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Syzygium australe extracts exhibit significant antioxidant and antidiabetic properties: a comprehensive analysis of the phytoconstituents

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Abstract

Background Medicinal plants are well known for their health benefits. *Syzygium australe* (Brush Cherry) is considered a health-promoting food due to its high antioxidant capacity, which may help prevent cancer, cardiovascular diseases, and neurological disorders. Additionally, *S. australe* exhibits antidiabetic and antiobesity properties.

Aim This study reviews the antioxidant and antidiabetic activities of *S. australe* fractions, along with their key phytoconstituents.

Materials and methods The antioxidant activity of *S. australe* crude extract and fractions was assessed using DPPH (2,2-diphenyl-1-picrylhydrazyl-hydrate), ABTS (2,2′-azinobis(3-ethylbenzothiazoline-6-sulfonic acid)), FIC (ferrozine iron metal chelation), and FRAP (ferric reducing antioxidant power) assays. Their antidiabetic activity was evaluated using *α*-glucosidase, *α*-amylase, and lipase inhibition assays. Additionally, their TFC (total flavonoid content) and TPC (total phenolic content) were determined. The secondary metabolites were analysed using Triple TOF UPLC-ESI–MS/MS (ultra-performance liquid chromatography-electrospray ionization-time of flight-mass spectrometry).

Results Our findings, for the first time, reveal that various *S. australe* extracts exhibit strong antidiabetic and antioxidant properties. The butanol and ethyl acetate fractions had the highest antidiabetic activity. Their respective IC_{50} values against *α*-glucosidase, *α*-amylase, and lipase were 0.11–0.14 µg/mL, 0.06–0.09 µg/mL, and 26.5–30.79 ng/mL, respectively. Also, they showed powerful antioxidant activity. The IC_{50} values of the ethyl acetate (19.93 ± 1 µg/mL) and butanol (38.7 µg/mL) fractions were significantly lower than those of the reference compounds, Trolox (24.42 ± 0.87 µg/mL) in the DPPH assay and EDTA (Ethylenediaminetetraacetic acid) (39.7 µg/mL) in the ferrozine iron metal chelation assay, respectively. They had a higher amount of TPC (397.65 ± 14.78, 253.32 ± 10.78 µg GAE/mg sample) and TFC (97.89 ± 4.98, 23.14 ± 1.11 µg RE/mg sample) of ethyl acetate and butanol, respectively. The significant phenolic and flavonoid substances found in these extracts may account for their strong antioxidant activity. Triple TOF UPLC-ESI–MS/MS analysis detected 18 phenolic acids, 19 derivatives, and 39 flavonoids. As a way to prevent or treat various disorders, these two extracts additionally served as a great source of antioxidant phytochemicals.

Conclusion Ultimately, our findings strongly suggest that the phenolics of *S. australe* may be valuable for the development of antioxidant and antidiabetic medications.

Keywords Antioxidant, Antidiabetic, *Syzygium australe* (J.C.Wendl. ex Link) B. Hyland, Phenolics

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Background

Diabetes mellitus is considered one of the leading causes of human mortality. The anomalies in fat, protein, and carbohydrate metabolism are the hallmarks of this chronic metabolic disease. It is caused by either an absolute or a relative deficiency of the insulin hormone. Due to insulin inefficiency, the body accumulates excess glucose. Advanced glycation end-products (AGEs) may form due to the nonenzymatic interaction of high glucose levels with plasma proteins. The accumulation of glycated haemoglobin and albumin in the kidney, retina, and other organs may lead to complications. Currently, synthetic antidiabetic medications often cause side effects such as kidney damage, gastrointestinal discomfort, diarrhoea, dizziness, and skin rashes [1]. In contrast, plant-derived hypoglycemic agents offer a safer, cost-effective alternative with improved accessibility. This study explores the potential antidiabetic properties of *S. australe*. Our plant is officially known by its scientific name, *S. australe* (J.C. Wendl. ex Link) B. Hyland family Myrtaceae [2]. Myrtaceae includes 140 genera and 3800–5800 species [3]. *Syzygium* is the sixteenth largest genus of evergreen flowering plants [4]. This genus is commonly found in rainforests, including peat swamps, bamboo forests, and monsoon-influenced coastal forests [5]. It is highly diverse and is grown for its juicy colourful fruits [6]. Plants from this family, particularly those from the *Eucalyptus, Syzygium, Eugenia,* and *Melaleuca* genera, are rich sources of essential oils, many of which possess antimicrobial activity [7]. One of them is our plant *S. australe.* Its tree is cultivated for its wood, edible fruit, and ornamental value [2]. Additionally, it has traditional medicinal uses due to its anaesthetic properties. Its leaves and fruits also have antioxidants, antimicrobial activities, and their essential oils are used for food preservation [8, 9]. The total antioxidant capacity of *S. australe* was previously estimated by DPPH assay and expressed as mg ascorbic acid equivalent (AAE)/g of plant material. The antioxidative potential of the aqueous, ethyl acetate, and methanolic leaves extracts were (2.6, 25, 40 mg AAE, respectively) and that of fruit were (55, 41, 9.2 mg AAE, respectively). The chloroform and hexane extracts of both organs were below the detection threshold [10]. Despite widespread recognition of *S. australe* as a medicinal plant, previous research has not extensively explored its antidiabetic and antioxidant properties, particularly its phytochemical composition. To date, no extensive research has examined the medicinal potential of its leaves. This study attempts to fulfil this gap by examining the plant's antioxidant and antidiabetic activities utilizing in vitro assays, as well as recognizing and measuring its phenolic components. The phenolics are assumed to contribute the plant's biological activity. By addressing this research gap, the study will give vital insights into the medical potential of *S. australe*, notably its function in controlling oxidative stress and diabetes.

Materials and methods

Materials

Plant material collection

In March 2020, fresh leaves of *S. australe*, as shown in Fig. 1, were collected from the Mazhar Botanical Garden in Giza, Egypt. The plant was authenticated, and a voucher specimen (serial number 25.12.2022) was deposited.

Chemicals and reagent

Methanol, sodium hydroxide, and formic acid, which were used to alter the pH, were supplied by Fisher Scientific, USA. The German company Sigma-Aldrich provided the rutin, gallic acid, acetonitrile, and ammonium formate. Millipore, USA, provided the water used in the Triple TOF UPLC-ESI–MS/MS analysis. For the *in vitro* antioxidant and antidiabetic tests, the following reagents were used: DPPH reagent (Sigma-Aldrich), ferrous sulphate (American Chemical Suppliers), ferrozine (MedChemExpress), Butylated hydroxyanisole (BHA) (American International Ingredients), potassium ferricyanide (Sigma-Aldrich), phosphate buffer (Sigma-Aldrich), trichloroacetic acid (Fisher Scientific), ferric chloride ($FeCl_{3)}$ (Univar Solutions), potassium persulphate (Thomasnet), and ABTS (Sigma-Aldrich). These reagents were sourced from reputable suppliers to ensure the accuracy and reliability of the assays.

Methods

Sample preparation

Two kilograms of dried, powdered *S. australe* leaves were macerated at room temperature (RT) in seven litres of 70% methanol. The extraction was performed three times with fresh solvent. 160 g of dry residue was obtained by evaporating the filtered extract in a rotating evaporator to no more than 40 °C. So its yield percentage was (8%) of 2 kg dried leaves. Ethyl acetate, petroleum ether, butanol saturated with water, and methylene chloride were used to fractionate the 150 g of crude methanol extract (ME). Following evaporation, the following fractions were obtained: butanol fraction (BF) (80 gm), methylene chloride fraction (MCF) (5 gm), ethyl acetate fraction (EAF) (18 gm), and petroleum ether fraction (PEF) (10 gm). At 20 °C 10 g dried crude extract and its 4 fractions were kept for biological investigations and additional analysis.

Analytical methods

In vitro antioxidants and antidiabetic tests.

DPPH assay

As described in Boly et al. (2016) A 100 µL sample was mixed with 100 µL of DPPH reagent (0.1% in methanol) in 96-well plates (n = 6). The mixture was incubated at RT in the dark for 30 min before measuring absorbance at 540 nm [11].

FIC assay (ferrozine iron metal chelation)

According to Santos et al. (2017), the experiment was performed with slight alterations in microplates. On 96-well plates (n = 6), 50 mL sample was added to 20 mL ferrous sulphate (0.3 mM). After mixing, 30 µl (0.8 mM) of ferrozine was added to each plate before incubation at RT for 10 min. After the end of incubation period, we measured the reduction of colour intensity at 562 nm [12].

Ferric iron reducing power (FRAP assay)

As shown in Younis et al. (2023), methanolic extract and its fractions (in different concentrations) were added to BHA (0–480 µg) in 1 mL of distilled water + 2.5 mL of potassium ferricyanide (1%) + 2.5 mL of phosphate buffer (0.2 M, pH 7.6). Then, the ended mixtures were incubated for 30 min at 50 °C. After incubation, 2.5 mL of 10% trichloroacetic acid was added, and the mixture was centrifuged at 3000 rpm for 10 min. 2.5 mL of the resulted upper layer was mixed with 2.5 mL distilled water + 0.5 mL 0.1% $FeCl_3$. Finally, the absorbance was measured at 700 nm, and BHA was utilized as the reference antioxidant. Higher absorbance indicates stronger reducing power [13].

ABTS radical-scavenging assay

With minor adjustment to Arnao et al. (2001), the stock solutions were prepared by adding 2.4 mM potassium persulphate to 7 mM ABTS. Then, equal portions of 2 stock solutions were combined for 14 h in dark RT. After 2 mL of ABTS solution was diluted by 50 mL methanol, 0.305 ± 0.01 units absorbance was measured at 734 nm by a spectrophotometer. Each assay began with a new ABTS solution. After 5 min, 1 mL of extract, fractions, and BHT (0.025–2.0) µg/mL were combined with 2 mL of ABTS solution and at 734 nm their absorbance was detected [14]. The scavenging capability was determined by:

$$\text{ABTS scavenging capacity (\%)} = [(\text{control absorbance}(A1) - \text{sample absorbance}(A2)/A1] \times 100$$



Fig. 1 Photograph of *S. australe* leaves (Magnification scale of Fig. 1 is 5.76)

Total phenolic content

TPC was evaluated using Attard et al. (2013) technique. In a 96-well microplate, 10µL of standard or sample was mixed to (1:10) diluted 100µL Folin–Ciocalteu reagent. Then, 80µL of 4 N Na2 CO3 was added. After that, we incubated them at dark RT for 20 min. At the end, we used the FLUOstar Omega microplate reader to measure the blue colour absorbance at 630 nm. We used gallic acid as standard [15].

Total flavonoid content

According to Kiranmai et al. (2011), TFC was determined. To summarize, 2.8 mL distilled water, 1.5 mL methanol, 0.1 mL potassium acetate solution, 0.1 mL aluminium chloride, and 0.5 mL of total extract and each fraction stock solution were combined properly. Blanks were prepared using distilled water rather than aluminium chloride. Extract and fractions were prepared as blanks and samples. By using the FLUOstar Omega microplate reader, their absorbance was measured against the standard rutin at 630 nm [16].

α-Amylase inhibition assay

The 2 U/mL enzyme solution of α-amylase (from *Aspergillus oryzae*, Sigma-Aldrich) was prepared using buffer sodium phosphate with pH 6.9 as described in Wickramaratne et al. (2016) with some changes. 200 µl of the extract, fractions, or acarbose (0.05–0.4 mg/mL) was added to the enzyme solution in a test tube. Then, it was pre-incubated in a water bath for 10 min at 30 °C. After that, to each tube the reaction was initiated by adding 200 µl of substrate starch solution (1% in phosphate buffer w/v). Then, the tubes were incubated for 3 min at 30 °C. We stopped the reaction by adding 200 µl DNSA colouring reagent (12 g sodium potassium tartate tetrahydrate in 8 mL of 2 M NaOH and 20 mL of 96 mM 3, 5-dinitrosalicylic acid solution) with boiling in a water bath for 10 min at 85 °C. After that we cooled the mixture with 5 mL distilled water. Finally, their absorbance at 540 nm was measured by Shimadzu UV–Visible spectrophotometer (Japan) against sodium phosphate buffer (blank) [17]. The α-glucosidase inhibition activity was calculated by:

Inhibition (%) = 100 [control absorbance (A1)–sample absorbance (A2)]/A1).

α -Glucosidase inhibition assay

According to Zheng et al. (2010), 50 µl *S. australe* extract, fractions, and acarbose (0.05–0.4 mg/mL) were pre-incubated with 50 µl α-glucosidase for 1 h. By adding 50 µl of 0.1 M Na2 CO3 for 30 min at 37 °C, the enzymatic reaction was permitted to continue. Then, the absorbance at 405 nm was detected with UV–Visible spectrophotometer. Also, the negative (−ve) control activity was tested with and without an inhibitor. Finally, the inhibition activity was determined by this equation [18].

$$\text{Inhibition}(\%) = (1 - [A2/A1]) \times 100$$

$A1$ = the reactants with the sample absorbance.
$A2$ = blank absorbance (reactants only).

Lipase inhibition assay

The porcine pancreatic lipase (PPL, type II) activity was evaluated according to Zheng et al. (2010) method with slight modification with the substrate p-nitrophenyl butyrate (p-NPB). We prepared PPL stock solutions (1 mg/mL) by using a 0.1 mM potassium phosphate buffer (pH 6.0) and kept it at −20 °C. To test PPL activity, 50 µL of extract and fractions (0.05–0.4 mg/mL) or orlistat (0–400 ug/mL) were added to (0.1 mM, pH 7.2, 0.1% Tween 80) potassium phosphate buffer at 30 °C for 1 h. The reaction began with a substrate addition (0.1 µL NPB) in a 100 µL final volume. Following five minutes of incubation at 30 °C, a UV–Visible spectrophotometer (BioTek Synergy HT, Winooski, Vermont, USA) was used to measure the amount of *p*-nitrophenol generated in the reaction at 405 nm. The negative control performance was also measured with an inhibitor and without [18]. We estimated the inhibitory activity (I) using this calculation:

$$I\% = 100 - ((B - b)/(A - a) \times 100)$$

where A: the −ve control without inhibitor (DMSO activity).

B: the activity + inhibitor.

b: the −ve control + inhibitor.

Metabolic profiling using triple TOF UPLC-MS/MS

It was conducted using an Exion LC system (AB Sciex, Framingham, MA, USA) with an autosampler and an X select HSS T3 column (2.5 µm, 2.1 ×150 mm, Waters Corporation, Milford, MA, USA) as described by Mohammed et al. (2021). The mobile phase gradient flow was established by adding 0.1% formic acid to both acetonitrile (ACN) and water. After the first 20 min of the experiment, ACN increased by 10%, which increased to 90% between 21 and 25 min. The ACN level was kept at 10% for 25.01 min until the experiment end. The flow rate was maintained at 0.3 mL/min for 28 min. The Triple TOF 5600 + system (AB SCIEX, Concord, ON, Canada) was used with a Duo-Spray for mass spectrometry and as a source operating in electrospray ionization (ESI) mode, respectively. The Analyst-TF 1.7.1 application conducted the LC-Triple TOF control [19].

Statistical analysis

The antioxidant assays were expressed as following: For DPPH the inhibitory concentration 50 (IC_{50}) value was calculated by GraphPad Prism 5®. Also, the data for FIC and ABTS radical-scavenging assay were recorded with the FLUOstar Omega microplate reader. The antidiabetic inhibition assays were expressed for α-Amylase, α-Glucosidase, and lipase as IC_{50} value. TPC and TFC were calculated in mg per gram of extract as mean ± standard deviation. PeakView2.2 software (Sciex) was used for metabolite identification by LC–MS analysis. Additionally, MS-DIAL 4.6, an open-source programme, was used for peak identification based on fragment analysis, utilizing datasets such as ReSpect positive (+ve) (2737 records) and ReSpect negative (−ve) (1573 records). After the existing compounds were initially identified, were compared to the reference literature for verification.

Results

TPC and TFC of *S. australe* leaves extracts

The two most common types of plant phenolics are phenolic acids and flavonoids. The crude methanol extract

and its fractions were first analysed for TPC and TFC, followed by comprehensive chemical profiling. All fractions of *S. australe* leaves contained large amounts of phenolic and flavonoid chemicals, as shown in Fig. 2 and Table 1. The methanol extract contained 186.99 ± 2.43 µg GA eq/mg and 10.71 ± 0.9 µg rutin eq/mg. The ethyl acetate fraction exhibited the highest total phenolic content (397.65 ± 14.78 µg GA eq/mg) and flavonoid content (97.89 ± 4.98 µg rutin eq/mg), followed by the butanol fraction (253.32 ± 10.78 µg GA eq/mg and 23.14 ± 1.11 µg rutin eq/mg, respectively). The total phenolic (TPC) and flavonoid (TFC) contents increased in the following order: petroleum ether < methylene chloride < butanol < ethyl acetate (see Table 1).

Metabolic profiling of leaves using triple TOF UPLC-ESI–MS/MS

S. australe leaf extract was selected for further investigation due to its significant antioxidant and antidiabetic properties. A comprehensive analysis using Triple TOF UPLC-ESI–MS/MS identified seventy compounds across different chemical classes, in both −ve and +ve ionization modes, such as shown in Table 2 and illustrated in Figs. 4. Among these, a total of 46 polyphenols were identified, which included 39 flavonoids, 5 phenolic acids, 1 coumarin, and 1 anthocyanidin, making polyphenols the predominant group. Additionally, the analysis revealed the presence of other compound classes, including 9 amino acids and their derivatives, 1 terpenoid, 1 fatty acid, 7 organic acids, and 6 miscellaneous compounds. These findings are systematically presented in Figs. 3, 4, 5, 6, 7, and 8, providing a comprehensive overview of the diverse chemical composition of leaves extract.

Phenolic acids and their derivatives

Our investigation results revealed various phenolic acids and their derivatives (Fig. 5). Notably, p-hydroxybenzoic acid (peak 23) was detected with a molecular ion $[M–H]^-$ at m/z 137.0238 and product ions at m/z 93 for $[M–H–CO_2]^-$ [20]. Jasmonic acid (peak 25) was detected as $[M+H]^+$ at m/z 225.148, with product ions observed at m/z 95 (attributable to the loss of COOH, C_5H_{10}, and CH_3)

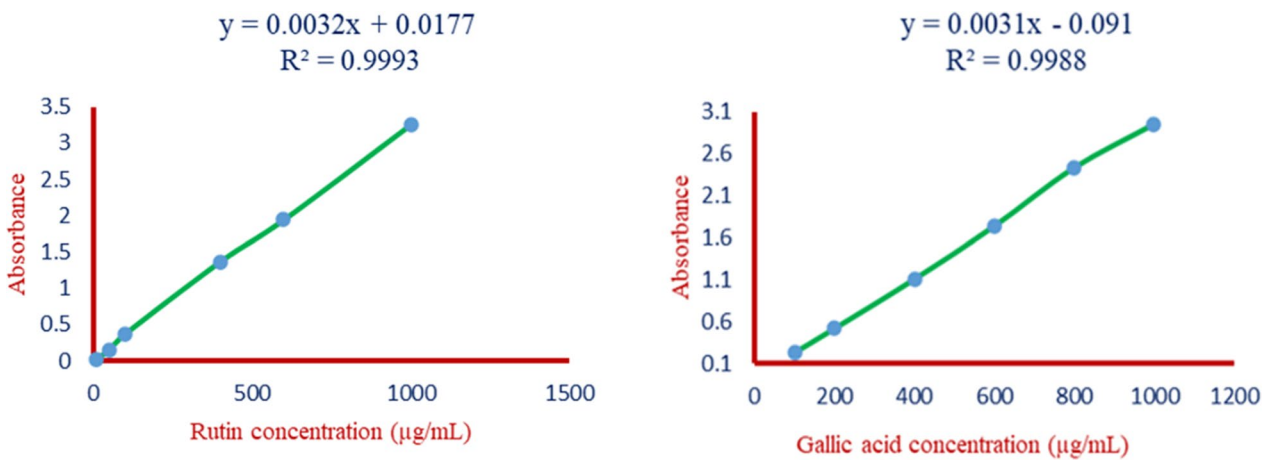


Fig. 2 Calibration curve of standard gallic acid in total phenolic and standard rutin in total flavonoid contents of *S. australe* leaves extracts

Table 1 TPC and TFC of *S. australe* leaves extract and fractions

	Methanolic extract	Petroleum ether	Methylene chloride	Ethyl acetate	Butanol
TF (µg rutin eq/mg sample)	10.71 ± 0.9[a]	5.88 ± .42[a]	10.37 ± 1.34[a]	97.89 ± 4.98[a]	23.14 ± 1.11[a]
TP (µg Gallic acid eq/mg sample	186.99 ± 2.43[b]	21.58 ± 1.32[b]	52.13 ± 0.66[b]	397.65 ± 14.78[b]	253.32 ± 10.78[b]

Data shown are mean ± standard deviation of the number of observations within each treatment. Data followed by the same letter are not significantly different at P ≤ 0.05. F for one-way ANOVA test, pairwise comparison between each two groups was done using a post hoc test (Tukey). The high significant levels of the parameters were in the order of a < b < c < d < e < f. Data with superscript alphabet "a" are significantly lower than data with superscript alphabet "b" while data with superscript "b" are lower than data with superscript alphabet "c and d" at *p < 0.05

Data shown are mean ± standard deviation of the number of observations within each treatment. Data followed by the same letter are not significantly different at P ≤ 0.05. F for one-way ANOVA test, pairwise comparison between each two groups was done using a post hoc test (Tukey). The high significant levels of the parameters were in the order of a < b. Data with superscript alphabet "a" are significantly lower than data with superscript alphabet "b" at *p < 0.05

TP: total phenolic, TF: total flavonoid

Table 2 Characterization of methanolic extract compounds using Triple TOF UPLC-MS/MS analysis in −ve and +ve mode

Peak #	RT	Precursor.m.z	ESI ±	Identified compounds	Molecular Formula	Error (ppm)	Fragment Ions
1	1.01	190.0562	[M + H] +	Quisqualate	C5H7 N3O5	− 1.8	68, 79, 97, 125, 144, 190
2	1.02	110.0089	[M + H] +	4-Aminophenol	C6H7 NO	− 0.6	68
3	1.04	133.014	[M–H]–	Malic acid	C4H6O5	− 1.9	71, 89, 115, 133
4	1.05	149.009	[M–H]–	Tartaric acid	C4H6O6	0.5	59, 72, 75, 87, 103, 105, 130, 148 149
5	1.06	259.0245	[M–H]–	Monosaccharide phosphates	C6H13O9P	4.2	259
6	1.07	175.1171	[M + H] +	L-Arginine	C6H14 N4O2	− 1	60, 70, 175
7	1.11	162.1116	[M + H] +	Carnitine	C7H15 NO3	2.2	57, 58, 72, 88, 102, 162
8	1.14	104.1064	[M + H] +	Choline	C5H14 NO	0.8	58, 59, 60, 104
9	1.15	135.0283	[M–H]–	ɣ-terpinene	C10H16	− 1.1	135
10	1.16	148.0337	[M + H] +	Methylaspartic acid	C5H9 NO4	5	58, 74, 69, 78, 82, 94, 98, 102, 130, 148
11	1.22	132.1003	[M + H] +	Creatine	C4H9 N3O2	4.9	55, 58, 132
12	1.23	129.0197	[M–H]–	Citraconic acid	C5H6O4	−4.2	85, 129
13	1.27	179.0569	[M–H]–	Hexose	C6H12O6	− 4.7	59, 71, 85, 89, 119, 141, 161, 179
14	1.28	159.0303	[M–H]–	β-Homolysine	C7H16 N2O2	− 1.9	115, 159
16	1.35	229.1555	[M + H] +	Resveratrol	C14H12O3	− 1	70, 132, 142, 184, 229
17	1.36	433.1139	[M–H]–	Quercetin pentoside	C20H18O11	0.2	229, 297, 365
18	1.37	283.1017	[M–H]–	Acacetin	C16H12O5	3.6	59, 146, 237, 283
19	1.84	339.095	[M–H]–	Aesculin	C15H16O9	− 1.8	163, 173, 177
20	1.87	130.0504	[M + H] +	L-5-Oxoproline	C5H7 NO3	− 0.6	84, 130
21	2.05	240.9489	[M + H] +	L-Cystine	C6H12 N2O4S2	4.7	224, 240, 241
22	2.84	299.0768	[M–H]–	kaempferide	C16H12O6	0.6	179, 299, 300, 302
23	2.93	137.0238	[M–H]–	P-hydroxybenzoic acid	C7H6O3	− 0.4	93, 137
24	4.16	447.1866	[M–H]–	Quercitrin	C21H20O11	0.9	446, 447, 448, 449, 450, 451
25	4.24	225.148	[M + H] +	Methyl Jasmonate	C13H20O3	0.8	95, 121, 225
26	4.35	301.0903	[M–H]–	Hesperetin	C16H14O6	− 4.7	300, 301
27	4.38	137.0245	[M–H]–	Urocanic acid	C6H6 N2O2	− 1.6	137
28	4.78	481.1707	[M + H] +	Gossypin	C21H20O13	− 3.6	481
29	4.85	183.0285	[M–H]–	3,4-Dihydroxymandelate	C8H8O5	3.7	124, 140, 168, 183
30	4.99	433.1686	[M + H] +	Vitexin	C21H20O10	0.9	433
31	5.19	431.1909	[M–H]–	Afzelin	C21H20O10	2.5	179, 269, 362, 367, 430, 431
32	5.45	415.1581	[M–H]–	Puerarin	C21H20O9	3.6	253, 415
33	6.04	609.1922	[M + H] +	Diosmin	C28H32O15	0	609
34	6.08	126.0907	[M + H] +	5-Methylcytosine	C5H7 N3O	− 0.2	96, 126
35	6.12	209.1532	[M + H] +	Sinapyl aldehyde	C11H12O4	0.6	151, 209
36	6.13	427.1739	[M + H] +	Leupeptin hemisulphate salt	C20H38 N6O4	− 1.9	139, 149, 165, 191, 427
37	6.28	609.1476	[M–H]–	Delphinidin-rutinoside	C27H31O16	− 0.8	300, 301, 609

Table 2 (continued)

Peak #	RT	Precursor.m.z	ESI ±	Identified compounds	Molecular Formula	Error (ppm)	Fragment Ions
38	6.47	595.1292	[M–H]–	Neoeriocitrin	C27H32O15	1.2	271, 316, 593
39	6.59	507.0775	[M–H]–	Syringetin-O-hexoside	C23H24O13	0.8	218, 286, 316, 331, 344, 354, 394, 462, 506, 507
40	6.60	463.0903	[M–H]–	(Spiraeoside) Quercetin hexoside	C21H20O12	– 2.6	271, 286, 300, 301, 316, 326, 462, 463
41	6.65	319.044	[M + H] +	Myricetin	C15H10O8	1.4	153, 165, 189, 213, 217, 245, 269, 301, 316, 319
42	6.68	465.1009	[M + H] +	Myricitrin	C21H20O12	2.1	71, 85, 129, 303, 319, 465
43	6.73	451.12347	[M + H] +	Eriodictyol-O-hexoside	C21H22O11	4	153, 163, 271, 289, 451
44	6.79	609.1481	[M–H]–	Hesperidin	C28H34O15	– 1.2	300, 608
45	6.81	465.1007	[M + H] +	Hyperoside	C21H20O12	2.5	85, 129, 165, 229, 257, 303, 319, 447, 465
46	6.82	609.1074	[M–H]–	Luteolin-di-O-hexoside	C27H30O16	2.7	300, 608, 609
47	6.83	449.1095	[M–H]–	Isookanin-hexoside	C21H22O11	– 0.7	135, 151, 287, 313, 448, 449
48	6.90	593.1526	[M–H]–	Datiscin	C27H30O15	– 0.8	285, 592, 593
49	6.96	447.1868	[M–H]–	Luteolin-O-hexoside	C21H20O11	0.7	239, 285, 401, 447, 446, 447
50	6.98	579.1154	[M + H] +	Procyanidin B2	C30H26O12	– 4.5	579
51	7.20	625.1748	[M + H] +	Isorhamnetin-O-rutinoside	C28H32O16	– 0.2	85, 147, 317, 478, 479, 623, 625
52	7.23	287.0519	[M + H] +	Luteolin	C15H10O6	1.6	270, 287
53	7.24	271.0789	[M + H] +	Genistein	C15H10O5	– 0.7	241, 243, 271
54	7.32	447.0912	[M–H]–	Quercetin-O-deoxyhexoside	C21H20O11	4.8	245, 255, 271, 300, 301, 445, 447
55	7.58	479.1163	[M + H] +	Isorhamnetin-O-hexoside	C22H22O12	1.3	61, 85, 91, 145, 153, 229, 274, 285, 302, 316, 317, 479
56	7.64	435.1281	[M + H] +	Prunin	C21H22O10	– 0.9	153, 273
57	7.72	591.1323	[M–H]–	Acaciin	C28H32O14	– 0.8	590, 591
58	7.84	407.1841	[M–H]–	Cholic acid	C24H40O5	0.3	407
59	8.25	479.083	[M + H] +	Quercetin glucuronide	C21H18O13	– 1	73, 85, 113- 141- 153, 159, 165, 229, 257, 285, 303, 315, 317, 479
60	8.76	665.1674	[M-H]–	Nystose Trihydrate	C24H42O21	3.1	528, 596, 664, 665
61	9.05	287.0577	[M-H]–	Eriodictyol	C15H12O6	0.2	135, 151, 218, 286, 287
62	9.39	405.1774	[M-H]–	Astringin	C20H22O9	– 0.4	405
63	9.63	447.0891	[M + H] +	Baicalein-O-glucuronide	C21H18O11	0.2	271, 447
64	9.81	303.0491	[M + H] +	Quercetin	C15H10O7	0	67, 68, 93, 111, 117, 121, 123, 131, 137, 143, 149, 153, 163, 165, 173, 179, 184, 195, 201, 205, 228, 229, 247, 257, 274, 275, 285, 302, 303
65	10.35	271.06	[M-H]–	Naringenin	C15H12O5	3.8	119, 151, 177, 271
66	10.49	149.0959	[M + H] +	trans-Cinnamate	C9H8O2	0.9	64, 65, 77, 79, 88, 91, 93, 105, 121, 123, 149
67	10.92	345.0617	[M-H]–	Gibberellin A3	C19H22O6	0.6	344, 345
68	11.11	315.051	[M-H]–	Isorhamnetin	C16H12O7	0.7	151, 216, 227, 255, 272, 300, 315
69	12.77	181.1233	[M + H] +	o-Phenanthroline	C12H8 N2	– 2.6	79, 91, 93, 105, 107, 121, 135, 139, 145, 181
70	14.07	387.1807	[M + H] +	1-O-b-D-glucopyranosyl sinapate	C17H22O10	– 0.9	105, 121, 387

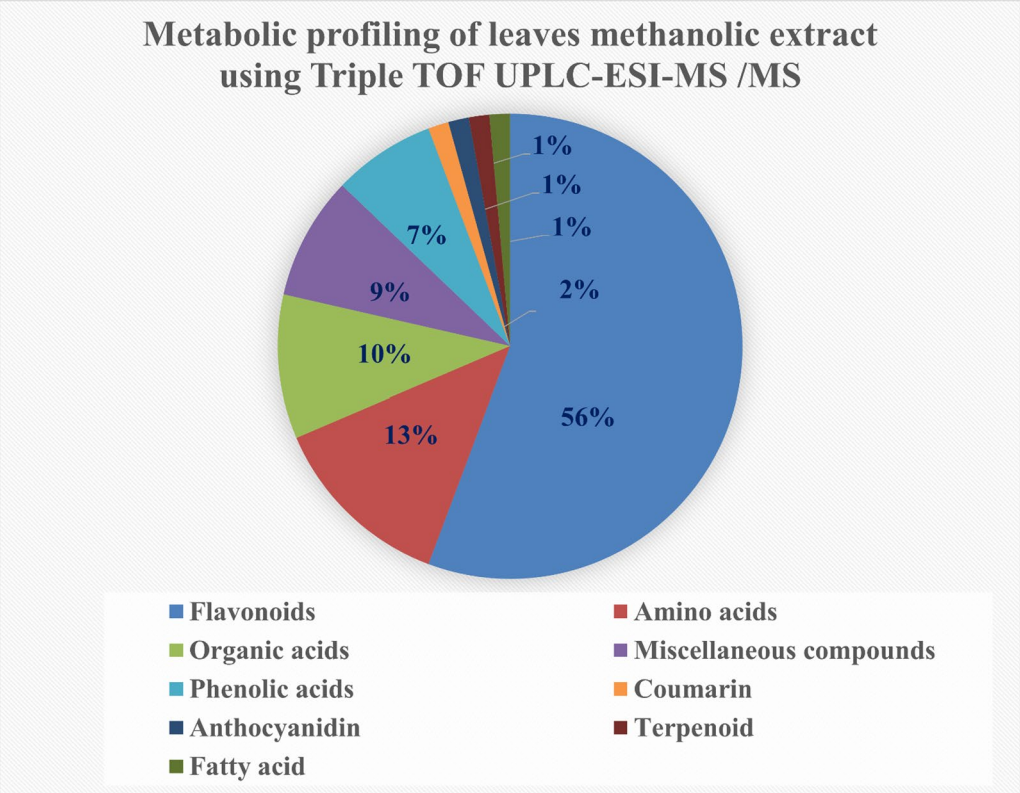


Fig. 3 Phytochemical composition of *S. australe* leaves methanolic extract determined using Triple TOF UPLC-ESI–MS/MS

and at m/z 121 (corresponding to the loss of COOH, CH_3, H_2O, and CO) [21]. In addition, trans-cinnamate (peak 66) was observed with $[M–H]^+$ at m/z 149.0959, product ions at m/z 121 $[M+H–CO]^+$ and m/z 105 $[M+H–COOH]^+$ [22]. Glucopyranosyl sinapate (peak 70) was detected as $[M+H]^+$ at m/z 387.1807, with product ions at m/z 121 and 105 corresponding to sequential losses (including that of a glucose unit and additional neutral fragments) [20]. Sinapyl aldehyde (peak 35) was detected by $[M+H]^+$ at m/z 209.1532 and product ion at m/z 151 $[M+H–C_3H_6O]^+$ [23]. Jasmonic acids and p-hydroxybenzoic acid were isolated and identified in genus [24, 25], but it was the first time to be identified in *S. australe*.

Flavonoids

They were the majority identified in *S. australe* as 39 peaks assigned to flavonols, flavones, flavanonols, isoflavones, and flavanones which mainly were O-glycosidic form as shown in Fig. 6. A hexose sugar moiety was indicated by a mass loss of 162 amu, while losses of 146, 132, and 308 amu corresponded to deoxyhexose, pentose, and rutinoside, respectively.

Table 2 displays the detected flavonoids and their aglycones. Using + ve ionization mode, (peak 51) at m/z 625.1748 and (peak 55) at m/z 479.1163 were identified, respectively, as isorhamnetin-*O*-rutinoside and isorhamnetin-*O*-hexoside. Their aglycone was identified by its distinctive fragment at m/z 317. Also, isorhamnetin (peak 68) showed molecular ion $[M–H]^-$ at m/z 315 [26, 27].

Various quercetin derivatives were identified in − ve and + ve mode with product ion at m/z 301 or 303, respectively, for the aglycone.

- Peak 17 ($[M–H]^-$ at m/z 433.1139) was identified as a quercetin pentoside [19].
- Peak 40 ($[M–H]^-$ at m/z 463.0903) yielded a product ion at m/z 301 ($[M–H–glucose]^-$) was assigned as a quercetin hexoside [27].
- Peak 54 ($[M–H]^-$ at m/z 447.0912) was identified as a quercetin –O–deoxyhexoside [28].
- Peak 59 ($[M+H].^+$ at m/z 479.083) was identified as a quercetin glucuronide [29].
- Peak 64 ($[M+H]^+$ at m/z 303.0491) yielded a product ion at m/z 165,229 (corresponding to the loss of H_2O and 2 CO), 247 (corresponding to the loss of 2 CO), 257 (corresponding to the loss of H_2O and CO), and 285 (corresponding to the loss of H_2O) was assigned as quercetin [30].

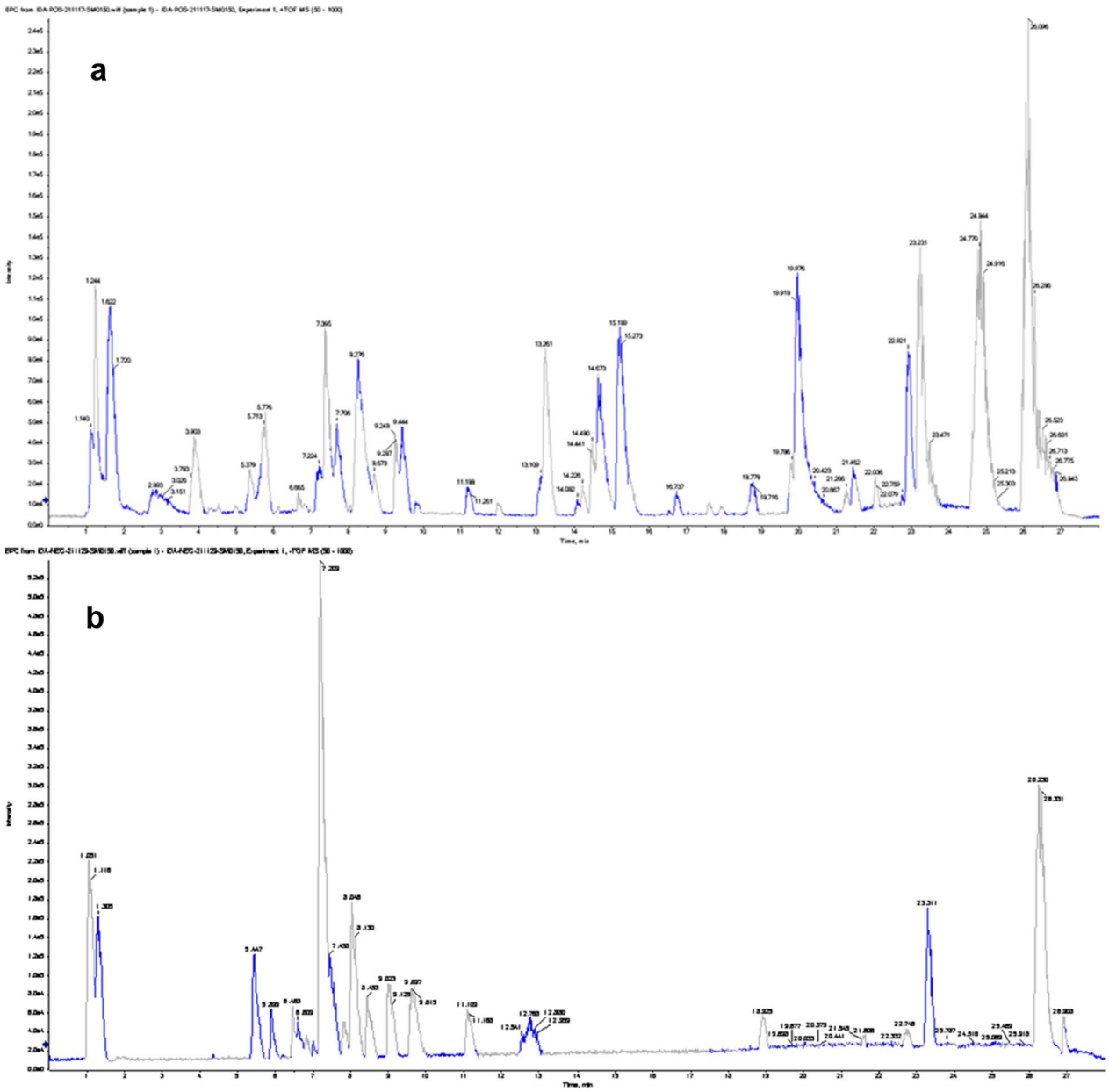


Fig. 4 Base peak chromatogram (BPC) of Triple TOF UPLC-ESI–MS/MS analysis of *S. australe* methanolic extract. **a** +ve mode, **b** -ve mode

- Quercitrin was also identified at peak 24 ($[M–H]^-$ at m/z 447.1866) and product ion at m/z 451. Although quercetin pentoside [30], quercetin glucuronide [31], and quercitrin [32] have been previously isolated from other species of the genus *Syzygium*, this is the first report of its detection in *S. australe*.

The analysis showed a number of flavonol metabolites: afzelin (peak 31) [28], hyperoside (peak 45) [27], and kaempferide (peak 22) [19] with molecular ions $[M–H]^-$ at m/z 431.1909, $[M+H]^+$ at m/z 465.1007, and $[M–H]^-$ at m/z 299.0768. Although hyperoside, isorhamnetin-3-O-glucoside, isorhamnetin 3-O-rutinoside, afzelin, and kaempferol-3-rhamnoside have been previously isolated from other species of the genus *Syzygium* [33–36], this is the first report of its detection in *S. australe*.

Vitexin (peak 30) was detected by $[M+H]^+$ at m/z 433.1686 [37]. Peak 18 and peak 57 were respective identified as acacetin and acaciin by $[M–H]^-$ at m/z 283.1017 [19] and 591.1323 [19]. Luteolin aglycone (peak 52) [27] and its O-glycoside; monohexoside (peak 49) [19] or di-O-hexoside (peak 46) [38] were observed with $[M+H]^+$

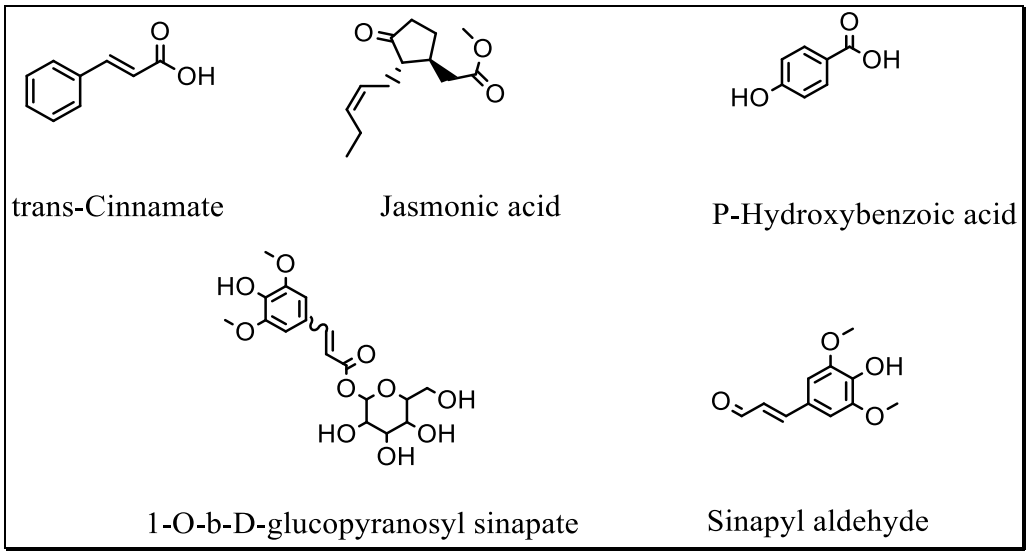


Fig. 5 Selected phenolic acids identified in *S. australe* leaves extracts

at 287.0519 m/z, $[M–H]^-$ at m/z 447.1868, and $[M–H]^-$ at m/z 609.1074. Although acacetin and apigenin have been isolated from other species of the genus *Syzygium* [33, 35], this is the first report of detection in *S. australe*.

Naringenin (peak 65) [26] and hesperetin (peak 26) [33] were detected, respectively, with $[M–H]^-$ ion at m/z 271.06 and 301.0903. The molecular ion of prunin (peak 56) [26] was shown at m/z 435.1281 and its fragment ion 273 due to hexoside loss. The deprotonated isoflavonoid ion at m/z 415.1581 was detected as puerarin (peak 32) [27] by hexose neutral loss (162 Da) at m/z 253 $[M–H–glc]^-$. Procyanidin (peak 50) was detected with parent ion $[M+H]^+$ at m/z 579.1154 [19]. Although hespertin, naringenin, Naringenin-7-O-glucoside, puerarin, procyanidin B2 as procyanidin B1 were isolated from other species of the genus *syzygium* [33, 35], this is the first report of detection in *S. australe*.

Organic acids

Malic acid (peak 3) [39], tartaric acid (peak 4), citraconic acid (peak 12) [19], urocanic acid (peak 27) [19], 3,4-dihydroxymandelate (peak 29) [21], cholic acid (peak 58) [39], and gibberellin A3 (peak 67) [40] as shown in Fig. 7 were identified at $[M–H]^-$ at m/z 133.014, 149.009, 129.097, 137.0245, 183.0285, 407.1841, 345.0617, respectively, for the first time in *S. australe*.

Coumarins and other derivatives

One coumarin: esculin (peak 19) [21] was detected by $[M–H]^-$ at m/z 339.095 and fragment at m/z 177 $[M–H–glc]^-$. Stilbene's derivative was detected (peak 62) [19] E-3,4,5'-trihydroxy-3'-glucopyranosyl stilbene (astringin), presenting $[M–H]^-$ at m/z 405.1774 as shown in Fig. 8.

There were many active constituents already identified in genus *Syzygium* and family Myrtaceae but it is the first time to identify all these compounds in *S. australe*.

Biological in vitro assays

Antidiabetic activity

In contrast to the well-known inhibitors acarbose and orlistat, *S. australe* leaves extract and fractions inhibited α-amylase, lipase, and α-glucosidase enzymes. The butanol and ethyl acetate fractions exhibited lower IC_{50} values (IC_{50}= 0.11 and 0.14 mg/mL for α-glucosidase inhibition, respectively) compared to acarbose (0.24 mg/mL), indicating stronger inhibition. The highest IC_{50} values were for methanolic extract (IC_{50}= 0.407 mg/mL). The butanol and ethyl acetate fractions exhibited lower IC_{50} values (0.06 and 0.09 mg/mL for α-amylase inhibition, respectively) compared to acarbose (0.276 mg/mL), indicating stronger inhibition. The methanolic extract exhibited the least action with higher IC_{50} values (IC_{50}= 0.304 mg/mL). Orlistat IC_{50} to inhibit lipase was 4.1 ng/mL and acarbose IC_{50} to inhibit lipase was 32.05 ng/mL, with the butanol and ethyl acetate fractions displaying again the strongest action (IC_{50}= 26.5 and 30.79 ng/mL) and the methanolic extract demonstrating the least activity (IC_{50}= 54.2007 ng/mL), Fig. 9, Table 3.

Antioxidant activity

S. australe leaf methanolic extract antioxidant activity and its four fractions (butanol, ethyl acetate, methylene

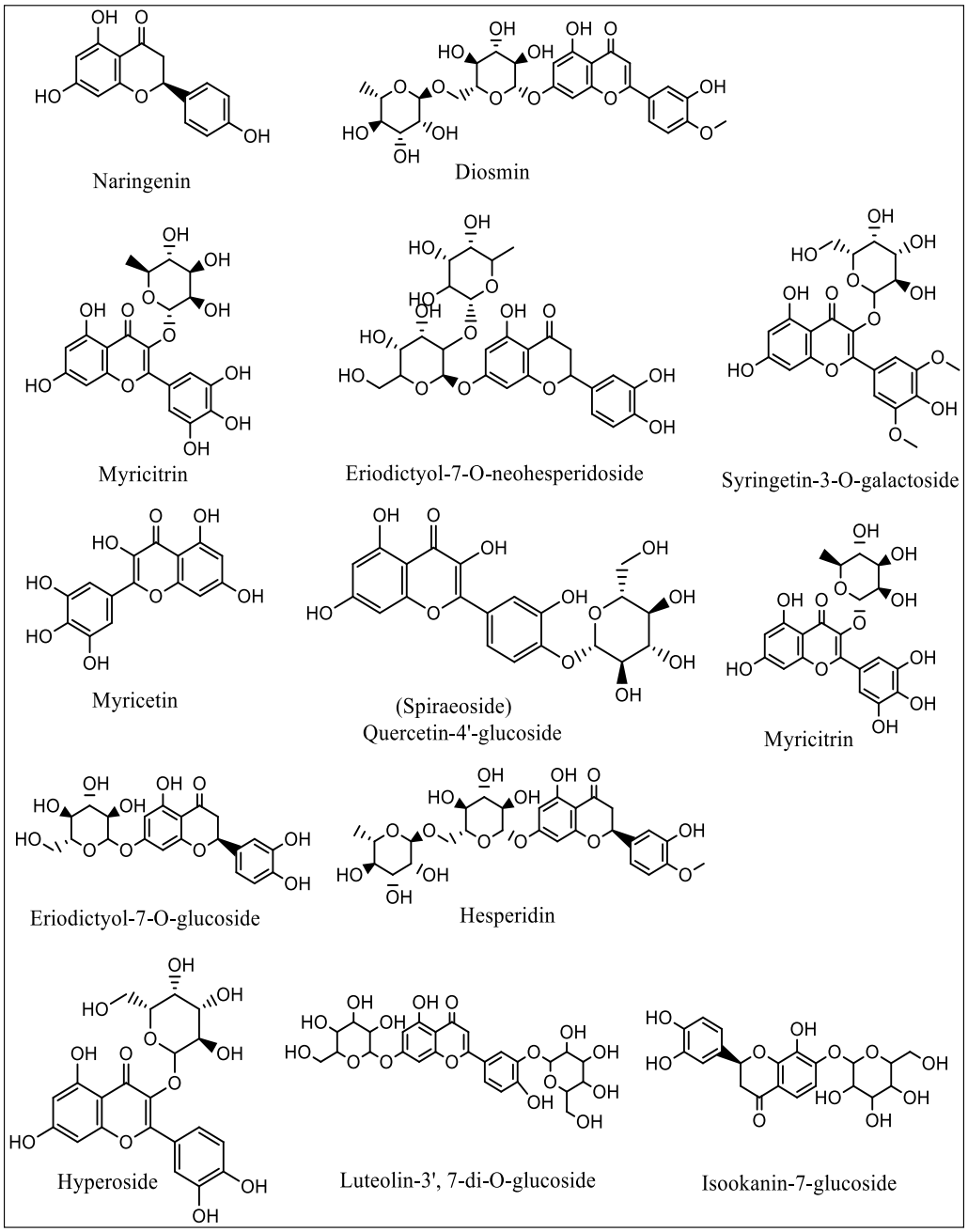


Fig. 6 Selected flavonoids identified in *S. australe* leaves extracts

chloride, and petroleum ether) were examined utilizing DPPH, ferrosin iron metal chelation, FRAP, and ABTS tests. Across all experiments, the butanol and ethyl acetate fractions revealed powerful antioxidant activity. The ethyl acetate IC_{50} (19.93 ± 1 µg/mL) and butanol (38.7 µg/mL) fractions were significantly higher than the reference medicines Trolox (24.42 ± 0.87 µg/mL) and EDTA (39.7 µg/mL) in DPPH and ferrosin iron metal chelation examinations, respectively. In FRAP technique (at 360 µg/mL), butanol and ethyl acetate fractions exhibited antioxidant activity with absorbance values of (0.55 ± 0.030 and 0.37 ± 0.0473, respectively) compared to 0.84 ± 0.02 for BHA. In the ABTS experiment, the butanol and ethyl acetate fractions showed inhibition percentages of 57.46 ± 1.7% and 44.06 ± 1.42%, respectively, at a concentration of 0.1 µg/mL, compared to 84.2 ± 1.22% for BHT. Table 4 shows that when comparison between the fractions and reference drugs in all investigations, the petroleum ether and

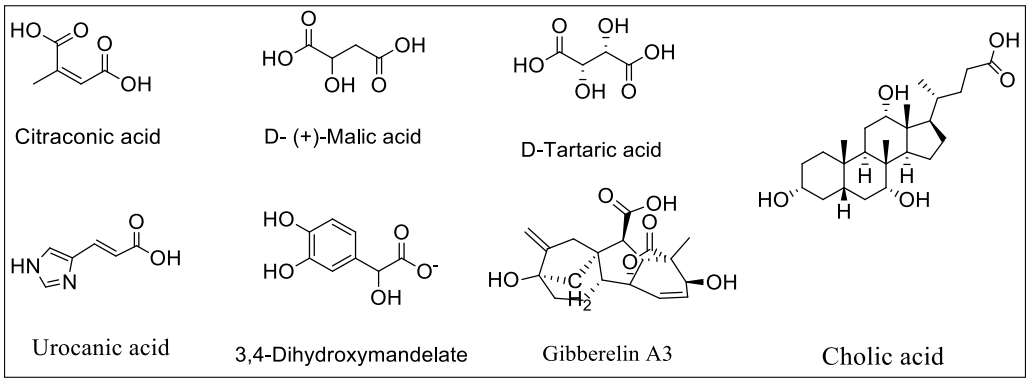


Fig. 7 Selected organic acids identified in *S. australe* leaves extracts

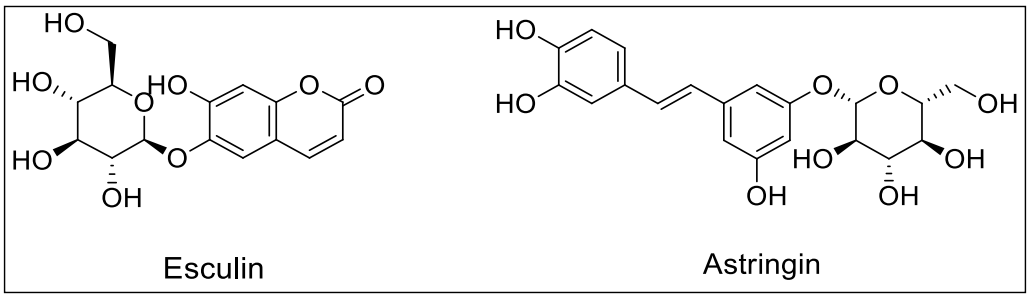


Fig. 8 Selected coumarins identified in *S. australe* leaves extracts

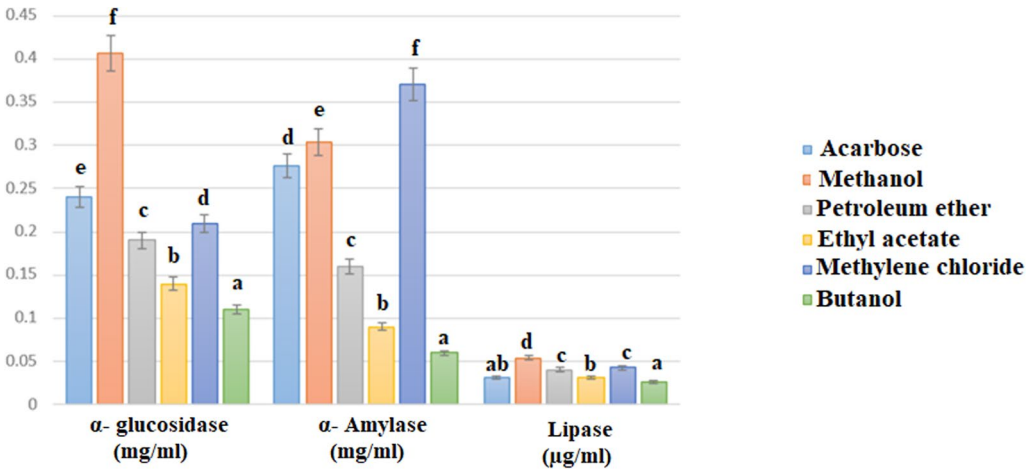


Fig. 9 Antidiabetic potential of *S. australe* leaves extracts *via* multiple pathways

methylene chloride fractions had the lowest antioxidant activity.

Discussion

This study provides the phytochemical content, antioxidant activity, and antidiabetic benefits of *S. australe* leaves. The plant's elevated levels of polyphenols and flavonoids are advantageous. The research indicates that *S. australe* may naturally alleviate diabetes and oxidative stress, fulfilling the demand for safer antidiabetic agents. The Triple TOF UPLC-ESI–MS/MS metabolic profile reveals the presence of polyphenols, flavonoids, and phenolic acids. So there are discrepancy in activity which is due to different phenolic and flavonoid contents in each

Table 3 Antidiabetic potential of *S. australe* leaves extract and fractions via multiple pathways

	Standard	Methanolic extract	Petroleum ether extract	Ethyl acetate extract	Methylene chloride extract	Butanol extract
α-glucosidase IC50 (mg/ml)	Acarbose 0.24	0.407 c	0.19 b	0.14 a	0.21 b	0.11a
α-amylase IC50 (mg/ml)	Acarbose 0.276	0.304 c	0.16 b	0.09 a	0.37 d	0.06 a
Lipase IC50 (ng/ml)	Acarbose 32.05 Orlistat 4.1	54.2007 d	40.57 c	30.79 b	42.52c	26.5 a

Data followed by the same letter are not significantly different at $P \leq 0.05$. F for one-way ANOVA test, pairwise comparison between each two groups was done using a Post Hoc Test (Tukey). The high significant levels of the parameters were in the order of a < b < c < d. Data with superscript alphabet "a" are significantly lower than data with superscript alphabet "b" while data with superscript "b" are lower than data with superscript alphabet "c and d" at *p < 0.05

Table 4 Antioxidant activity of *S. australe* leaves via multiple pathways

Extract	DPPH (IC50 µg/ml)	Ferrosin iron metal chelation (IC50 µg/ml)	FRAP (360 µg/ml)	ABTS˙ inhibition % (0.10 µg/ml)
Methanol	36.81 ± 1.01 c	70.04 b	0.36 ± 0.02 b	32.53 ± 1.62 a
Petroleum ether	9093 ± 1.04 f	89.60 c	0.36 ± 0.030 b	36.56 ± 2.90 b
Methylene chloride	593.6 ± 1.02 e	111.28 d	0.26 ± 0.01a	40.83 ± 2.57 c
Ethyl acetate	19.93 ± 1.03a	70.00 b	0.37 ± 0.0473 b	44.06 ± 1.42 d
Butanol	40.19 ± 1.00 d	38.70 a	0.55 ± 0.030 c	57.46 ± 1.7 e
Trolox	24.42 ± 0.87 b	ND	ND	ND
EDTA	ND	39.70 a	ND	ND
BHA	ND	ND	0.84 ± 0.02 d	
BHT	ND	ND	ND	84.20 ± 1.22 f

DPPH: 2, 2 diphenyl-1-picrylhydrazyl—ABTS˙: 2,2′-Azinobis (3-ethylbenzothiazoline-6-sulfonic acid) diammonium salt—FRAP: Ferric ion reducing antioxidant power—EDTA: Ethylenediaminetetraacetic acid—BHT: Butylated hydroxytoluene—BHA: butylated hydroxyanisole—ABTS: 2,2′-azinobis (3-ethylbenzothiazoline-6-sulfonic acid); ND: None detectable

Data followed by the same letter are not significantly different at $P \leq 0.05$. F for one-way ANOVA test, pairwise comparison between each two groups was done using a post hoc test (Tukey). The high significant levels of the parameters were in the order of a < b < c < d < e. Data with superscript alphabet "a" are significantly lower than data with superscript alphabet "b" while data with superscript "b" are lower than data with superscript alphabet "c and d" at *p < 0.05

extract. The elevated TPC and TFC render these fractions exceptional antioxidants that mitigate reactive oxygen species (ROS) and oxidative damage [41]. Ethyl acetate and butanol fractions had the highest quantities of these beneficial chemicals, as seen in Table 1, suggesting the biological activity. According to the DPPH, ABTS, FRAP, and ferrous ion chelation assays, they demonstrate the radical-scavenging and metal-chelating capabilities of *S. australe* extracts. The methanolic extract and other fractions exhibited less antioxidant activity compared to ethyl acetate and butanol. Due to the potential of phenolics and flavonoids to attach to proteins, they block carbohydrate-hydrolyzing enzymes. They may protect against oxidative stress-induced pancreatic beta-cell dysfunction, thereby lowering the risk of type 2 diabetes onset. The greatest TPC and TFC fractions exhibited the most potent antioxidant and antidiabetic properties. Researchers discovered that polyphenols enhance insulin secretion, reduce oxidative stress, and inhibit carbohydrate-digesting enzymes [42]. Quercetin, hesperetin, naringenin, kaempferol, luteolin, and apigenin can inhibit key enzymes such as α-amylase, lipase, α-glucosidase, and oxidative stress [22, 33]. From phenolics which have antidiabetic activity are trans-cinnamate, p-hydroxybenzoic acid [22]. In comparison with the methanolic extract, the butanol and ethyl acetate fractions demonstrate superior inhibition with lower IC_{50} values than standards. *S. australe* fractions inhibit α-amylase and α-glucosidase more effectively than acarbose, providing a natural and efficient choice for glycaemic management. Additionally, lipase is essential for the digestion of fats; hence, the lipase suppression tests of *S. australe* substantiate its potential in obesity treatment. The IC_{50} values of both butanol and ethyl acetate fractions are equivalent to those of orlistat, a clinically used lipase inhibitor, indicating their potential impact on lipid metabolism. Given the association between obesity and type 2 diabetes, *S. australe*'s dual inhibition of carbohydrate and lipid-metabolizing enzymes renders it a viable antidiabetic agent. This work is among the first evaluations of *S. australe*'s antioxidant and antidiabetic characteristics after other *Syzygium* species have been investigated. Flavonoid and polyphenolic components clearly inhibited α-glucosidase and α-amylase in research on *S cumini* and *S. aromaticum* [43]. The medicinal value

of *S. australe* is shown by these studies. Together with the new flavonoids and phenolic acids, the bioactivity sets *S. australe* apart from other *Syzygium* species. These natural medicines that inhibit α-Glucosidase are more cost-effective and have fewer adverse effects than synthetic drugs. Additionally, they exhibit a range of biological actions, such as antimicrobial and anticancer properties [33].

Conclusions

Our study provides novel insights into that *S. australe* leaves extracts have potential antidiabetic and antioxidant properties. The presence of quercetin and cinnamic acid in the methanolic fraction suggests that the extract can inhibit key enzymes such as α-amylase, lipase, and α-glucosidase. These findings provide compelling evidence that its leaves are rich in phenolic compounds and serve as a potent natural antidiabetic agent. These results emphasize the therapeutic potential of *S. australe* and pave the way for further pharmaceutical investigations.

Plant authentication

In March 2020, *S. australe* fresh leaves were gathered at the Mazhar Botanical Garden in Giza, Egypt. Agriculture Engineer Therese Labib provided the authentication of our plant *S. australe.* She is a former director of El-Orman Botanic Garden in Giza, Egypt, and a Plant Taxonomy Consultant at the Agriculture Ministry. A vouchered specimen (serial number 25.12.2022) was deposited at Cairo University Pharmacognosy Department, Faculty of Pharmacy.

Abbreviations

ABTS	2,2′-Azinobis (3-ethylbenzothiazoline-6-sulfonic acid)
CAN	Acetonitrile
BF	Butanol fraction
BHA	Butylated hydroxyanisole
BHT	Butylated hydroxytoluene
DNSA	3, 5-Dinitrosalicylic acid
DPPH	2, 2-Diphenyl-1-picrylhydrazyl-hydrate
EAF	Ethyl acetate fraction
EDTA	Ethylenediaminetetraacetic acid
$FeCl_3$	Ferric chloride
FIC	Ferrozine iron metal chelation
FRAP	Ferric iron reducing antioxidant power
GA	Gallic acid
GAE	Gallic acid equivalent
HSS	High strength silica
IC_{50}	Inhibitory concentration 50
MCF	Methylene chloride fraction
ME	Methanol extract
Mm	Millimolar
−ve	Negative
PEF	Petroleum ether fraction
p-NPB	P-nitrophenyl butyrate
+ ve	Positive
PPL	Porcine pancreatic lipase
RE	Rutin equivalent
RT	Room temperature
Rpm	Rotation per minutes
S. australe	*Syzygium australe*
TFC	Total Flavonoid contents
TOF UPLC-ESI–MS/MS	Ultra-performance liquid chromatography-electrospray ionization-time of flight-mass spectrometry
TPC	Total phenolic contents
U/mL	Units per millilitre
W/V	Weight per volume

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It is not applicable.

Author contributions
Samah A. Youssef performed the investigation, resources, visualization, and writing the original draft. Hala M. El Hefnawy, Ahmed H. Elosaily, Nermeen F. Farag, and Nabil Mohamed Selim were involved in conceptualization, supervision, visualization, and writing—review and editing of the manuscript. Mohammed A. Hussein helped us in the application of in vitro assays.

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Data Availability
All data generated and analysed during the current study are available in this published article.

Declarations

Ethics approval and consent to participate
Not applicable.

Consent for publication
Not applicable.

Competing interests
No competing interests are disclosed by the authors.

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