

Bioactive Flavonol C-Glycoside from Sida cordifolia L. and its Molecular Docking Study

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Phytochemical studies of the aerial parts of *Sida cordifolia* L. has led to the isolation of a new flavonol C-glycoside, $3'-(3'',7''-dimethyl-2'',6''-octadiene)-8-C-\beta-D-glucosyl-kaempferol-3-O-\beta-D-galactoside (1) together with two known flavonoids, luteolin and quercetin. The structures of all the compounds were established on the basis of chemical and spectroscopic studies. Compound 1 was assessed to check the analgesic and anti-inflammatory activities and showed significant activities. Molecular docking study was conducted for compound 1 against 4O1Z protein receptor, which strongly support the$ *in vitro*biological findings.

Keywords: Sida cordifolia, Malvaceae, Flavonol C-glycoside, Bioactivity, Molecular docking.

INTRODUCTION

Sida cordifolia L. (Malvaceae) is one of the indigenous herbal drugs and distributed throughout Bangladesh and India. It is widely used to treatment of different ailments and improving health conditions as an Ayurvedic medicine [1]. In Indian subcontinent, various fragments of these plants are used for the treatment of asthma, chronic dysentery, gonorrhea, skin disease, nasal congession, urinary diseases, obesity, cardiac diseases, bleeding hemorrhoids and regeneration of liver growth [2]. The crude extracts of different parts of *Sida cordifolia* were reported to possess analgesic, anti-inflammatory, antioxidant, acute toxicity, hypoglycemic, antispasmodic, hepatoprotective and antibacterial activities [3-9]. *Sida cordifolia* extract is also used as green corrosion inhibitor for mild steel in 0.5 M H₂SO₄ [10].

The different classes of compounds such as glycosides, alkaloids, steroids, flavonoids and amino acids were reported from genus *Sida* [11-17] and ephedrine, quinazoline alkaloids, vasicine, vasicinol, vasicinone and *N*-methyl tryptophan were also isolated from the species *Sida cordifolia* [13,18-21]. The isolation of various kinds of flavonoids, alkaloids and glycosides from *Sida cordifolia* were also reported in the literature [22-24]. As a part of our ongoing research, we have reported herein, a new flavonol C-glycoside **1** together with two known

flavonoids luteolin and quercetin from 80% ethanol extract of the aerial parts followed by partitioning with *n*-butanol. In this study, the isolation and structure elucidation of a new flavonol C-glycoside **1** and its analgesic and anti-inflammatory activities are reported. Molecular docking study was also performed to explore the possible binding mode of the flavonol C-glycoside **1**.

EXPERIMENTAL

The IR spectra were recorded on Shimadzu IR spectrophotometer (KBr pellets). ¹H NMR, ¹³C NMR, DEPT-135, COSY and HMBC spectra were recorded on a Bruker BPX-200 spectrometer. CDCl₃ and DMSO- d_6 were used as NMR solvent. The FAB mass spectra were recorded by Varian MAT CH₅ instrument. Melting points were recorded by open capillary tube method in electrothermal melting point apparatus (Model No. MPH-H2 90-264). Solvents and chemicals used in the extractions and experiments were collected from E. Merck (Germany) and BDH (England). Thin-layer chromatography (TLC) was carried out on Merck silica gel 60F₂₅₄ sheet (Germany) and column chromatography was carried out on Merck silica gel (100-200 mesh, Germany).

Plant material: The selected plant *Sida cordifolia* was collected from the hilly region of Chittagong, the south-eastern

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region of Bangladesh and their identification was done by taxonomists Mrs. Bushra Begum. The voucher specimen (Herbarium accession no. 31238) has been placed in Bangladesh National Herbarium (BNH) Dhaka.

Extraction and isolation: Air-dried plant material (3 Kg) were powdered and extracted with 80% EtOH (3×72 h) at room temperature. The filtrate was concentrated to 1 L under reduced pressure at 40 °C, which was then partitioned sequentially with *n*-hexane and *n*-BuOH. Removal of solvent *n*-BuOH extract yielded a yellowish mass (5 g). The *n*-BuOH extract (3 g) was eluted with CHCl₃:EtOAc:MeOH (1:1:1) by column chromatography using silica gel as adsorbent. The progress of elution was monitored by TLC and separated into three fractions as F1 (1-15), F2 (16-26) and F3 (27-48). Fractions F1 and F2 gave luteolin (155 mg) and quercetin (122 mg), respectively on crystallization. Fraction F3 yielded a pure compound **1** (250 mg) on repetitive crystallization from EtOAc: EtOH (2:1).

Compound 1: Brown amorphous solid, m.p.: 195-196 °C. UV λ_{max} (MeOH) nm: 269, 307, 331; +AlCl₃: 277, 306, 331; + AlCl₃/HCl: 278, 308, 332; NaOMe: 271, 322, 334, 348, 366, 378; NaOAc: 282, 311, 331. IR (KBr, v_{max}, cm⁻¹): 3398 (OH), 1654 (α,β-unsaturated ketone), 1604, 1262, 1077. ¹H NMR $(DMSO-d_6) \delta ppm: 6.75 (1H, s, H-6), 7.26 (1H, d, J = 1.3, H-2'),$ 6.85 (1H, d, J = 6.3, H-5'), 7.46 (1H, dd, J = 1.3, 6.2, H-6'),2.78 (2H, d, H-1", 5.34 (1H, t, H-2", 2.56 (2H, t, H-4"), 2.65 (2H, m, H-5"), 5.46 (1H, t, H-6"), 1.27 (3 × 3H, br s, H-8", 9", 10"), 4.28 (1H, d, H-1""), 3.54 (1H, m, H-2""), 3.84 (1H, m, H-3""), 3.58 (1H, m, H-4""), 3.75 (1H, m, H-5""), 3.59 (2H, m, H-6""), 5.49 (1H, d, H-1""), 3.58(1H, m, H-2""), 3.58 (1H, m, H-3""), 3.69 (1H, m, H-4""), 3.49 (1H, m, H-5""), 3.77 (2H, m, H-6""). ¹³C NMR (DMSO-d₆) δ ppm: 158.6 (C-2), 135.2 (C-3), 178.7 (C-4), 161.1 (C-5), 99.8 (C-6), 162.4 (C-7), 105.7 (C-8), 158.6 (C-9), 107.9 (C-10), 123.1 (C-1'), 133.1 (C-2'), 120.3 (C-3'), 160.6 (C-4'), 116.3 (C-5'), 132.5 (C-6'), 50.4 (C-1"), 121.5 (C-2"), 134.9 (C-3"), 35.2 (C-4"), 34.4 (C-5"), 122.0 (C-6"), 136.3 (C-7"), 30.8 (C-8"), 31.1 (C-9"), 31.1 (C-10"), 71.7 (C-1""), 72.4 (C-2""), 78.1 (C-3""), 71.5 (C-4""), 80.6 (C-5""), 63.5 (C-6""), 105.3 (C-1"""), 73.4 (C-2"""), 76.4 (C-3""), 70.4 (C-4""), 79.2 (C-5""), 63.6 (C-6""). FAB mass (positive ion mode): m/z (%) = 747.5 (5.2) [M+H]⁺(C₃₇H₄₆O₁₆), 585.3 (30.3) [M-162+H]⁺, 465.2 (12.5) [M-162-120+H]⁺, 401.2 (90.1), 391.2 (48.2), 315.2 (5.5), 273.1 (6.3), 257.4 (100), 239.1 (10.2), 193.5 (22.4), 185.1 (62.4), 163.2 (26.1), 95.2 (40.2), *etc.* HR-FABMS m/z [M+H]⁺ 747.1626 for C₃₇H₄₆O₁₆.

Pharmacology: Swiss albino mice (26-30 g) and Long Evans rats (145-165 g) of either sex maintained standard conditions (temperature of 20 ± 1 °C, relative humidity 50 ± 5 % and 12 h dark-light cycle for at least one week) and fed standard food and water *ad libidum*. Before starting the experiment, the animals were weighed by keeping them overnight fasting and the experiment was performed according to the International guidelines [25,26]. Analgesic activity of the plant extract was evaluated by acetic acid induced writhing inhibition method using aminopyrine as a standard analgesic agent. Carrageenan induced rat paw edema model [27] was employed to determine the anti-inflammatory activity with standard phenylbutazone.

RESULTS AND DISCUSSION

The dried powder (3 kg) of the aerial parts of plant was extracted with 80% EtOH. The EtOH extract was partitioned with *n*-hexane and *n*-butanol successively. *n*-Butanol extract (3 g) was chromatographed on column chromatography (silica gel, CHCl₃:EtOAc:MeOH (1:1:1) to produce a new compound 1 along with two known compounds, luteolin and quercetin. Compound 1 was obtained as a brown amorphous solid. It gave positive colour reactions for flavanol [28] and also gave positive test for sugar [29]. The ¹³C NMR spectrum of **1** showed the presence of 37 carbon signals in the molecule. HR-FABMS of 1 showed a protonated molecular ion peak $[M+H]^+$ at m/z747.1626, which established its molecular formula as $C_{37}H_{46}O_{16}$. The UV spectra of **1** in methanol (λ_{max} 269, 307, 331 nm) and the position of the peak shifted due to the addition of shift reagents, which confirmed the existence of free hydroxyl groups at C-5 and C-7 [30-32]. The IR spectrum of 1 exposed characteristic absorption bands at 3398 cm⁻¹ for O-H stretching and 1654 cm⁻¹ for α , β -unsaturated ketone. Proton absorption pattern of **1** in ¹H NMR spectrum indicating, ring A is substituted at 5, 7 and 8 positions [30], one proton attached to carbon C6 appeared as singlet at δ 6.75 ppm [30]. In ring B, three one-proton signals at δ 7.26 ppm (d, J = 1.2, H-2'), 6.85 (d, J= 6.2, H-5') and 7.46 (dd, J = 1.2, 6.2, H-6') confirming meta and ortho coupling of protons H-2' and H-5' with H-6', respectively, which is the characteristic of 3',4'-disubstituted flavonoids [30]. Two olefinic proton absorptions at δ 5.34t and 5.46t along with nine methyl proton $(3 \times CH_3)$ absorptions as a broad singlet at δ 1.27 ppm in the ¹H NMR spectrum suggested that 1 contains aside chain equivalent to two isoprene units. HMBC correlations indicated the site of the linkage of the side chain at C'-3 shown in Fig. 1. Compound 1 exposed two anomeric protons at δ 4.28 and 5.49 ppm signifying the existence of two sugar moieties. C-Glycosidic linkage is at C-8 supported by the HMBC correlation peaks detected between the anomeric proton H-1"" (\$ 4.28) and C-7 (\$162.4), C-8 (\$ 105.7) and C-9 (δ 158.6) of the aglycon. The O-Glycosidic linkage is at C-3 also supported by the HMBC correlation peaks in Fig. 1. Compounds 1 showed four main product ions at m/z 163.2,



Fig. 1. Important COSY and HMBC correlations of compound 1

465.2, 315.2 and 273.1, which is the characteristic cleavage pattern of flavonoid moiety [31-33]. Compound **1** is thus considered as $3'-(3'',7''-dimethyl-2'',6''-octadiene)-8-C-\beta-D-glucosyl-kaempferol 3-O-\beta-D-galactoside. Additionally, two known flavonoids namely luteolin and quercetin were isolated from this plant and their structures were confirmed by comparing with previous spectral data [34,35].$

Biological activities: The analgesic activity of compound **1** exhibited a remarkable reduction in the number of writhing with 39.48% (p < 0.05) and 51.28% (p < 0.01), respectively for doses of 25 and 50 mg/kg body weight (Table-1) and compared to standard drug aminopyrine (67.69% inhibition) at the dose of 30 mg/kg body weight. In carrageenan induced rat paw edema test for acute inflammation, compound **1** showed significant inhibition at 15.29% (p < 0.05) and 26.18% (p < 0.01) for doses of 25 and 50 mg/kg body weight, respectively (Table-2) as compared to standard drug phenylbutazone (32.98% inhibition) given at the dose of 80 mg/kg body weight at 3rd hour of carrageenan administration.

TABLE-1 ANALGESIC ACTIVITY OF COMPOUND 1			
Treatment	Dose (mg/kg)	Writhing	Inhibition (%)
Control (vehicle, 10 mL/kg)	-	30.8 ± 2.28	-
Commed 1	25	$19.66 \pm 1.89^*$	39.48
Compu. I	50	$15.83 \pm 2.08^{**}$	51.28
Aminopyrine	30	$10.50 \pm 0.76^{**}$	67.69
Note: Values are mean \pm SEM (n = 6); ^{**} $p < 0.01$, [*] $p < 0.05$ compared to control.			

Molecular docking study: Molecular docking study of isolated compound **1** (Fig. 2) was executed against the antiinflammatory target, cyclooxygenase receptor (COX-1) [PDB ID: 401Z] [36]. The crystal structure of the targeted receptor 401Z was obtained from protein data bank (www.rcsb.org).



Fig. 2. Optimized structure of compound 1

The PDB file of the target receptor was made after removing all water molecules, heteroatoms and inhibitors through PyMol (version 2.4). Compound **1** was optimized by DFT method on basis of B3LYP/6-31+G (d,p) level using Gaussian 09 software package [37] and optimized structure is presented in Fig. 2. The binding energy score was expressed in terms of negative energy equal to -7.6 Kcal. The poses with the highest negative binding energy scores were chosen for final presentation that imply the best affinities of the compounds towards the target receptors. The pictorial representation of docked compound displayed in Fig. 3 and their preferred interactions shown in Table-3. Higher bioactivity of compound is dependent on number of H-bond interaction with amino acid residue. The diagrammatic view of ligand interaction revealed the interaction with amino acid residues by H-bonding, hydrophobic

TABLE-2 ANTI-INFLAMMATORY ACTIVITY OF COMPOUND 1						
Group	Dose	Carrageenan induced rat paw edema Mean ± SEM (% inhibition of paw volume)				
- (mg/kg	(mg/kg)	1 h	2 h	3 h	4 h	24 h
Control	-	103.7 ± 2.33	108.5 ± 3.83	95.5 ± 4.62	92.8 ± 2.46	70.5 ± 3.44
Compd. 1	25	$101.16 \pm 3.5 (5.45)$	$100.33 \pm 3.02 (10.41)$	$82.16 \pm 4.71^{*} (15.29)$	8266 ± 4.95 (11.11)	67.33 ± 5.28 (2.42)
Compd. 1	50	96.80 ± 4.21 (9.53)	$92.20 \pm 4.88^{**} (17.67)$	$71.60 \pm 4.06^{**} (26.18)$	$71.00 \pm 3.22^{**}$ (24.26)	$66.16 \pm 2.12 (4.11)$
PBZ	80	$72.50 \pm 1.32^{**}(32.32)$	$65.00 \pm 2.84^{**}(36.60)$	$71.00 \pm 4.04^{**} (32.98)$	$66.00 \pm 3.80^{**} (29.75)$	$60.66 \pm 2.09^{*} (12.08)$
Note: Values are mean + SEM (n = 6): Paw volume is expressed in change of height (mm) of Hg bath (in parentheses % inhibition of edema) $**p < \infty$						

Note: Values are mean \pm SEM (n = 6); Paw volume is expressed in change of height (mm) of Hg bath (in parentheses, % inhibition of edema). "p < 0.01, "p < 0.05 compared to control.

TABLE-3 DOCKING RESULTS OF MOST ACTIVE ANALGESIC AND ANTI-INFLAMMATORY COMPOUND 1

Binding affinity (Kcal/mol)	Hydrogen bond AA…compd. (distance: Å)	Hydrophobic interaction (distance: Å)	Electrostatic interaction (distance: Å)
-7.6	Gly 38 (3.02) N-H…O-H	Ala 43 (3.78)	Lys 84 (2.83)
	Gly 38 (1.80) N-HO-H	His 47(4.36)	
	Asp 195 (2.66) N-H-O-C	His 50 (4.48)	
	Asp 195 (2.51) N-H-O-C	Trp 241 (5.12)	
	Arg 88 (2.59) N-H…O…C		
	Lys 84 (2.83) N-H-OC		



Fig. 3. Interaction (2D and 3D) of compound 1 with cyclooxygenase (COX-1)

and electrostatic interactions with the active site of cyclooxygenase receptor (COX-1). It exhibited H-bonding with Gly 38 (distance: 3.02 Å), Gly 38 (distance: 1.80 Å), Asp 195 (distance: 2.66 Å), Asp 195 (distance: 2.51Å), Arg 88 (distance: 2.59 Å), Lys 84 (distance: 2.83 Å), respectively. In addition to H-bonding compound showed hydrophobic interactions with Ala 43 (distance: 3.78 Å), His 47 (distance: 4.36 Å), His 50 (distance: 4.48 Å) and Trp 241 (distance: 5.12 Å) and electrostatic interaction with Lys 84 (distance: 2.83 Å), respectively. The docking analysis revealed a good correlation with the anti-inflammatory tests results and the active compound may be used as a lead for drug designing.

Conclusion

The principal objective of this project was to isolate steroids and flavonoids along with other secondary metabolites from the aerial parts of *Sida cordifolia* L as well as to determine the molecular architecture and their biological activities. A bioactive flavonol C-glycoside (1) together with two known flavonoids were isolated successfully. Flavonol C-glycoside is known to possess significant analgesic and anti-inflammatory properties. Molecular docking study of compound 1 also exhibited good docking score with its better potency of anti-inflammatory activities. The active compound 1 may act as useful leads for future development of analgesic and anti-inflammatory agent.

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CONFLICT OF INTEREST

The authors declare that there is no conflict of interests regarding the publication of this article.

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