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Effects of low doses of Latrunculins from the Red Sea Marine Sponge *Negombata corticata* on Intraocular pressure in Normotensive Rabbits

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Latrunculins, C-20 and C-22 macrolides primarily derived from marine sponges of the *Negombata* genus, exhibit a range of bioactivities, including antitumor, antiviral, antimicrobial, antiangiogenic, and antimigratory effects. In this study, we focused on purifying and identifying Latrunculins from the sponge *Negombata corticata* and assessing their impact on intraocular pressure (IOP) in normotensive rabbits. Two Latrunculins, latrunculol A (1), and latrunculin A (2), were isolated from the extract of the sponge, and their structures were determined using NMR and (+)-HRESIMS spectral data. The IOP-lowering effects of latrunculol A were compared with timolol and latrunculin A. IOP was measured at baseline (0 hours) and at 1, 3, and 24 hours after treatment on both experimental days. The results showed that latrunculol A (0.02%) significantly reduced IOP one hour after administration, with a notable decrease in delta IOP compared to baseline values ($p < 0.05$) on the first day. This suggests that latrunculol A has a potent IOP-lowering effect in normotensive rabbits. Minimal ocular side effects were observed, indicating a favourable safety profile. These findings highlight latrunculol A as a promising candidate for glaucoma treatment. Its efficacy in reducing IOP, combined with its safety profile, warrants further investigation into its possible application as scaffolds for managing elevated intraocular pressure, a key factor in glaucoma pathogenesis.

Keywords: Red Sea sponge, *Negombata corticata*, macrolides, latrunculol A, latrunculin A, IOP lowering effect.

INTRODUCTION

Glaucoma is a main cause of permanent blindness, primarily considered by advanced impairment to the optic nerve. It is frequently linked with elevation of the intraocular pressure (IOP), though the condition is multifactorial in origin. Age, genetic predisposition, history of the family, non-Caucasian ethnicity, and elevated IOP represent the key risk factors in glaucoma. As a global health concern, glaucoma affects diverse populations worldwide; with estimates suggesting that approximately 3% of the global population aged 40–80 years is affected. Projections indicate a rising prevalence, which could have a profound impact on the quality of life of those affected. Early diagnosis and management are particularly challenging due to the asymptomatic nature of the disease in its early stages (Quigley and Broman, 2006; Tham et al. 2014). Current therapeutic approaches primarily aim to reduce IOP to slow disease progression. Medications like alpha-agonists, prostaglandin analogs, carbonic anhydrase, and beta-blockers inhibitors are frequently prescribed to reduce IOP. Surgical interventions, including laser trabeculoplasty and trabeculectomy, may be recommended when medications are not sufficient. While these treatments can be effective, challenges remain; highlighting the need for ongoing research to develop more targeted and personalized therapies for glaucoma. Elevated IOP continues to be the primary modifiable risk factor in glaucoma, driving disease progression. Consequently, therapeutic strategies are centered on IOP reduction, with

the 2020 American Academy of Ophthalmology Preferred Practice Pattern guidelines recommending a 20%-30% reduction in IOP as an appropriate target, even in normotensive eyes (Weinreb et al. 2014). Advancements in glaucoma pharmacotherapy have led to the introduction of more effective and safer medications, such as topical application of carbonic anhydrase inhibitors (CAIs), beta blockers, prostaglandin analogs, alpha agonists, and more recently, Rho-kinase inhibitors. These newer agents have demonstrated improved safety and efficacy compared to older treatments, such as pilocarpine and systemic oral CAIs (Wagner et al. 2022). However, Rho-kinase inhibitors mainly focus on the Schlemm's canal (SC) and the trabecular meshwork (TM), a unique class of agents—latrunculins—has emerged as a promising alternative. Latrunculins exert their effects through prevention of the assembly of actin microfilaments in a 1:1 molecular binding of free actin monomers in the cytoplasm of the cell. (Rasmussen et al. 2014).

Latrunculins are a fascinating group of marine-derived macrolides primarily sourced from sponges of the genus *Negombata*. These compounds have garnered significant attention due to their unique mechanisms of action and potential therapeutic applications. Latrunculin A has been extensively studied for its ability to disrupt the actin cytoskeleton. Sourced from the Red Sea sponge *Latrunculia* (now *Negombata*) *magnifica* (Groweiss et al. 1983; Kashman et al. 1980), latrunculins exert their effects by binding to free actin monomers in the cellular cytoplasm, forming a 1:1 molecular complex, and subsequently preventing the assembly of actin microfilaments. This mechanism of action makes latrunculins intriguing for their potential applications in diverse biomedical fields, including cancer research and neurobiology (Coué et al. 1987; Crews et al. 1986; El Sayed et al. 2006; Hayot et al. 2006; Spector et al. 1983). Furthermore, latrunculins have demonstrated their ability to lower IOP by impeding the assembly of actin microfilaments in ocular tissues (Hayot et al. 2006; Spector et al. 1983). A study in the central region of Saudi Arabia estimated a glaucoma prevalence of 5.6%, underscoring the importance of developing novel therapeutic approaches (Khandekar et al. 2019).

In this study, we describe the identification of latrunculol A and latrunculin A from the Red Sea sponge *Negombata corticata*. Furthermore, the effects of latrunculol A on intraocular pressure (IOP) in normotensive rabbits at various low doses (0.005%, 0.01%, and 0.02% w/v) were assessed and its efficacy was compared to that of latrunculin A and timolol. These results are presented and discussed.

MATERIALS AND METHODS

General Experimental Procedures

Optical rotations of 1 and 2 were measured using a digital polarimeter DIP-370. NMR spectra were recorded on 600 MHz spectrometer (DRX Bruker Avance). (+)-HRESIMS data were obtained using a Micromass Q-ToF mass spectrometer.

Biological Materials

The sponge *Negombata corticata* (Figure S1) (formerly *Latrunculia corticata* Carter, 1879, Family: Latrunculiidae) (Carter 1979) was collected using SCUBA diving at depths of 13-17 m off the coast of Yanbu, in the Saudi Red Sea. Phylogenetic revisions, supported by chemical investigations (Antunes et al. 2005; Kelly et al. 2016; Laubenfels, 1936; Samaai et al. 2006; Samaai and Krasokhin, 2002), have reclassified the genus to *Negombata*, now belonging to the family Podospongiidae Laubenfels, 1936 (order Poecilosclerida, suborder Mycalina).

Purification of Compounds 1 and 2

The freeze-dried sponge (98 g) was extracted three times with 1200 mL of MeOH. The combined extracts were evaporated under vacuum, and the residue was dissolved in a MeOH: H_2O (4:6) mixture followed by partition with CH_2Cl_2. The combined CH_2Cl_2 fractions were dried, and the residue (1.7 g) was partitioned on a Sephadex (LH-20), using a CH_2Cl_2-MeOH (1:1) solvent mixture, yielding four subfractions (Fr. 1-4). Fraction 3 (489 mg) was further partitioned on a reversed-phase silica column with a water-methanol gradient, resulting in five main fractions (A-E). Final purification of fraction D (115 mg) was performed on a YMC-Triart C18 column (250 × 6.0 mm, S-5 µm, 12 nm) using 60% acetonitrile (CH_3CN) at 1 mL/min, which led to the isolation of compounds 1 (2.4 mg) and 2 (5.7 mg).

Evaluation of the IOP-Lowering Effects of 1 and 2

Preparation of Solutions for the Treatment

Compounds 1 and 2 were dissolved in polyethylene glycol (PEG) at three concentrations: 0.005%, 0.01%, and 0.02%. Timolol maleate (0.5%) was obtained from a local pharmacy (Timoptol-XE®). Polyethylene glycol was obtained from Sigma-Aldrich.

Animal Studies

All procedures adhered to the standards outlined in the Health Guide of the National Institutes for the Laboratory Animals use and care. Male adult New Zealand albino rabbits (weighing 2.5 to 3 kg) were kept in the Unit of Animal Facility at King Fahd Medical Research Center, where they were maintained in a regulated environment with a consistent temperature and a 12-hour light-dark cycle. The rabbits had unrestricted access to food and water. The experimental protocol received approval from both the Institutional Animal Care and Use

Committee and the CEGMR Bioethics Committee at King Fahd Medical Research Center (Permit # 26-CEGMR-Bioeth-2021).

Treated Animal Groups

Latrunculol A (1) and latrunculin A (2) were evaluated as eye drops in healthy, normotensive rabbit eyes at three different concentrations (0.005%, 0.01%, and 0.02% w/v) for each compound.

Groups 1-3 (G1-G3)**:** 15 rabbits were treated with three different concentrations of latrunculol A (0.005%, 0.01%, and 0.02% w/v), with each concentration assigned to a separate group (n = 5 per group).

Groups 4-6 (G4-G6)**:** 15 rabbits were treated with three different concentrations of latrunculin A (0.005%, 0.01%, and 0.02%), with each concentration assigned to a separate group (n = 5 per group).

Control Animal Groups

Group 7 (G7, Positive Control, n = 5)**:** Rabbits were treated with commercial timolol eye drops (as timolol maleate, 0.5% w/v, equivalent to 0.5% timolol).

Group 8 (G8, Negative Control, n = 5): Rabbits were administered polyethylene glycol (PEG) eye drops using the same procedure, serving as intact controls.

Intraocular Pressure (IOP) Measurements

Before the experiment, 1–2 drops of proparacaine HCl sterile solution (Alcaine®, 0.5% w/v) were instilled into the eyes as a local anesthetic. The mean pre-treatment IOP for control and experimental eyes was 12.3 mmHg. Intraocular pressure (IOP) was measured before drug application and at 1, 3, and 24 hours on both day 1 and day 2 to align with the optimal function time of timolol (Lee et al. 2022). IOP was measured using a calibrated Tono-Pen AVIA® Tonometer (Reichert Technologies®, Buffalo, New York, USA). For each point, IOP of the right eye was measured three times to ensure accuracy. The variation in IOP (ΔIOP) was determined by subtracting the baseline IOP (recorded at 0 hours) from the IOP at each designated time point. The percentage change in ΔIOP was expressed as the ratio of ΔIOP to the baseline IOP at 0 hours, as shown in the following equations:

ΔIOP = IOP at time point − IOP at 0 hours

Percentage (%) of ΔIOP = (ΔIOP / IOP at 0 hours) × 100

During the acclimation period, the animals underwent training to reduce stress and improve the accuracy of IOP measurements. IOP was measured 5–10 consecutive times, beginning with the right eye. To account for circadian rhythm effects, all IOP measurements were consistently performed in the morning.

Normotensive Rabbit Studies

The effect of compounds 1 and 2 on intraocular pressure (IOP) was evaluated at three different doses: 0.005%, 0.01%, and 0.02%, corresponding to 110, 220, and 441 µM for compound 1, and 118, 237, and 474 µM for compound 2, respectively. The study was conducted in normotensive rabbits, with five animals in each group. To assess the time-dependent impact on IOP, the compounds, as well as the positive control timolol (0.5%), were administered unilaterally to the right eye as drops at a fixed 10 µL volume. IOP evaluation was then taken at 1-, 3-, and 24-hours post-treatment. Two baseline IOP measurements were recorded prior to compound administration. The control group received 10 µL of polyethylene glycol (vehicle). IOP was monitored for up to 48 hours following treatment. All experiments were conducted in a blinded design, with the experimenter unaware of the identity of the applied solution.

Statistical Analysis

Statistical analysis was conducted using IBM SPSS Statistics version 25 (SPSS 25). The data are presented as mean (±)-standard deviation (SD). One-way ANOVA, one-way repeated measures ANOVA, and Tukey's HSD post hoc tests were used for multiple comparisons. Graphs were generated with GraphPad Prism version 8 (ISI® Software, USA). A p-value of ≤ 0.05 was regarded as statistically significant.

RESULTS AND DISCUSSION

Structural Determination of Compound 1

Compound 1 (Figure 1) was isolated as white solid, exhibiting an optical rotation of $[\alpha]_D$ = +66.5° (c 1.0, MeOH), with the molecular formula $C_{22}H_{33}NO_7S$, as determined from the (+)-HRESIMS peak at *m/z* 478.1872 $[M + Na]^+$. In comparison to latrunculin A (2), compound 1 differs by having one bond equivalent less and two additional hydroxyl groups. The structure of 1 was determined by analyzing its 1D and 2D NMR spectra (Figures 2-7). In contrast to the ^1H and ^{13}C NMR data for compound 2 (latrunculin A), compound 1 showed several notable differences (Tables 1 and 2). Notably, the ^1H and ^{13}C NMR signals corresponding to the olefinic moiety at C-6/C-7 ($\delta_{C/H}$ 131.7/5.73 and 126.0/6.40 ppm) in latrunculin A were absent in compound 1.

Instead, new signals appeared for oxygenated methine groups of a vicinal diol at $\delta_{C/H}$ 75.8/3.36 (ddd, *J* = 9.0, 4.8, and 1.8 Hz) (CH-6) and 69.4/4.38 (d, *J* = 9.6 Hz) (CH-7).

The COSY experiment of 1 supported a continuous coupling system from the protons at C-4 (δ_H = 2.67 and 2.50 ppm) to the protons at C-16 (δ_H = 2.12 and 1.92 ppm). Additionally, a vicinal COSY correlation was observed between H-18 (δ_H = 3.81 ppm) and the protons at C-19 (δ_H = 3.46 and 3.39 ppm).

Table 1: **NMR data of latrunculol A (1)[a] ($CDCl_3$).**

position	δ_C, type	δ_H (mult., *J* in Hz)	HMBC (H→C)
1	165.7, C		
2	117.1, CH	5.66 (brs)	C-1, C-3
3	158.5, C		
4	31.0, CH_2	2.67 (dt, 11.4, 4.8), 2.50 (dt, 11.4, 5.4)	C-2, C-3, C-6
5	34.1, CH_2	1.89 (dd, 15.0, 3.6), 1.72 (m)	
6	75.8, CH	3.36 (ddd, 9.0, 4.8, 1.8)	C-8
7	69.4, CH	4.38 (d, 9.6)	C-5, C-8, C-9
8	128.9, CH	5.62 (dd, 10.8, 9.6)	C-6, C-7
9	138.7, CH	5.24 (t, 10.8)	C-10, C-22
10	29.5 CH	2.57 (m)	
11	30.9, CH_2	1.75 (m), 1.15 (m)	
12	32.0, CH_2	1.46 (m)	
13	62.0, CH	4.03 (m)	C-17
14	35.4, CH_2	1.83 (m), 1.53 (ddd, 15.0, 12.0, 3.0)	
15	68.0, CH	5.37 (quin., 3.0)	
16	31.3, CH_2	2.12 (td, 15.0, 1.8), 1.92 (m)	
17	97.1, C		
18	61.4, CH	3.81 (ddd, 8.4, 6.5, 0.6)	C-17, C-20
19	28.6, CH_2	3.46 (dd, 11.4, 8.4), 3.39 (dd, 11.4, 6.5)	
20	174.9, C		
21	25.1, CH_3	1.89 (d, 1.2)	C-3
22	22.4, CH_3	0.98 (d, 6.6)	C-9, C-10
N*H*		5.79 (brs)	C-20
O*H*		3.49 (s)	

[a] Acquired at 600 MHz for ^1H and 150 MHz for ^{13}C; [b] Signals were assigned from HSQC experiment.

Table 2: NMR data of latrunculin A (2)[a] ($CDCl_3$).

position	δ_C, type[b]	δ_H (mult., *J* in Hz)	HMBC (H→C)
1	165.4, C		
2	117.2, CH	5.69 (s)	C-1, C-3
3	158.4, C		
4	32.6, CH_2	2.90 (m), 2.66 (m)	C-2, C-3, C-6
5	30.4, CH_2	2.26 (m)	
6	131.7, CH	5.73 (m)	C-8
7	126.0, CH	6.40 (dd, 15.0, 11.4)	C-5, C-8, C-9
8	127.1, CH	5.97 (t, 10.8)	C-6, C-7
9	136.5, CH	5.01 (t, 10.8)	C-10, C-22
10	29.2, CH	2.72 (m)	
11	31.0, CH_2	1.72 (m), 1.08 (m)	
12	31.7, CH_2	1.42 (m)	
13	62.2, CH	4.26 (m)	C-17
14	34.9, CH_2	1.78 (qd, 14.4, 2.4), 1.47 (m)	
15	68.1, CH	5.42 (quin-like, 3.0)	
16	31.5, CH_2	2.06 (td, 15.0, 2.4), 1.93 (m)	
17	97.2, C		
18	61.3, CH	3.85 (ddd, 9.0, 6.0, 0.6)	C-17, C-20
19	28.7, CH_2	3.48 (dd, 11.4, 9.0), 3.42 (dd, 11.4, 6.0)	
20	174.7, C		
21	24.5, CH_3	1.93 (d, 1.2)	C-3
22	21.5, CH_3	0.98 (d, 6.6)	C-9, C-10
N*H*		5.71 (brs)	C-20
O*H*		3.90 (brs)	

[a] Acquired in $CDCl_3$ at 600 MHz for ^1H and 150 MHz for ^{13}C; [b] Signals were assigned from HSQC experiment.

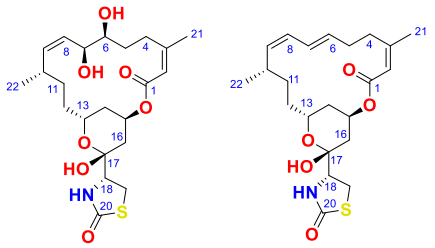

Figure 1: Chemical structures of compounds 1 and 2.

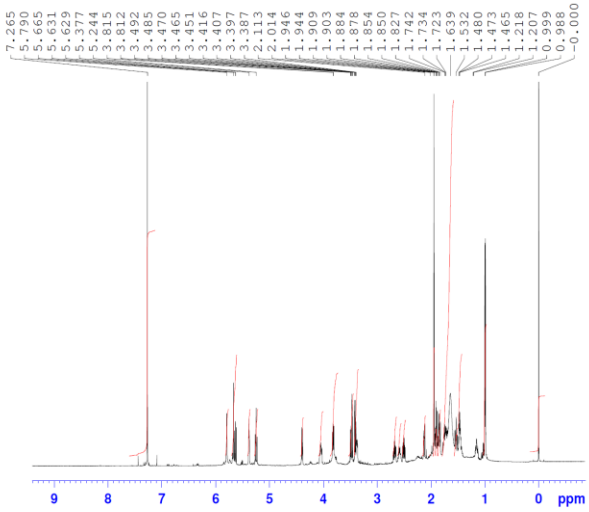

Figure 2: ^{1}H NMR spectrum of latrunculol A (1).

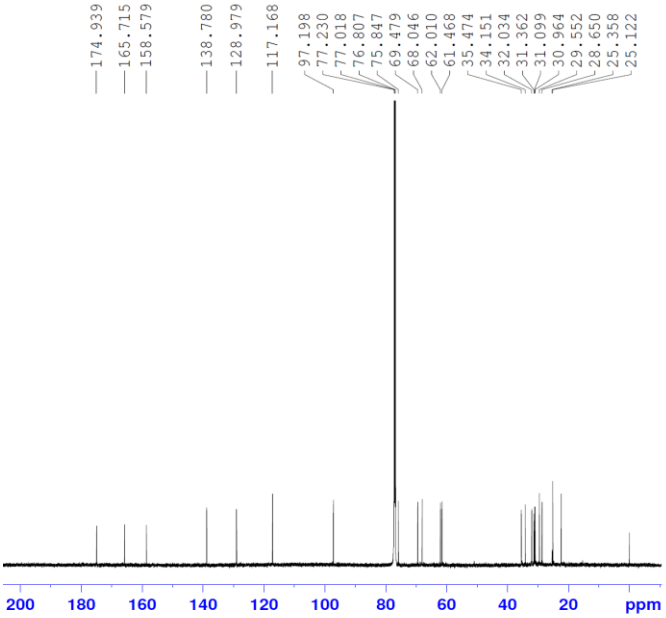

Figure 3: ^{13}C NMR spectrum of latrunculol A (1).

The position of this vicinal diol was confirmed by COSY correlations between H_2-5 and H-6, between H-6 and H_2-7, and between H-7 and H-8. The residual ^{1}H and ^{13}C signals for compound 1 were like those of latrunculin A. The assignment of the protonated carbons in 1 was achieved through the HSQC experiment.

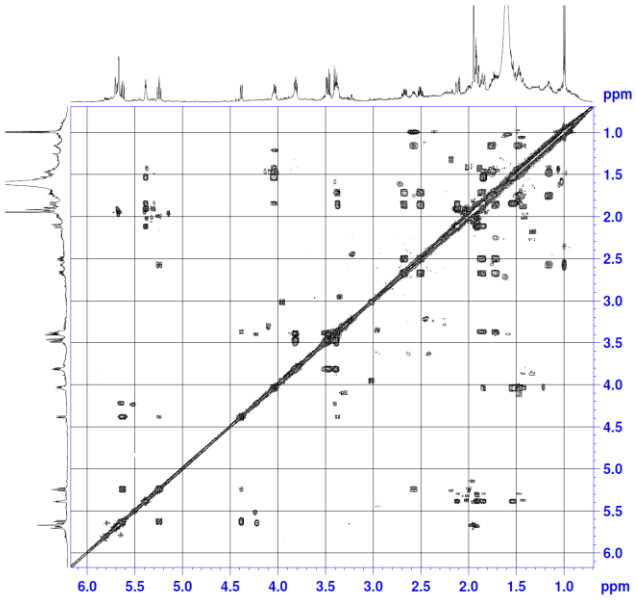

Figure 4: ^{1}H-^{1}H COSY spectrum of latrunculol A (1).

The non-protonated carbons (C-1, C-3, C-17, and C-20) were clearly assigned based on long-range correlations in the HMBC experiment. Similar configuration of the hydroxyl moieties at C-6 and C-7 were determined from the ROESY cross-peaks between H-6 and H-7 (Figures 2-7), Finally, the ^{1}H and ^{13}C NMR data of **1** were consistent with those of latrunculol A as reported in the literature (Amagata et al. 2008). Based on this evidence, compound **1** was identified as latrunculol A.

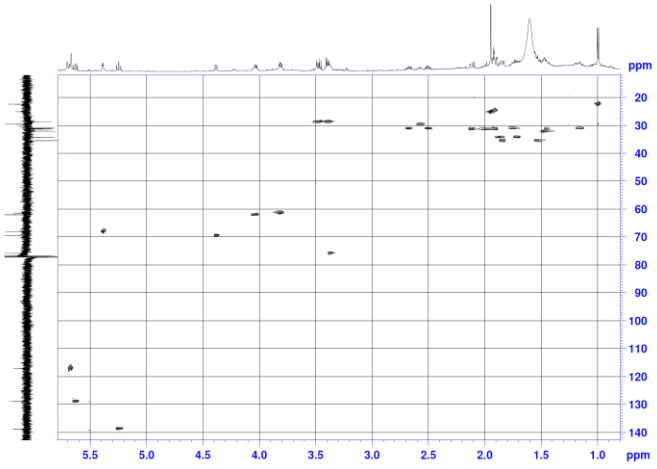

Figure 5: HSQC spectrum of latrunculol A (1).

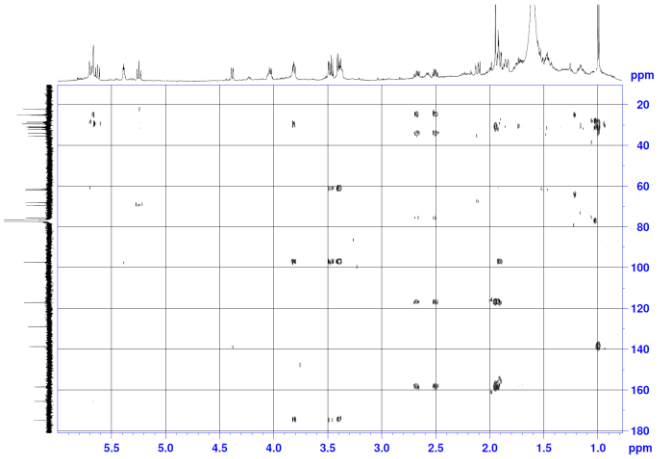

Figure 6: ^{1}H-^{13}C HMBC spectrum of latrunculol A (1).

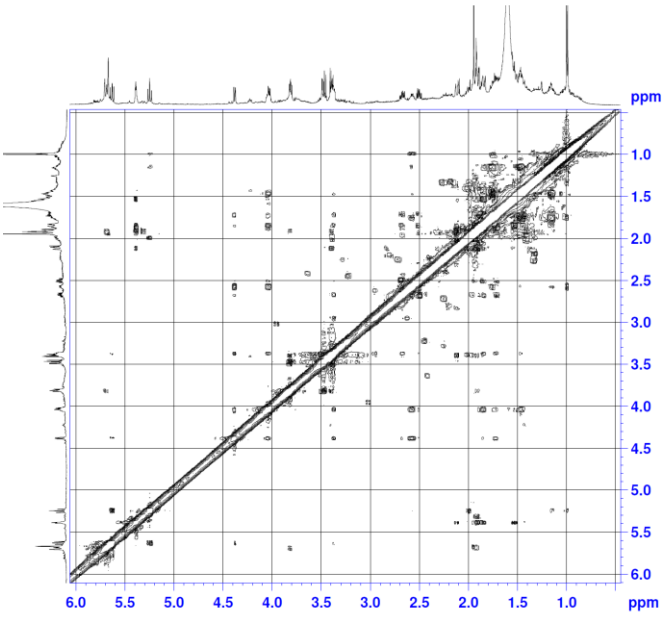

Figure 7: ^{1}H-^{1}H ROESY spectrum of latrunculol A (1).

Structural Determination of Compound 2

Compound 2 (Figure 1) was isolated as white solid, with a specific rotation of $[\alpha]_D$ = +143.1° (c 1.0, MeOH). Its molecular formula, $C_{22}H_{31}NO_5S$, was confirmed by the (+)-HRESIMS peak at *m/z* 444.1817 $[M + Na]^+$. The structure of compound 2 was determined through the analysis of its 1D and 2D NMR spectra (Figures 8-12). The NMR data of compound 2 (Table 2) are like those of latrunculin A (Amagata et al. 2008; Groweiss et al. 1983). Thus, compound 2 was identified as latrunculin A.

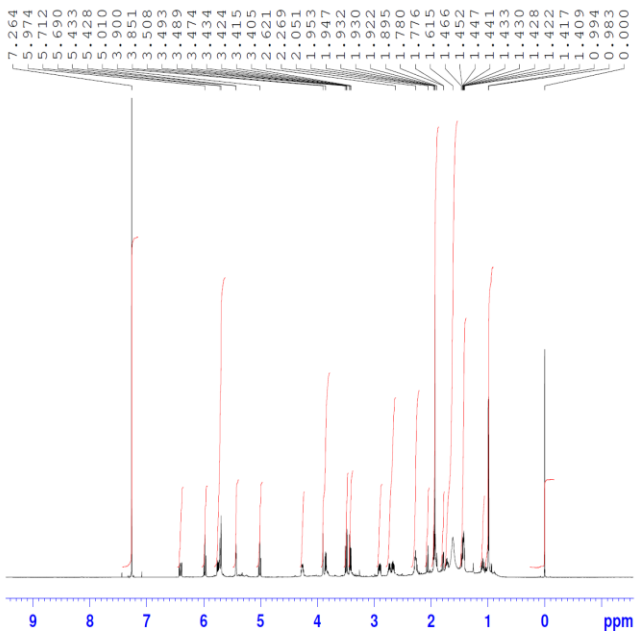

Figure 8: ^{1}H NMR spectrum of latrunculin A (2).

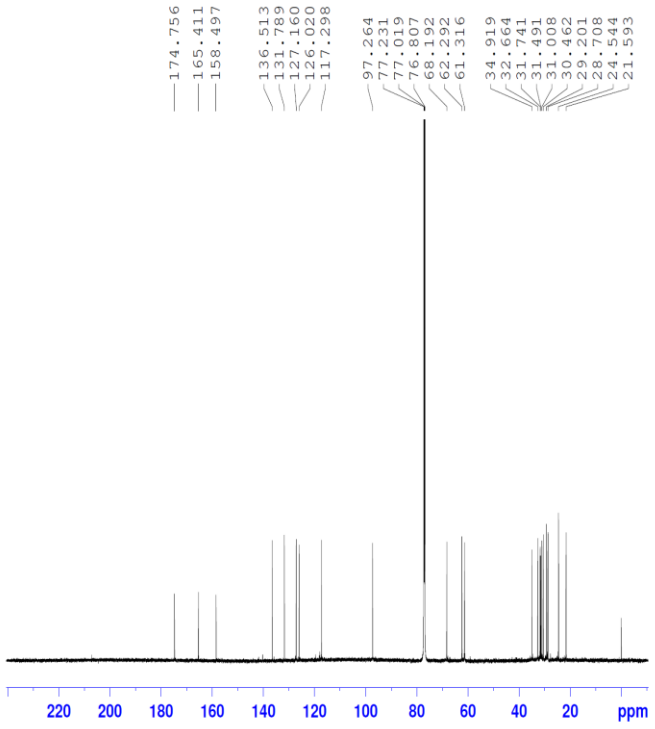

Figure 9: ^{13}C NMR spectrum of latrunculin A (2).

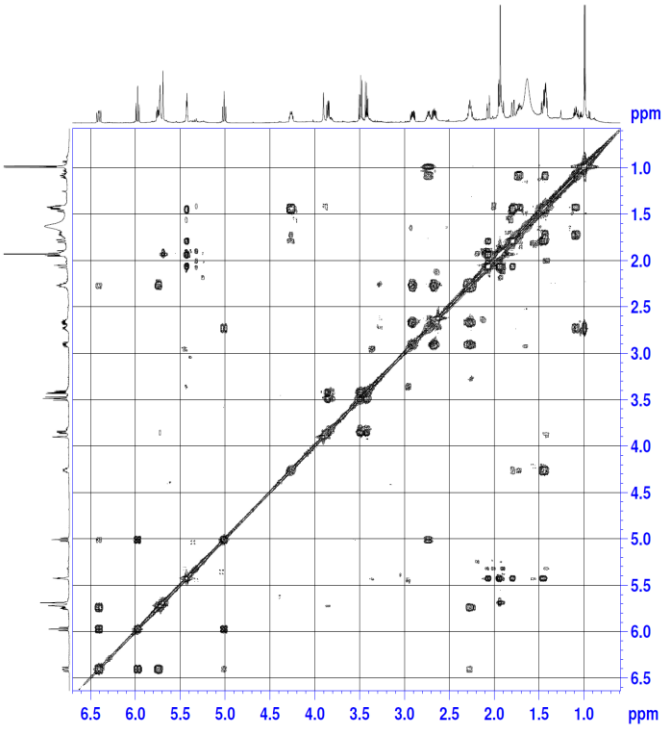

Figure 10: ^{1}H-^{1}H COSY spectrum of latrunculin A (2).

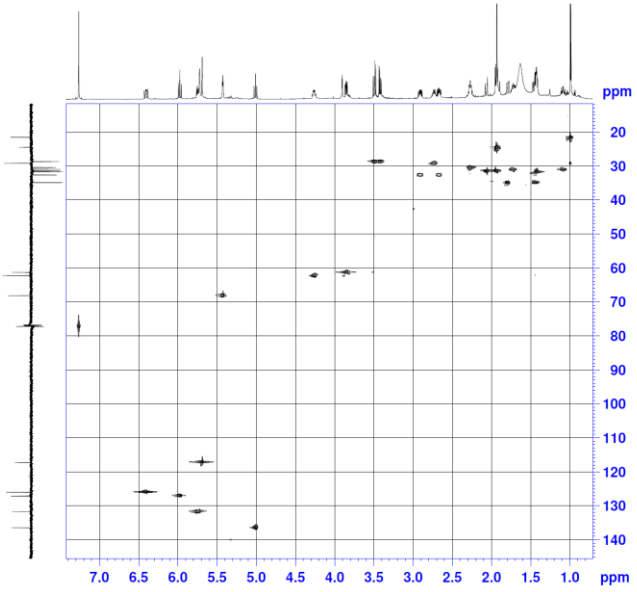

Figure 11: HSQC spectrum of latrunculin A (2).

Evaluation of the IOP-Lowering Effects of Compounsds 1 and 2

Timolol, a β-adrenergic receptor blocker approved for the treatment of glaucoma, served as a positive control. The compounds tested were latrunculol A (1) and latrunculin A (2), which were administered at the following concentrations: latrunculol A at 110, 220, and 441 µM (equivalent to 0.005%, 0.01%, and 0.02% w/v, respectively), and latrunculin A at 118, 237, and 474 µM (equivalent to 0.005%, 0.01%, and 0.02% w/v, respectively). In comparison, the positive control drug, timolol maleate, was used at its highest concentration of 1175.4 µM (equivalent to 0.5%). It is expected that higher concentrations or more frequent dosing of the tested compounds may lead to a greater reduction in intraocular pressure (IOP). In this experiment, latrunculol A caused a significant, dose-dependent decrease in intraocular pressure (IOP) in rabbit eyes one hour after administration ($p > 0.05\%$) (Figures S2 and S3).

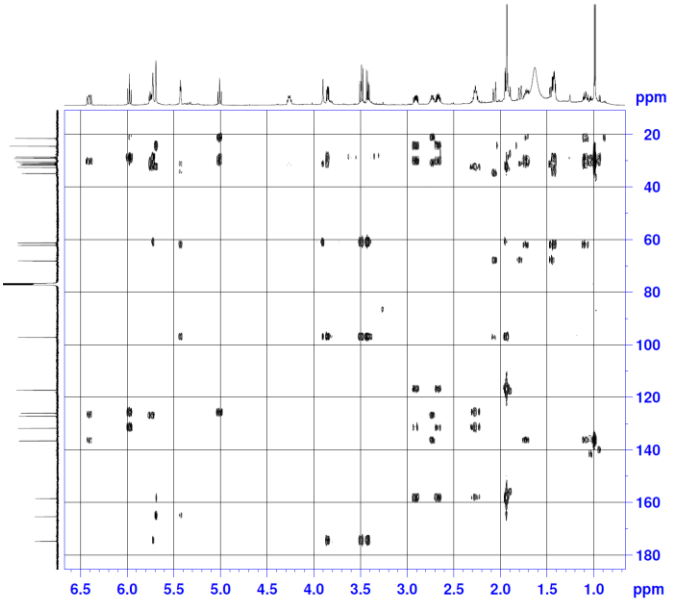

Figure 12: ^{1}H-^{13}C HMBC spectrum of latrunculin A (2).

This effect was immediate but not sustained beyond one hour, suggesting a quick onset of action. In contrast, latrunculin A significantly reduced IOP three hours after treatment ($p > 0.05\%$), suggesting a delayed onset of action. Notably, this effect was reproducible the following day. Timolol also had a noticeable effect on the second day, with a slight increase in IOP, which aligns with its enhanced performance in hypertensive eyes, as reported in previous studies (Abdulsahib and Abood, 2020; Jacob et al. 2018).

The mechanism underlying the IOP-lowering effect of latrunculins can be explained as follows: Actin filaments are present in nearly all body cells, with junctional complexes typically found in the internal wall of Schlemm's canal and the juxtacanalicular endothelial meshwork. Latrunculins act as actin-disrupting or -depolymerizing agents, which can open these junctions, leading to the separation of cells from the extracellular matrix and from each other. This disruption alters the structural integrity of the meshwork. As a result, the endothelial cells lining the internal wall of Schlemm's

canal become flattened, the trabecular meshwork (TM) relaxes, and the juxtacanalicular endothelial meshwork expands. This sequence of events causes dilation of the canal and a reduction in IOP. It is important to note, however, that this effect is reversible (Peterson et al. 1999; Rasmussen et al. 2014).

The ocular safety of these compounds was also evaluated. No abnormal findings were observed, except for mild conjunctival redness, which was primarily noted one hour after timolol administration. This redness gradually diminished after three hours. In contrast, latrunculol A and latrunculin A did not cause similar effects, suggesting that both compounds have comparable safety profiles for potential ocular use. In conclusion, this study serves as a preliminary investigation, providing a foundation for future research to further validate the antiglaucoma activity of latrunculol A. Future studies should focus on factors such as repeated dosing of ocular drops, the use of hypertensive animal models, and the inclusion of long-duration models to offer more comprehensive insights.

CONCLUSIONS

In this study, two latrunculins, latrunculol A (1) and latrunculin A (2), were purified from the CH_2Cl_2 fraction of the MeOH extract of the sponge *Negombata corticata* and their structures identified. The effect of latrunculol A on intraocular pressure (IOP) in normotensive rabbits was evaluated and compared to latrunculin A and timolol, a well-established IOP-lowering agent. The results revealed that latrunculol A (0.02% w/v) significantly reduced IOP one hour after administration on the first day, demonstrating a rapid onset of action. In comparison, latrunculin A (0.02% w/v) lowered IOP three hours post-administration, while timolol effectively reduced IOP, with the most significant effects seen at one and three hours. Importantly, latrunculol A induced substantial IOP reduction with minimal ocular side effects, indicating its potential as a promising glaucoma treatment.

Future research should aim to assess the durable efficacy and safety of latrunculol A, including trials in hypertensive animal models to better mimic glaucomatous conditions. Additionally, exploring the effects of repeated dosing and alternative administration routes could offer valuable insights for its clinical application. Further research into the cellular and molecular mechanisms of latrunculol A will be crucial to fully understand its therapeutic potential in managing elevated IOP, a key factor in glaucoma progression.

Supplementary materials

The supplementary material / supporting for this article can be found online and downloaded at: https://www.isisn.org/BR-25-1-2025/34-42-22(1)2025BR25-114-Supl-Mat.pdf

Author contributions

Conceptualization, D.T.A.Y. and L.A.S.; methodology, M.M.A., A.T.A., U.A.A., L.A.S., Y.A.A., T.A. and M.E.R.; software, Y.A.A.; validation, Y.L. and W.L.; formal analysis, D.T.A.Y and Y.A.A.; investigation, M.M.A., A.T.A., U.A.A., L.A.S., Y.A.A., T.A. and M.E.R.; resources, R.T.A.Y.; data curation, D.T.A.Y., M.M.A., Y.A.A.; writing-original draft preparation, D.T.A.Y., M.M.A. and Y.A.A.; writing-review and editing, D.T.A.Y., L.A.S. and M.E.R.; visualization, D.T.A.Y. and L.A.S.; supervision, D.T.A.Y. and L.A.S.; project administration, D.T.A.Y.; funding acquisition, D.T.A.Y. All authors have read and agreed to the published version of the manuscript.

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Institutional Review Board Statement

The study was approved by the Bioethical Committee of the Institutional Animal Care and Use Committee and the CEGMR Bioethics Committee at King Fahd Medical Research Center (Permit # 26-CEGMR-Bioeth-2021).

Informed Consent Statement

Not applicable.

Data Availability Statement

All of the data is included in the article/Supplementary Material.

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Conflict of interest

The authors declared that present study was performed in absence of any conflict of interest.

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