Research Article

Evaluation of the Antioxidant, Antibacterial, and In Vivo Wound-Healing Activities of 9-Isopropyl-3,6-Dimethoxy-9-Methyl-9H-Fluorene, a Bioactive Compound Isolated from the Marine Bacterium Shewanella algae

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Abstract

Background: Marine bacteria are valuable sources of structurally diverse secondary metabolites with potential pharmaceutical applications. The present study evaluated the antioxidant, antibacterial, antifungal, and wound-healing properties of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene isolated from the marine bacterium Shewanella algae. Methods: Antioxidant activity was assessed using the DPPH radical-scavenging assay at concentrations ranging from 1.56 to 100 µg/mL, with ascorbic acid as the reference standard. Antibacterial activity was evaluated against Staphylococcus aureus and Escherichia coli by agar well diffusion, followed by determination of the minimum inhibitory concentration (MIC). Morphological changes in MIC-treated S. aureus were examined using high-resolution transmission electron microscopy (HR-TEM). Antifungal activity was assessed against Candida albicans. Wound-healing activity was investigated in Wistar albino rats treated with 50 and 100 mg of the compound, using simple ointment and silver sulfadiazine as controls. Results: The compound demonstrated concentration-dependent DPPH scavenging, increasing from 10.63% at 1.56 µg/mL to 73.13% at 100 µg/mL. A 16 mm inhibition zone was observed against S. aureus, with an MIC of 100 µg/mL, whereas no inhibition was detected against E. coli or C. albicans. HR-TEM revealed substantial morphological and structural alterations in treated S. aureus cells. In the wound model, the 100 mg treatment produced 93.86 ± 2.45% wound closure on day 21, significantly exceeding the simple ointment group (88.02 ± 3.12%) and approaching silver sulfadiazine treatment (99.21 ± 0.42%). Histopathological findings supported improved tissue regeneration. Conclusion: 9-Isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene exhibited promising antioxidant, selective antibacterial, and wound-healing activities, particularly at the 100 mg dose. These findings support further investigation of this marine-derived compound as a potential bioactive agent for wound management.

Keywords: Shewanella algae; 9-Isopropyl-3,6-Dimethoxy-9-Methyl-9H-Fluorene; Antioxidant Activity; Antibacterial Activity; Wound Healing.

1. Introduction

Marine environments represent an exceptionally diverse source of microorganisms capable of producing chemically distinct secondary metabolites with considerable pharmaceutical potential. Among marine bacteria, members of the genus *Shewanella* have attracted increasing scientific interest because of their metabolic versatility and ability to survive under diverse environmental conditions. These microorganisms produce a broad range of bioactive metabolites that may possess antioxidant, antimicrobial, anti-inflammatory, cytoprotective, and other pharmacological properties. The exploration of marine bacterial metabolites is therefore an important approach for identifying structurally novel compounds with potential applications in drug discovery and biomedical research. In the present investigation, 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene was isolated as a bioactive compound from the marine bacterium *Shewanella algae* and subjected to biological evaluation.

Oxidative stress is closely associated with the generation of reactive oxygen and nitrogen species that can damage cellular lipids, proteins, and nucleic acids. Excessive accumulation of free radicals may disturb normal cellular functions and contribute to tissue injury and delayed recovery from pathological conditions. Antioxidant compounds can counteract these effects by neutralizing reactive species and thereby reducing oxidative damage. Natural products,

particularly those obtained from microorganisms, are considered valuable sources of structurally diverse antioxidant molecules. The DPPH radical-scavenging assay is widely employed as an initial in vitro method for assessing the free-radical-neutralizing capacity of bioactive compounds. Therefore, evaluating the antioxidant activity of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene may provide preliminary evidence of its ability to participate in antioxidant defense mechanisms.

Bacterial infections remain an important complication in wound management and can substantially interfere with normal tissue repair. The increasing occurrence of antimicrobial resistance has further emphasized the need to identify alternative antimicrobial molecules with activity against clinically relevant microorganisms. Marine-derived metabolites have received considerable attention in this context because of their unique chemical diversity and biological activities. *Staphylococcus aureus* is an important Gram-positive pathogen frequently associated with wound infections, whereas *Escherichia coli* represents a clinically relevant Gram-negative organism. Determining the antibacterial spectrum of newly isolated marine metabolites against these organisms can provide useful information regarding their potential therapeutic applications.

Wound healing is a complex biological process involving overlapping phases of inflammation, proliferation, tissue formation, and remodeling. Successful repair requires coordinated interactions among inflammatory cells, fibroblasts, keratinocytes, extracellular matrix components, and newly developing blood vessels. Oxidative stress and microbial infection can adversely affect these processes and consequently delay tissue regeneration. Compounds possessing both antioxidant and antimicrobial properties may therefore offer particular advantages in wound management. In vivo evaluation using an experimental wound model provides an opportunity to determine whether the biological activities observed in vitro translate into measurable improvement in wound contraction and tissue restoration.

The present study was designed to comprehensively evaluate the antioxidant, antibacterial, and wound-healing properties of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene isolated from marine *Shewanella algae*. Antioxidant activity was investigated using the DPPH radical-scavenging assay, while antibacterial activity was assessed against *S. aureus* and *E. coli*, including determination of the minimum inhibitory concentration against the susceptible organism. High-resolution transmission electron microscopy was further employed to examine morphological changes in MIC-treated bacterial cells. The wound-healing potential of the compound was evaluated in a Wistar albino rat model through assessment of wound contraction and histopathological changes.

1. Material and Methods

1.1. Antioxidant activity of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene isolated from the Shewanella Algae marine bacteria.

The antioxidant activity of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene was evaluated using the DPPH radical-scavenging method. A 0.1 mM solution of 2,2-diphenyl-1-picrylhydrazyl (DPPH) was prepared in methanol, and 1 mL was mixed with 1 mL of the test compound at concentrations of 1.56, 3.125, 6.25, 12.5, 25, 50 and 100 µg/mL. The mixtures were incubated in darkness at room temperature for 30 minutes, and absorbance was measured at 517 nm. Ascorbic acid was used as standard. Measurements were performed in duplicate (n=2), and percentage inhibition was calculated using the DPPH control absorbance.

1.2. Antibacterial activity of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene.

Double strength Mueller–Hinton agar was prepared, sterilized by autoclaving, and poured into sterile Petri plates. Fresh cultures of *Escherichia coli* and *Staphylococcus aureus* were prepared and adjusted to 0.5 McFarland turbidity. The standardized bacterial suspensions were uniformly spread over the agar surface using sterile cotton swabs. Sterile wells of 6 mm diameter were made aseptically in the inoculated plates. 9-Isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene was prepared in a DMSO solvent and introduced into the wells 100 µg/mL concentrations. A solvent control and standard antibiotic control were included. The plates were allowed to stand for approximately 30 min for diffusion and incubated at 37°C for 18–24 hours. After incubation, the diameter of each inhibition zone was measured in millimetres using a Himedia zone reader and the results were recorded.

1.3. Minimum inhibitory concentration (MIC) of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene.

MIC of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene was determined against *Staphylococcus aureus* using a broth

microdilution method. Serial two-fold dilutions of the test compound were prepared in sterile Mueller–Hinton broth using dimethyl sulfoxide (DMSO) as the solvent, covering an appropriate concentration range. Each dilution was inoculated with a standardized bacterial suspension adjusted to approximately 0.5 McFarland turbidity. A growth control containing inoculated broth without test compound and a solvent control were included. The microplates were incubated under appropriate conditions, and bacterial growth was assessed by visual turbidity or absorbance measurement. The MIC was recorded as the lowest concentration of the test compound showing no visible bacterial growth. The assay was performed in duplicate (n=2).

1.4. HR-TEM observation of the MIC concentration treated *Staphylococcus aureus*

The HR-TEM observation of *Staphylococcus aureus* treated with the minimum inhibitory concentration (MIC) of the test sample was performed to evaluate alterations in bacterial morphology and ultrastructural integrity. The MIC-treated bacterial suspension was collected by centrifugation and washed gently with sterile phosphate-buffered saline. The resulting pellet was fixed with an appropriate primary fixative, followed by dehydration using a graded ethanol series. A small volume of the processed suspension was placed onto a carbon-coated copper grid and allowed to dry under suitable conditions. The prepared grids were examined using high-resolution transmission electron microscopy (HR-TEM). Untreated cells were observed in parallel as controls, and differences in cell-wall integrity, membrane continuity, cytoplasmic organization, and cellular morphology were recorded.

1.5. Antifungal activity of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene.

Double-strength Potato dextrose agar media was prepared, sterilized by autoclaving, and aseptically poured into sterile Petri plates. A fresh culture of *Candida albicans* was prepared. The standardized fungal suspension was uniformly inoculated over the agar surface using a sterile cotton swab. Sterile wells measuring 6 mm in diameter were prepared aseptically in the inoculated plates. 9-Isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene was dissolved in dimethyl sulfoxide (DMSO) and introduced into the wells at a concentration of 100 µg/mL. DMSO was included as the solvent control, while an appropriate standard antifungal agent was used as the positive control. The plates were allowed to stand for approximately 30 min to facilitate diffusion and were subsequently incubated at 48 hours room temperature. Following incubation, the diameter of the inhibition zones was measured in millimetres using a HiMedia zone reader, and the observations were recorded.

1.6. *In vivo* Wound healing activity of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene.

A wound excision model was used to evaluate the wound-healing activity of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene. The animals were divided into four groups: G1 received simple ointment, G2 received 50 mg of the test compound, G3 received 100 mg of the test compound, and G4 received 10 mg/g silver sulfadiazine as the standard treatment. The respective treatments were applied externally to the wound area. Wound healing was assessed by measuring wound contraction on post-wounding days 2, 6, 12, 16, and 21, and the percentage of wound closure was calculated. The results were expressed as mean ± SEM (n = 6). Statistical analysis was performed using one-way ANOVA followed by Dunnett's multiple comparison test, with $p < 0.05$ considered statistically significant.

2. Results and Discussion

2.1. Antioxidant activity of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene

The DPPH radical-scavenging activity of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene increased progressively with concentration. At 1.56 µg/mL, replicate absorbances were 0.710 and 0.720, giving a mean absorbance of 0.715 and 10.63% inhibition. At 3.125, 6.25, 12.5, 25, 50 and 100 µg/mL, mean absorbances were 0.665, 0.595, 0.505, 0.405, 0.305 and 0.215, corresponding to 16.88%, 25.63%, 36.88%, 49.38%, 61.88% and 73.13% inhibition, respectively. In comparison, ascorbic acid produced mean absorbances of 0.725, 0.675, 0.555, 0.385, 0.235, 0.135 and 0.085 at the corresponding concentrations, with inhibition values of 9.38%, 15.63%, 30.63%, 51.88%, 70.63%, 83.13% and 89.38%, respectively. Thus, both test compound and standard exhibited concentration-dependent DPPH scavenging activity.

Table 1. DPPH radical-scavenging activity of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene at different concentrations, showing duplicate optical density (OD) readings, mean absorbance, and percentage inhibition.

Concentration (µg/mL)	Replicate 1 (OD)	Replicate 2 (OD)	Mean Absorbance	9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene (%)
100	0.21	0.22	0.215	73.13
50	0.3	0.31	0.305	61.88
25	0.4	0.41	0.405	49.38
12.5	0.5	0.51	0.505	36.88
6.25	0.59	0.6	0.595	25.63
3.125	0.66	0.67	0.665	16.88
1.56	0.71	0.72	0.715	10.63

Table 2. DPPH radical-scavenging activity of ascorbic acid at different concentrations, showing duplicate optical density (OD) readings, mean absorbance, and percentage inhibition.

Concentration (µg/mL)	Replicate 1 (OD)	Replicate 2 (OD)	Mean Absorbance	Ascorbic acid (%)
100	0.08	0.09	0.085	89.375
50	0.13	0.14	0.135	83.125
25	0.23	0.24	0.235	70.625
12.5	0.38	0.39	0.385	51.875
6.25	0.55	0.56	0.555	30.625
3.125	0.67	0.68	0.675	15.625
1.56	0.72	0.73	0.725	9.375

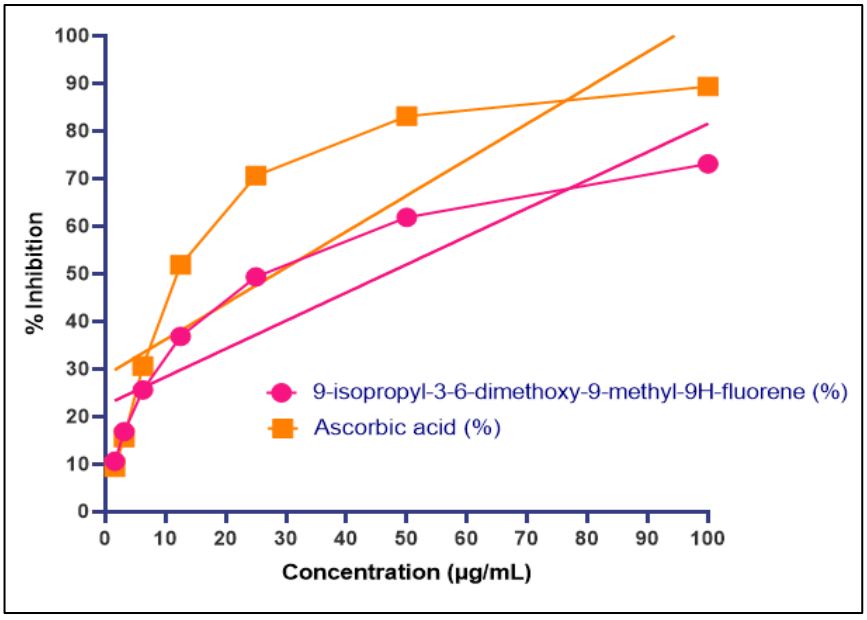


Figure 1: Concentration-dependent DPPH radical-scavenging activity of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene compared with ascorbic acid.

Antibacterial activity of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene

The antibacterial activity of the test drug was evaluated against *Staphylococcus aureus* and *Escherichia coli* using the

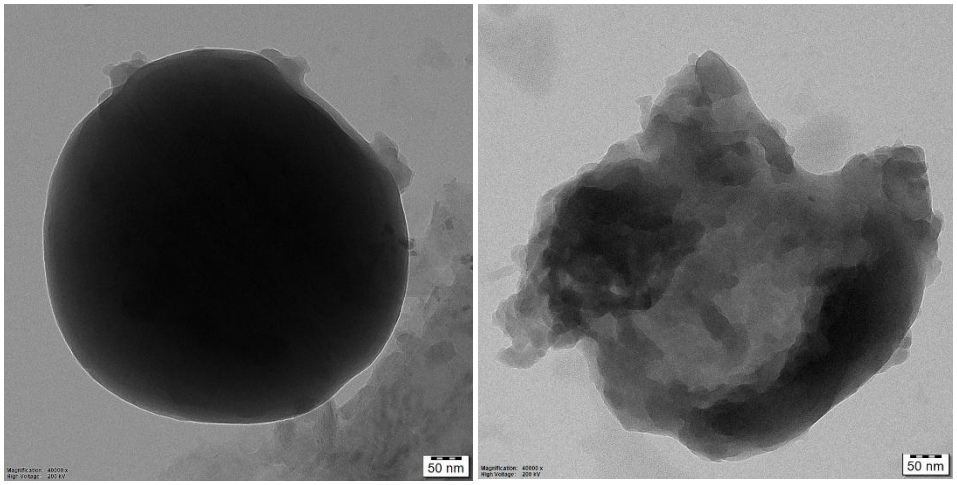
agar well diffusion method, and the findings are presented in Table 2 and Figure 2. The test drug produced a distinct zone of inhibition measuring 16 mm against *S. aureus*, indicating appreciable antibacterial activity. In contrast, no visible zone of inhibition was observed against *E. coli* under the tested conditions. The absence of inhibition against the Gram-negative organism suggests that the antibacterial effect of the test drug may be influenced by differences in bacterial cell-envelope architecture. The relatively greater susceptibility of *S. aureus* may be associated with its exposed peptidoglycan-rich cell wall, which could facilitate interaction of active constituents with cellular targets. The DMSO solvent control showed no inhibitory effect, confirming that the observed activity was attributable to the test drug rather than the solvent. Overall, the results demonstrate selective antibacterial activity, particularly against *S. aureus*.

Minimum inhibitory concentration (MIC) of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene.

The MIC evaluation demonstrated that 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene exhibited antibacterial activity against *Staphylococcus aureus* at a minimum inhibitory concentration of 100 µg/mL. At this concentration, no visible bacterial growth was observed, indicating effective inhibition of *S. aureus*.

HR-TEM observation of the MIC concentration treated *Staphylococcus aureus*

The HR-TEM images demonstrated distinct morphological differences between untreated and MIC-treated *Staphylococcus aureus*. The control cells exhibited a predominantly intact, smooth, and well-defined spherical morphology with a continuous cellular outline, indicating preserved structural integrity. Cells exposed to 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene at the MIC concentration showed pronounced structural alterations, including irregular cell morphology, surface disruption, aggregation, and loss of the characteristic smooth appearance. The treated cells also displayed increased electron-dense regions and apparent disorganization of the cellular structure. These changes suggest that the compound may interfere with bacterial envelope integrity and cellular organization, contributing to the observed antibacterial activity against *S. aureus*.



Control Treated

Figure 3: HR-TEM images of *Staphylococcus aureus* showing the untreated control cell and the morphological alterations observed following treatment with 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene at its minimum inhibitory concentration (MIC).

Antifungal activity of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene

The antifungal evaluation showed that 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene did not produce a measurable zone of inhibition against *Candida albicans* at the tested concentration. The absence of a clear inhibition zone indicates that the compound exhibited no detectable antifungal activity under the experimental conditions. The assay was performed in duplicate (n=2).

Table 2. Antifungal activity of *Test drug against Candida albicans*

S.NO	Test organism	Zone of Inhibition (mm) n=2
		9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene
1	*Candida albicans*	-

***In vivo* assessment of the wound-healing activity of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene using a Wistar albino rat model.**

The wound healing activity of 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene was evaluated at doses of 50 mg (G2) and 100 mg (G3) and compared with simple ointment (G1) and silver sulfadiazine (G4). A progressive increase in wound closure was observed in all groups from day 2 to day 21. G1 showed 5.06 ± 2.81%, 33.32 ± 3.89%, 46.60 ± 8.24%, 84.65 ± 6.21%, and 88.02 ± 3.12% closure on days 2, 6, 12, 16, and 21, respectively. Treatment with G2 increased wound closure to 9.70 ± 3.26%, 36.27 ± 3.26%, 46.39 ± 7.46%, 86.29 ± 6.19%, and 91.34 ± 3.91%, with significant improvement on days 16 and 21 ($p < 0.05$). G3 demonstrated 10.65 ± 3.12% to 93.86 ± 2.45% closure, with significant effects on days 16 ($p < 0.05$) and 21 ($p < 0.01$). G4 produced the highest closure, reaching 99.21 ± 0.42% on day 21, indicating superior activity.

Table 9: G1: Simple ointment, G2: 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene (50 mg), G3: 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene (100 mg). G4: A 10 mg/g silver sulfadiazine formulation was applied externally to the wound area.

Post-wounding days	2	6	12	16	21
Simple ointment-G1	5.06 ± 2.81	33.32 ± 3.89	46.6 ± 8.24	84.65 ± 6.21	88.02 ± 3.12
9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene (50 mg)-G2	9.70 ± 3.26	36.27 ± 3.26	46.39 ± 7.46	86.29 ± 6.19*	91.34 ± 3.91*
9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene (100 mg)-G3	10.65 ± 3.12	39.80 ±11.70	53.62 ± 12.90	89.73 ± 4.11*	93.86 ± 2.45**
Silver sulfadiazine (10 mg)-G4	13.82 ± 7.30	48.26 ± 6.79	57.77 ± 5.74*	94.61 ± 5.23**	99.21 ± 0.42**

All data are presented as mean ± SEM for six samples. Statistical evaluation was conducted using one-way ANOVA followed by Dunnett's multiple comparison test. Values showing *$p < 0.05$ were considered significant, while **$p < 0.01$ indicated a higher level of significance compared with the control group.

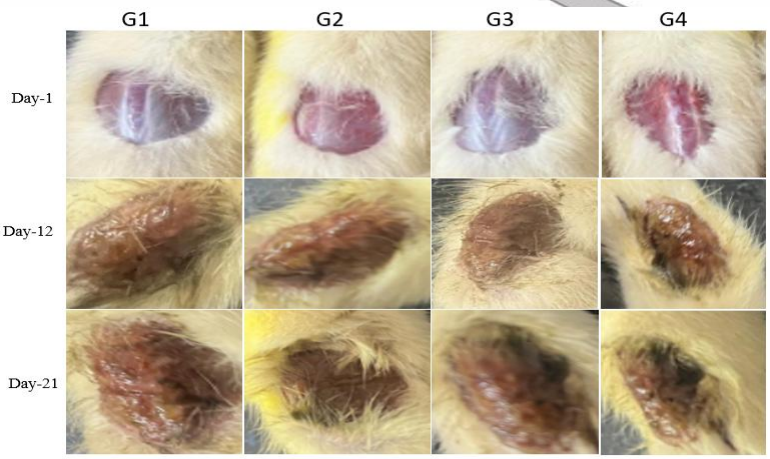


Figure 1: Representative macroscopic images showing progressive wound healing in experimental groups G1–G4 on post-wounding days 1, 12, and 21. G1: simple ointment; G2: 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene (50 mg); G3: 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene (100 mg); G4: silver sulfadiazine (10 mg/g).

The macroscopic observations demonstrated progressive wound contraction in all treatment groups, with notable differences in the extent of healing by day 21. On day 1, the wounds appeared as distinct open lesions in all groups. By day 12, visible reduction in wound area and formation of a developing tissue layer were evident, particularly in G3 and G4. By day 21, G2 and G3 exhibited substantial wound contraction compared with G1, while G4 showed the most pronounced closure and comparatively advanced surface restoration. These observations are consistent with the quantitative wound-contraction results, where G2, G3, and G4 achieved 91.34 ± 3.91%, 93.86 ± 2.45%, and 99.21 ± 0.42% closure, respectively, compared with 88.02 ± 3.12% in G1.

Histopathological examination of the wound.

Histopathological examination further supported the macroscopic findings. G1 showed comparatively incomplete tissue organization, whereas G2 and G3 demonstrated improved tissue reconstruction and greater restoration of the wound region. The G3 section appeared comparatively more organized than G2, suggesting a dose-related improvement in tissue repair. G4 displayed the most advanced healing pattern among the groups, corresponding with its highest wound-closure percentage. The findings indicate that 9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene, particularly at 100 mg, promoted wound repair and approached the activity observed with the reference silver sulfadiazine treatment.

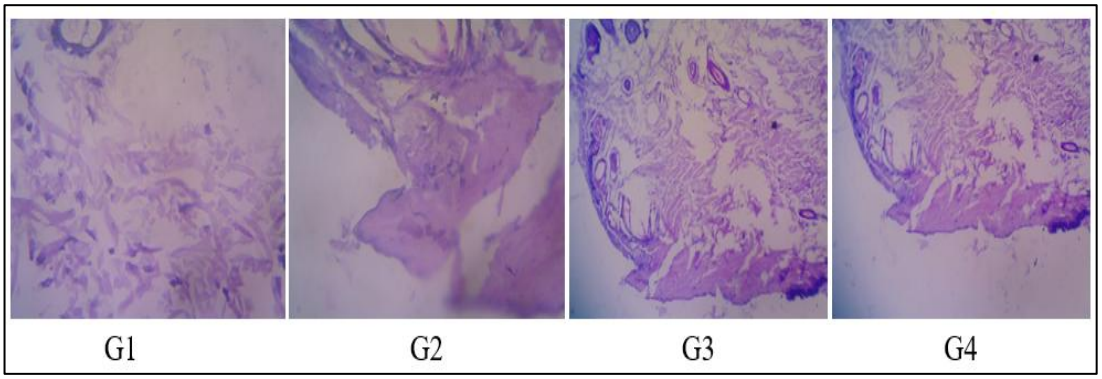


Figure 1: Histopathological examination of wound tissues (H&E-stained sections) showing tissue repair in G1–G4 (40X). G1: incomplete tissue regeneration; G2: improved tissue organization; G3: enhanced tissue reconstruction and regeneration; G4: comparatively advanced tissue repair with improved structural restoration. Overall, G3 demonstrated greater histological improvement than G2 and approached the healing pattern observed with G4.

3. Conclusion

9-isopropyl-3,6-dimethoxy-9-methyl-9H-fluorene demonstrated promising biological activities in the present investigation. The compound exhibited concentration-dependent DPPH radical-scavenging activity, with 73.13%

inhibition at 100 µg/mL, although its activity was lower than that of ascorbic acid. It showed selective antibacterial activity against *Staphylococcus aureus*, producing a 16 mm inhibition zone and an MIC of 100 µg/mL, while no activity was detected against *E. coli* or *Candida albicans*. HR-TEM findings supported the antibacterial effect by revealing marked structural alterations in treated bacterial cells. In vivo, the compound enhanced wound contraction and tissue regeneration, particularly at 100 mg, indicating considerable wound-healing potential. These findings support further investigation of this compound as a potential antioxidant, antibacterial, and wound-healing agent.

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