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Research Article

Effect of the hydroethanolic extract of *Terminalia catappa L.* bark against the overproduction of cytokines TNF-α and IL-6 during neuroinflammation

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ABSTRACT

The use of medicinal plants is experiencing a particularly marked resurgence of scientific interest, especially in the face of the increasing scale of neurodegenerative diseases. The general objective of our study is to evaluate *in vitro* the ability of *Terminalia catappa L.* bark to reduce the overproduction of pro-inflammatory molecules (TNF-α, IL-6) in primary rat astrocytes. The plant material consisted of dried bark of *Terminalia catappa L.* Ethanol extraction was performed by maceration. Four newborn rat pups (P14) were used for primary astrocyte culture. A density gradient centrifugation step using Ficoll was performed to obtain the astrocytes, which were then cultured for 14 days. Inflammation was induced using *Escherichia coli* lipopolysaccharide (LPS) on primary astrocyte cells. A *T. catappa* extract at a concentration of 50 µg/ml was chosen as the protective concentration. Ficoll density gradient separation generated three distinct fractions : astrocytes at the 0-10% interface (well-defined opalescent ring). By Day 14, a confluent monolayer (100%) of mature astrocytes had formed. Pretreatment of the cells with *T. catappa* extract at 50 µg/mL significantly reduced the LPS-induced increase in TNF-α from 4660 ± 0.13 pg/mL to 2685 ± 0.38 pg/mL. IL-6 decreased significantly from 5469 ± 1.58 pg/mL to 4861 ± 0.25 pg/mL. The anti-inflammatory activity of the hydroethanolic extract of *Terminalia catappa L.* is exceptional, with a major inhibition of TNF-α (95.6%) and IL-6 (91.5%) overproduction.

Keywords:
Neuroinflammation ; Primary astrocytes ; *Terminalia catappa L.* ; Côte d'Ivoire

1. INTRODUCTION

The use of medicinal plants is one of humanity's oldest therapeutic practices, employed for millennia by numerous civilizations. Today, this traditional approach is experiencing a particularly marked resurgence of scientific interest, especially in light of the growing scale of neurodegenerative diseases, which now represent a global health emergency. In 2021, 57 million people worldwide suffered from dementia. This figure is all the more concerning given the nearly 10 million new cases per year[1]. Moreover, this rapid increase fuels particularly alarming projections : 78 million patients expected in 2030, then 139 million in 2050[2]. This epidemiological reality underscores the urgent need to develop innovative therapeutic strategies. However, current treatments for neurodegenerative diseases are revealing their limitations in the face of the complexity of the underlying pathophysiological mechanisms.

In this regard, neuroinflammation is emerging as a central process that needs to be better understood and targeted. This reaction is characterized by the chronic activation of glial cells and the sustained secretion of pro-inflammatory mediators[3]. Chronic activation of astrocytes, particularly in response to pathological stimuli, leads to excessive secretion of pro-inflammatory cytokines

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such as Interleukin-1, Interferon-α, and Interleukin-6 (IL-1, TNF-α, and IL-6), creating a deleterious cycle that contributes to the progression of diseases such as Alzheimer's, Parkinson's, and multiple sclerosis[4].

In this context, the exploration of plant resources is emerging as a promising therapeutic avenue. *Terminalia catapa L.*, commonly known as the Indian almond tree, is emerging as a promising candidate. This tropical species from the Combretaceae family is traditionally used in various pharmacopoeias to treat inflammatory conditions. Moreover, some recent scientific studies tend to confirm this therapeutic potential. On the one hand, the beneficial properties observed *in vitro* of the ethanolic extract of *T. catappa* stem bark appear to be attributable to its immunomodulatory and anti-inflammatory capacities, conferred by the identified phenolic compounds[5]. On the other hand, research conducted on the aqueous extract of the leaves suggests that this extract improves oxidative stress and inflammation induced by hyperglycemia by activating the Nrf-2 gene, an essential transcription factor in the regulation of oxidative stress [6]. Nevertheless, despite these promising advances, a major scientific gap remains : the specific effects of *T. catappa* bark on the inflammatory response of astrocytes are still unexplored. This problem is all the more crucial given that these glial cells are central players in neuroinflammation in neurodegenerative diseases. Consequently, this gap raises a fundamental research question : can *Terminalia catappa* bark extracts modulate the inflammatory response of astrocytes by inhibiting lipopolysaccharide (LPS)-induced overproduction of TNF-α and IL-6 ? The general objective of our study will be to evaluate *in vitro* the ability of *Terminalia catappa* L. bark to reduce the overproduction of pro-inflammatory molecules (TNF-α, IL-6) in primary rat astrocytes.

2. MATERIALS AND METHODS

2.1. Plant material

The plant material consisted of dried bark from *Terminalia catappa L.* The samples were collected in the Abidjan region, specifically in Yopougon Niangion, Cité Verte, in March 2025.

2.2. Animal material

Four (4) two-week-old Wistar rats, weighing 25 g each, were used in this study. The rats were provided by the animal facility of the UFR Biosciences of Félix Houphouët-Boigny University of Côte d'Ivoire.

2.3. Obtaining dried plant powder

The day after harvesting, the plant material was transported in canvas bags to allow for optimal ventilation. Drying took place in the Biochemistry Laboratory of Félix Houphouët Boigny University, in the open air and protected from sunlight, for 14 days. The dried plant material was then ground using a blender until a homogeneous powder was obtained. The particle size was standardized by sieving to optimize the contact surface during extraction and ensure the reproducibility of the process. The resulting powder was stored in labeled, airtight containers, protected from light and humidity (17°C).

2.4. Preparation of the hydroalcoholic extract

The ethanolic extraction was carried out by maceration using the method of [7] according to the following protocol: one hundred grams (100 g) of plant powder were dissolved in 1 liter of a hydroalcoholic solution (70°) using a blender for 5 minutes. The resulting macerate or homogenate was then drained and filtered three times through cotton and once through 3 mm Whatman filter paper. The filtrate was then dried in an oven at 45°C for 24 hours. Finally, after drying, the extract was weighed and stored in hermetically labeled bottles, then refrigerated at 17°C for future use.

The extraction yield was calculated using the formula :

$$\text{Yield (\%)} = \frac{(\text{Mass of dry extract obtained}) \times 100}{(\text{Mass of plant material used})}$$

2.5. Phytochemical screening

To identify and characterize the different chemical groups in our *T. catappa* bark extracts, several analytical methods were used. These include: concentrated sulfuric acid for the detection of sterols and polyterpenes ; 10% ferric chloride for polyphenols [8] ; 10% lead acetate for flavonoids; Stiasny's reagent for catechins and sodium acetate for gallic tannins ; NH4OH for anthocyanins; hydrochloric alcohol for coumarin; ammonia for quinones ; and Dragendorff and Wagner's reagents for alkaloids.

2.6. Primary astrocyte culture from rat pups cortical tissue preparation by dissection

Newborn rat pups (P14) were sacrificed according to the Laboratory's ethical protocols. The brain was then rapidly dissected in 7 ml of sterile, cold HBSS medium to preserve cell viability. The cerebellum and olfactory bulbs were then carefully removed to specifically isolate the cerebral cortex. Simultaneously, particular attention was paid to the complete removal of the meninges, which could otherwise contaminate the culture with fibroblasts. Finally, the cortical tissue was

finely chopped using a sterile scalpel to facilitate the subsequent enzymatic dissociation step. Each raccoon was dissected.

2.6.1. Cell dissociation

Tissue dissociation combined an enzymatic and mechanical approach to optimize cell yield while preserving astrocyte integrity [9]. Tissue fragments were incubated in a 0.05% trypsin solution for 5 minutes at 37°C. The addition of DNase I at a concentration of 100 µg/mL prevented cell aggregation by degrading the DNA released from the lysed cells.

Once this step was completed, enzymatic digestion was stopped by adding 1 mL of fetal bovine serum (FBS) to inhibit trypsin activity. The mixture was then centrifuged for 5 minutes at 2100 rpm at 4°C. After centrifugation, the supernatant was discarded, and the cell pellet was resuspended in cold HBSS. Subsequently, gentle trituration was performed using a pipette to homogenize the suspension and complete the mechanical dissociation of the cell aggregates. This step was carried out carefully to avoid damaging the fragile cells. Finally, the cell suspension was filtered through a sterile 70 µm sieve to remove residual cell aggregates and tissue debris, thus ensuring a homogeneous cell suspension.

After dissociation, a density gradient centrifugation step using Ficoll was performed to obtain the astrocytes. The astrocytes were cultured for 14 days [10-11].

2.7. Cytotoxicity evaluation by the CCK-8 test

Principle and Objective : The intrinsic cytotoxicity of the hydroethanolic extract of *T. catappa* bark was evaluated on primary astrocytes to determine non-toxic concentrations. This test allows for the differentiation of beneficial from deleterious effects of the extract on healthy astrocytes and the assessment of its safety for use [12].

Four concentrations of *T. catappa* extract: 1.5; 8; 40; 200 µg/mL were prepared by dilutions in DMEM medium from the stock solution (1 mg/mL) according to the protocols of [13].

2.8. Cell viability

After 48 hours of exposure to different extract concentrations, astrocyte viability was measured using the CCK-8 assay according to the manufacturer's protocol.

Ten microliters (10 µL) of CCK-8 solution were added to each well containing 100 µL of culture medium. The plates were then incubated for 2 hours at 37°C in a CO_2 incubator. The absorbance in each well was measured at 450 nm using a microplate reader.

The percentage of viability was calculated using the formula :

$$\% \text{ Viability} = \frac{(\text{Absorbance treatment with extract})}{(\text{Absorbance negative control})} \times 100$$

This method allows for a direct assessment of the cytotoxic effect of each extract concentration compared to untreated control astrocytes [14].

2.9. Evaluation of anti-inflammatory activity

Inflammation was induced using *Escherichia coli* lipopolysaccharide (LPS) on primary astrocytes. *T. catappa* extract at a concentration of 50 µg/ml was chosen as the protective concentration. Primary astrocytes were seeded (20,000 cells/well) into 6-well plates at a concentration of 4 ml per well. After 4 hours of incubation, *T. catappa* extract (50 µg/ml) and LPS (1 µg/ml) were added sequentially to the cell cultures for a total volume of 100 µL per well. The plates were then incubated for 48 hours at 37°C in a CO2 incubator. The experimental design included the following groups :

- Control group : primary astrocytes + culture medium
- LPS-only group : primary astrocytes + culture medium + LPS (1 µg/mL)
- Treatment group : primary astrocytes + culture medium + extract (50 µg/mL) + LPS (1 µg/mL).

After the incubation period, the contents of each well were centrifuged at 2100 rpm for 5 minutes. The supernatants were collected, aliquoted, and stored at -80°C for subsequent use in cytokine assays.

2.10. IL-6 and TNF-α cytokine assay

IL-6 and TNF-α cytokine assays were performed using the FineTest kit.

Test Principle : The test is based on sandwich enzyme immunoassay technology. The anti-IL-6 (or TNF-α) antibody was pre-coated onto a 96-well plate. The biotin-conjugated anti-IL-6 (or TNF-α) antibody was used as the detection antibody.

The percentages of inhibition were calculated using the following formula :

$$1\% = \frac{(\text{LPS Absorbance alone} - \text{Treated Absorbance})}{[(\text{LPS Absorbance alone} - \text{Control Absorbance})]} \times 100$$

The percentages of reduction and increase in inflammation were calculated using the following formulas :

$$\% \text{ Reduction} = \frac{(\text{LPS Absorbance alone-Absorbance treated}}{\text{LPS Absorbance alone}} \times 100$$

$$\% \text{ Increase} = \frac{(\text{LPS Absorbance alone} - \text{Control Absorbance})}{\text{LPS Absorbance alone}} \times 100$$



Figure 1. Hydroethanolic extract of *Terminalia catappa L.* bark [33].

With :
- LPS Absorbance alone : primary astrocytes + culture medium + LPS (1 µg/mL)
- Treated Absorbance : primary astrocytes + culture medium + extract (50 µg/mL) + LPS (1 µg/mL)
- Control Absorbance : primary astrocytes + culture medium.

2.7. Statistical analysis of data

Statistical tests were performed using GraphPad Prism version 8.0 (GraphPad Software, San Diego, CA, USA). Results are presented as means ± standard deviations of the mean. Data were evaluated using one-way ANOVA followed by Dunnett's multiple comparison test at a significance level of 5% to assess the significance of observed differences. A difference of $P < 0.0001$ is considered significant, and a difference of $P > 0.0001$ is not significant.

2.8. Ethics

The study was approved by the Laboratory of Biology and Health of the UFR Biosciences of the Félix Houphouet Boigny University of Côte d'Ivoire. Ethical approval number is : RCI/004-27/02/2025.

3. RESULTS

3.1. Extract characterization

3.1.1. Extraction yield

From 100 g of *T. catappa* bark powder, we obtained 11.31 g of dry hydroethanolic extract, representing an extraction yield of 11.31%.

3.1.2. Appearance and color of the extract

Physical appearance

After evaporation of the hydroethanolic solvent, the extract is a dry residue with a homogeneous texture. At room temperature (20°C ± 17°C), the dry hydroethanolic extract has a crystalline consistency (Figure 1).

Colorimetric characteristics

The hydroethanolic extract has a characteristic color ranging from light brown to dark brown, with a dominant dark brown hue. The extract exhibits intense color intensity.

3.2. Phytochemical screening

Phytochemical analysis revealed the presence of several groups of secondary metabolites. Certain compounds stood out due to their abundance: flavonoids, gallic tannins, and total polyphenols were identified in relatively high quantities in the extract (Table 1).

3.3. Primary astrocyte cultures

Enzymatic and mechanical dissociation of the cortical tissue of newborn rat pups (P14) yielded a homogeneous cell suspension. Ficoll density gradient separation generated three distinct fractions : astrocytes at the 0-10% interface (well-defined opalescent ring). Three successive washes in HBSS effectively removed Ficoll residues.

Cell adhesion occurred after 4 hours. On Day 0, the cells exhibited a dispersed morphology with

Table 1. Chemical composition of hydroethanolic extracts of the bark of *Terminalia catappa L.*

CHEMICAL GROUPS	OBSERVATIONS
Sterols et polyterpenes	++
Total polyphenols	+++
Flavonoids	+++
Catechetical tannins	++
Gallic tannins	+++
Anthocyanins	-
Leucoanthocyanes	+
Coumarins	-
Quinones	++
Alkaloids	+
Saponins	++

(-) **:** Absence
(+) : Presence
(++) : Abundant
(+++) : Very abundant

progressive adhesion to the substrate. A change of medium at 24 hours eliminated non-adherent cells.

On Day 7, the astrocytes showed approximately 80-90% confluence with a characteristic mature stellate morphology. The cells had developed extensive cytoplasm with multiple branched extensions.

On Day 14, a confluent monolayer (100%) of mature astrocytes was formed. The cells exhibited a sprawling fibroblastic morphology with well-developed and interconnected extensions (Figure 2).

The purity of the astrocytes was verified using the specific marker GFAD. All astrocytic cells were negative for GFAD.

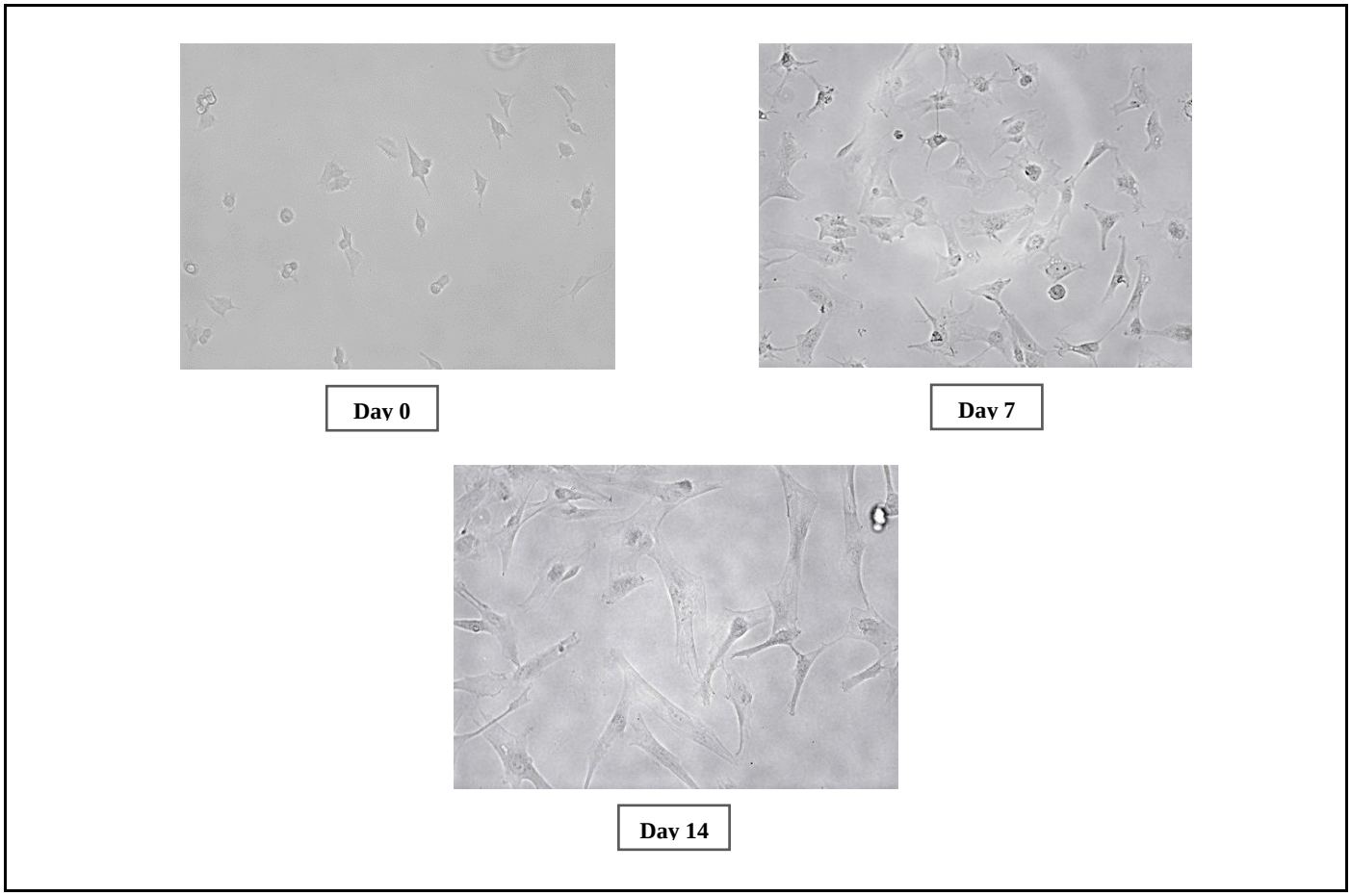


Figure 2. Primary astrocyte cells in culture.

3.4. Cytotoxicity evaluation

The results of the cytotoxicity evaluation of *T. catappa* bark extract on primary astrocytes are presented as a curve in Figure 3. These results show that all concentrations tested (1.5 ; 8 ; 40 ; 200 µg/mL) maintain cell viability superior to the control (100%).

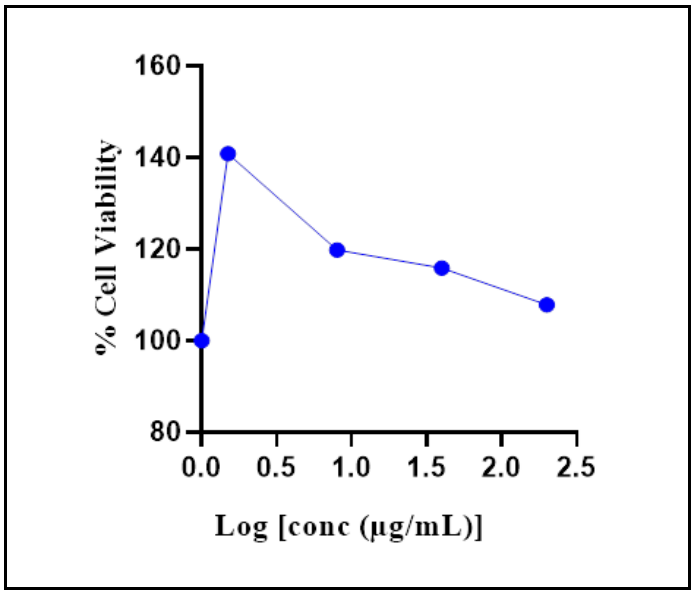


Figure 3. Cell viability curve.

3.4. Evaluation of anti-inflammatory activity

3.4.1. Effect of T. catappa extract on TNF-α overproduction

The results of the evaluation of the anti-inflammatory activity of *T. catappa* bark extract on TNF-α overproduction are presented as histograms in Figure 4.

These results show that exposure to LPS alone (negative control group) induced a drastic increase in TNF-α production, from 2593 ± 0.03 pg/mL in the normal control group to 4660 ± 0.13 pg/mL, representing a 44.35% increase compared to the control ($p < 0.0001$). Pretreatment of the cells with *T. catappa* extract at 50 µg/mL significantly reduced this inflammatory production. This reduction is highly significant, with TNF-α levels falling to 2685 ± 0.38 pg/mL, representing a 42.38% decrease compared to the LPS-only group and statistically identical to the normal control group. The percentage of inhibition achieved is remarkable, with a 95.6% reduction in LPS-induced TNF-α production. ANOVA analysis reveals highly significant differences between all groups ($p < 0.0001$) with a perfect coefficient of determination ($R^2 = 1.000$), confirming the excellent goodness of fit of the model. Dunnett's multiple comparisons test confirms the significance of all comparisons performed, demonstrating the exceptional anti-inflammatory efficacy of the extract on this major pro-inflammatory cytokine.

3.4.2. Effect of Terminalia catappa L. extract on IL-6 overproduction

The results of the evaluation of the anti-inflammatory activity of *T. catappa* bark extract on IL-6 overproduction are presented as histograms in Figure 5.

These results show that exposure to LPS alone (negative control group) caused a moderate but significant increase in IL-6 production, from 4804 ± 0.07 pg/mL in the normal control group to 5469 ± 1.58 pg/mL, representing a 12.16% increase compared to

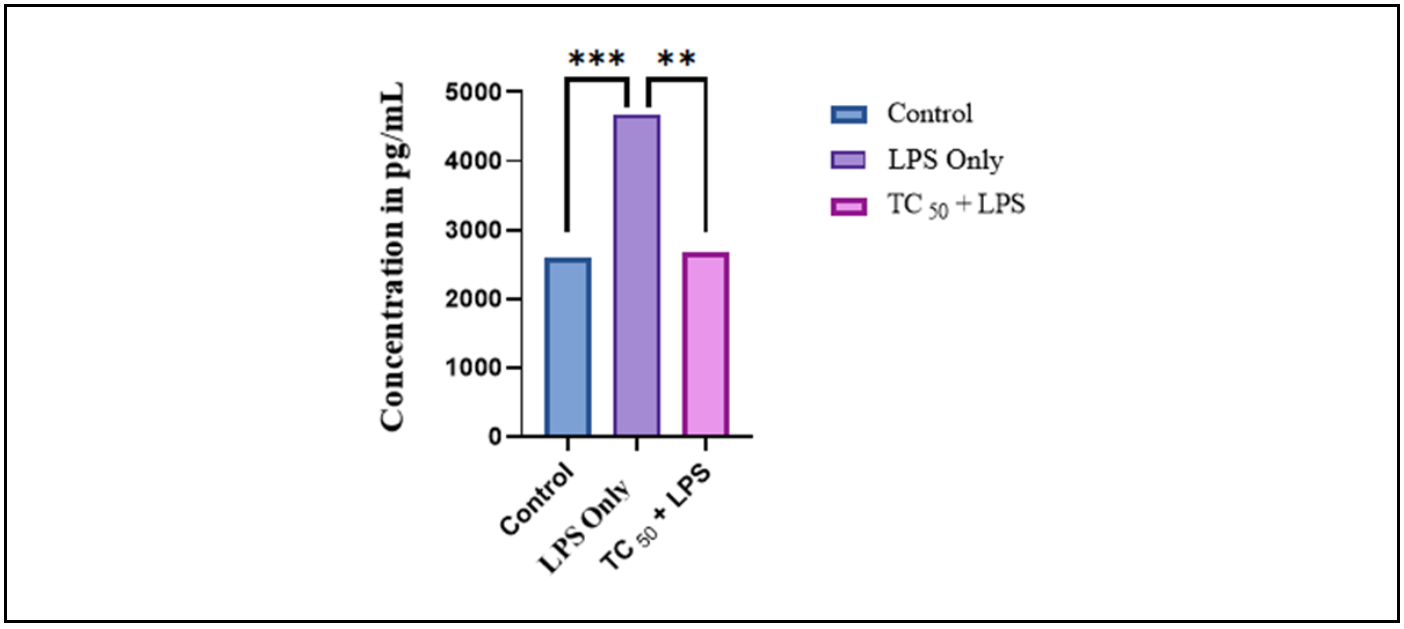


Figure 4. Effect of *Terminalia catappa L.* extract on TNF-α production.

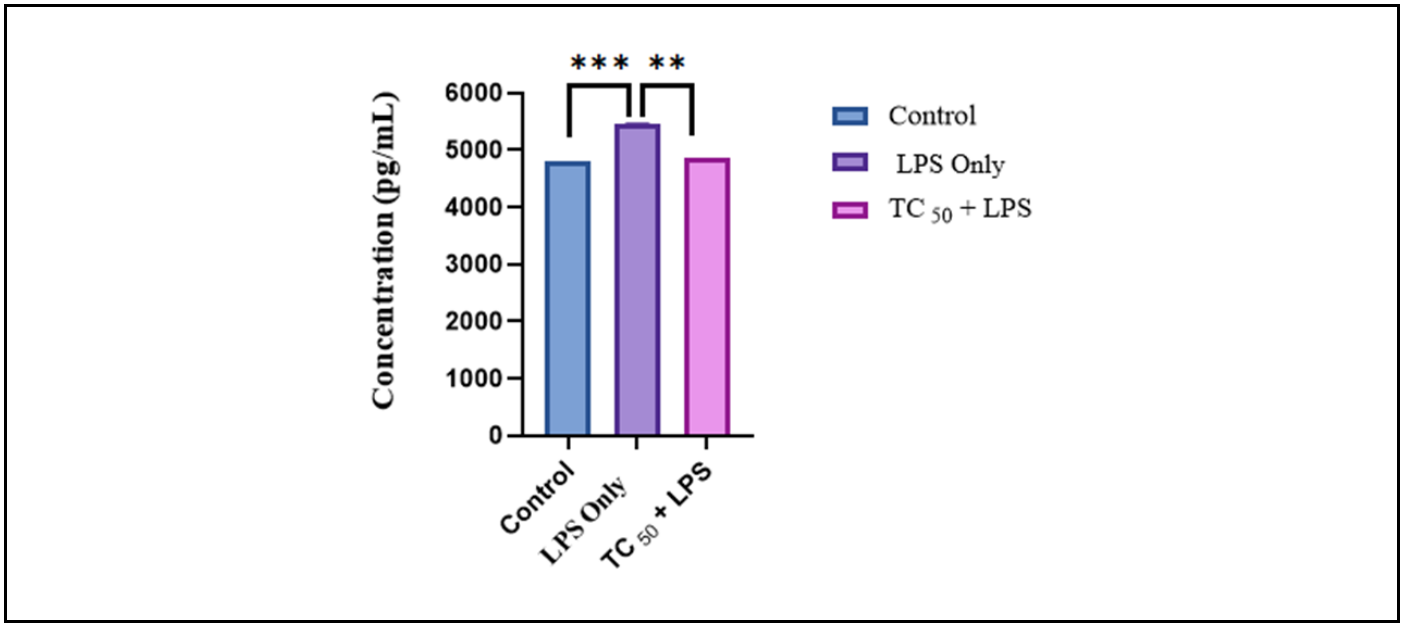


Figure 5. Effect of *Terminalia catappa L.* extract on IL-6 production.

to the control ($p < 0.0001$). Pretreatment of the cells with *T. catappa* extract at 50 µg/mL effectively counteracted this inflammation. This reduction is significant, with IL-6 levels falling to 4861 ± 0.25 pg/mL, representing an 11.11% decrease compared to the LPS-only group and levels close to those of the normal control group. The calculated percentage of inhibition compared to the control is 91.5%, demonstrating the extract's efficacy in neutralizing LPS-induced IL-6 production. Statistical analysis by ANOVA reveals highly significant differences between all groups ($p < 0.0001$) with a perfect coefficient of determination ($R^2 = 1.000$), confirming the excellent goodness of fit of the model.

4. DISCUSSION

The general objective of this study was to evaluate *in vitro* the ability of *Terminalia catappa L.* bark to reduce the overproduction of pro-inflammatory molecules (TNF-α, IL-6) in primary rat astrocytes. Indeed, neuroinflammation is one of the central pathophysiological mechanisms in the initiation and progression of neurodegenerative diseases such as Alzheimer's and Parkinson's [14]. Given the therapeutic limitations of current conventional molecules[15], there is an urgent need to develop new therapeutic strategies, including the use of medicinal plants.

T. catappa is widely used in traditional medicine for its anti-inflammatory, antioxidant, antibacterial, and other properties [16-17]. In this study, hydroethanolic (70°) extraction of *T. catappa* bark yielded 11.31%. This result is satisfactory for this type of plant organ and falls within the upper range of values reported in the scientific literature.

This high yield can be explained by the bark's specificity as the organ containing the most secondary metabolites. Indeed, [18] obtained a yield of 5.77% with *T. catappa* leaves extracted using a hydro-alcoholic solvent (70°). Furthermore, [19]obtained yields of 7.1% with a methanolic extract of the leaves, and 18.3% with an aqueous extract. These differences illustrate the major impact of experimental parameters on extraction efficiency and suggest that the barks, richer in secondary metabolites, constitute a particularly interesting matrix for pharmacological applications.

Furthermore, overall data on the genus Terminalia confirm this variability: yields can range from less than 5% to more than 20%, depending on the species studied, the organ analyzed, and the experimental conditions [20]. In this context, the yield obtained in the present study (11.31%) is a robust result, which supports the potential of *T. catappa* bark as a source of bioactive compounds potentially involved in modulating neuroinflammatory processes.

Phytochemical analysis of this extract revealed a diverse chemical profile rich in secondary metabolites, characterized by a particular abundance of total polyphenols, gallic tannins, and flavonoids. This high polyphenol concentration forms the biochemical basis for the antioxidant and anti-inflammatory activities documented in this species.

The *in vitro* study of neuroinflammation required the culture of primary rat astrocytes.The results obtained confirm the effectiveness of the Ficoll density gradient separation method for isolating primary astrocytes. The purity obtained, exceeding 80%, is consistent with data reported in the literature for this technique. [9] established reference protocols for the isolation and culture of murine cortical astrocytes,

demonstrating the efficiency of this approach compared to traditional differential shaking methods, which require 7–10 days of culture before purification. This approach offers several advantages over conventional methods based solely on differential adhesion, enabling early separation of cell populations and reducing the time required to obtain a pure culture. The observed morphological evolution, from an initial spherical shape to a star-shaped form with multiple extensions, reflects the adaptation of astrocytes to the culture environment and their maturation process. This star-shaped morphology constitutes a reliable morphological marker of astrocytic identity, and the formation of intercellular contacts partially replicates the native tissue organization of astrocytes, suggesting the maintenance of certain functional properties important for future studies.

Newborn rat pups (P14) were chosen because, in rodents, astrocyte proliferation and differentiation begin late in gestation and accelerate sharply after birth, reaching their peak during the first two postnatal weeks (around P14). At 14 days, astrocytes are in the midst of a phase of local expansion and structuring, allowing for the collection of an extremely active cell population representative of this dynamic process.

In this study, Escherichia coli lipopolysaccharide (LPS), used as a pro-inflammatory molecule, induced cytokine overproduction of approximately 12.16% for IL-6 and 44.35% for TNF-α in primary rat astrocytes. This stimulation is well-documented in the literature, as LPS classically induces glial cell activation and increased secretion of pro-inflammatory cytokines [22]. This cytokine overproduction was reduced by the hydroethanolic extract of *T. catappa* bark. The drastic reduction in TNF-α overproduction, with an inhibition rate of 95.6% for the LPS-induced increase (including the control) and 91.5% for IL-6, positions this extract among the most effective natural anti-inflammatory agents [12,23]. This efficacy is remarkably high compared to data from the literature on other plant species with anti-inflammatory potential [24]. This efficacy is particularly relevant because astrocytes have the capacity to secrete TNF-α in response to various biological stimuli, and this modulation confirms the broad-spectrum anti-inflammatory effect of the extract [4,25]. The use of primary astrocytes as an experimental model reinforces the relevance of these results, as these cells represent a validated model for the study of neuroinflammation [26]. The extract's ability to restore cytokine levels to near-normal values suggests not only an anti-inflammatory effect but also a potential for restoring cellular homeostasis [27].

These remarkable effects can be attributed to the synergy between the various polyphenolic compounds present in the hydroethanolic bark extract, particularly flavonoids and gallic tannins, known for their inflammatory pathway-modulating properties [28]. The use of a hydroethanolic solvent promotes the selective extraction of bioactive hydrolyzable tannins, flavonoids, and glycosylated phenolic compounds, which are the main contributors to the documented biological activities [29]. The extraction yield of 11.31% obtained, combined with this rich composition, suggests efficient recovery of bioactive secondary metabolites from *T. catappa* bark [30].

Taken together, these results position the hydroethanolic extract of *Terminalia catappa* bark as a promising candidate for the development of natural neuroprotective agents. The combination of a favorable safety profile and exceptional anti-inflammatory efficacy of this extract on key neuroinflammation targets suggests potential applications in the prevention or treatment of neurodegenerative diseases associated with chronic inflammation [27]. These multiple properties illustrate the advantage of complex plant-based preparations over isolated molecules, where the therapeutic effect results from the synergistic action of multiple bioactive compounds rather than a single active ingredient [31].

These results must nevertheless be interpreted within the context of the inherent limitations of *in vitro* models. Although primary astrocyte cultures offer a more physiological cellular environment than cell lines, they do not fully reproduce the complexity of cellular interactions present *in vivo* [32].

5. CONCLUSION

This study investigated the *in vitro* effect of the hydroethanolic extract of *T. catappa* bark against neuroinflammation. The anti-inflammatory activity of this extract is exceptional, with a major inhibition of the overproduction of TNF-α (95.6%) and IL-6 (91.5%). An *in vivo* study could be considered to confirm the neuroprotective nature of *Terminalia catappa L.* bark.

6. ACKNOWLEDGEMENTS

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Author contributions

T A : Conceptualization, Methodology, Execution, Data collection, Supervision, Writing of the article. K G : Conceptualization, Methodology, Supervision. S M : Methodology and Data collection.

Funding

None to declare.

Conflict of interest

None to declare.

Ethics approval

The study was approved by the Laboratory of Biology and Health of the UFR Biosciences of the Félix Houphouet Boigny University of Côte d'Ivoire. Ethical approval number is : RCI/004-27/02/2025.

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