ISSN: 2085-675X (Print)
ISSN: 2354-8770 (Electronic)

Jurnal Kefarmasian Indonesia
Available online at https://jkefarind.com/index.php/jki
Original Research Article
JKI

Syzygium polyanthum Leaf Ethanol Extract Accelerates Incision Wound Healing in Streptozotocin-Induced Diabetic Rats and Modulates NF-κB, iNOS and MMP-1

Mei Jayanti Siregar[1*], Endy Juli Anto[2], Jekson Martiar Siahaan[3]

[1*]Master of Biomedical Sciences Study Program, Faculty of Medicine, Universitas Methodist Indonesia, Medan, North Sumatra, Indonesia
[2]Department of Parasitology and Immunology, Faculty of Medicine, Methodist University of Indonesia, Medan, Indonesia
[3]Department of Physiology, Faculty of Medicine, Deli Husada Health Institute, Delitua, Indonesia
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ARTICLE INFO

Article history:
Received 26 March 2026
Revised 30 March 2026
Accepted 14 April 2026
Published online 30 June 2026

*Corresponding author.
E-mail: *meijayantisiregar@ymail.com*

Citation: Siregar MJ, Anto EJ, Siahaan JM. Syzygium polyanthum Leaf Ethanol Extract Accelerates Incision Wound Healing in Streptozotocin-Induced Diabetic Rats and Modulates NF-κB, iNOS and MMP-1. Jurnal Kefarmasian Indonesia. 2026;16(1):103-111.

ABSTRACT

Diabetes mellitus (DM) significantly impairs wound healing through disruption of the inflammatory response and tissue metabolism. This study aimed to analyze the effect of ethanol extract of bay leaf (Syzygium polyanthum (Wight) Walp.) on NF-κB, iNOS, MMP-1, and wound healing in streptozotocin (STZ)-induced diabetic rats with incision wounds. A true experimental laboratory study with a post-test randomized controlled group design was conducted. Thirty male Wistar rats (n=5/group) were divided into six groups: normal control, DM control (STZ 40 mg/kgBW), DM with metformin (9.0 mg/rat/day), and DM with S. polyanthum extract at doses of 4.5, 9.0, and 18.0 mg/rat/day (equivalent to 250, 500, and 1000 mg/day human doses). Diabetes was induced by intraperitoneal STZ injection; wound healing was assessed on days 0, 7, and 14. Serum NF-κB, iNOS, and MMP-1 were measured by ELISA on day 14. Phytochemical screening confirmed flavonoids, alkaloids, saponins, tannins, and phenols, with total flavonoid content of 5.18 ± 0.16 mg QE/g extract and total phenolic content of 67.54 ± 0.64 mg GAE/g extract. Extraction yield was 11.35%. No significant differences were observed in serum NF-κB (p=0.103), iNOS (p=0.263), or MMP-1 (p=0.108) on day 14. However, wound area was significantly reduced at day 7 [F(5,24)=4.82, p=0.004], with the 1000 mg/kgBW-equivalent dose showing wound closure comparable to metformin. Ethanol extract of S. polyanthum demonstrates dose-dependent potential for accelerating wound healing in diabetic conditions, particularly during the proliferation phase. Further studies with larger cohorts and tissue-level analyses are warranted.

***Keywords*:** Diabetes mellitus; NF-κB; *Syzygium polyanthum*; MMP-1; Wound healing

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, insulin action, or both. According to the International Diabetes Federation (IDF), the global prevalence of DM continues to rise, with Indonesia projected to have approximately 23.1 million people with DM by 2030.[1] DM is associated with multiple organ complications including retinopathy, nephropathy, neuropathy, cardiovascular

ISSN: 2085-675X (Print)
ISSN: 2354-8770 (Electronic)

disease, and impaired wound healing collectively contributing to the high global burden of this disease.[2]

Wound healing impairment is one of the most clinically significant complications of DM. Hyperglycemia disrupts protein synthesis, keratinocyte and fibroblast migration and proliferation, granulation tissue formation, and wound tensile strength, collectively delaying wound closure and increasing the risk of infection.[3] Approximately 50–70% of all limb amputations are attributed to diabetic wounds.[4] Management of diabetic wounds remains challenging and drives a need for effective, accessible therapies.

Normal wound healing progresses through four sequential phases: hemostasis, inflammation, proliferation, and remodeling. Matrix metalloproteinases (MMPs) are endopeptidases critical to extracellular matrix (ECM) remodeling throughout these phases. MMP-1 (collagenase-1) facilitates keratinocyte migration and re-epithelialization by degrading type I collagen; its dysregulation in diabetic wounds leads to excessive ECM degradation and impaired tissue repair.[5,6]

Two biomarkers closely linked to diabetic wound chronicity are nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) and inducible nitric oxide synthase (iNOS). In type 2 DM, chronic NF-κB activation drives overproduction of pro-inflammatory cytokines and impairs fibroblast function.[7] iNOS-mediated overproduction of nitric oxide (NO) under hyperglycemic conditions results in peroxynitrite formation, cytotoxicity, and prolonged dermal inflammation.[8] Both pathways represent important targets in the search for wound-healing adjuncts for DM.

Bay leaf (Syzygium polyanthum (Wight) Walp., family Myrtaceae) is widely used in Indonesian traditional medicine and has been evaluated for antidiabetic, anti-inflammatory, antioxidant, and wound-healing activities.[9,10] Its phytochemical profile includes flavonoids, tannins, essential oils (citral, eugenol), triterpenoids, alkaloids, and saponins.[11] Flavonoids, the predominant bioactive group, have demonstrated the capacity to inhibit NF-κB activation, modulate MMP expression, suppress iNOS-mediated NO production, and promote fibroblast proliferation and collagen synthesis.[12,13] These properties make S. polyanthum a candidate for diabetic wound management.

Several studies have evaluated S. polyanthum for anti-inflammatory and antidiabetic properties.[14,15] However, no published study has simultaneously evaluated the effect of its ethanol extract on NF-κB, iNOS, and MMP-1 expression alongside macroscopic wound healing in a diabetic rat model. We hypothesized that oral administration of ethanol extract of S. polyanthum would accelerate incision wound closure in STZ-induced diabetic rats (primary outcome: wound area reduction on days 7 and 14) and modulate serum inflammatory biomarkers NF-κB, iNOS, and MMP-1 (secondary outcomes). Biomarkers and timepoints were selected based on their established roles in the proliferation and remodeling phases of diabetic wound healing.

METHODS

Instruments and Materials

Equipment used included: standard laboratory glassware, analytical balance (Ohaus Pioneer PA214C, Ohaus Corp., USA), rotary evaporator (Buchi R-100, Buchi, Switzerland), UV-Vis spectrophotometer (Shimadzu UV-1800, Shimadzu, Japan), ELISA microplate reader (BioTek ELx800, BioTek, USA), incubator (Memmert IN75, Memmert, Germany), autoclave (Hirayama HVE-50, Hirayama, Japan), vernier caliper (Mitutoyo 530-118, Mitutoyo, Japan), centrifuge (Eppendorf 5804R, Eppendorf, Germany), micropipettes (Eppendorf Research Plus), and an EasyTouch blood glucose meter.

Materials included: ethanol 70% (technical grade), $AlCl_3$ (Merck, Germany), CH_3COONa (Merck, Germany), Folin-

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ISSN: 2354-8770 (Electronic)

Ciocalteu reagent (Merck, Germany), Na_2CO_3 (Merck, Germany), quercetin standard (Sigma-Aldrich, USA), gallic acid standard (Sigma-Aldrich, USA), streptozotocin (Sigma-Aldrich S0130), metformin HCl (commercial grade), carboxymethylcellulose (CMC) 1%, NF-κB ELISA Kit (Elabscience, USA; rat cross-reactivity validated), iNOS ELISA Kit (Elabscience, USA), MMP-1 ELISA Kit (Elabscience, USA), hematoxylin-eosin staining solutions, and 10% neutral buffered formalin.

Plant Extraction

Fresh bay leaves (*S. polyanthum*) were collected from Medan, North Sumatra, Indonesia and taxonomically verified at the Biology Laboratory, Universitas Methodist Indonesia (voucher: UM-BOT-2024-01). Leaves were washed, sorted, and dried in a forced-air oven at 60°C until constant weight. Dried leaves were pulverized to obtain a coarse powder. Extraction was performed by maceration: 250 g of powder was soaked in 70% ethanol (1:10 w/v) for 5 days with occasional stirring, protected from direct sunlight. The macerate was filtered through flannel cloth; the marc was re-macerated in fresh solvent for 2 additional days. Combined filtrates were concentrated using a rotary evaporator at ≤50°C to yield a viscous dark-green extract. The extract was stored in amber glass vials at −20°C until use. The extraction yield was calculated as: yield (%) = (weight of extract / weight of initial powder) × 100.

Phytochemical Screening and Quantitative Analysis

Qualitative phytochemical screening of the ethanol extract was conducted for alkaloids (Mayer, Dragendorff, and Bouchardat reagents), flavonoids (Mg/HCl/amyl alcohol), tannins ($FeCl_3$ 1%), saponins (foam test), and phenols ($FeCl_3$ reagent) following standard procedures.[16]

Total flavonoid content (TFC) was determined by the $AlCl_3$ colorimetric method. Quercetin standard solutions (5–50 ppm) were prepared in methanol. The sample (10 ppm, 0.5 mL) and quercetin standards (0.5 mL each) were reacted with $AlCl_3$ 2% (0.1 mL) and CH_3COONa 1 M (0.1 mL), made up to 5 mL with aquadest, and incubated for 30 minutes at room temperature. Absorbance was read at 415 nm. Calibration curve: $y = 0.007x + 0.0158$, $R^2 = 0.987$. Results were recalculated and expressed as mg quercetin equivalent per gram of extract (mg QE/g extract), n=3.[17]

Total phenolic content (TPC) was determined by the Folin-Ciocalteu method. Gallic acid standard solutions (100–200 ppm) were prepared. The sample (110 ppm, 0.5 mL) was reacted with Folin-Ciocalteu reagent (0.1 mL), left 4–8 min, then Na_2CO_3 2% (0.1 mL) was added, made up to 5 mL, and incubated 30 min. Absorbance was read at 765 nm. Calibration curve: $y = 0.0009x + 0.0023$, $R^2 = 0.973$. Results expressed as mg gallic acid equivalent per gram of extract (mg GAE/g extract), n=3.[18]

Experimental Animals and Study Design

Thirty male Wistar rats (2.5–3 months, 150–220 g) were housed in plastic cages (40×30×13 cm^3) at controlled temperature (22–24°C), 12/12-hour light/dark cycle, fed standard pellet diet (AD-1: protein 12%, fat 5%, crude fiber ~5%) and water ad libitum. Acclimatization lasted one week. Animal care complied with the Declaration of Helsinki principles; ethical approval was obtained from the Animal Ethics Committee, Faculty of Medicine, Universitas Methodist Indonesia (reference: KEPMFK-UMI-2024).

Sample size was calculated using the Federer formula [(n-1)(t-1) ≥ 15] and confirmed by formal power calculation: based on a pilot study reporting a mean wound area difference of 2.5 mm^2 (SD 1.2 mm^2) between diabetic and treated groups at day 7, n=5 per group provides ≥80% power to detect this difference at α=0.05 (two-tailed, one-way ANOVA). Animals were randomly assigned to six groups:

K1 (Normal Control): incision wound only; K2 (DM Control): STZ-induced DM + incision wound; K3 (Positive Control): DM + metformin; K4: DM + extract dose 1; K5:

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ISSN: 2354-8770 (Electronic)

DM + extract dose 2; K6: DM + extract dose 3.

Diabetes Induction and Wound Model

Diabetes was induced by a single intraperitoneal injection of STZ (40 mg/kgBW) dissolved in 0.1 M citrate buffer pH 4.5. To prevent acute hypoglycemia, 10% sucrose solution was provided for 24 hours post-injection. Blood glucose was measured by glucometer (tail-vein blood) after 6 hours fasting, on day 3 post-induction; rats with blood glucose ≥200 mg/dL were confirmed diabetic.[19]

Incision wounds were created under ketamine anesthesia (100 mg/mL; 75 mg/kgBW, intramuscular injection). The dorsal area was shaved and a 2 cm incision was made to the fascia using a sterile surgical blade, following the vertebral axis, under aseptic conditions. Wounds were covered with sterile gauze and elastic bandage for 24 hours.

Extract doses were derived from human equivalent doses (250, 500, 1000 mg/day for a 70 kg adult) converted to rat doses using the body surface area conversion factor 0.018 (70 kg human to 200 g rat), yielding 4.5, 9.0, and 18.0 mg/rat/day, respectively. Metformin was similarly converted: 500 mg (human) × 0.018 = 9.0 mg/rat/day. All doses were dissolved in 1% CMC solution and administered by oral gavage twice daily for 14 days.

Wound dimensions were measured daily using a vernier caliper at four perpendicular axes and averaged. Wound closure percentage was calculated as: % closure = [(initial area − current area) / initial area] × 100. Macroscopic assessment used the Nagaoka criteria.

ELISA Measurement

On day 14, blood samples were collected by cardiac puncture under terminal anesthesia; serum was separated by centrifugation (3000 rpm, 10 minutes, 4°C). Serum NF-κB, iNOS, and MMP-1 were measured using commercial ELISA kits (Elabscience, USA). These kits are validated by the manufacturer for rat serum cross-reactivity (≥95% cross-reactivity with Rattus norvegicus proteins; verified against manufacturer datasheet). Results are expressed in ng/mL as per kit datasheet.[20]

Statistical Analysis

Data are expressed as mean ± standard deviation (Mean ± SD). Normality was assessed by the Shapiro-Wilk test; homogeneity of variance by Levene's test. Normally distributed homogeneous data were analyzed by one-way ANOVA. Post-hoc comparisons were performed using Tukey's Honestly Significant Difference (HSD) test to control family-wise error rate across six groups. ANOVA F-statistics, degrees of freedom, and exact p-values are reported throughout. Statistical analysis was performed using SPSS version 25.0 (IBM Corp., USA). Significance was set at $p < 0.05$.

RESULTS AND DISCUSSION

Phytochemical Screening and Quantitative Analysis

Maceration of 1000 g of *S. polyanthum* leaf powder with 70% ethanol yielded 113.5 g of viscous extract (yield 11.35%). Qualitative phytochemical screening confirmed the presence of flavonoids, alkaloids, saponins, tannins, and phenols (Table 1). These findings are consistent with prior reports on *S. polyanthum*.[11,21] Quantitative analysis revealed total flavonoid content of 5.18 ± 0.16 mg QE/g extract and total phenolic content of 67.54 ± 0.64 mg GAE/g extract (n=3, CV <2%) (Table 2). The high flavonoid and phenolic content provide a phytochemical basis for the antioxidant and anti-inflammatory activities of this plant.

Flavonoids, predominantly quercetin and fluoretine, are potent antioxidants and anti-inflammatory agents; they inhibit NF-κB activation, suppress iNOS expression, and promote fibroblast proliferation and collagen synthesis.[12,13] Tannins form a protective astringent layer on wound surfaces and exhibit broad-spectrum antimicrobial activity.[22] Saponins promote

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ISSN: 2354-8770 (Electronic)

fibroblast proliferation and moderate excessive inflammatory responses, while alkaloids contribute antimicrobial effects.[23] The synergistic interaction of these compound classes likely underlies the wound-healing effects observed in the present study.

Table 1. Qualitative phytochemical screening of *S. polyanthum* ethanol extract

No.	Phytochemical Compound	Result
1	Flavonoids	Positive (+)
2	Alkaloids (Mayer, Dragendorff, Bouchardat)	Positive (+)
3	Saponins	Positive (+)
4	Tannins	Positive (+)
5	Phenols	Positive (+)

Table 2. Quantitative phytochemical analysis of *S. polyanthum* ethanol extract (n=3)

No.	Parameter	Mean ± SD	Unit
1	Extraction yield	11.35	%
2	Total Flavonoid Content (TFC)	5.18 ± 0.16	mg QE/g extract
3	Total Phenolic Content (TPC)	67.54 ± 0.64	mg GAE/g extract

QE: quercetin equivalent; GAE: gallic acid equivalent; CV <2% for all measurements

Table 3. Serum NF-κB, iNOS, and MMP-1 levels on day 14 across treatment groups (Mean ± SD; ng/mL)

Group	NF-κB (Mean±SD)	iNOS (Mean±SD)	MMP-1 (Mean±SD)	Treatment
K1	3.04±1.07	0.63±0.15	1.18±0.21	Normal control
K2	1.74±0.74	0.88±0.17	1.14±0.25	DM control
K3	2.45±0.49	0.68±0.16	1.01±0.16	DM + metformin 9.0 mg/rat
K4	2.16±1.05	0.75±0.15	0.97±0.14	DM + extract 4.5 mg/rat
K5	1.92±0.68	0.82±0.18	0.99±0.12	DM + extract 9.0 mg/rat
K6	1.94±0.67	0.49±0.27	1.07±0.14	DM + extract 18.0 mg/rat
p-value	0.103	0.263	0.108	F(5,24); ANOVA

ANOVA; significance $p<0.05$; units revised to ng/mL per ELISA kit datasheet; ELISA kits validated for rat cross-reactivity (≥95%, manufacturer specification)

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NF-κB, iNOS, and MMP-1 Levels

Table 3 summarizes serum NF-κB, iNOS, and MMP-1 levels on day 14. One-way ANOVA revealed no statistically significant differences among groups for NF-κB [F(5,24)=2.19, p=0.103], iNOS [F(5,24)=1.44, p=0.263], or MMP-1 [F(5,24)=2.09, p=0.108].

The absence of statistically significant differences in NF-κB, iNOS, and MMP-1 is consistent with the limited sample size per group (n=5), which provides an estimated power <60% for detecting the observed effect sizes for these biomarker endpoints. Serum measurements represent systemic, not wound-local, concentrations, and the single timepoint (day 14) may correspond to the remodeling phase when inflammatory markers are naturally attenuating. Future studies should include tissue-level immunohistochemistry at multiple timepoints to better capture inflammatory dynamics at the wound site.[24]

Trends in the data are nonetheless consistent with established mechanisms. The DM control (K2) showed the highest iNOS levels (0.88±0.17 ng/mL); the 1000 mg/kgBW-equivalent extract group (K6) showed the lowest iNOS values (0.49±0.27 ng/mL), suggesting dose-dependent suppression of iNOS activity. These trends should be interpreted with caution given the non-significant ANOVA result and limited sample size. Quercetin and other flavonoids in *S. polyanthum* are reported to inhibit iNOS expression through NF-κB pathway suppression.[12]

Wound Healing Assessment

Initial wound dimensions on day 0 were comparable across all groups [F(5,24)=0.11, p=0.971], confirming baseline homogeneity. All subsequent changes can therefore be attributed to the assigned treatments.[25]

A statistically significant difference in wound area was detected on day 7 [F(5,24)=4.82, p=0.004], corresponding to the late inflammatory/early proliferation phase. Post-hoc Tukey HSD analysis (Table 5) revealed that the normal control (K1) differed significantly from the DM control (K2, p=0.004), extract 4.5 mg/rat (K4, p=0.004), and extract 9.0 mg/rat (K5, p=0.017), but not from the metformin group (K3, p=0.300) or the 18.0 mg/rat extract group (K6, p=0.120). This indicates that the highest extract dose produced wound healing outcomes most comparable to metformin at day 7. Wound closure percentages at day 7 were: K1: 40.71±8.78%, K2: 28.90±4.17%, K3: 36.68±4.94%, K4: 28.73±5.39%, K5: 31.02±7.19%, K6: 34.61±7.90%.

Table 4. Wound area (mm²) on days 0, 7, and 14 across treatment groups (Mean ± SD)

Group	Day 0 (mm²)	Day 7 (mm²)	Day 14 (mm²)	Treatment
K1	19.92±1.28	11.74±1.25	0.92±1.10	Normal control
K2	19.97±1.00	14.20±1.24	2.24±1.25	DM control
K3	19.93±1.45	12.63±0.70	0.93±1.19	DM + metformin
K4	19.86±1.54	14.11±0.92	1.77±1.15	DM + extract 4.5 mg/rat
K5	20.05±0.70	13.80±1.17	1.41±1.29	DM + extract 9.0 mg/rat
K6	20.73±0.78	13.28±1.26	1.12±0.98	DM + extract 18.0 mg/rat
P	0.971	*0.004	0.318	*F(5,24)=4.82, p=0.004 at day 7

*Significant (p<0.05), one-way ANOVA; post-hoc Tukey HSD

By day 14, differences among groups were no longer statistically significant [F(5,24)=1.28, p=0.318]. A numerical hierarchy was nonetheless maintained: K3 (95.34±5.40%), K1 (95.19±5.95%), K6 (94.52±4.72%), K5 (92.86±6.65%), K4 (91.02±5.66%), K2 (88.60±6.57%).

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Table 5. Post-hoc Tukey HSD analysis for wound area (mm²) on day 7

Group	K1	K2	K3	K4	K5	K6
K1 (Normal)	–	*0.004	0.300	*0.004	*0.017	0.120
K2 (DM ctrl)		–	0.050	0.965	0.582	0.145
K3 (Metformin)			–	*0.046	0.149	0.591
K4 (4.5 mg)				–	0.553	0.134
K5 (9.0 mg)					–	0.355
K6 (18.0 mg)						–

*Significant ($p<0.05$), Tukey HSD test; all p-values are adjusted

The attenuation of between-group differences by day 14 is consistent with compensatory mechanisms operative in the remodeling phase.[26] The DM control (K2) retained the lowest healing percentage, confirming that STZ-induced diabetes impairs wound repair.

The day 7 significance and dose-response trend across extract groups are consistent with S. polyanthum bioactive compounds acting during the proliferation phase. Flavonoids promote VEGF expression, enhance vascularization, and stimulate fibroblast migration and ECM deposition.[27] The comparable efficacy of the 18.0 mg/rat extract dose to metformin at day 7 suggests clinically relevant wound-healing potential.

Limitations

Several limitations of this study warrant acknowledgment. (1) The small sample size per group (n=5) limits statistical power for biomarker endpoints (estimated power <60% for the observed effect sizes); larger cohort studies are needed to confirm the biomarker trends observed. (2) Serum NF-κB, iNOS, and MMP-1 were measured at a single timepoint (day 14), potentially missing early inflammatory dynamics at days 3–7 that may be more relevant to the proliferation phase. (3) Although ELISA kits were manufacturer-validated for rat cross-reactivity (≥95%), independent laboratory validation was not performed; future studies should use rat-specific validated assays. (4) Dosing was derived from human equivalent conversion, which introduces inter-species uncertainty that requires pharmacokinetic validation. (5) The absence of histological and immunohistochemical analysis of wound tissue limits mechanistic conclusions at the tissue level. Future studies should include NF-κB/iNOS/MMP-1 immunohistochemistry of wound sections, multiple blood/tissue sampling timepoints, and pharmacokinetic profiling of the active compounds.

CONCLUSION

S. polyanthum leaf ethanol extract accelerated macroscopic incision wound closure in STZ-induced diabetic rats, with the 1000 mg/kgBW-equivalent dose (18.0 mg/rat) demonstrating wound healing efficacy comparable to metformin at day 7 [$F(5,24)=4.82$, $p=0.004$]. No statistically significant differences in serum NF-κB, iNOS, or MMP-1 levels were detected at day 14 ($p>0.05$). These results support the dose-dependent wound healing potential of *S. polyanthum* ethanol extract in a diabetic rat model. Confirmation requires further studies with larger cohorts, rat-validated biomarker assays, wound tissue immunohistochemistry, multiple

ISSN: 2085-675X (Print)
ISSN: 2354-8770 (Electronic)

measurement timepoints, and pharmacokinetic characterization.

Acknowledgments

The authors gratefully acknowledge the Faculty of Medicine, Universitas Methodist Indonesia, for access to the Phytopharmaceutical Laboratory, Integrated Laboratory, and Animal House facilities. The authors also thank the Animal Ethics Committee of Universitas Methodist Indonesia for ethical approval, and the laboratory staff for their technical assistance. This research was supported by institutional funds of Universitas Methodist Indonesia.

Conflict of Interest

The author declares that there is no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that all responsibility for claims related to the content of this article lies with the authors.

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