Journal of Pharmaceutical and Sciences
Electronic ISSN: 2656-3088 DOI: https://doi.org/10.36490/journal-jps.com
Homepage: https://journal-jps.com
ORIGINAL ARTICLE JPS. 2025, 8(4), 2276-2284

Enhanced Anti-Inflammatory Effects of Multicomponent Etoricoxib Formulations on TNF-α Suppression

Peningkatan Efek Antiinflamasi Multikomponen Etorikoksib terhadap Penurunan TNF-α

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Abstract

Etoricoxib, a selective COX-2 inhibitor, is widely used for its anti-inflammatory effects but is associated with dose-dependent adverse events. Multicomponent formulations with coformers or solubilizing agents offer a potential strategy to improve efficacy while minimizing toxicity. This study aimed to evaluate the anti-inflammatory efficacy of pure etoricoxib and its multicomponent formulations with nicotinamide, N-methyl glucamine, and piperine using TNF-α as a coformer. A controlled laboratory experiment was conducted in Wistar rats using a carrageenan-induced granuloma pouch model. TNF-α levels were measured at baseline (0 hours) and at 6 hours post-treatment. Normality tests, two-way ANOVA, and Tukey HSD post-hoc analyses were applied to assess group differences and time effects. All treatment groups significantly reduced TNF-α levels compared to the control ($p < 0.001$). While pairwise comparisons between treatments were not statistically significant, the P4 formulation (etoricoxib–piperine) showed the most consistent reduction. P3 (etoricoxib–N-methyl glucamine) exhibited a near-significant difference from pure etoricoxib (P1), suggesting enhanced efficacy. The main effect of time confirmed the temporal decline of TNF-α ($p = 0.0101$), without significant group × time interaction. Multicomponent formulations, particularly those containing piperine and N-methyl glucamine, enhance the anti-inflammatory action of etoricoxib. These research support further development of bioenhanced etoricoxib as safer alternatives for antiinflammatory.

***Keywords*: Etoricoxib, Multicomponent, TNF-α suppression, Anti-inflammatory efficacy.**

Abstrak

Etorikoksib merupakan suatu inhibitor COX-2 selektif, digunakan karena efek antiinflamasinya, tetapi memiliki efek samping yang bergantung pada dosis. Formulasi multikomponen dengan koformer menawarkan strategi potensial untuk meningkatkan efikasi dan mungkin dapat meminimalkan toksisitas. Penelitian ini bertujuan untuk mengevaluasi efikasi antiinflamasi etorikoksib murni dan formulasi multikomponennya dengan nikotinamida, N-metil glukamine, dan piperin menggunakan TNF-α sebagai koformer. Eksperimen laboratorium terkontrol dilakukan pada tikus Wistar menggunakan model kantong granuloma yang diinduksi karagenan. Kadar TNF-α diukur pada awal (0 jam) dan 6 jam pascaperawatan. Uji normalitas, ANOVA dua arah, dan analisis post-hoc Tukey HSD diterapkan untuk menilai perbedaan kelompok dan efek waktu. Semua kelompok perlakuan mengalami penurunan kadar TNF-α secara signifikan dibandingkan dengan kontrol ($p < 0,001$). Meskipun perbandingan berpasangan antar perlakuan tidak signifikan secara statistik, formulasi P4 (etorikoksib–piperin) menunjukkan penurunan yang paling konsisten. P3 (etorikoksib–N-metil glukamine) menunjukkan perbedaan yang hampir signifikan dari etorikoksib murni (P1), menunjukkan peningkatan efikasi. Efek utama waktu mengonfirmasi penurunan temporal TNF-α ($p = 0,0101$), tanpa interaksi kelompok × waktu yang signifikan. Multikomponen, terutama dengan koformer piperin dan N-metil glukamine, meningkatkan efek antiinflamasi etorikoksib. Penelitian ini mendukung pengembangan lebih lanjut etorikoksib yang ditingkatkan secara biologis sebagai alternatif yang lebih baik sebagai antiinflamasi.

***Kata Kunci:** Etoricoxib, Multicomponent, TNF-α suppression, Anti-inflammatory efficacy*

Article History:
Received: 30/07/2025,
Revised: 14/10/2025,
Accepted: 17/10/2025,
Available Online: 22/10/2025.

QR access this Article

https://doi.org/10.36490/journal-jps.com.v8i4.1097

Introduction

Tumor necrosis factor-alpha (TNF-α) is a pro-inflammatory cytokine that plays a pivotal role in orchestrating immune responses and mediating inflammation. Produced predominantly by macrophages and other immune cells in response to pathogenic stimuli, TNF-α influences numerous physiological processes such as cell proliferation, differentiation, and apoptosis [1,2]. It also contributes significantly to the pathogenesis of chronic inflammatory diseases including rheumatoid arthritis and Crohn's disease [3].

A critical function of TNF-α during inflammation is its capacity to increase vascular permeability, thereby facilitating the transmigration of leukocytes to inflamed tissue. This is achieved through the upregulation of adhesion molecules on endothelial cells, allowing neutrophils and lymphocytes to extravasate into affected tissues[1,2]. Additionally, TNF-α can induce the secretion of other pro-inflammatory cytokines such as IL-1 and IL-6, amplifying and prolonging the inflammatory response [4].

Given its central role, TNF-α has become a therapeutic target in various inflammatory conditions. Pharmacological agents that inhibit TNF-α activity, including etanercept, adalimumab, and infliximab, have demonstrated significant efficacy in alleviating symptoms and improving clinical outcomes in diseases such as rheumatoid arthritis and Crohn's disease [3]. Monitoring TNF-α levels has thus become a useful biomarker for evaluating patient response to these therapies.

Etoricoxib, a selective cyclooxygenase-2 (COX-2) inhibitor, has been recognized for its efficacy in reducing TNF-α levels in both preclinical and clinical models. COX-2 converts arachidonic acid into prostaglandins, key mediators of pain and inflammation. By selectively inhibiting COX-2, etoricoxib diminishes prostaglandin synthesis, which in turn may attenuate TNF-α production indirectly [5,6].

Several studies have reported the anti-inflammatory properties of etoricoxib, indicating its ability to decrease TNF-α levels. For instance, preclinical animal models have shown significant suppression of inflammatory biomarkers including TNF-α following etoricoxib treatment. Moreover, in clinical contexts such as knee osteoarthritis, combination therapies involving etoricoxib and glucosamine sulfate have been associated with improved cartilage health and decreased inflammatory markers, further validating its therapeutic potential[5,7,8].

Etoricoxib has also demonstrated protective effects in inflammation-induced organ damage models, such as hepatic and cardiac injury, with marked reductions in serum TNF-α levels. Its long half-life and sustained COX-2 inhibition make it particularly suitable for chronic inflammatory conditions. However, concerns regarding its long-term safety, particularly cardiovascular and renal adverse effects, necessitate a balanced assessment of its therapeutic benefits versus risks[5,7].

In pursuit of enhanced efficacy and reduced side effects, multicomponent formulations are being explored. These approaches aim to exploit the synergistic effects of combining etoricoxib with other bioactive agents. Studies such as those by Li et al. (2022) and Smeriglio et al. (2020) have demonstrated that drug combinations or plant-derived polyphenolic mixtures can potentiate anti-inflammatory effects and improve pharmacological profiles [9]. Notably, Artemisia absinthium extracts, polymeric nanoparticles with citrus flavonoids, and Kunzea ericoides nanoemulgels have exhibited stronger TNF-α inhibition compared to single-agent therapies [10,11,12].

Among promising adjuvants are nicotinamide, N-methyl glucamine, and piperine, each offering unique anti-inflammatory mechanisms. Nicotinamide reduces TNF-α and IL-6 levels and modulates the NF-κB signaling pathway [13]. N-methyl glucamine, though less studied, may enhance cellular transport and

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energy metabolism relevant to immune modulation. Piperine, a known bioenhancer, not only inhibits inflammatory signaling pathways such as NF-κB and MAPK but also improves the bioavailability of co-administered drugs [14]

Piperine's mechanisms include intestinal absorption enhancement via P-glycoprotein inhibition, cytochrome P450 modulation, and gut microbiota regulation [15,16]. Its synergistic effects with anti-inflammatory agents make it an ideal candidate for multicomponent drug strategies. Such formulation strategies have been shown to provide not only greater therapeutic effects but also more sustained and systemic cytokine modulation.

Despite the growing body of research supporting the efficacy of multicomponent anti-inflammatory formulations, several gaps remain. First, direct comparative studies between monocomponent and multicomponent NSAID formulations are limited. Second, diverse experimental methodologies reduce cross-study comparability. Third, few studies have addressed how formulation differences impact bioavailability and cytokine modulation in vivo. Finally, safety profiles of multicomponent therapies require thorough evaluation to confirm hypothesized reductions in adverse effects.

Therefore, the present study seeks to address these gaps by evaluating the anti-inflammatory effectiveness of pure etoricoxib versus its multicomponent formulations with nicotinamide, N-methyl glucamine, and piperine, using TNF-α as a biomarker. We hypothesize that these multicomponent etoricoxib formulations will result in greater TNF-α suppression compared to pure etoricoxib, owing to their synergistic pharmacological mechanisms. This investigation aims to inform the rational design of enhanced anti-inflammatory therapies with improved efficacy and potential safety advantages.

Experimental Section

Prior to the commencement of this study, ethical clearance was obtained from the Ethics Committee of the Faculty of Pharmacy, as the research involved pharmacological interventions on living animal subjects. The study employed male Wistar rats (Rattus norvegicus), weighing between 200 and 250 grams. All animals were acclimatized under controlled environmental conditions for one week prior to experimentation to minimize physiological stress and ensure baseline homogeneity.

This study was designed to evaluate the anti-inflammatory efficacy of pure etoricoxib (P1) and its multicomponent formulations with nicotinamide (P2), N-methyl glucamine (P3), and piperine (P4). The multicomponent formulations were prepared using the solvent drop grinding technique, a solid-state method designed to enhance drug interaction and improve physicochemical characteristics.

The anti-inflammatory response was assessed using tumor necrosis factor-alpha (TNF-α) levels as the primary biomarker. A controlled laboratory experiment with a repeated measures design was conducted to compare TNF-α expression across five groups: a negative control group (K) and four treatment groups (P1–P4). All formulations were administered orally to simulate the intended route of administration in clinical settings.

Materials and Apparatus

ELISA Ryder, Rat male white rats of the Wistar strain (weight 200 – 250 g), ELISA kit for TNF-α, pure etoricoxib, etoricoxib-nicotinamide multicomponent , etoricoxib- N-methyl glucamine multicomponent, etoricoxib-piperine multicomponent, NaCMC 1%

Sample Preparation

Etoricoxib and its respective coformers were prepared using a solid-state grinding technique with specific molar ratios: 4:6 for etoricoxib–nicotinamide, and 1:1 for both etoricoxib–N-methyl glucamine and etoricoxib–piperine using the solvent-free solid-state grinding method. Each component was first triturated separately in a mortar for 10 minutes to reduce particle size. The components were then combined and ground together until a homogeneous physical mixture was obtained. The resulting mixtures were stored under ambient temperature and normal relative humidity conditions in a desiccator, following the protocol adapted from Berry and Steed [17].

Ethical Clearence

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All experimental procedures adhered to institutional and international ethical guidelines to ensure humane treatment and scientific integrity.

Animal Model Preparation

The male Wistar rats were fasted for 18 hours prior to treatment, while access to drinking water was maintained throughout the observation period. Body weights were recorded (200 – 250 kg), and male Wistar rats were randomly assigned into groups (n = 6 per group). The subplantar surface of the right forepaw was cleaned with 70% ethanol before injecting 0.2 mL of 1% carrageenan solution to induce local inflammation. One hour after carrageenan induction, the pre-prepared suspension formulations were administered orally to the respective groups, following the procedure described by Jensen et alThe temporal dynamics of tumor necrosis factor-alpha (TNF-α) expression were evaluated as a biomarker of the inflammatory response. TNF-α levels were measured at baseline (0 hours), immediately before drug administration, and at 6 hours post-treatment. This allowed for a comparative analysis of the anti-inflammatory efficacy of the tested formulations, based on the extent of TNF-α suppression during the early phase of inflammation.

Experimental Groups and Formulations

The experimental animals were divided into five groups, each receiving a distinct treatment regimen. The negative control group (K+) was induced with an inflammatory agent and subsequently administered 1% sodium carboxymethyl cellulose (NaCMC) suspension, with the volume adjusted to 1% of the rat's body weight. Treatment Group 1 (P1) was induced with the inflammatory agent and then administered pure etoricoxib at a dose of 1.8 mg per 200 g body weight. Treatment Group 2 (P2) received etoricoxib combined with nicotinamide, Treatment Group 3 (P3) received etoricoxib combined with N-methyl glucamine, and Treatment Group 4 (P4) received etoricoxib combined with piperine—each at an equivalent etoricoxib dose of 1.8 mg per 200 g body weight. All formulations were administered orally in a single dose with a fixed volume of 1 mL per rat.The dosage of etoricoxib in each formulation was standardized across groups to ensure consistency. The multicomponent formulations were developed through homogenization techniques, ensuring stable mixtures and bioavailability enhancement. Nicotinamide, N-methyl glucamine, and piperine were incorporated at concentrations based on previously published preclinical studies, targeting known therapeutic ranges for each bioactive compound.

Sample Collection and TNF-α Assay

Samples were collected at two time points: baseline (0 hours) and post-treatment (6 hours). TNF-α concentrations were measured using a validated ELISA (Enzyme-Linked Immunosorbent Assay) protocol, ensuring sensitivity and specificity for quantitative cytokine determination. All samples were processed in duplicate to reduce technical variability, and strict laboratory controls were maintained to ensure reproducibility.

Data Normality and Preliminary Statistical Testing

To evaluate the assumption of normality within each group and time point, the Shapiro–Wilk test was applied. The results indicated no significant deviation from normal distribution across all groups ($p > 0.05$), allowing for the use of parametric statistical tests. Despite small sample sizes (n=5 per group), K-S results suggested acceptable distribution properties for ANOVA application.

Two-Way ANOVA with Interaction

A two-way analysis of variance (ANOVA) was employed to evaluate the main effects of Group (K+, P1, P2, P3, P4), Time (0h vs 6h), and the Group × Time interaction on TNF-α concentrations.. The main effect of Group tested for differences in average TNF-α levels between formulations, irrespective of time. The main effect of Time evaluated whether TNF-α levels decreased significantly after 6 hours across all groups. The interaction term assessed whether the change over time varied significantly among the different formulations.

Post-Hoc Pairwise Comparison

Upon identifying significant main effects, Tukey's Honest Significant Difference (HSD) test was used for post-hoc pairwise comparisons across all group combinations. This method controls for Type I error across multiple comparisons and identifies which specific pairs of groups differ significantly. Additionally,

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subgroup analyses were performed using Welch's t-test for independent samples within each time point (0h and 6h), with Bonferroni correction to adjust for multiple comparisons.

Visualization and Statistical Display

TNF-α levels were plotted using mean values and 95% confidence intervals for each group at both time points. Graphs highlighted within-group changes over time and between-group differences at fixed time points. Visualizations were complemented by compact letter display (CLD) outputs from post-hoc analyses to aid in interpreting statistical groupings. The combination of statistical and graphical analyses enabled a comprehensive comparison of anti-inflammatory efficacy.

Software and Analytical Tools

All statistical analyses were conducted using All statistical analyses were conducted using GraphPad Prism version 9.5.1 (GraphPad Software Inc., San Diego, CA, USA). Data were expressed as mean ± standard deviation (SD), and a significance level of $\alpha = 0.05$ was applied to all tests. ELISA results were managed using Microsoft Excel before being transferred to software.

This rigorous methodological approach ensured that the data collection, statistical analysis, and interpretation of TNF-α suppression across experimental groups were performed systematically and transparently, supporting the validity and reproducibility of the study findings.

Results and Discussion

TNF-α Levels and Intergroup Differences

The primary aim of this study was to evaluate the anti-inflammatory efficacy of pure etoricoxib (P1) and its multicomponent formulations with nicotinamide (P2), N-methyl glucamine (P3), and piperine (P4), in a carrageenan-induced granuloma pouch model in rats. TNF-α levels were used as the biomarker of inflammatory response, measured at baseline (0 hours) and 6 hours after treatment administration. Normality of the data was assessed using the Shapiro–Wilk test. All groups showed p-values above 0.05, confirming normal distribution, except for P2 at 6 hours ($p = 0.0291$), which was slightly outside the threshold yet retained for parametric testing due to the overall consistency of the dataset.

Table 1. Normality Test Results (Shapiro-Wilk)

Sample	W-statistic	p-value	Normal (p > 0.05)
K+ (0)	0.881	0.31385	True
K+ (6)	0.932	0.61266	True
P1 (0)	0.929	0.59514	True
P1 (6)	0.982	0.94594	True
P2 (0)	0.809	0.09519	True
P2(6)	0.748	0.02910	False
P3 (0)	0.942	0.67795	True
P3 (6)	0.789	0.06669	True
P4 (0)	0.841	0.16823	True
P4 (6)	0.940	0.66804	True

Two-way ANOVA revealed a significant main effect of Group ($F = 24.63$, $p < 0.00001$), demonstrating substantial differences in TNF-α levels among treatment groups. Additionally, a significant effect of Time ($F = 21.82$, $p = 3.35 \times 10^{-5}$) was found, indicating that TNF-α levels declined significantly over time across all groups. However, the Group × Time interaction was not significant ($F = 1.84$, $p = 0.14$), suggesting that the rate and pattern of cytokine reduction over time were similar between groups.

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Table 2. Two Way ANOVA Results

Factor	F-value	p-value	Interpretation
Group	24.63	2.48e-10	Very significant – there are differences between groups.
Time (0 vs 6)	21.82	3.35e-05	significant – there is an influence of time (0 vs 6).
Interaksi Group×Time	1.84	0.14	No significant – time effect is independent of group.

Post-hoc Tukey HSD tests confirmed that all treatment groups (P1–P4) significantly lowered TNF-α levels compared to the negative control group (K+), with p-values < 0.001 for P1, P2, and P4, and p = 0.0001 for P3. These findings affirm the anti-inflammatory action of etoricoxib and its multicomponent formulations, consistent with its known role as a selective COX-2 inhibitor capable of downregulating pro-inflammatory cytokine expression [1,2].

Table 3. Tukey HSD Results Between Groups

Group1	Group2	Meandiff	P-adj	Lower	Upper	Reject
K+	P1	-33.4571	0	-46.4114	-20.5028	TRUE
K+	P2	-28.4444	0	-41.3987	-15.4901	TRUE
K+	P3	-22.2198	0.0001	-35.1741	-9.2655	TRUE
K+	P4	-25.0417	0	-37.996	-12.0874	TRUE
P1	P2	5.0127	0.8059	-7.9416	17.967	FALSE
P1	P3	11.2373	0.1171	-1.717	24.1916	FALSE
P1	P4	8.4154	0.3609	-4.5389	21.3697	FALSE
P2	P3	6.2246	0.6525	-6.7297	19.1789	FALSE
P2	P4	3.4027	0.9442	-9.5516	16.357	FALSE
P3	P4	-2.8219	0.9713	-15.7762	10.1324	FALSE

Time-Dependent TNF-α Suppression

Across all groups, TNF-α levels showed a significant temporal decrease from baseline to 6 hours (mean difference = −10.86, p = 0.0101). This pattern aligns with the expected pharmacodynamic profile of etoricoxib, whose cytokine modulation is typically evident within hours after administration [3,5].

Table 4. Tukey HSD Results Between Times

Group1	Group2	Meandiff	P-Adj	Lower	Upper	Reject
0	6	-10.8645	0.0101	-19.0155	-2.7135	True

Group-specific analyses demonstrated that the greatest reductions in TNF-α levels were observed in P1, P3, and P4, particularly at the 6-hour time point. In contrast, the K+ group exhibited minimal change, supporting the validity of the inflammation model.

Comparative Efficacy of Multicomponent Formulations

Although Tukey's post-hoc comparisons among treatment groups revealed no statistically significant differences, the comparison between P1 and P3 approached significance (p = 0.0809). This finding suggests that the multicomponent formulation of etoricoxib with N-methyl glucamine may offer enhanced anti-inflammatory efficacy compared to pure etoricoxib. N-methyl glucamine has been reported to improve solubility and dissolution profiles of NSAIDs by acting as a hydrophilic coformer [17], potentially increasing systemic absorption of etoricoxib.

P4, the combination of etoricoxib with piperine, showed the most consistent TNF-α suppression, aligning with previous studies that highlight piperine's role as a bioenhancer and modulator of inflammatory pathways such as NF-κB and MAPK [14,15]. Piperine is known to increase intestinal permeability and reduce drug efflux, thereby enhancing bioavailability and pharmacological activity [16].

In contrast, the P2 formulation (etoricoxib–nicotinamide) yielded more modest reductions in TNF-α. While nicotinamide has mild anti-inflammatory properties and has been used to enhance solubility in

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pharmaceutical co-crystals [17], its effect appears less potent compared to piperine and N-methyl glucamine in this study.

Implications for Anti-Inflammatory Therapy

These results support the strategic use of multicomponent formulations to improve the pharmacodynamic efficacy of etoricoxib. The enhanced cytokine suppression observed in P3 and P4 suggests potential clinical applications where lower doses of etoricoxib may achieve therapeutic effects comparable to higher doses, possibly reducing adverse outcomes such as cardiovascular or renal toxicity [1,6].

Furthermore, the consistency of TNF-α suppression across all formulations despite the lack of significant interaction with time indicates that the coformers do not alter the kinetics of etoricoxib action, but may enhance its magnitude of effect. This observation could inform future formulation strategies in anti-inflammatory drug development.

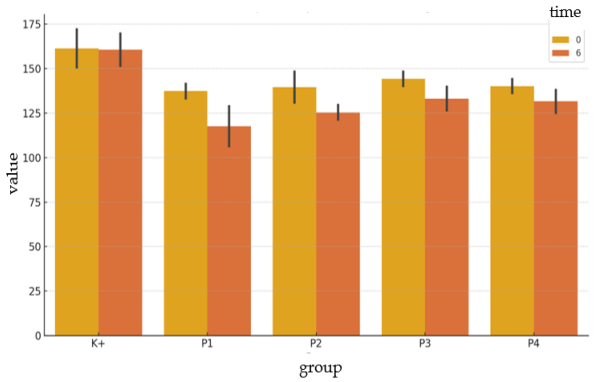

Figure 1. Average Value per Group and Time

Study Limitations and Future Directions

This study is limited by the small sample size (n = 5–6 per group), which may restrict the statistical power to detect subtle intergroup differences. Additionally, TNF-α was measured at only two time points, limiting the ability to capture full cytokine response dynamics. The near-significant difference between P1 and P3 highlights the need for further investigation with a larger cohort and more time points.

Future studies should incorporate extended pharmacokinetic-pharmacodynamic profiling, molecular mechanism assays, and clinical safety assessments of multicomponent etoricoxib formulations to validate and expand on these findings. Exploring other coformers or delivery systems may further enhance the therapeutic potential of etoricoxib-based treatments.

Conclusions

This study demonstrated that both pure etoricoxib and its multicomponent formulations with nicotinamide, N-methyl glucamine, and piperine significantly reduced TNF-α levels in an acute carrageenan-induced granuloma pouch model in rats. Among the treatment groups, the etoricoxib–piperine combination exhibited the most consistent suppression of TNF-α, likely due to piperine's bioenhancing properties and direct anti-inflammatory effects. The etoricoxib–N-methyl glucamine formulation showed a trend toward higher efficacy compared to pure etoricoxib, suggesting improved drug solubility and absorption. While the nicotinamide-based formulation also demonstrated anti-inflammatory activity, its effects were relatively modest.

These findings support the hypothesis that multicomponent formulations can enhance the pharmacodynamic profile of NSAIDs like etoricoxib. Clinically, such strategies may enable lower therapeutic doses, potentially minimizing adverse events associated with long-term NSAID use. Further studies with larger sample sizes, expanded time points, and molecular mechanism assessments are warranted to validate these preliminary results and explore translational potential.

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Conflict of Interest

The authors declare no conflict of interest. The research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Acknowledgment

The authors would like to acknowledge the Faculty of Pharmacy for providing laboratory facilities and technical assistance during the course of this research. Special thanks are extended to the Ethics Committee of the Faculty of Pharmacy for granting ethical clearance prior to the initiation of the study.

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