Suppression of B Cell Activating Factor by *Physalis angulata* Extract in a Doxorubicin-Induced Rat Model of Nephrotic Syndrome: Exploring Its Role as Adjunctive Therapy

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CURRICULUM VITAE

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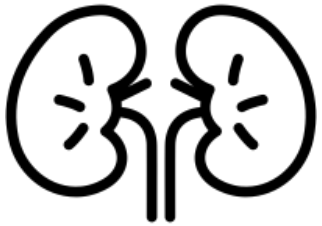
EDUCATIONAL BACKGROUND

- Doctoral Degree, Brawijaya University, 2023 - 2025
- Pediatric Nephrology Sub-Specialist Program, Airlangga University, Indonesia, 2018-2020
- Pediatric Residency Program, Brawijaya University, Indonesia, 2009-2013
- Magister of Biomedical Science, Faculty of Medicine, Brawijaya University, Indonesia, 2009-2013
- Medical Doctor Degree, Brawijaya University, Indonesia, 2001-2007

CLINICAL AND RESEARCH INTEREST

- Pediatric Glomerulopathies
- Interventional Pediatric Nephrology
- Critical Care Pediatric Nephrology

INTRODUCTION



The **most common** glomerular disorder in children

Nephrotic Syndrome

Tapia *et al.*, 2022; Forero-Delgadillo *et al.*, 2022)

Nephrotic Syndrome

Persistent challenges in the region

Many children experiences frequent relapse or become steroid-dependent, leading to significant long-term steroid toxicity.

This is the key concern that highlights the **urgent need for safe and effective adjunctive therapies**

Veltkamp et al., 2021; Tapia *et al.*, 2022; Forero-Delgadillo *et al.*, 2022

Steroids remain the mainstay of therapy, but their **side-effects accumulate over years** of repeated relapses.

(Kshirsagar *et al.*, 2013; Hjorten *et al.*, 2016; Schijvens *et al.*, 2017; Jang *et al.*, 2018; Wang *et al.*, 2018a; Kallash *et al.*, 2019; Cui *et al.*, 2021; Chan *et al.*, 2022; Vivarelli *et al.*, 2022)

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Adjunctive Therapy

Several phytomedicne have been shown to reduce relapse rates and the side effects of long-term corticosteroid therapy

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Drug of choice

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Target Therapy

New paradigm of B cell involvement in the pathogenesis of nephrotic syndrome

(Kshirsagar *et al.*, 2013; Hjorten *et al.*, 2016; Schijvens *et al.*, 2017; Jang *et al.*, 2018; Wang *et al.*, 2018a; Kallash *et al.*, 2019; Cui *et al.*, 2021; Chan *et al.*, 2022; Vivarelli *et al.*, 2022)

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New paradigm of B cell involvement in the pathogenesis of nephrotic syndrome

BAFF

Cytokine for B cell survival and activation, has been implicated in podocyte injury and disease progression in nephrotic syndrome

(Kshirsagar *et al.*, 2013; Hjorten *et al.*, 2016; Schijvens *et al.*, 2017; Jang *et al.*, 2018; Wang *et al.*, 2018a; Kallash *et al.*, 2019; Cui *et al.*, 2021; Chan *et al.*, 2022; Vivarelli *et al.*, 2022)

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The gap become foundation of this study

Can we **modulate BAFF** using **a safe, plant-based compound**?

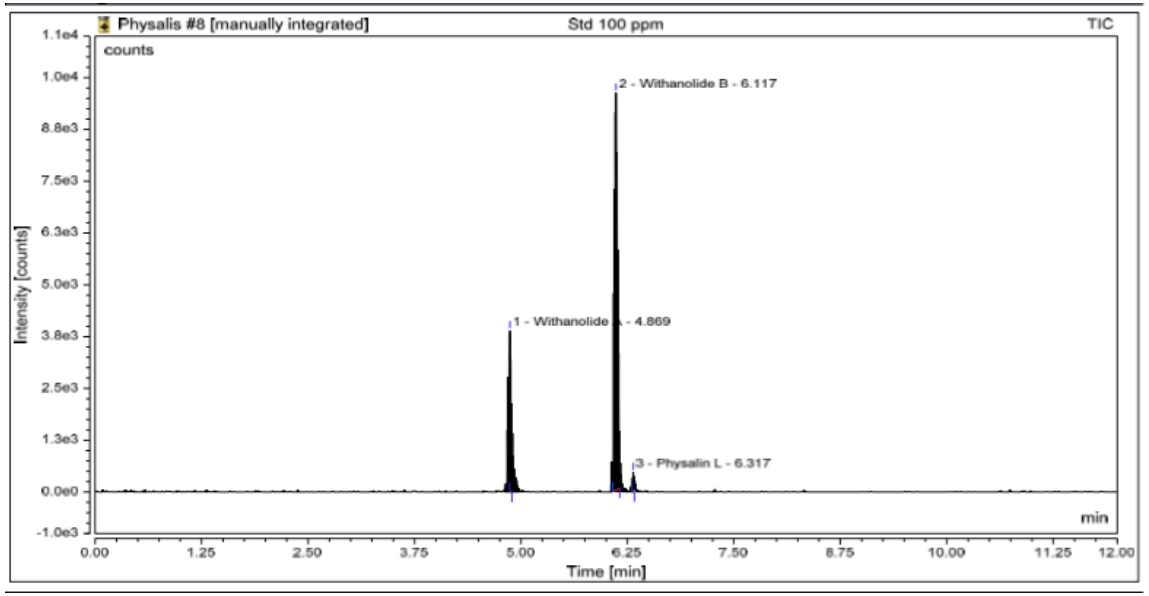
Can we **identify a bioactive molecule** from this plant that could be further developed into a potential therapeutic agent?

Commonly found in Indonesia, it contains several **phytosteroid compounds such as withanolides.**

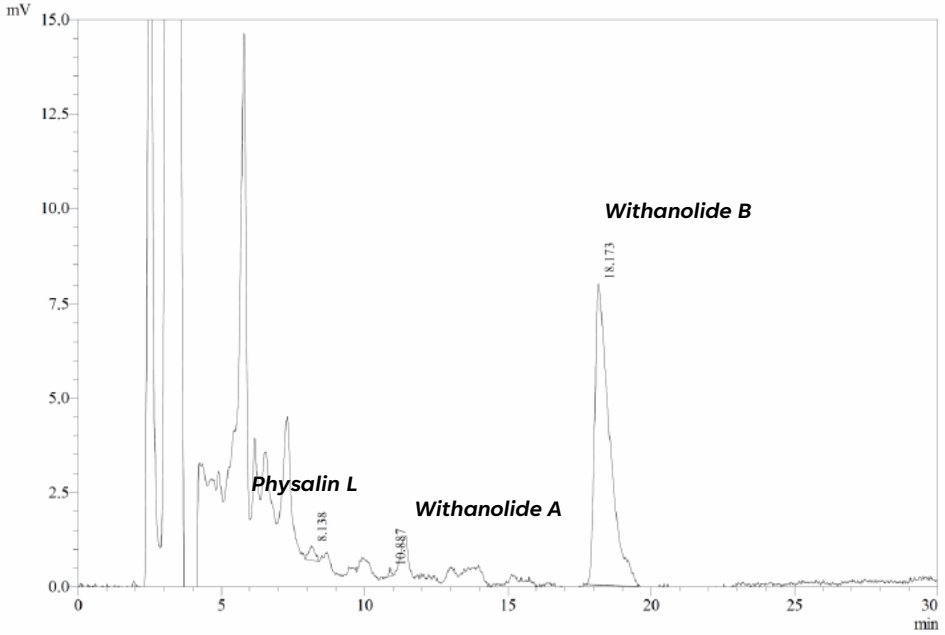
Physalis angulata

Jang *et al.*, 2018; Wang *et al.*, 2018a; Kallash *et al.*, 2019; Cui *et al.*, 2021; Chan *et al.*, 2022; Vivarelli *et al.*, 2022

Preliminary study



Liquid Chromatography/Mass Spectrometry (LC/MS)



High Performance Liquid Chromatography (HPLC)

HPLC and LC-MS analyses consistently identified **Withanolide A, Withanolide B, and Physalin L** in Physalis angulata, with **Withanolide B emerging as the dominant** and **primary bioactive compound**.

Jang *et al.*, 2018; Wang *et al.*, 2018a; Kallash *et al.*, 2019; Cui *et al.*, 2021; Chan *et al.*, 2022; Vivarelli *et al.*, 2022

Previous study

Physalis angulata

In combination **with methylprednisolone, it reduces inflammation and improves kidney function** in lupus model rats through NF-κB pathway inhibition.

In lupus model rats, it also **suppresses immune responses** by inhibiting macrophage nitric oxide (NO) production and tumor necrosis factor-α (TNF-α)level.

No studies have yet examined the effects of Physalis angulata in nephrotic syndrome.

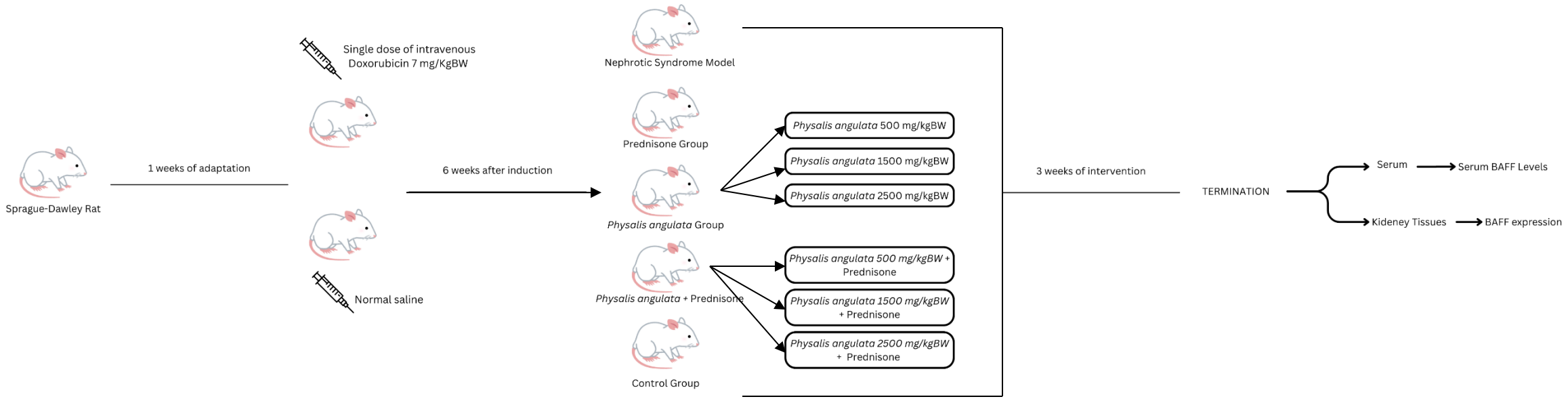
Jang *et al.*, 2018; Wang *et al.*, 2018a; Kallash *et al.*, 2019; Cui *et al.*, 2021; Chan *et al.*, 2022; Vivarelli *et al.*, 2022

Evaluate the effect of Physalis angulata extract on BAFF levels in the serum and kidney tissue of doxorubicin-induced nephrotic syndrome rats, and **assess whether combining it with prednisone would enhance its effects.**

METHOD

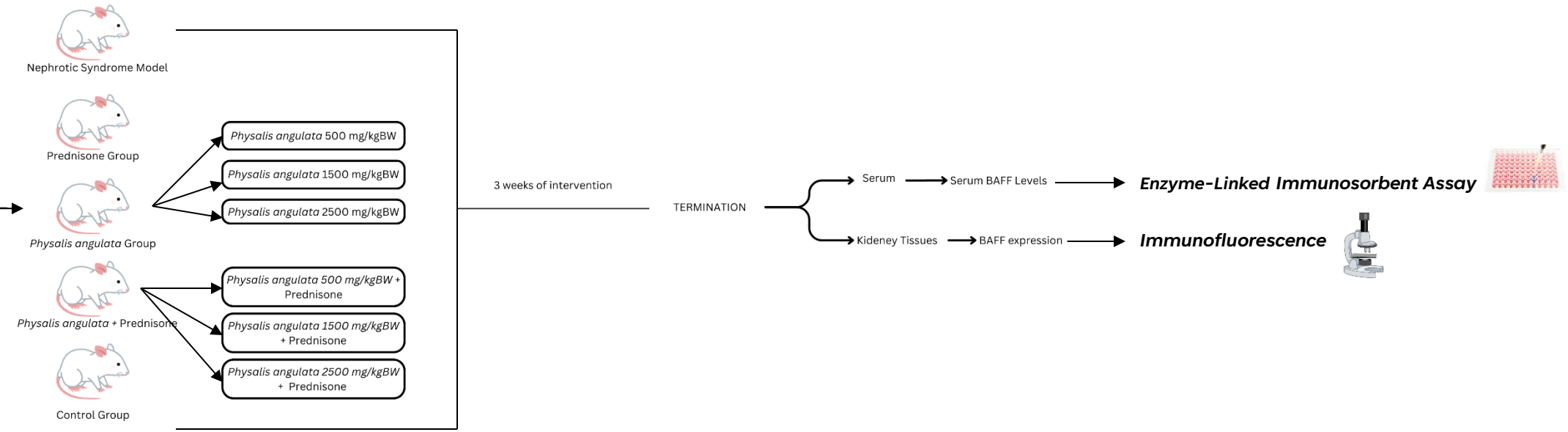
Preliminary study

Single **7 mg/kg** dose of **doxorubicin produced the most consistent nephrotic syndrome** model after **six weeks** of observation



Preliminary study

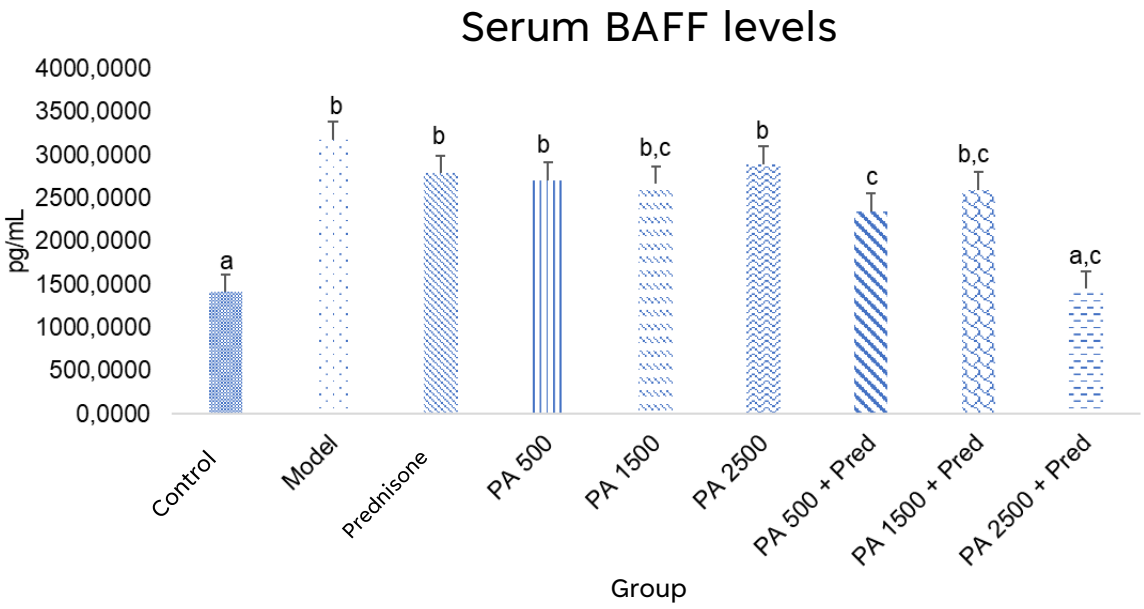
Single **7 mg/kg** dose of **doxorubicin produced the most consistent nephrotic syndrome** model after **six weeks** of observation



RESULTS

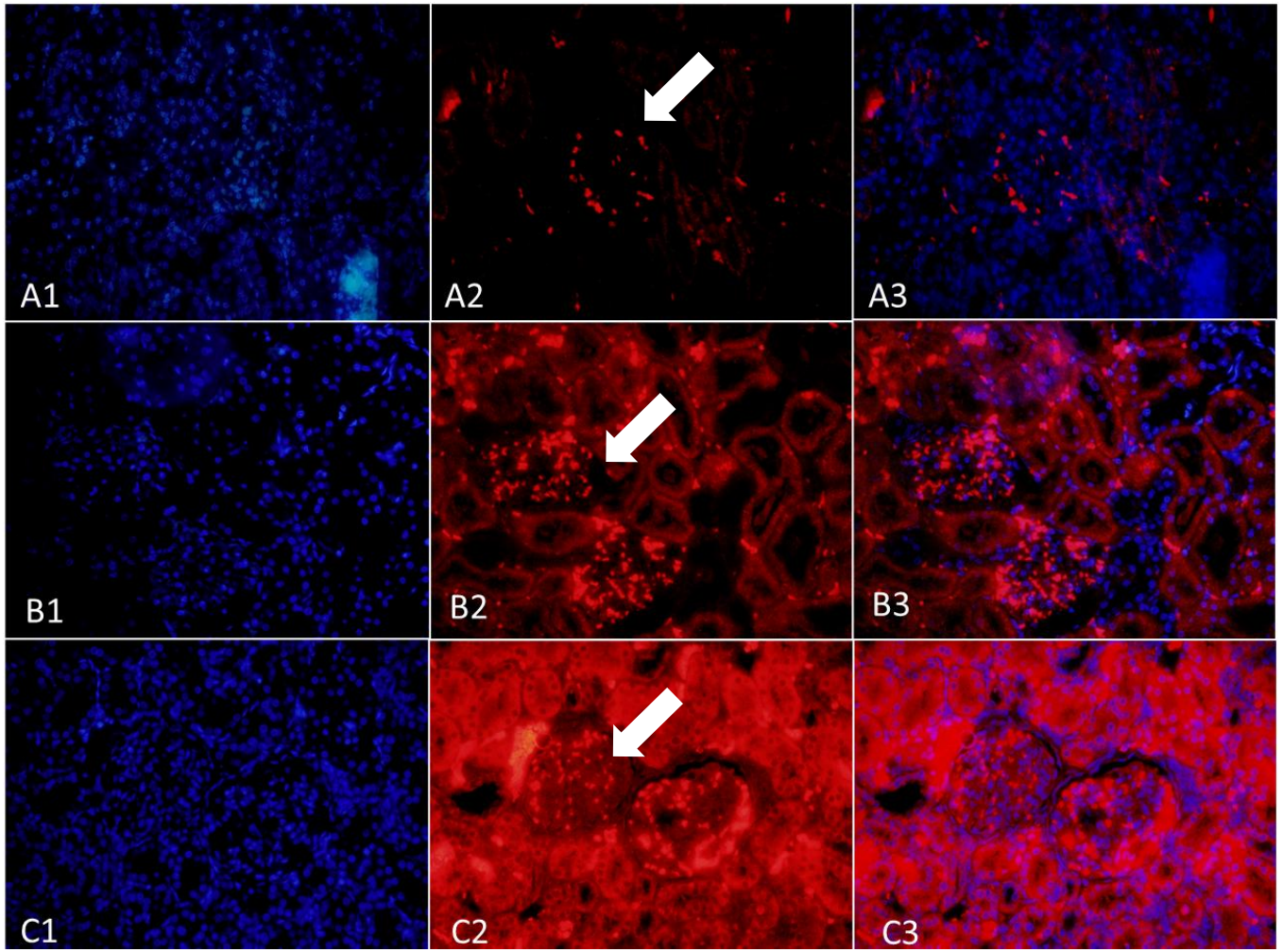
In the **serum analysis,** BAFF was **clearly elevated in the nephrotic syndrome model**

Treatment with **Physalis angulata reduced BAFF levels**, and the **reduction was even greater when combined with prednisone.**



a: control; b. model; c.PA 500+prednisone.

- The negative control and nephrotic syndrome model groups showed a significant difference.
- PA 500 + Prednisone and PA 2500 + Prednisone were significantly different from the nephrotic syndrome model group.
- The greatest reduction was observed in the PA 2500 + Prednisone group.



ImageJ was used to provide objective fluorescence intensity values.

Description:
1: DAPI, 2: Antibody, 3: Composite.
(A) Negative control;
(B) Nephrotic syndrome model
(C) Prednisone

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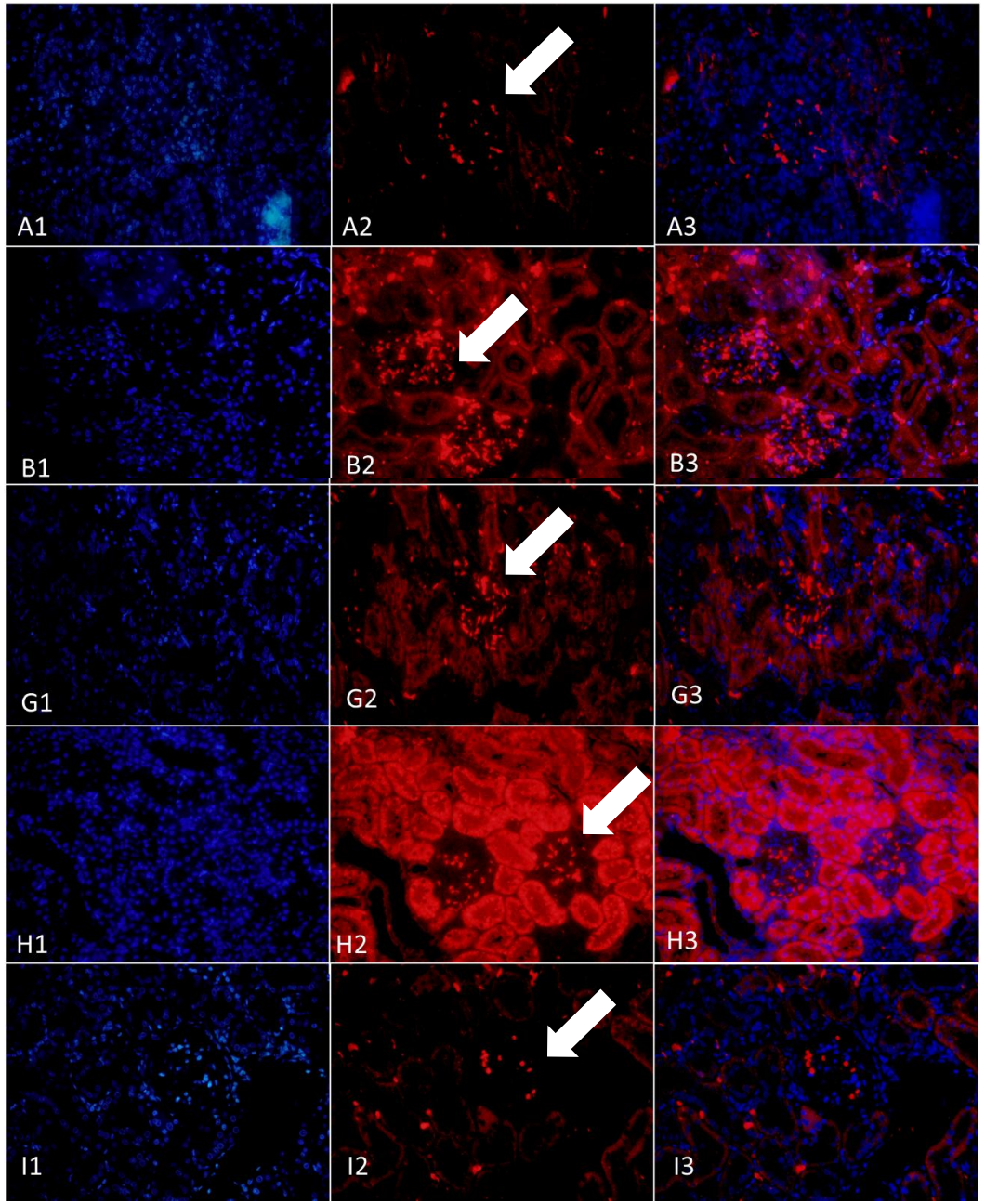
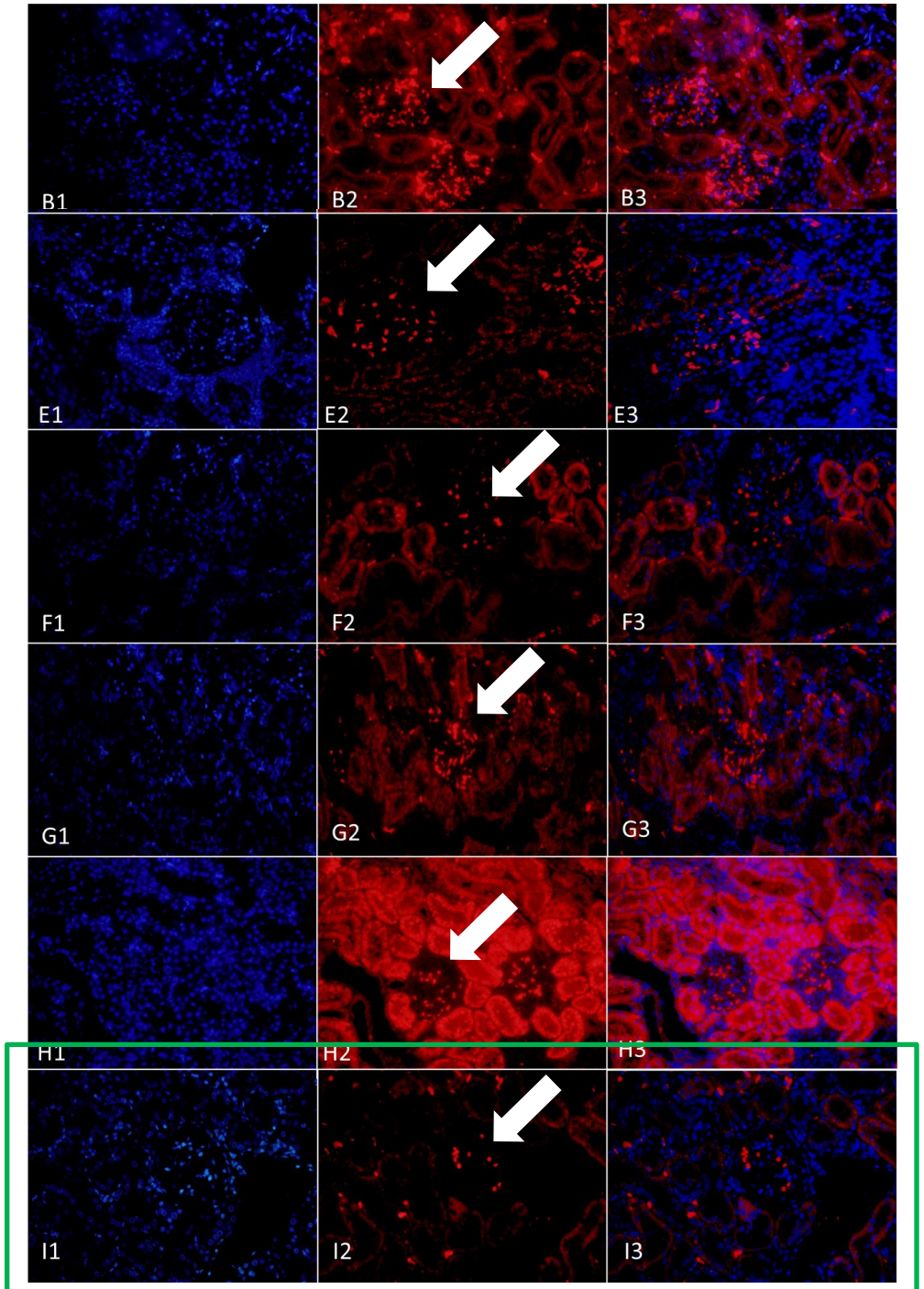


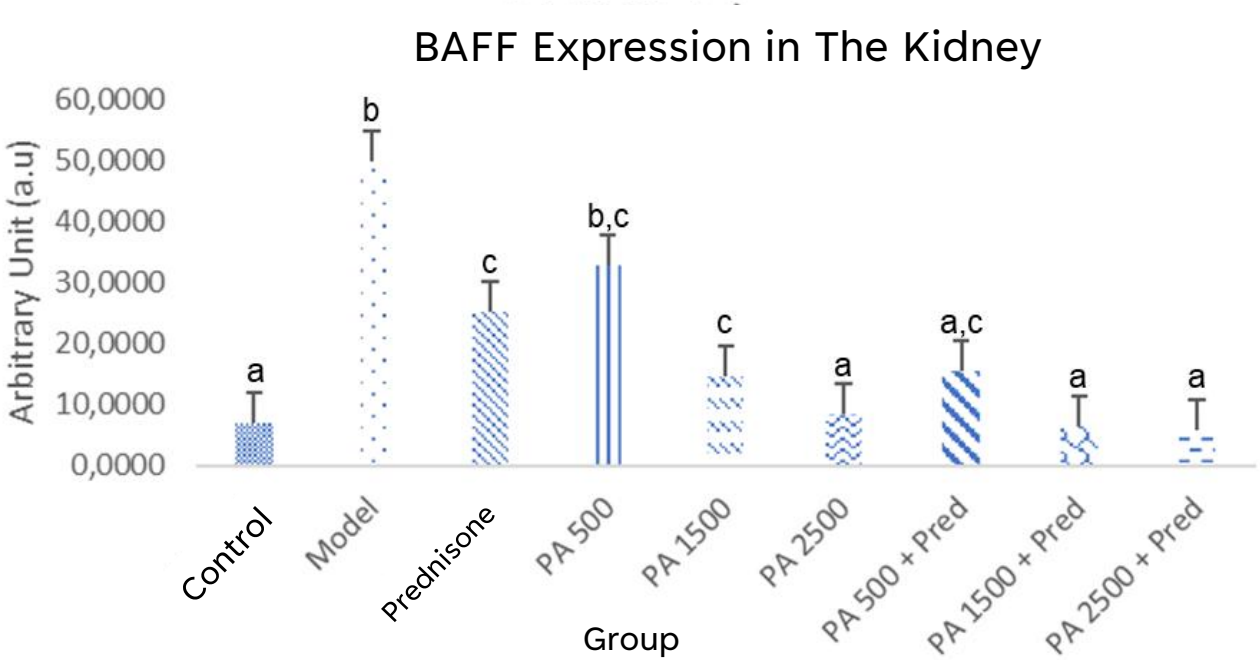
Description:
1: DAPI, 2: Antibody, 3: Composite.
(A)Negative control;
(B) Nephrotic syndrome model
(D) Physalis angulata 500 mg/kg BW
(E) Physalis angulata 1500 mg/kg BW
(F) Physalis angulata 2500 mg/kg BW

A similar pattern was observed in the kidney.

BAFF expression was **strongly upregulated** in the model group and progressively decreased with Physalis angulata treatment, with the **greatest reduction** seen in **the PA2500 combined with prednisone group.**

RESULTS





a: control; b. model; c.PA 500+prednisone.

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Description:
1: DAPI, 2: Antibody, 3: Composite.
(B) Nephrotic syndrome model
(E) Physalis angulata 1500 mg/kg BW
(F) Physalis angulata 2500 mg/kg BW
(G) Physalis angulata 500 mg/kg BW + prednisone
(H) Physalis angulata 1500 mg/kg BW + prednisone
(I) Physalis angulata 2500 mg/kg BW + prednisone

DISCUSSION

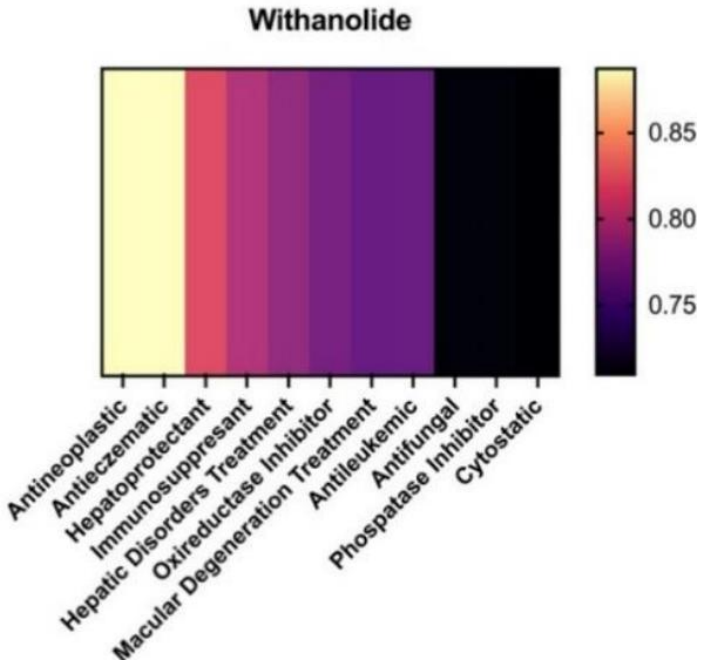
DISCUSSION

Our findings support the important role of BAFF in the pathogenesis of nephrotic syndrome, as BAFF was significantly elevated in our animal model.

We also found a strong positive correlation between serum BAFF levels and renal BAFF expression, reinforcing BAFF as a biologically relevant marker.

Physalis angulata demonstrated a clear inhibitory effect on BAFF, with the strongest suppression seen in the PA2500 combined with prednisone group.

These results are consistent with our previous in silico analysis, which showed that withanolide compounds in Physalis angulata can modulate immune activation by inhibiting BAFF and BCMA, while physalin F inhibits TACI.



Kardani AK, Fitri LE, Samsu N, Subandiyah K, Endharti AT, Nugrahenny D, Wibowo S. Inhibition of B-cell activating factor activity using active compounds from Physalis angulata in the mechanism of nephrotic syndrome improvement: A computational approach. Narra J. 2024 Dec;4(3):e859.

CONCLUSION

Physalis angulata extract shows **promising potential as an adjunctive therapy** for nephrotic syndrome, underscoring the **need for further studies to evaluate its clinical safety and effectiveness,** as well as its relevance in exploring **BAFF as an emerging therapeutic target.**

Further animal studies to evaluate the safety, toxicity, and dose optimization of Physalis angulata before moving toward clinical translation.

Identify and isolate the key bioactive compounds, such as withanolides, from the extract and evaluate them as single, purified molecules.

Evaluate the interaction of Physalis angulata with adipose-derived stem cells in an in vitro podocytopathy model to better understand its immune-regulating mechanisms.

These steps will help bridge our findings toward **potential drug development** and **future clinical application.**


THANK YOU