standard procedures described by Legbosi and Ellis [25].

2.5.2. Estimation of Immunological and Allergic Response Markers

Serum IgE levels were measured using an enzyme-linked immunosorbent assay (ELISA) kit (Abcam, UK) following the manufacturer's protocol. Histamine levels were quantified using a fluorometric assay kit (Sigma-Aldrich, USA) to assess mast cell degranulation and allergic response intensity. Cytokine profiling for IL-4, IL-6, TNF-α, and IL-10 was conducted using ELISA kits (R&D Systems, USA) to evaluate pro-inflammatory and anti-inflammatory responses.

2.6. Statistical Analysis

Data were expressed as mean ± standard deviation (SD). Statistical analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey's post hoc test for multiple comparisons. Differences were considered statistically significant at $P < 0.05$.

3. Results and Discussion

3.1. Effects of Treatments on selected haematological parameters

Table 3.1 presents the haematological parameters of Wistar rats subjected to different treatment groups. As shown in Table 3.1, significant alterations in haematological parameters across treatment groups. The normal (G1) and negative control (G2) groups remained comparable, confirming baseline stability. In contrast, the positive control (G3; Ampicloxacillin) demonstrated reduced PCV, Hb, and platelet counts, alongside elevated WBC, eosinophils, and basophils ($P<0.05$), consistent with drug-induced immune activation and β-lactam–associated hypersensitivity reactions.

Administration of A. indica extract alone produced dose-dependent effects, with minimal changes at 200 mg/kg (G4) and significant alterations at 400 mg/kg (G5). The combination groups (G6 and G7) exhibited the most pronounced responses, including marked reductions in PCV, Hb, and platelet counts, and significant increases in WBC and differential counts ($P < 0.05$), suggesting a potentiated interaction effect.

The observed leukocytosis, eosinophilia, and basophilia are characteristic of drug-induced hypersensitivity syndromes, which are driven by aberrant immune activation involving T-cell signaling, IgE-mediated pathways, and cytokine dysregulation [26,27]. The amplified response observed in the combination groups may therefore

reflect synergistic immunomodulation [28], where phytochemicals in *A. indica* enhance immune signaling pathways [29] and potentiate antibiotic-induced hypersensitivity [30].

Furthermore, the reductions in PCV and haemoglobin may be attributed to inflammation-mediated suppression of erythropoiesis, a process increasingly linked to cytokine-driven pathways involving IL-6 and TNF-α in recent immunological models of systemic inflammation [31]. Similarly, the observed thrombocytopenia may be associated with immune-mediated platelet destruction or bone marrow suppression, both of which are recognised features of drug-induced hypersensitivity reactions and related syndromes such as drug reaction with eosinophilia and systemic symptoms (DRESS) syndrome [32,33].

Collectively, these findings suggest that the combined exposure to *A. indica* extract and Ampicloxacillin promotes a dose-dependent amplification of immune and haematological disturbances, consistent with emerging models of herb–drug interaction-induced hypersensitivity and systemic inflammatory dysregulation [22,35].

Table 3.1. Effects of Treatments on selected haematological parameters in Wistar rats.

Group	**PCV (%)**	**Hb (g/dL)**	**Platelets (×10⁹/L)**	**WBC (×10⁹/L)**	**Eosinophils (%)**	**Basophils (%)**
G1 (Normal Control)	42.0 ± 2.1	14.1 ± 0.8	250 ± 15	7.2 ± 0.5	3.1 ± 0.3	0.6 ± 0.1
G2 (Negative Control)	43.0 ± 2.2	14.3 ± 0.9	255 ± 16	7.5 ± 0.6	3.5 ± 0.4	0.7 ± 0.1
G3 (Positive Control)	39.0 ± 2.0*	12.8 ± 0.7*	220 ± 14*	10.8 ± 0.9*	6.3 ± 0.5*	1.2 ± 0.2*
G4 (*A. indica* 200 mg/kg)	40.5 ± 2.0	13.5 ± 0.8	235 ± 14	8.6 ± 0.7	4.2 ± 0.5	0.9 ± 0.2
G5 (*A. indica* 400 mg/kg)	38.5 ± 1.9*	12.6 ± 0.7*	215 ± 13*	11.2 ± 0.9*	6.8 ± 0.6*	1.3 ± 0.2*
G6 (*A. indica* 200 mg/kg + Ampicloxacillin)	36.0 ± 1.8**	11.5 ± 0.6**	190 ± 13**	14.2 ± 1.1**	9.1 ± 0.7**	2.0 ± 0.3**
G7 (*A. indica* 400 mg/kg + Ampicloxacillin)	34.0 ± 1.6**	10.2 ± 0.5**	170 ± 12**	16.8 ± 1.3**	11.3 ± 0.9**	a. ± 0.4**

Values are expressed as Mean ± Standard Deviation (SD); n = 5 per group. *P<0.05 vs Negative Control (G2).* ** P<0.05 vs Positive Control (G3) and Negative Control (G2)

3.2. Effects of Treatments on Some Immunological and Allergic Response Markers

The results in Table 3.2 show marked alterations in immunological and allergic response markers across treatment groups. The normal (G1) and negative control (G2) groups maintained comparable baseline values, while the positive control (G3; Ampicloxacillin) exhibited significant increases in IgE, histamine, and pro-inflammatory cytokines (IL-4, IL-6, and TNF-α), alongside a reduction in IL-10 ($P < 0.05$), indicating drug-related immune activation [36].

Administration of *A. indica* extract alone produced dose-dependent effects, with moderate changes at 200 mg/kg (G4) and significant increases at 400 mg/kg (G5). The combination groups (G6 and G7) showed the highest levels

of IgE, histamine, IL-4, IL-6, and TNF-α, together with the lowest IL-10 levels ($P < 0.05$), demonstrating a pronounced interaction effect.

The elevated IgE and histamine levels suggest increased mast cell activation and release of allergic mediators [37,38]. The rise in IL-4 indicates stimulation of Th2 immune responses, which promotes IgE production and sustains allergic inflammation [39–41]. The elevated IL-6 and TNF-α levels may reflect increased inflammatory signaling and enhanced recruitment of immune cells, whereas the reduction in IL-10 reflects compromised anti-inflammatory regulation, thereby permitting sustained and uncontrolled inflammatory activity [42–45].

The greater changes observed in the combination groups suggest that *A. indica* extract enhances immune responses triggered by Ampicloxacillin, resulting in amplified release of cytokines and allergic mediators. This pattern is consistent with immune dysregulation observed in allergic and drug-induced hypersensitivity conditions [46–49].

Table 3.2. Effects of Treatments on selected Immunological and Allergic Response Markers in Wistar rats.

Group	IgE (ng/mL)	Histamine (ng/mL)	IL-4 (pg/mL)	IL-6 (pg/mL)	TNF-α (pg/mL)	IL-10 (pg/mL)
G1 (Normal Control)	45.2 ± 3.1	18.3 ± 1.2	12.5 ± 1.0	10.2 ± 0.9	9.8 ± 0.7	15.4 ± 1.1
G2 (Negative Control)	48.5 ± 3.3	20.1 ± 1.4	14.2 ± 1.2	11.4 ± 1.1	10.5 ± 0.8	14.8 ± 1.0
G3 (Positive Control: Ampicloxacillin)	76.4 ± 4.5*	35.6 ± 2.1*	22.7 ± 1.8*	18.6 ± 1.5*	17.2 ± 1.3*	12.1 ± 0.9*
G4 (*A. indica* 200 mg/kg)	60.3 ± 3.8	25.4 ± 1.6	17.6 ± 1.3	13.8 ± 1.2	12.4 ± 1.0	13.9 ± 1.1
G5 (*A. indica* 400 mg/kg)	88.7 ± 5.2*	41.2 ± 2.5*	26.9 ± 2.0*	21.5 ± 1.7*	19.6 ± 1.4*	11.8 ± 0.8*
G6 (*A. indica* 200 mg/kg + Ampicloxacillin)	98.2 ± 5.7**	48.9 ± 2.8**	30.5 ± 2.2**	26.4 ± 1.9**	22.8 ± 1.6**	10.3 ± 0.7**
G7 (*A. indica* 400 mg/kg + Ampicloxacillin)	115.7 ± 6.4**	62.3 ± 3.5**	38.1 ± 2.6**	33.7 ± 2.3**	28.5 ± 1.9**	9.1 ± 0.6**

Values are expressed as Mean ± Standard Deviation (SD); n = 5 per group. *$P<0.05$ vs Negative Control (G2).* ** $P < 0.05$ vs Positive Control (G3) and Negative Control (G2).

4. Clinical Implications of the Study

The findings of this study highlight the need for caution when herbal medicines are used concurrently with conventional antibiotics, particularly Ampicloxacillin. The observed increases in eosinophils, basophils, IgE, and histamine indicate activation of allergic response pathways, suggesting a higher risk of hypersensitivity reactions, including conditions such as dermatitis, asthma, and, in severe cases, anaphylaxis [49].

The reductions in packed cell volume (PCV), haemoglobin, and platelet counts further raise concerns about the potential development of anaemia and thrombocytopenia, especially in individuals with underlying haematological

disorders or impaired bone marrow function. These changes point to possible suppression of blood cell production or increased peripheral destruction associated with sustained inflammatory activity [50,51].

The enhanced responses observed with combined administration suggest that A. indica extract may intensify immune reactions triggered by β-lactam antibiotics, potentially increasing susceptibility to drug hypersensitivity [52]. This interaction may also contribute to sustained inflammatory signaling and reduced immune regulation, thereby increasing the risk of prolonged or exaggerated immune responses [53,54].

5. Conclusion

The concurrent use of herbal medicines and conventional antibiotics is increasing worldwide, highlighting the need to understand potential herb–drug interactions. However, the findings of this study suggest that such combinations may influence immune function in ways that warrant careful consideration.

Wistar rats exposed to A. indica extract and Ampicloxacillin showed marked increases in eosinophils, basophils, IgE, histamine, and pro-inflammatory cytokines, alongside reductions in anti-inflammatory signaling. These changes reflect enhanced allergic-type immune activity and sustained inflammatory responses. In parallel, the observed reductions in packed cell volume, haemoglobin, and platelet counts suggest disturbances in haematological homeostasis, including features consistent with anaemia and thrombocytopenia.

The stronger effects observed in the combination groups indicate that co-administration may amplify immune responses beyond those seen with individual treatments. This pattern highlights the potential for herb–drug interactions to intensify hypersensitivity reactions and alter normal immune regulation.

These findings underscore the importance of cautious use of herbal–antibiotic combinations, particularly in individuals with underlying immune or haematological conditions. However, future studies should:

1. Elucidate the molecular and cellular mechanisms underlying the interaction between Azadirachta indica phytochemicals and β-lactam antibiotics in the development of hypersensitivity reactions.

2. Investigate the long-term safety and toxicological effects of repeated co-administration of A. indica extracts with Ampicloxacillin and other commonly prescribed antibiotics.

3. Determine the optimal dosage, duration, and formulation of A. indica that minimise adverse herb–drug interactions while preserving its therapeutic benefits.

4. Conduct detailed histopathological and immunophenotypic studies to evaluate the effects of the combined treatment on immune organs, bone marrow, and other target tissues involved in immune regulation and haematopoiesis.

5. Validate these findings through well-designed clinical studies to establish the safety, efficacy, and clinical relevance of concurrent A. indica and antibiotic use in human populations.

Declaration

Source of Funding

This study has not received any funds from any organization.

Conflict of Interest

The authors declare that they have no conflict of interest.

Consent for Publication

The authors declare that they consented to the publication of this study.

Authors' Contribution

All the authors took part in literature review, analysis, and manuscript writing equally.

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