

Bioactive Polyphenolic and Terpenoid Compounds from Stem Bark and Flowers of *Terminalia brownii*



Sebastian M. Ikiiki^{1,*} , Josiah O. Odalo¹, Aloice O. Ogwen¹ and Matthias Heydenreich²

¹Department of Pure and Applied Sciences, Technical University of Mombasa, P.O. Box 90420 – 80100, Mombasa, Kenya

²Institut für Chemie, Universität Potsdam, Potsdam, Germany

Abstract:

Introduction: *Terminalia brownii* Fresen (Combretaceae) extensively used in Eastern, Southern, and Western Africa herbal remedies in treatment of variety of diseases including liver cirrhosis. Bioassay – guided fractionation was used to isolate the compounds responsible for these actions.

Aim of the Study: The study sought to extract, characterize and determine the antimicrobial activities of the components of the commonly used stem bark and hitherto uninvestigated regeneratable flowers of *T. brownii*.

Materials and Methods: Column chromatography was used to fractionate and isolate the compounds followed by thin layer chromatography. The isolates were structurally elucidated using FTIR, ¹H NMR, ¹³C NMR and HRESI-MS spectral data. The isolated compounds' antimicrobial activities were evaluated against *Candida albicans*, *Staphylococcus aureus*, *Pseudomonas aeruginosa* and *Escherichia coli*.

Results: Bioassay – guided fractionation of methanol and 50% dichloromethane: methanol extracts of *Terminalia brownii* stem bark and flowers yielded seven known metabolites; termiglaucoside (1), arjunglucoside-I (2), sericoside (3), 23-galloyl arjungenin (4), 28-O-β-D-glucopyranosyl-2,3,6-trihydroxy-23-galloylolean-12-dien-28-oate (5), 3,3',4',5'-tetrahydroxy-7-methoxyflavone (9), 3,3',4',5,7-pentahydroxyflavone (10) and three new metabolites: 1,4,7-tri-O-galloyl hept-6-deoxyheptose (6), 1,2,4-tri-O-galloyl-8,9-dideoxynonose (7), Rhamnetin-3-O-(2,3,6-trigalloyl)-β-D-glucopyranoside (8). Among these molecules, compound (6) was extremely potent toward *E. coli* (16.5±0.7 mm) while (1) showed substantial inhibitory effects on *Candida albicans* (16.0±5.7 mm). Compounds 6, 7, 8, 9, and 10 were extracted and identified for the first time from 50% dichloromethane/methanol flower extract. The extract yielded three novel bioactive compounds (6, 7 and 8) that shown substantial activity on *P. aeruginosa*, *E. coli*, *C. albicans*, *S. aureus*.

Conclusion: For the first time, the results of this investigation demonstrate that flower extract possess strong antibacterial and antifungal qualities, akin to those of stem bark extract. As a result, more environmentally friendly flower extracts should be considered for treatment of bacterial and fungal infection.

Keywords: Regeneratable, *Terminalia brownii*, Antimicrobial activity, Thin layer chromatography, Bioassay, Herbal remedies.

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*Address correspondence to this author at the Department of Pure and Applied Sciences, Technical University of Mombasa, P.O. Box 90420 – 80100, Mombasa, Kenya; E-mail: ikiiki@sebastian@tum.ac.ke

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1. INTRODUCTION

The management of prevalent illnesses such as flu, fatal acute respiratory syndrome and diarrhea remains jeopardized due to the advent of multidrug resistance pathogens [1]. It's estimated that infectious diseases account for almost half of all deaths in tropical countries [2]. Plants constitute a storehouse of naturally occurring metabolites with medicinal traits and they have been extensively utilized in treating an array of maladies around the globe since time immemorial [3, 4] hence they are regarded as goldmine for development of potent pharmaceuticals [5]. Plant-based drugs are believed to be secure and cost-effective when juxtaposed with artificial drugs/conventional medicine and thus, their demand is rapidly increasing. Even though multiple studies have certified the use of plants for medical purposes through exploring secondary metabolites found in them, barely 15% of available medicinal plants have undergone scientific investigation to ascertain their phytochemical makeup and potential for medicinal purposes [6-8].

The genus *Terminalia* (Combretaceae) has a diverse range of plants prevalent in tropical and subtropical climates across the globe, encompassing Africa, Asia and Australia [9]. The trees are primarily employed in ancient systems of medicine across different cultures providing health benefits and treatment of various ailments such as geriatric, wound healing, flu, reducing oxidative stress and inflammation in the body, improve digestion, improve memory, relieve constipation and promote bowel movements, regulate blood pressure, managing blood sugar levels, management of dental caries and gum diseases [10, 11]. The prominent secondary metabolites that have been confirmed from this genus are triterpenoids, tannins, glycosidic derivatives and flavonoids. A few are reported to embody diverse biological traits notably antiretroviral, antibacterial, antifungal, antimalarial and antioxidant effects [12]. *T.brownii* has been used to manage a wide range of ailments notably flu, geriatric and back pain [13]. Concoctions of roots are utilized in management of back pain while chewing of stem bark relieves cough and arthritis [14]. Notwithstanding the reported ethnopharmacological usage of various *Terminalia* species, very few research have been carried out to comprehensively investigate the medicinal potential of different parts of *T.brownii*. This study aimed at isolation and structural elucidation of isolates from *T.brownii* stem bark and flowers. The obtained isolates were also tested for antibacterial activity against bacterial pathogens.

2. METHODOLOGY

2.1. Plant Materials, Extraction and Isolation

Stem bark and flowers of *T. brownii* were collected in April, 2021 in Mwingi; Kitui County, Kenya (1°02'18.7"S 37°55'01.9"E) and identified at the Herbarium of South Eastern Kenya University (voucher number SKU.JULY/2023/01). The plant name was checked with the plant list database (<http://www.theplantlist.org>) to confirm plant

taxonomy. The air-dried plant materials were powdered and sequentially extracted using *n*-hexane, dichloromethane, 50% dichloromethane/methanol and methanol through maceration [15].

50% dichloromethane/methanol and methanol extracts of *T. brownii*'s stem bark and flowers which exhibited strong antimicrobial activity [16], were separately subjected to column chromatography on a silica gel and eluted with gradient of ethyl acetate/*n*-hexane (40:60, 50:50, 60:40, 70:30, 80:20, 90:10, 100:0, v/v) and methanol/ethyl acetate (5:95, 10:90, 15:85, 20:80, v/v). The fractions were purified by preparative thin layer chromatography and pure isolates characterized using ¹H NMR, ¹³C NMR, IR, and HRESI-MS.

3. RESULTS AND DISCUSSION

3.1. Isolated Compounds

Bioassay-guided study of 50% dichloromethane/methanol and methanol fractions led to separation and detection of seven known metabolites and three new compounds. The isolates were assessed using ¹H NMR, ¹³C NMR, IR, HRESI-MS and results compared with previously reported data for the seven known compounds, termiglaucoscin, 69 mg (1) [17], arjunglucoside - I, 130 mg (2) [18], sericoside, 23 mg (3) [19], 23-galloyl arjungenin, 95 mg (4) [17], 28-O-β-D-glucopyranosyl-2,3,6-trihydroxy-23-galloylolean-12-dien-28-oate, 48 mg (5) [20], 3,3',4',5-tetrahydroxy-7-methoxy flavone, 61 mg (9) [21] and 3,3',4',5,7-penta hydroxy flavone, 98 mg (10) [22]. The three newly isolated compounds were identified as 1,4, 7-tri-O-galloyl-6-deoxyheptose, 11mg (6) [23] 1,2,4-tri-O-galloyl-8,9 dideoxynonose, 10 mg (7) [24] and rhamnetin-3-O-2,3,6-tri-galloyl-β-D-glucopyranoside, 40 mg (8) [25]. Fig. (1) illustrates the molecular structures of the isolates.

Compounds 1 - 3 and 4 -5 were isolated from methanol and 50% dichloromethane/methanol extract of *T.brownii* stem bark respectively while compound 6 - 10 were obtained from 50% dichloromethane:methanol extract of *T.brownii* flower. Compound 1, 4,5,6,7 and 8 were eluted by 15% methanol/ethyl acetate while compound 2, 3, 9 and 10 were eluted by 20% methanol/ethyl acetate solvent system.

Compound 6 identified as 1,4, 7-tri-O-galloyl-6-deoxyheptose was isolated as light brown amorphous substance (11 mg) with melting point range of 176 - 178 °C and molecular formula C₂₈H₂₆O₁₈ as determined by HRESIMS (m/z 650.1106). The infrared Absorption at 3295, 1708 and 1611 cm⁻¹ revealed existence of hydroxyl, ester carbonyl and C=C functional group respectively in the molecule.

Compound 6 was generated based on spectral data evaluation [23, 26]. C - 6 substitution evidenced by lack of hydroxyl proton at C-6, ¹H NMR spectrum (Fig. 2) which is typically diagnostic of hydroxyl group on C - 6 in heptose [27, 28]. The ¹H NMR signal at C - 1, C - 4 and C - 7 of heptose moiety were significantly downfield compared to

those of 6-deoxyheptose [23]. ^{13}C NMR spectrum (Table 1) exhibited seven aliphatic carbon indicating presence of 6-deoxyheptose and 15 sp^2 carbon signals corresponding to

three galloyl groups. COSY and HMBC correlations (Fig. 3) revealed the atomic connectivity within the 6-deoxyheptose framework and confirmed the substitution pattern, supporting the identification of Compound 6.

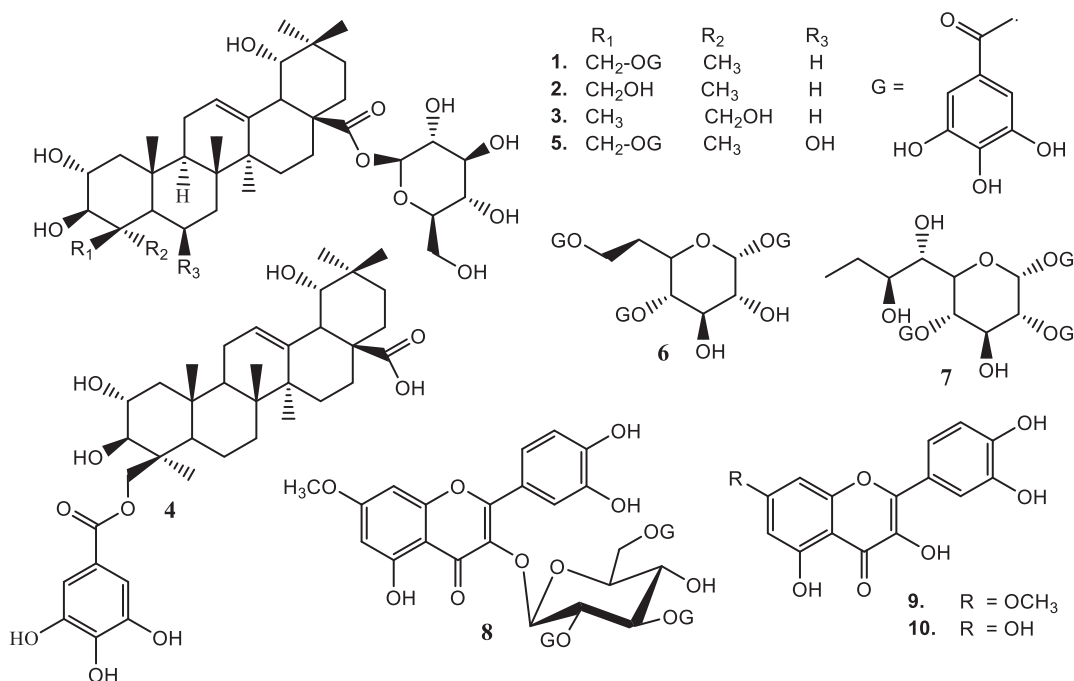


Fig. (1). Molecular structures of compounds 1-10.

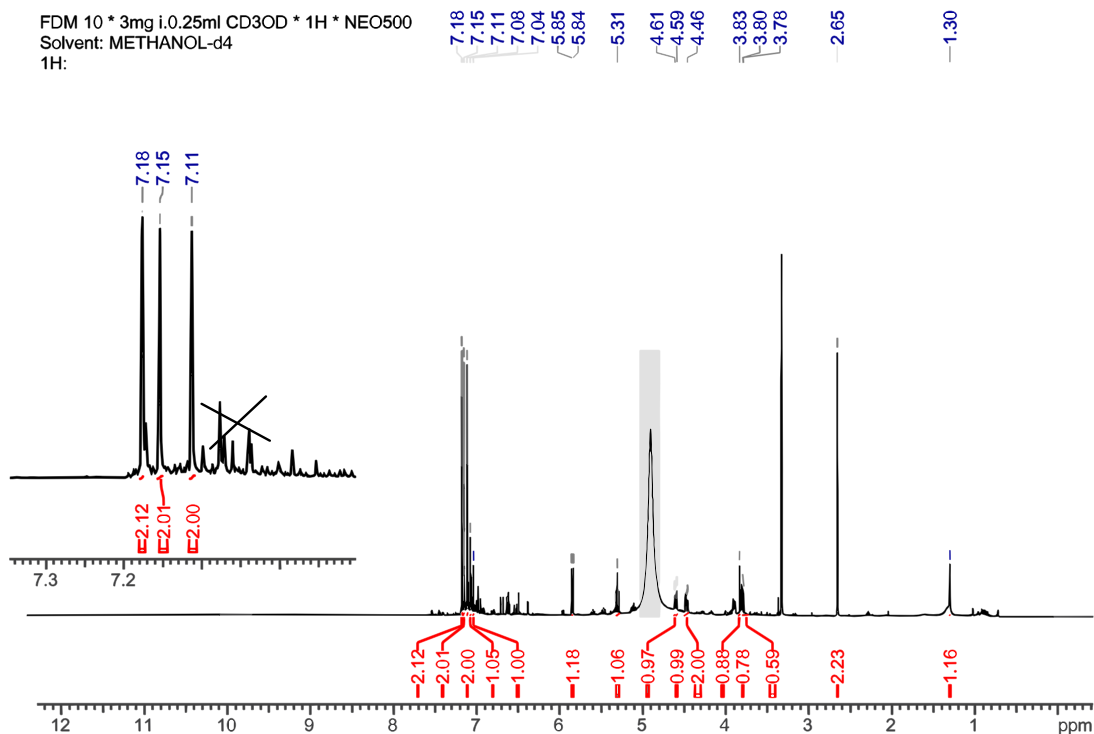


Fig. (2). ^1H NMR spectrum of structure 6 (MeOH d_4 , 500 MHz).

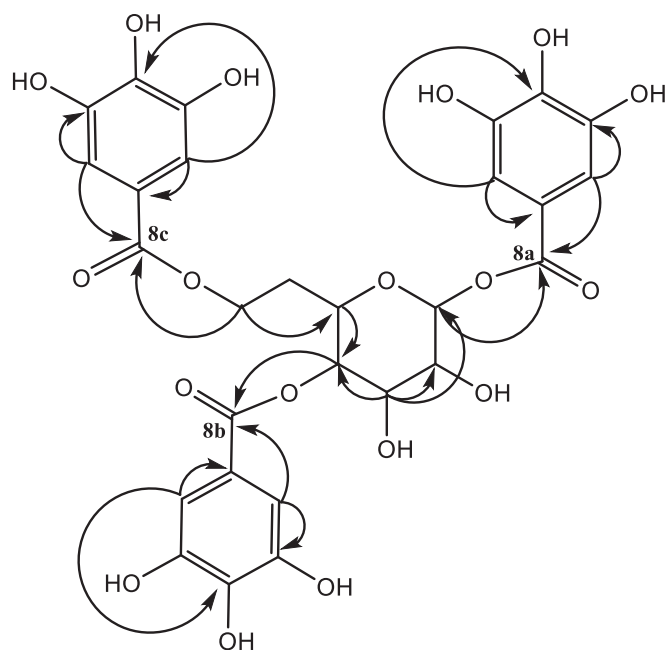


Fig. (3). Key H/C HMBC correlations of compound 6.

Compound 7 for 1,2,4-tri-O-galloyl-8,9 dideoxynonose was retrieved as brown powder (10 mg) with melting point range of 186 - 188 °C and molecular formula $C_{30}H_{30}O_{18}$ as determined by HRESIMS analysis (m/z 678.1536). The identification of compound 7 was based on spectral data analysis [24, 29]. The 1H NMR spectrum (Fig. 4) three aromatic proton signifying existence of three galloyl units. In the sugar regions, three protons were observed

significantly downfield compared to those of nonose moiety implying the attachment of galloyl entities to their respective carbons [30]. ^{13}C NMR spectrum (Table 1) revealed eight aliphatic carbons associated with 8,9 dideoxynonose moiety and 15 sp^2 carbon representing the three galloyl groups. HMBC correlations (Fig. 5) showed the inter - atomic interaction of 8,9 dideoxynonose and galloyl skeletons and the substitution pattern of the 8,9 dideoxynonose system, thus confirming compound 7.

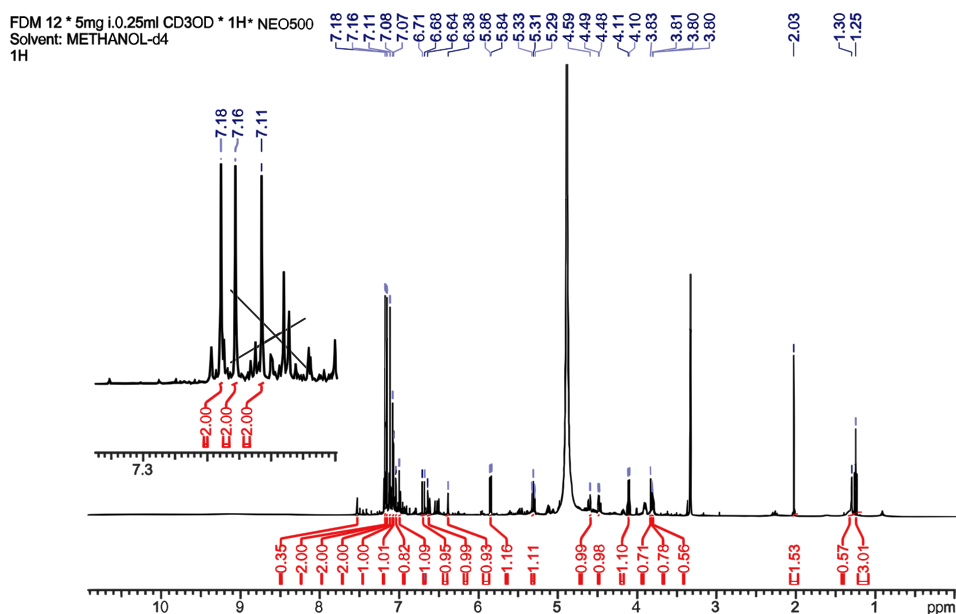


Fig. (4). 1H NMR spectrum of structure 7 (MeOH d_4 , 500 MHz).

Compound **8** for rhamnetin-3-O-(2,3,6-tri-galloyl)- β -D-glucopyranoside was acquired as pale green powder (40 mg) with melting point range of 156 - 157 °C and molecular formula $C_{43}H_{34}O_{24}$ as confirmed by HRESIMS analysis (m/z 934.1524). Infrared absorption at 3201, 1705 and 1607 cm^{-1} confirmed the existence of hydroxyl, carbonyl and C-C stretching at aromatic system respectively. The compound was established based on

spectroscopic data analysis [25, 31]. The 1H NMR signal (Fig. 6) at C - 2 and C - 3 of the glucosyl moiety were significantly downfield compared to those of rhamnetin-3-O-6-galloyl)- β -D-glucopyranoside [31, 32]. The ^{13}C NMR data (Table 2) indicated three galloyl groups. HMBC correlations interactions (Fig. 7) revealed inter - atomic interactions in rhamnetin-3-O-6-galloyl)- β -D-glucopyranoside framework and substitution on glucosyl moiety, confirming the structure of compound 8.

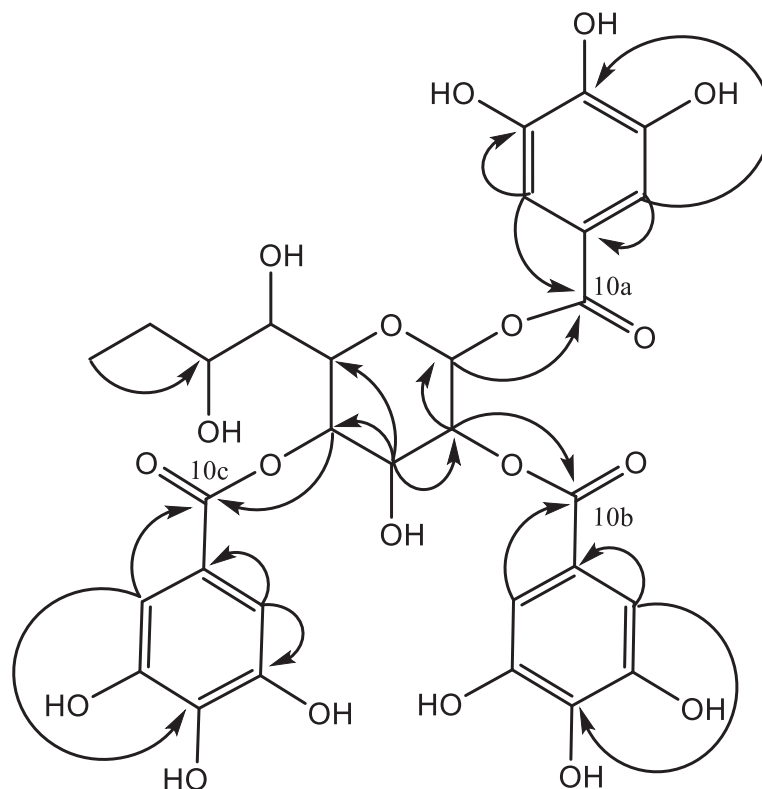


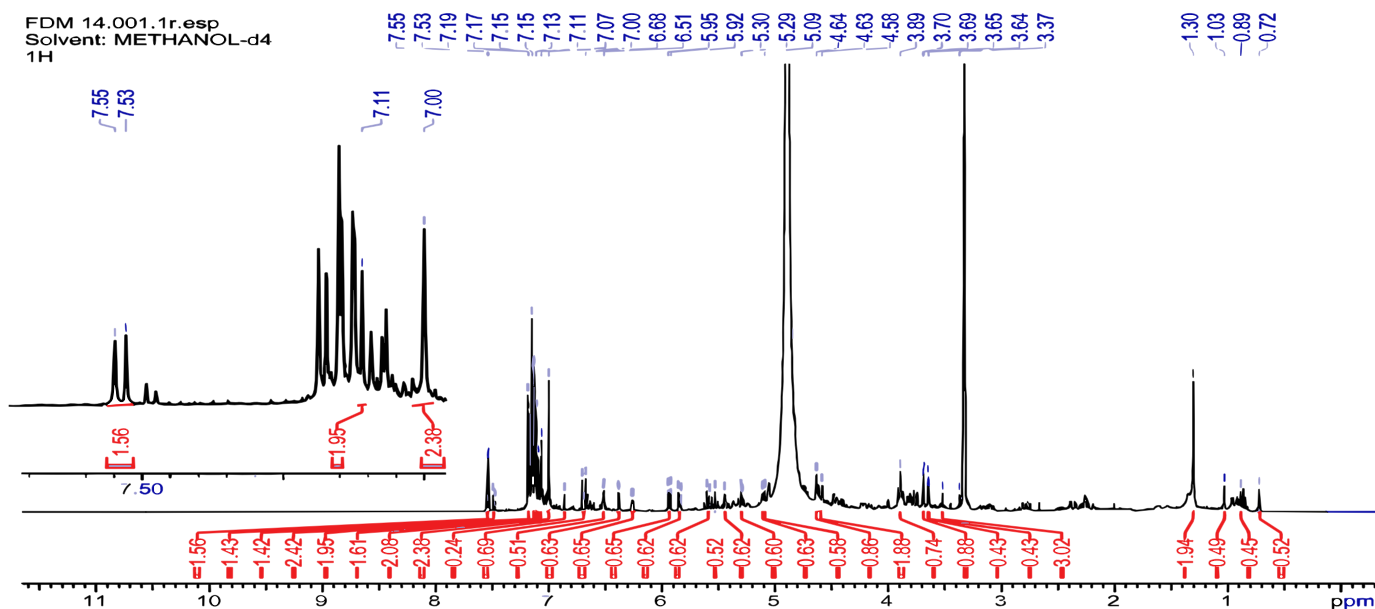
Fig. (5). Key H/C HMBC correlations of compound 7.

Table 1. 1H and ^{13}C NMR of structure 6 and 7 (MeOH d_4 , 500 MHz).

Structure 6					Structure 7			
S/No.	^{13}C (ppm)	1H NMR δ (ppm)	HMBC Correlations		S/No.	^{13}C	1H δ (ppm)	HMBC Correlations
1	94.5	5.9 (d, 1H, 8.2)	3, 8a		1	94.5	5.9 (d, 1H, 8.2)	10a
2	71.2	3.8 (s, 1H)	-		2	71.2	3.8 (d, 1H, 1.2)	1, 3, 5, 10b
3	75.0	3.8 (d, 1H, 1.2)	1, 2, 4, 5		3	75.0	3.8 (d, 1H, 3.1)	4, 6
4	68.3	3.8 (m, 1H)	2, 3, 8b		4	68.3	3.8 (m, 1H)	1, 3, 5, 6, 10c
5	77.5	5.3 (t, 2H, 9.3)	1, 2, 3, 4, 8b		5	77.5	5.3 (d, 1H, 9.3)	2, 4, 10c
6	39.0	2.7 (s, 2H)	-		6	62.8	4.6 (d, 1H, 1.8)	-
7	62.8	4.5 (dd, 2H, 12.1; 4.8)	3, 4, 5, 7c, 8c		7	60.2	4.5 (d, 1H, 4.7)	-
Galloyl unit - 1					8	19.5	2.0 (s, 2H)	-
8a	165.4	-	-		9	13.1	1.3 (t, 3H, 7.2)	7
9a	120.2	-	-		Galloyl unit - 1			

(Table 1) contd.....

Structure 6				Structure 7			
S/No.	13C (ppm)	1H NMR δ (ppm)	HMBC Correlations	S/No.	13C	1H δ (ppm)	HMBC Correlations
10a	109.0	7.2 (s, 2H)	8a, 9a, 11a, 12a	10a	165.5	-	-
11a	145.1	-	-	11a	120.2	-	-
12a	138.4	-	-	12a	109.0	7.2 (s, 2H)	10a, 11a, 13a, 14a
Galloyl unit - 2				13a	145.0	-	-
8b	166.7	-	-	14a	138.4	-	-
9b	119.1	-	-	Galloyl unit - 2			
10b	108.9	7.1 (s, 2H)	8b, 9b, 11b, 12b	10b	169.0	-	-
11b	145.0	-	-	11b	120.6	-	-
12b	139.1	-	-	12b	109.2	7.2 (s, 2H)	10b, 11b, 13b, 14b
Galloyl unit - 3				13b	145.1	-	-
8c	166.8	-	-	14b	138.2	-	-
9c	119.9	-	-	Galloyl unit - 3			
10c	109.2	7.2 (s, 2H)	8c, 9c, 11c, 12c	10c	166.8	-	-
11c	145.1	-	-	11c	119.1	-	-
12c	138.5	-	-	12c	108.9	7.1 (s, 2H)	10c, 11c, 13c, 14c
-	-	-	-	13c	145.0	-	-
-	-	-	-	14c	139.1	-	-

Fig. (6). ¹H NMR spectrum of structure 8 (MeOH d₄, 400 MHz).

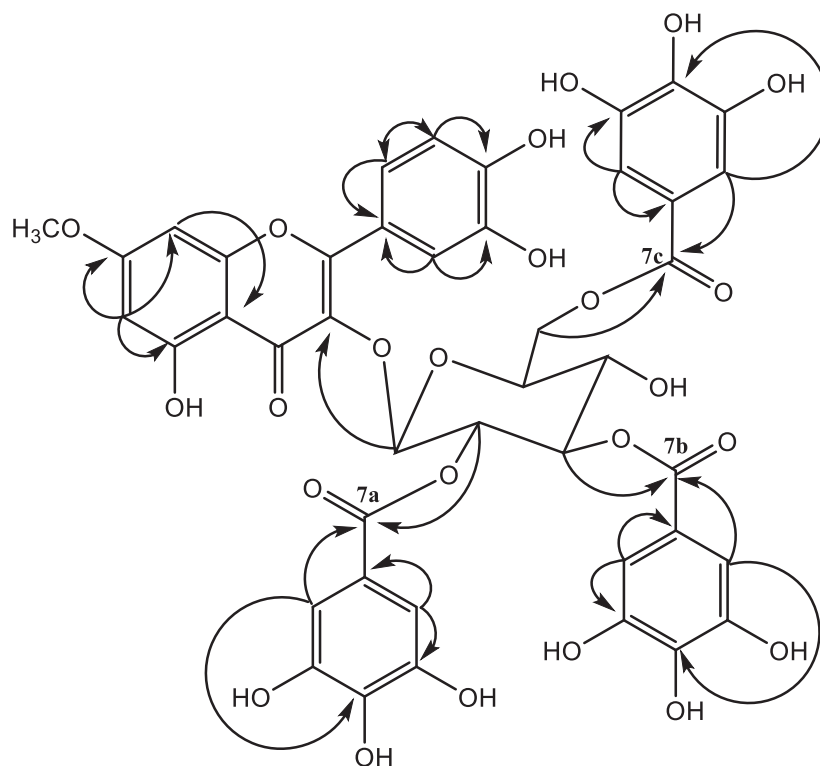


Fig. (7). Key H/C HMBC correlations of compound 8.

Table 2. ¹H and ¹³C NMR of compound 8 (MeOH d₄, 400 MHz).

S.No.	¹³ C δ(ppm)	¹ H δ(ppm)	HMBC Correlations
2	148.2	-	-
3	136.3	-	-
4	173.5	-	-
5	164.7	-	-
6	97.1	6.3 (d, 1H, 1.2)	-
7	168.9	-	-
8	94.5	6.4 (d, 1H, 1.6)	-
9	164.9	-	-
10	108.9	-	-
7 O-CH ₃	51.8	3.3 (br s, 1H)	168.9
1'	121.4	-	-
2'	109.3	7.2 (d, 2H, J = 5.4)	-
3'	145.1	-	-
4'	148.3	-	-
5'	109.0	5.8 (d, 1H, 8.3)	-
6'	109.3	7.1 (dd, 1H, 8.3, 2.2)	-
Sugar unit			
1"	106.9	6.7 (br d, 1H, 0.9)	136.3
2"	72.7	4.2 (br d, 1H, J = 0.9)	164.9
3"	76.9	4.6 (d, 1H, J = 1.3)	166.6
4"	70.3	5.4 (m, 1H)	-
5"	75.0	5.6 (m, 1H)	-
6"	62.5	4.8 (br s, 2H)	166.5
Galloyl unit - 1			
7a	164.9	-	-
8a	120.7	-	-

(Table 2) contd.....

S.No.	¹³ C δ(ppm)	¹ H δ(ppm)	HMBC Correlations
9a	110.2	7.6 (d, 2H, 8.0)	120.7, 139.9, 145.0, 164.9
10a	145.0	-	-
11a	139.9	-	-
Galloyl unit - 2			
7b	166.6	-	-
8b	120.0	-	-
9b	109.1	7.1 (s, 2H)	120.0, 138.8, 145.1, 166.6
10b	145.1	-	-
11b	138.8	-	-
Galloyl unit - 3			
7c	166.5	-	-
8c	119.0	-	-
9c	108.8	7.0 (s, 2H)	119.0, 138.7, 145.5, 166.5
10c	145.5	-	-
11c	138.7	-	-

Table 3. Antimicrobial activity of isolated compounds from *T. brownii*.

Zone of Inhibition in mm (mean ± SD)				
Isolated Compounds	<i>E. coli</i>	<i>P. aeruginosa</i>	<i>S. aureus</i>	<i>C. albicans</i>
1	10.50±0.7	10.8±1.1	10.5±0.7	16.00±2.7
2	10.5±0.7	10.0±2.8	12.5±0.7	15.0±2.2
3	8.5±0.7	8.5±0.7	10.8±1.1	13.0±1.4
4	9.3±0.4	9.5±0.7	12.3±0.4	5.5±1.8
5	12.8±0.4	11.8±0.4	10.5±0.7	14.0±1.4
6	16.5±0.7	9.5±0.7	10.0±1.4	10.5±0.7
7	12.5±0.7	13.0±2.7	10.0±2.8	12.5±2.5
8	10.5±0.7	8.0±2.8	11.5±0.7	11.5±0.7
9	9.5±2.1	11.5±0.7	10.5±0.7	12.8±1.1
10	10.5±0.7	9.5±0.7	8.8±1.1	11.8±0.4
Amoxillin	15.2±2.4	20.0±0.7	15.3±2.2	-
Fluconazole	-	-	-	23.0±5.7
Distilled water	-	-	-	-

Note: (-) mean no activity All values presented as mean ± SD.

3.2. Antimicrobial Activity

All isolated compounds showed activity against the tested pathogens (Table 3). *E. coli*, was more susceptible to compound 6 (16.5±0.7). Compound 1 exhibited excellent antifungal activity, with zone of inhibition of 16.0±2.7 mm. All the identified compounds had reduced antimicrobial efficacy compared to the positive control. According to [33], plant extracts containing flavonoids and phenolic exhibit antibacterial activity against a wide spectrum of harmful bacteria due to their chemical structures and biological properties. Flavonoids and phenolics contain hydroxyl group that interact with bacterial cell wall and membranes, creating disruption of cell integrity, inhibition of enzyme function and interference with bacterial DNA and protein synthesis [34]. Additionally, these compounds may act as antioxidants reducing oxidative stress in cells inhibiting bacterial growth hence making them effective against various bacterial strains [35, 36]. Terpenes and their derivatives exhibit potent antimicrobial activity against

drug - resistant pathogens bacteria and fungi owing to their ability to erode microbial cell membranes and obstruct integral cellular process [13, 37]. These results align with previous studies that documented the antimicrobial properties of termiglaucoscin (**1**), arjunglucoside - I (**2**), Sericoside (**3**), 23-galloyl arjungenin (**4**) [17, 38]. This corroboration reinforces the potential of these compounds as viable option for developing new antimicrobial agent particularly in the face of rising drug resistance.

The study proposes the isolation and characterization of n-hexane, chloroform and ethylacetate extract of *T.brownii* flowers and carry out toxicity and antioxidant tests on *T.brownii* flowers extracts.

CONCLUSION

This study investigated the antimicrobial activity of stem bark and flowers of *T.brownii*, a plant traditionally used in ethnomedicine to treat various ailments. Bioassay guided fractionation through silica gel column chromatography, three new compounds were isolated and

characterized 1,4, 7-tri-O-galloyl-6-deoxyheptose, 1,2,4-tri-O-galloyl-8,9 dideoxynonose and rhamnetin-3-O-(2,3,6-tri-galloyl)- β -D-glucopyranoside alongside seven existing compounds.

Evaluation of antimicrobial activities of the identified compounds against the test pathogens indicated that compounds 1 - 5 demonstrated relatively high antimicrobial effects, implying that terpenes and their derivatives constitute promising candidate for development of antimicrobial drugs targeting both susceptible and resilient pathogens. The findings underscores the potential of *T. brownii* as a repository of bioactive compounds with promising antimicrobial properties. The results support the plant's traditional uses in treating infections and highlight its value in developing new antimicrobial agents. In conclusion this study has demonstrated that flower extracts possess potent antimicrobial properties comparable to those found in stem bark. As a result, more environmentally friendly flower extracts should be considered for treatment of bacterial and fungal infection.

AUTHORS' CONTRIBUTION

It is hereby acknowledged that all authors have accepted responsibility for the manuscript's content and consented to its submission. They have meticulously reviewed all results and unanimously approved the final version of the manuscript.

LIST OF ABBREVIATIONS

COSY	= Correlation Spectroscopy
HMBC	= Heteronuclear Multiple Bond Correlation
HRESMS	= High - Resolution Electrospray Ionization Mass Spectrometry
HSQC	= Heteronuclear Single Quantum Coherence Spectroscopy
NMR	= Nuclear Magnetic Resonance
FTIR	= Fourier Transform Infrared

ETHICS APPROVAL AND CONSENT TO PARTICIPATE

Not applicable.

HUMAN AND ANIMAL RIGHTS

Not Applicable.

CONSENT FOR PUBLICATION

Not applicable.

AVAILABILITY OF DATA AND MATERIAL

All data generated or analyzed during this study are included in this published article.

FUNDING

None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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