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model.

Moringa oleifera Extract Attenuates Lipopolysaccharide-Driven Systemic Cytokine Dysregulation in Rats

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ABSTRACT:

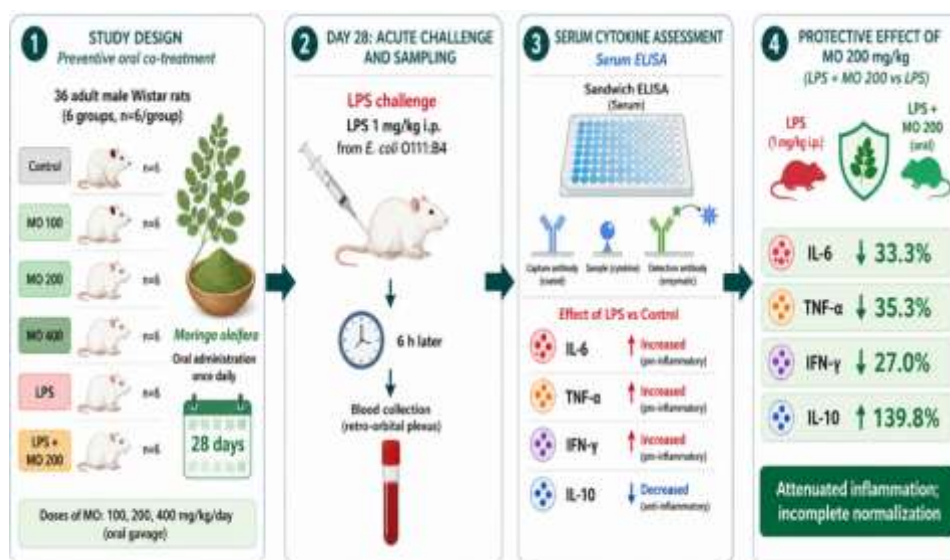
Background: Overactive Toll-like receptor 4 (TLR4) response to lipopolysaccharide (LPS) creates a program of cytokines that can trigger systemic inflammatory damage. Polyphenols, flavonoids and isothiocyanate-containing glucosinolates are redox-sensitive and inflammatory signaling node-active components of *Moringa oleifera*. This study aimed to assess the effect of *M. oleifera* on basal cytokine tone and its protection against LPS-induced systemic cytokine dysregulation in rats.

Methods: The rats were divided into six groups ($n=6$) and were subjected to a 28-day protocol; the concentration of serum interleukin (IL)-6, tumour necrosis factor alpha (TNF- α), IL-10, and interferon gamma (IFN- γ) was measured using rat-specific sandwich ELISA. The experimental calibration curves were found to be linear with R^2 values ranging from 0.9998 to 0.9999. One-way analysis of variance followed by Tukey's test were used to compare the groups.

Results: LPS increased IL-6 (113.58 ± 6.29 vs 36.51 ± 3.58 pg/mL), TNF- α (125.01 ± 11.63 vs 40.19 ± 2.89 pg/mL), and IFN- γ (98.02 ± 4.82 vs 32.58 ± 1.60 pg/mL), while reducing IL-10 (20.00 ± 3.07 vs 28.39 ± 2.48 pg/mL) relative to control (all Tukey-adjusted $p \leq 0.004$). Co-treatment with 200 mg/kg *Moringa* reduced LPS-associated IL-6 by 33.3%, TNF- α by 35.3%, and IFN- γ by 27.0%, and increased IL-10 by 139.8% (all $p < 0.001$). The treatment group effects ranged from very large ($\eta^2 = 0.888-0.985$) across all markers. In non-challenged rats, 400 mg/kg reduced IL-6, and TNF- α , and increased IL-10 compared to control while having no effect on IFN- γ .

Conclusion: The immunomodulatory signature of *M. oleifera* was coherent and showed a significant downmodulation of LPS-induced levels of IL-6, TNF- α , and IFN- γ , followed by a restoration and overshoot of IL-10, but not full reversal or clinical efficacy; validation was done at pathway and tissue level.

Graphic Abstract



1. INTRODUCTION

The inflammatory response is an integral component of a defence programme which is responsible for the recognition of pathogens, recruitment of leukocytes, and repair of tissues. However, inflammatory signalling is a cause of organ damage and chronic disease when over- or unresolved. LPS, a component of the Gram-negative bacterial cell wall, is an activator of Toll-like receptor 4 (TLR4) and of the downstream nuclear factor kappa B (NF- κ B) and mitogen-activated protein kinase pathways, causing a rapid release of cytokines, of which the major ones are tumor necrosis factor (TNF) and IL-6 [1,2]. IFN- γ may also potentiate the production of other cytokines that are induced by endotoxin; IL-10 is an important counter-regulatory mechanism that helps to regulate inflammatory damage [3,4].

Moringa oleifera Lam. is a food medicinal plant that contains various polyphenolic compounds (phenolic acid, flavonoids, glucosinolates, and isothiocyanate) [5–7] which are beneficial for human health. Experimental studies have shown that preparations of *Moringa* can inhibit the production of nitric oxide and pro-inflammatory cytokines in LPS stimulated macrophages, and block degradation of I κ B and nuclear signalling of NF- κ B [8–11]. However, the composition of extracts depends on different parts of the plants, solvents, processing, geographical location and dosage; and there are many results that are model-specific [12]. In-vivo controlled studies that study pro-inflammatory and counter-regulatory cytokines simultaneously are thus useful to establish direction and dose pattern of immunomodulation.

One important question that remains unanswered is whether *Moringa* is simply reducing isolated inflammatory markers or reshaping the overall inflammatory amplification/counter-regulation in vivo. In this study, the effect of graded doses of *M. oleifera* on basal serum levels of IL-6, TNF- α , IL-10, and IFN- γ was determined, as well as whether 200 mg/kg was able to alleviate the bidirectional alteration of cytokine activity observed after LPS. We hypothesized that LPS would trigger an up-regulation of IL-6, TNF- α and IFN- γ and down-regulation of IL-10, while *Moringa* co-treatment would induce a down-regulation of inflammatory amplification and up-regulation of counter-regulatory mechanisms.

2. MATERIALS AND METHODS

2.1 Study design and experimental animals

A controlled laboratory trial was carried out with 36 adult male Wistar rats aged 8–10 weeks and weighing 200–230 g. Animals were maintained in standard polypropylene cages in a controlled environment (22 ± 2 °C, relative humidity $55 \pm 5\%$, 12 hours light/12 hours dark) with access to a standard pelletized diet for rodents and drinking water as required. Acclimatisation period of 7 days for the rats. All procedures followed the ARRIVE guidelines and international standards for the care and use of laboratory animals and were approved by the Institutional Animal Ethics Committee.

2.2 Preparation and phytochemical characterisation of *Moringa oleifera* extract

The fresh leaves of *M. oleifera* Lam. were confirmed by a taxonomist and a voucher specimen was kept in the institution's herbarium. The plant material was thoroughly washed using distilled water, shade dried till constant weight and mechanically pulverised into fine powder. The dried powder was extracted at 1:10 ratio (dried powder to ethanol) using 70% ethanol and continuous shaking at room temperature for 48 h. The mixture was filtered through Whatman No. 1, concentrated under reduced pressure at 40 °C with a rotary evaporator and lyophilised to get a dry crude extract. The extract was stored at –20 °C till it was daily reconstituted in physiological saline (0.9% NaCl). The total phenolics content was assessed by a colorimetric Folin–Ciocalteu assay and the chemical profile and the presence of the major bioactive compounds such as chlorogenic acid and glucomoringin have been confirmed by HPLC.

2.3 Treatment allocation and in-vivo LPS challenge

Table 1. Experimental groups, *Moringa* dosing regimens, and acute LPS challenge

Group	n	Moringa dose	Days 1–28: oral regimen	Day 28: acute challenge
Control	6	0 mg/kg	Saline vehicle	Saline, i.p.
Moringa Low	6	100 mg/kg	<i>M. oleifera</i> , 100 mg/kg/day	Saline, i.p.
Moringa Medium	6	200 mg/kg	<i>M. oleifera</i> , 200 mg/kg/day	Saline, i.p.
Moringa High	6	400 mg/kg	<i>M. oleifera</i> , 400 mg/kg/day	Saline, i.p.
LPS only	6	0 mg/kg	Saline vehicle	LPS, 1 mg/kg, i.p.
LPS + Moringa	6	200 mg/kg	<i>M. oleifera</i> , 200 mg/kg/day	LPS, 1 mg/kg, i.p.

The 36 rats were randomly divided into six parallel groups (N = 6/ group) based on a randomisation sequence generated on a computer. The moringa extract and saline vehicle were given orally for 28 days (once a day) by oral gavage. On day 28, systemic acute inflammation was triggered in the LPS-only and LPS-plus-Moringa groups, with a single injection of lipopolysaccharide (LPS) from the organism *Escherichia coli* O111:B4 (1 mg/kg) 2 h after the last oral dose. There were non-challenged groups in which an equivalent amount of sterile saline was administered by the intraperitoneal route. Biomarker assays and statistical analyses were conducted in a blinded fashion by investigators conducting downstream assays. There were no deaths or exclusions of any of the 36 animals during the study.

2.4 Serum collection and cytokine quantification by sandwich ELISA

Six hours after the LPS or saline challenge, terminal blood collection was performed under deep anaesthesia. Blood was collected by cardiac puncture into serum-separator tubes, allowed to clot at room temperature for 30 min, and centrifuged at 2,000 × g for 15 min at 4 °C. Serum supernatants were separated, aliquoted, and immediately stored at –80 °C until analysis. Serum IL-6, TNF-α, IL-10, and IFN-γ concentrations were measured using rat-specific sandwich ELISA kits (Sunlong Biotech Co., Ltd., China) in accordance with the manufacturer's instructions. Standards, experimental blanks, and serum samples were assayed in technical triplicate. Immediately after addition of the acidic stop solution, absorbance was recorded at 450 nm (OD450) using an automated microplate reader. Technical triplicates were averaged to establish one biological observation per animal.

2.5 Standard-curve generation and concentration calculations

Standard calibration curves were established within the range of 0 – 500 pg/mL by linear regression of OD450 against known standard concentrations (C pg/mL). The equations were $OD = 0.001554C + 0.0535$ for IL-6 ($R^2 = 0.9998$), $OD = 0.001481C + 0.0588$ for TNF- α ($R^2 = 0.9998$), $OD = 0.001622C + 0.0485$ for IL-10 ($R^2 = 0.9999$), and $OD = 0.001511C + 0.0575$ for IFN- γ ($R^2 = 0.9998$). Biological sample concentration was determined by dividing the OD450 minus the intercept by the slope and multiplying by the dilution factor. All ELISA measurements had intra-assay and inter-assay CoVs of less than 8% and 10% respectively.

2.6 Statistical analysis

The independent experimental unit (I.E.U.) was the individual rat ($n = 6/\text{Group}$). The Shapiro–Wilk test was used to determine distributional normality and Levene's test was used to determine the homogeneity of variance between groups. For numerical presentation of data, the mean and standard deviation (SD) are shown; for graphic presentation of the data, the mean and standard error of the mean (SEM) are shown.

One-way analysis of variance (ANOVA) and Tukey's honestly significant difference (HSD) post hoc test were used to compare differences between the six experimental groups by cytokine. Control versus LPS alone was prespecified as the primary contrast for validation of the inflammatory model, LPS versus LPS plus Moringa was the primary contrast for evaluation of Moringa's protective efficacy and control versus the Moringa-only groups at 100, 200 and 400 mg/kg were prespecified for evaluation of Moringa's baseline immunomodulatory effects. The magnitude of the omnibus effect was standardised as eta squared (η^2). Cohen's d was used to describe the standardised pairwise effects. A 2-tailed p value < 0.05 was used as a cut-off for statistical significance. All the statistical calculations were done in python 3.11 with scipy.stats 1.11 and statsmodels 0.14.

3. RESULTS

3.1 ELISA calibration performance

The four calibration curves were all linear over the specified range of standards. Coefficients of determination were 0.9998 for IL-6, 0.9998 for TNF- α , 0.9999 for IL-10, and 0.9998 for IFN- γ . This calibration performance allowed for interpolation of the serum concentrations of cytokines from the measured OD450.

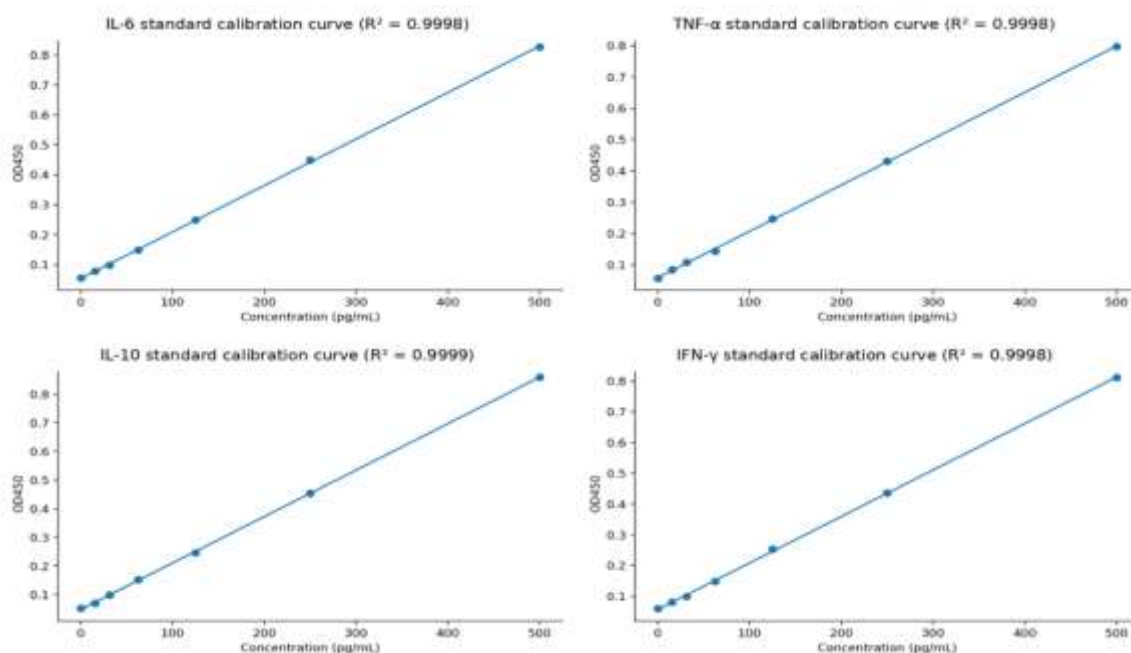


Figure 1. ELISA standard calibration curves (generated experimentally for quantification of cytokines in serum). Calibration curves are shown for (A) IL-6, (B) TNF- α , (C) IL-10, and (D) IFN- γ . The absorbance was determined at 450 nm. The values of coefficient of determination varied from 0.9998 to 0.9999.

3.2 LPS produced a pronounced inflammatory cytokine profile

In the provided data set, there were 36 animals and all of the animals had values for cytokines. Compared with control, LPS increased mean IL-6 by 211.1%, TNF- α by 211.0%, and IFN- γ by 200.9%, and decreased IL-10 by 29.6%. Tukey-adjusted comparisons were significant for IL-6, TNF- α , and IFN- γ (all $p < 0.001$) and IL-10 ($p = 0.004$). These changes validated an LPS challenge with a robust systemic cytokine response.

3.3 Moringa partially attenuated the LPS response

Relative to LPS alone, co-treatment with 200 mg/kg Moringa reduced IL-6 from 113.58 ± 6.29 to 75.78 ± 5.63 pg/mL (33.3%), TNF- α from 125.01 ± 11.63 to 80.88 ± 7.61 pg/mL (35.3%), and IFN- γ from 98.02 ± 4.82 to 71.53 ± 7.17 pg/mL (27.0%). Conversely, IL-10 increased from 20.00 ± 3.07 to 47.95 ± 5.82 pg/mL (139.8%). No adjustments were made for multiple comparisons for each LPS vs. combination comparison, which all remained significant ($p < 0.001$). The combination group did not return to control concentrations for the three pro-inflammatory markers, and thus there was partial, not full, normalisation for these markers, and IL-10 increased above the control mean.

3.4 Moringa modified basal cytokines in a dose-related pattern

IL-6, TNF- α and IFN- γ did not differ significantly between 100 mg/kg and control for non-LPS groups; however, IL-10 was elevated in 100 mg/kg compared to control ($p = 0.023$). At 200 mg/kg, IL-6 decreased ($p = 0.041$) and IL-10 increased ($p = 0.015$), while TNF- α and IFN- γ were unchanged. At 400 mg/kg, IL-6 ($p = 0.002$) and TNF- α ($p = 0.006$) were lower and IL-10 was higher ($p < 0.001$) than control; IFN- γ remained unchanged ($p = 0.405$). This pattern can be accommodated by dose responsive immunomodulation, but a model for the trend was not requested nor specifically mentioned in the pairwise testing, and should not be assumed from this pattern alone.

Table 2. Serum cytokine concentrations by experimental group (mean $\pm$ SD; $n = 6$).

Group	IL-6	TNF- α	IL-10	IFN- γ
Control	36.51 ± 3.58	40.19 ± 2.89	28.39 ± 2.48	32.58 ± 1.60
Moringa Low	34.46 ± 2.57	35.82 ± 1.73	35.35 ± 2.34	34.47 ± 3.37
Moringa Medium	28.71 ± 3.67	33.28 ± 2.22	35.74 ± 2.23	30.96 ± 2.45
Moringa High	25.76 ± 2.72	26.60 ± 3.00	43.53 ± 4.11	27.93 ± 3.14
LPS only	113.58 ± 6.29	125.01 ± 11.63	20.00 ± 3.07	98.02 ± 4.82
LPS + Moringa	75.78 ± 5.63	80.88 ± 7.61	47.95 ± 5.82	71.53 ± 7.17

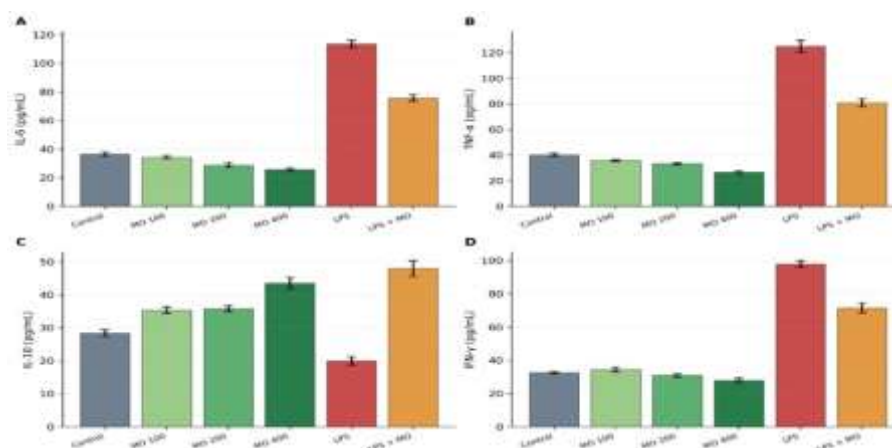


Figure 2. Graphical representation of Table 1: serum concentrations of cytokines in experimental groups. Panels show (A) IL-6, (B) TNF- α , (C) IL-10, and (D) IFN- γ . Bars are mean $\pm$ SEM (n = 6 independent animals/group). MO 100, MO 200, and MO 400 denote Moringa doses of 100, 200, and 400 mg/kg; LPS + MO received Moringa at 200 mg/kg.

Table 3. One-way ANOVA results and omnibus effect sizes.

Marker	F(5,30)	p value	η^2
IL-6	396.315	1.94e-26	0.985
TNF- α	244.255	2.37e-23	0.976
IL-10	47.760	2.17e-13	0.888
IFN- γ	286.781	2.26e-24	0.980

All omnibus tests were statistically significant: $p < 0.05$. The very large η^2 values suggest that the variance in these cytokines observed among the animals was related to treatment group for this data set; this should not be taken at face value as the group means were widely spread and n was small.

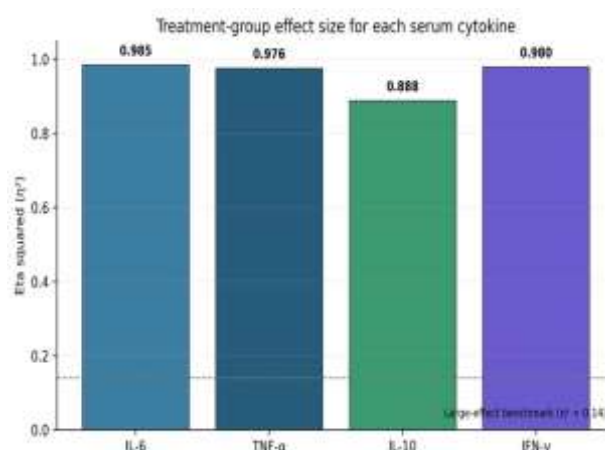


Figure 3. Graphical depiction of omnibus treatment-group effect sizes for the four serum cytokines. eta squared (η^2) values from one way ANOVA are indicated with bars. The dotted regression line represents the conventional threshold for large effects ($\eta^2 = 0.14$). All observed effects were far greater than this benchmark, and the exact F statistics, and p values, are provided in Table 3.

Table 4. Prespecified contrasts and standardized effect magnitudes.

Marker	Contrast	Mean difference	Cohen's d	Adjusted p
IL-6	LPS only – Control	77.07	15.06	<0.001
IL-6	LPS + Moringa – LPS only	-37.81	-6.34	<0.001
TNF- α	LPS only – Control	84.82	10.01	<0.001
TNF- α	LPS + Moringa – LPS only	-44.14	-4.49	<0.001
IL-10	LPS only – Control	-8.39	-3.01	0.0040
IL-10	LPS + Moringa – LPS only	27.94	6.00	<0.001
IFN- γ	LPS only – Control	65.44	18.22	<0.001
IFN- γ	LPS + Moringa – LPS only	-26.49	-4.34	<0.001

The difference between the second group and the first group in the indicated contrast is a mean difference. LPS minus Moringa numbers are negative if cytokine is reduced compared to LPS alone, positive if counter-regulation is increased. LPS minus Moringa values are negative if cytokine is reduced compared to LPS alone, positive if counter-regulation is increased. The Cohen's d values are only descriptive magnitudes because they are only based on a small number of animals per group per contrast.

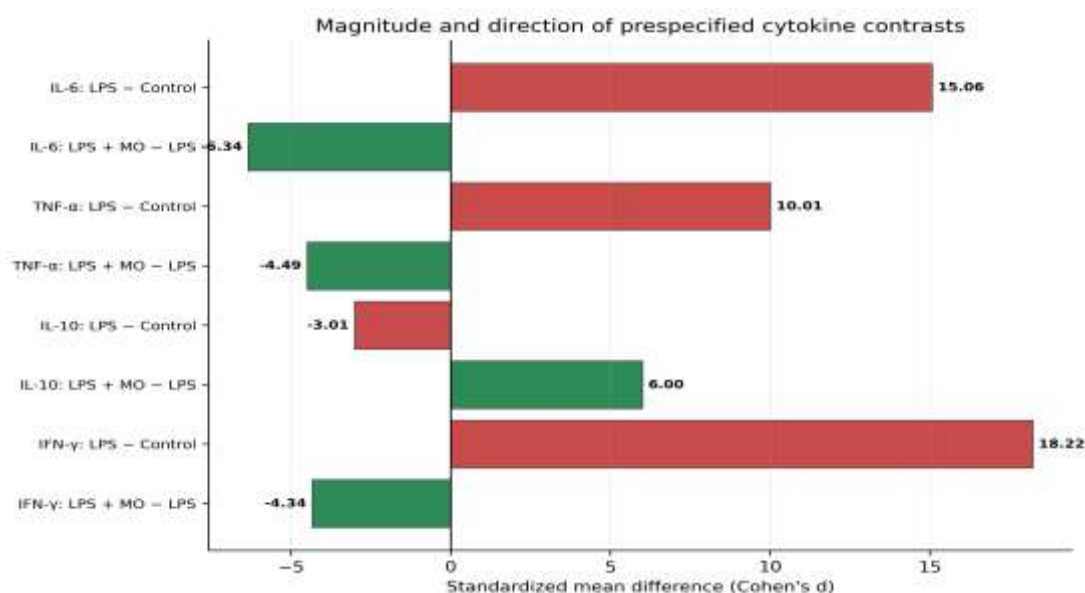


Figure 4. Table 4 shows standardized effect magnitudes for the prespecified cytokine contrasts graphically. Red bars indicate the effect of LPS on compared with control; Green bars indicate the effect of Moringa co-treatment on compared with LPS alone. Positive values will show an increase in concentration in the second group while a negative value will show a decrease in concentration. The levels of IL-10 should be read as an inverse response to the pro-inflammatory cytokines, and thus as an increase in counter-regulation.

3.5 Integrated cytokine response

The treatment effect did not occur with just one biomarker. LPS shifted three pro-inflammatory mediators in the same direction, and it reduced the level of IL-10, while Moringa co-treatment oppositely shifted all four mediators. Coordinate response further reinforces the inference of coordinated immunomodulation, within the measured cytokine panel. However, the presence of IL-6, TNF- α , and IFN- γ values above control points suggest that there is still a persistent inflammatory activity, whereas IL-10 values above control point suggest rather a compensatory response, than a mere return to control values.

4. DISCUSSION

In this study, we obtained quantitative signal in-vivo that *M. oleifera* has the potential to reshape LPS driven cytokine dysregulation. LPS caused a greater than threefold rise in the levels of IL-6, TNF- α , and IFN- γ and a reduction in the level of IL-10, creating a phenotype of combined inflammatory-amplification and counter-regulatory-deficit. All three mediators were lowered and IL-10 was significantly increased in moringa co-treatment. Very large omnibus effects and the directionally concordant four cytokine response is more convincing than a change in any individual cytokine. An ongoing increase in IL-6, TNF- α and IFN- γ , however, indicates that the intervention did not completely inhibit inflammatory signalling.

The results are consistent with well-known LPS signalling in a biological context. Upon TLR4 activation, MyD88- and TRIF-dependent pathways are stimulated, which results in activation of NF- κ B and MAPK and TNF- α and IL-6 production [13-15]. LPS-associated interferon gamma (IFN- γ) can be involved in a feed-forward inflammatory pathway and can enhance the response to tumor necrosis factor-alpha (TNF- α) and Interleukin-6 (IL-6) [16-18]. Concurrently lowering these three mediators following Moringa treatment thus indicates an effect at a common upstream regulatory site and/or at the point of interaction between innate and adaptive immune pathways, without providing any information regarding the site(s) of action in the serum.

The following constituents of *M. oleifera* are likely to be responsible for the mechanism. Within the leaves, quercetin and kaempferol derivatives, chlorogenic acids, glucosinolates, and rhamnosylated isothiocyanate are found [19-21]. Hydroethanolic leaf extracts have been seen to inhibit nitric oxide, prostaglandin E2, tumor necrosis factor -alpha, interleukins (IL-6, IL-1beta) in LPS stimulated macrophages [22]. Other studies have shown that Moringa bioactives can inhibit I κ B- α degradation and NF- κ B activation [22-24] and that Moringa isothiocyanates might be involved with activation of the Nrf2 pathway of antioxidant response [25]. These mechanisms are consistent with the decrease in IL-6 and TNF- α that was seen here and are not the subjects of direct measurement, but are hypotheses to test.

The architecture of the cytokines observed here allows for the development of a more specific interpretation of the mechanism. TNF- α is an early amplifier of endothelial activation and further downstream inflammatory recruitment, IL-6 are involved in acute phase and metabolic responses and IFN- γ strengthens macrophage activation and can potentiate the production of TNF- α and IL-6 by endotoxin [26]. Concurrently suppressing them is thus compatible with the interruption of a mutually reinforcing inflammatory network. At the same time, activation of Nrf2 may decrease the oxidation support for NF- κ B signalling [27]. All of these possibilities can only be distinguished by direct measurements of phosphorylated I κ B- α , nuclear p65, MAPKs, Nrf2 targets, and cellular sources of each of the cytokines.

Significant increases were observed in IL-10 levels in the LPS plus moringa group. IL-10 regulates inflammatory gene expression and helps to prevent immunopathology [28-30]. There is a clear correlation between a coordinated decrease in TNF- α /IL-6 and an increase in IL-10, which indicates that balanced immune suppression rather than indiscriminate suppression is necessary. Simultaneously, levels of serum IL-10 higher than those of the untreated control should not be equated with beneficial effects – high/during too long counter-regulation can have a negative effect on antimicrobial defence. Whether this response is adaptive would be determined by time-course experiments, cellular phenotyping and pathogen-clearance outcomes.

Efficacy can also be interpreted in different ways depending on the size of the increase in IL-10. The combination group was not only returned to the control state, but to a state of elevated IL-10, with residual elevation of all three pro-inflammatory cytokines. This can be active resolution, compensatory counter-regulation or concurrent presence of inflammatory and regulatory programmes. No single terminal measurement is able to differentiate between these states. This reaction would be better understood in terms of its kinetics and functional significance by serial sampling and ratios, (e.g. IL-10/TNF- α), with cell counts and tissue injury indices.

Arms with only Moringa show evidence of dosing under basal conditions. The high dose decreased IL-6 and TNF- α and increased IL-10 while IFN- γ did not significantly change. However, the high dose of Moringa in combination with LPS was not included in the experiment so, it is difficult to determine the protective dose response in inflammatory conditions. Furthermore, the combination group was made up of the medium dose, which was chosen without a pharmacological comparator. The present data are thus indicative of a signal and a working dose, but not an optimum dose.

4.1 Biological and translational implications

The results suggest the potential immunomodulatory nature of Moringa as a precursor of potential therapeutic anti-inflammatory drugs, but do not establish it as a clinically proven drug. The bioavailability, metabolism and interactions between multiple constituents of whole extracts can differ from those of isolated constituents. Translation, however, needs to be chemically standardised, pharmacokinetic characterised, target engaged, safe and replicated in disease conditions. Modification of cytokines in healthy rats challenged with LPS is essential proof of biological activity, but is insufficient evidence to confirm efficacy in infection, chronic inflammatory disease and in humans.

4.2 Strengths and limitations

The advantages are an LPS-only comparator, measurements at the animal level for four complementary cytokines, technical triplicate measurement, experimentally generated calibration curves, and multiplicity adjusted pairwise comparisons. The small group size, single terminal sampling point, lack of organ-specific and histopathological outcomes, lack of oxidative stress and pathway measurements, and absence of anti-inflammatory positive control makes it difficult to draw conclusions from serum cytokines alone regarding tissue protection. The study report should also include information on randomisation, concealment of allocation, blinded assessment of outcome, performance of the assays, raw data from the plate-reader, and full details of the animals, extracts and LPS prior to submission.

5. CONCLUSION

The treatment of rats with *M. oleifera* extract (200 mg/kg) resulted in a strong and uniform immunomodulatory response. Specifically, there were significant decreases in the concentrations of IL-6, TNF- α and IFN- γ and significant increases in the concentration of IL-10. In summary, the graded Moringa exposures under baseline conditions showed a similar pattern, but with the most significant reduction in inflammation at 400 mg/kg – which is not enough to support full normalisation or clinical efficacy. The most important additional investigations should involve a chemically standardised extract, several doses of Moringa during LPS challenge, longitudinal cytokine sampling, tests of target engagement of NF- κ B and Nrf2, and a good pharmaceutical comparator.

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