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Antioxidant Chemical Constituents from Lychee Seed (*Litchi chinensis* Sonn.)

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Authors' contributions

This work was carried out in collaboration between all authors. Authors XH, YW and XD designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors XD and YW managed the analyses of the study. Author XD managed the literature searches. All authors read and approved the final manuscript.

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ABSTRACT

Aims: To research non-flavonoids chemical constituents from the lychee seed.
Study Design: Chemical constituents were isolated and elucidated from the lychee seed and their antioxidant activities were also estimated.
Place and Duration of Study: School of Pharmacy, Guangdong Pharmaceutical University, between September 2015 and March 2018.
Methodology: All compounds were isolated by Silica gel, Sephadex LH-20, ODS as well as HPLC chromatography and confirmed by 1D and 2D NMR. The DPPH radical scavenging capacities of these isolated compounds were measured using the DPPH assay.
Results: Seventeen compounds were isolated and identified from the lychee seed (**1**–**17**). Among them, amentoflavone (**1**), (7*R*,8*S*)-dihydrodehydrodiconiferyl alcohol 9′-O-β-D-glucopyranoside (**3**), arjunglucoside I (**5**), 3β-hydroxy-7α-methoxy-24β-ethyl-cholest-5-ene (**7**), 4-hydroxy-5-(9′-oxo-8′-pyrrolidinyl)-benzoic acid (**8**), 1-pyrrolidineacetic methyl ester (**9**), phenylalanine methyl ester (**10**),

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2-hydroxyquinoline-4-carboxyic acid (**11**), 3,4-dihydroxy-cyclohexanecarboxylic acid-methyl ester (**13**), 1,1-cyclopropanediacetic acid,1-methyl ester (**15**), cyclopropaneacetic acid, 2-(methoxycarbonyl) (**16**) were first isolated from lychee seed and **3** and **17** exhibited antioxidant capacities on DPPH radical scavenging.

Conclusion: This study suggests that compounds from the seed of *Litchi chinensis* Sonn. showed potential antioxidant properties, which mean that lychee seed could be utilized as a natural antioxidant for health care.

Keywords: Litchi chinensis Sonn; chemical constructions; antioxidant.

ABBREVIATIONS

NMR: Nuclear Magnetic Resonance spectrum; ODS: Octadecyl Silane; HPLC: High-performance liquid chromatography; DPPH: 1-diphenyl-2-picrylhydrazyl; HSQC: Heteronuclear single quantum coherence spectroscopy; HMBC: Heteronuclear multiple bond correlation spectroscopy.

1. INTRODUCTION

Lychee (*Litchi chinensis* Sonn.) is an important evergreen and tropical plant which belong to the sole member of the Sapindaceae family. It is native to southeast of China and now cultivated as an economic crop in many countries due to the global consumption of its fruit. This dolce fruit, prevalent by the worldwide market as its sweet arils and high nutritional value, posses white and semilucent flesh aril which was covered by a red and attractive pericarp [1-3]. Not only delicious taste, lychee has been utilized for traditional medicine in many cultures to treat stomach ulcers, flatulence, gastralgia, diabetes and obesity. In Chinese traditional medicines, lychee seeds were applied to relieve symptoms of testicular swelling, hernia-like conditions, and epigastric and neuralgic pains as a paregoric agent [4-5]. In Ayurveda, lychee was applied to alleviating ulcer and the digestive, and reproductive systems disorder [5]. As a tissue of lychee, lychee seed has been noticed as a high-quality resource for phenolics, such as flavonoids, which showed variety health care benefits including antioxidant and anti-tumor activities. Previous biological activity studies suggested that lychee seed possessed antioxidant, antitumor, antibacterial, antivirus, anti-hyperglycemic, liver protection, and immune-stimulating activities [6-7]. Furthermore, recent research provides that lychee seed saponins also showed neuroprotection effects, which could significantly be improving the learning and memory capacities of model mice [8]. Previous chemical investigations on lychee seeds suggested that it contained various bioactive compounds including flavonoids, phenolic acids, sesquiterpene, oligosaccharides, polysaccharides and triterpenes [5-7]. Furthermore, lychee seed contain large amount of oil, which are including oleic acid, palmitic, dihydrosterculic acid, stearic acid and linoleic acid and so on [9]. Moreover, abundant flavonoids, such as epicatechin, catechin and a series of proanthocyanidins, from lychee seed were considered to take lead responsibility for its excellent antioxidant and antineoplastic activity. [10] However, our previous work suggested that the outstanding antioxidant activities of lychee seeds were not simply due to these flavonoids derivatives [11] and further phytochemical constituents studies of lychee seed is needed for better medicine utilization.

The main objective of this research was to isolate and concentrate the non-flavonoids compounds from the lychee seed, to assess their antioxidant activities.

2. MATERIALS AND METHODS

2.1 Chemicals and Reagents

Methanol for HPLC was purchased from Oceanpak Chemical Co. (Gothenburg, Sweden). Silica gel (200–300 and 300-400 mesh, Anhui Liangchen Silicon Material Co. Ltd. Lu'an, China), ODS (40–60 μm, Merck KGaA, Darastadt, Germany) and Sephadex LH-20 (Amersham Biosciences, Uppsala, Sweden) were utilized for column chromatography. All other reagents and analytical chemicals were provided by Sinopharm Chemical Reagent Co. Ltd. (Shanghai, China).

2.2 Instrumentation

All NMR spectra were tested with a Bruker AV-400 NMR spectrometer. Optical rotations were

measured with a Rudolph II digital polarimeter. Semi-preparative HPLC was obtained by a Waters 2535 pump equipped with a Waters 2489 UV/Visible detector (Waters Corp., Milford, MA, USA) and a C_{18} column (Cosmosil $5C_{18}$-AR-II, 5 μm, 10ID × 250 mm, Nacalai Tesque, Kyoto, Japan).

2.3 Plant Material

Seeds of lychee (20 kg) were purchased from Qingping herbal market, Guangzhou on Aug. 2015 and were confirmed to be *Litchi chinensis* Sonn. by Prof. X. J. He of Guangdong Pharmaceutical University. A voucher specimen was deposited at the Lead Compounds Laboratory, Guangdong Pharmaceutical University.

2.4 Extraction and Purification

The dried pieces of lychee seeds (20 kg) were extracted with 70% ethanol (65 L × 3) and 4 h at 60 – 65°C. The crude extract, was concentrated under reduced pressure to get rid of ethanol, sequentially partitioned with cyclohexane, chloroform, ethyl acetate and n-butanol to obtain their corresponding fractions, and then the EtOAc soluble extract (120.11 g) was subjected to a silica gel C.C. elution with an increasing polarity $CHCl_3$-MeOH (100:0 to 1:1, v/v) to gain seventeen fractions.

Fraction E4 (2.89 g) was isolated by silica gel C.C. elution with cyclohexane-ethyl acetate, followed by Sephadex LH-20 column ($CHCl_3$/MeOH, 2:1, v/v), and then purified with the preparative HPLC (32% MeOH/H_2O, v/v) to get compounds **6** (12.8 mg), **9** (21.3 mg), **10** (5.5 mg).

Fraction E7 (3.38 g) was separated with a silica gel C.C. elution with cyclohexane-ethyl acetate (100:0 to 2:1, v/v) to get subtraction E7-1–E7-8. Subtraction E7-4 was purified by HPLC (47% MeOH/H_2O, v/v) to yield compound **15** (8.1 mg) and **16** (6.3 mg). Subtraction E7-5 was followed by a Sephadex LH-20 column ($CHCl_3$/MeOH 2:1, v/v) and then purified with the HPLC (38% MeOH/H_2O, v/v) to afford compound **7** (8.9 mg). Compound **11** (9.6 mg) was recrystallized from subtraction E7-4.

Fraction E8 (3.92 g) was subjected to a silica gel C.C. eluted with $CHCl_3$-MeOH (100:0 to 2:1, v/v) to yield subtraction E8-1 to E8-10. Subtraction E8-2 followed by a Sephadex LH-20 column ($CHCl_3$/MeOH 1:1, v/v) , and then purified with the HPLC (35% MeOH/H_2O, v/v) to afford compound **8** (9.5mg), **14** (5.3 mg). Subtraction E8-5 through by a ODS column with MeOH/H_2O (10% to 70%, v/v) and then purified with the HPLC (42% MeOH/H_2O, v/v) to afford compound **2** (27.4mg), **4** (15.2 mg) and **5** (12.2 mg).

Fraction E12 (6.53g) was subjected to a silica gel C.C. elution with $CHCl_3$-MeOH (100:0 to 1:1, v/v) to provided subtraction E12-1–E12-10. Subtraction E12-2 through by Sephadex LH-20 column with MeOH/H_2O (80%, v/v) and then purified with the HPLC (32% MeOH/H_2O, v/v) to afford compound **13** (10.8mg). Subtraction E12-6 through by ODS column with MeOH/H_2O (10% to 70%, v/v) and then purified with the HPLC (35% MeOH/H_2O, v/v) to afford compound **1** (17.4 mg) and **12** (50.5mg). Subtraction E12-6 purified with the HPLC (28% MeOH/H_2O, v/v) to afford compound **3** (17.4 mg).

2.5 DPPH Radical Scavenging Activity

The DPPH radical scavenging was determined by utilizing the DPPH assay as previously described [12]. Briefly, 100 μL of each of the tested sample (in methanol, 6.25 to 200 μM) were mixed with 100μL of the DPPH solution (in methanol, 0.2mmol/L) in a 96-well flat-bottom plate. After 0.5 h of incubation in the dark condition at room temperature, the OD value was measured at 510 nm, respectively. Ascorbic acid was implemented as positive control.

3. RESULTS AND DISCUSSION

3.1 Structure Identification of the Purified Phenolics

The ethanol extract of lychee seed was fractionated with different solvents, and then successively chromatographed on silica gel, ODS, Sephadex LH-20 and HPLC to obtain seventeen compounds (Fig. 1).

Compound **10** was obtained as a white powder from the EtOH extract of lychee seed. The molecular formula was identified to be $C_{12}H_{15}NO_3$ dependence on the ^1H NMR and ^{13}C NMR. According to the ^1H and ^{13}C NMR spectrum, with the HSQC spectrum, an N-H proton signals at δ_H 8.34 (1H, d, J = 7.7 Hz); signals at δ_H 7.28 (2H, m) and 7.21 (3H, t, J = 5.5 Hz) with δ_C 137.3, 129.0, 128.2, 126.5 suggested the presences of one substituted benzene group, a methoxy proton signal at δ_H 3.58 (3H, s) with δ_C 51.8,

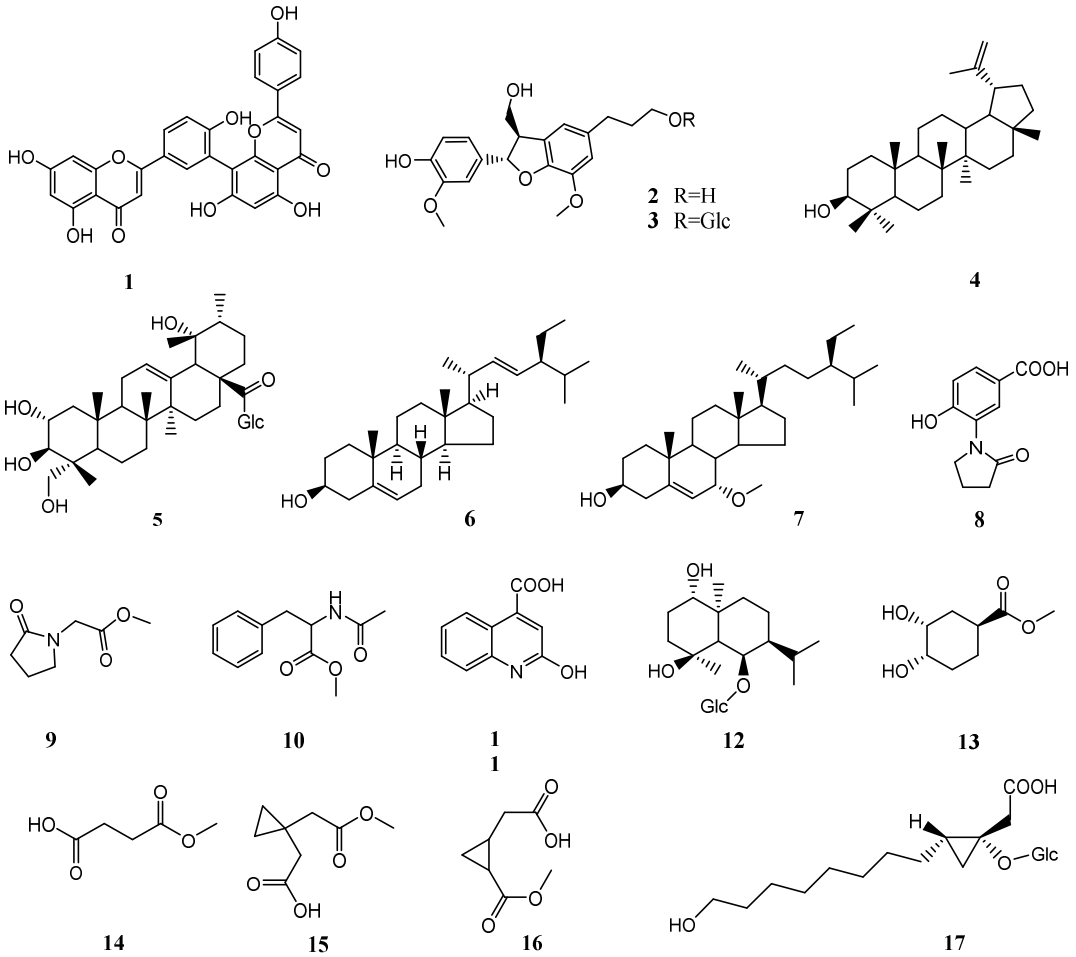

Fig. 1. Structures of phenolics 1-15 isolated from lychee seed

a methene proton signal at δ_H 3.00 (1H, dd, *J* = 13.7, 5.6 Hz) , 2.86 (1H, dd, *J* = 13.7, 9.3 Hz) and δ_C 36.7, as well as a methyl proton signal at δ_H 1.78 (3H, s) and δ_C 22.2, two carbonyl carbon signals at δ_C 169.3 and 172.2, respectively. In the HMBC spectrum, (Fig. 2-A), the correlations of H-5/9(δ_H 7.21) with C-3 (δ_C 36.7), and H-2 (δ_H 4.44) coupled with C-4 (δ_C 137.3)/ C-1 (δ_C 172.2), as well as H-3(δ_H 2.86) correlated with C-2 (δ_C 53.6)/ C-1 (δ_C 172.2) were observed. Above all, combined with the ^{1}H-^{1}H COSY spectrum correlations both N-H with H-2 and H-2 with H-3, indicated that phenylpropanoic acid methyl ester linkage formamide moiety at C-2. According to a described protocol [13], compound **10** was eventually elucidated to be phenylalanine methyl ester.

Compound **17** was compiled as faint yellow oil from the EtOH extract of lychee seed. The molecular formula was established to be $C_{19}H_{34}O_9$ based on the ^{1}H NMR and ^{13}C NMR. According to the ^{1}H and ^{13}C NMR spectrum, with the aid of HSQC spectrum, signal at δ_c 174.9 showed the existence of one carboxyl carbon; signals at δ_H 4.25 (2H, d, *J* = 7.9 Hz) and δ_C 103.1 (C-1') indicated the existence of an β-glucopyranosyl moiety; one oxygenated quaternary carbon signal at δ_C 63.3 (C-3); and δ_H 3.36 (2H, d, *J* = 6.4 Hz) with δ_C 60.9 (C-12) displayed the presence of one oxygenated, and signals at δ_H 2.77 (1H, d, *J* = 16.2 Hz), 2.43 (1H, d, *J* = 16.2 Hz) with δ_C 38.0 (C-2) exhibited the presence of one methene. The existence of a methine with highly shielded signal at δ_H 1.01 (1H, d, *J* = 6.7 Hz) and δ_C 23.8 (C-4), as well as a methylene protons at δ_H 1.14 (1H, dd, *J* = 9.7, 5.0 Hz), 0.27 (1H, t, *J* = 5.7 Hz) and δ_C 18.7 (C-13), all those signals demonstrated a moiety of 1,1,2-trisubstituted cyclopropyl. In the HMBC spectrum, (Fig. 2-B), the correlations of H_a-2(δ_H 2.77) with C-1 (δ_C 174.9)/ C-3/ C-13, and H_b-2(δ_H

2.43) coupled with C-1 (δ_C 174.9)/ C-3/ C-4, as well as H-11(δ_H 1.39) with C-7 (δ_C 29.0); H-12(δ_H 3.38) with C-10 (δ_C 25.6)/ C-11(δ_C 32.6) were noticed. All these data, together with the ^1H-^1H COSY spectrum correlations of H-12 with H-11, H-11 with H-10 and H-5 with H-4, indicated that a cyclopropyl ring get involved in a dodecanoic acid at C-2 and C-5 and a hydroxyl function

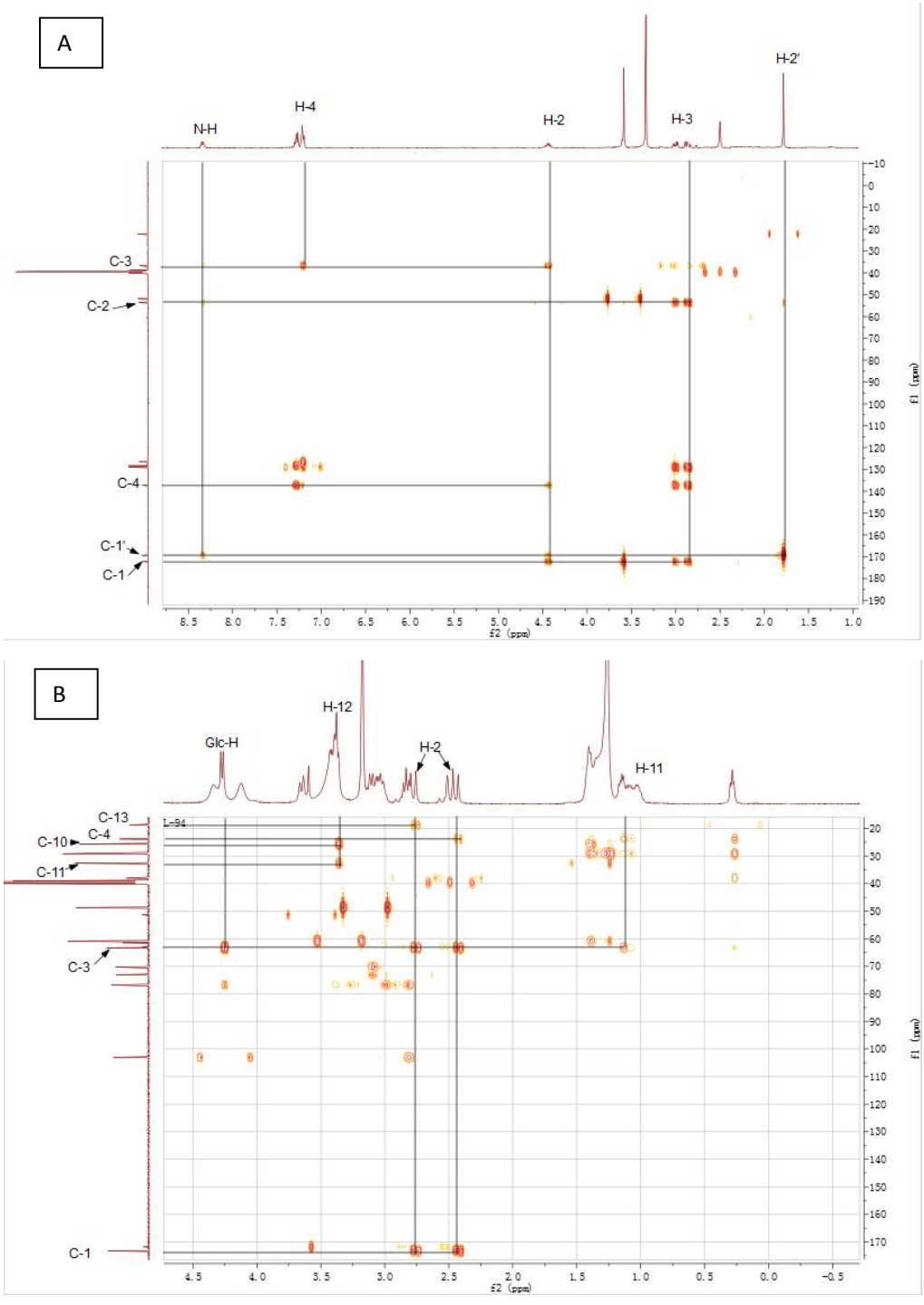

Fig. 2. Enlarged HMBC of compound 10 (A) and 17 (B)

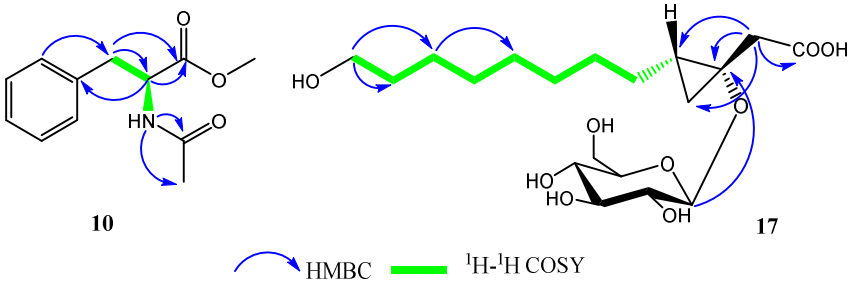

Fig. 3. HMBC and ^{1}H-^{1}H COSY correlations of compound 10 and 17

linking at C-12. Anymore, the correlation between H_{Glc}-1(δ_H 4.25) and C-3 suggested that a glucopyranosyl group located at C-3. Depending on these NMR spectral data and comparison with literature [9], consequently compound **17** was concluded to be litchioside C.

Other compounds was determined to be amentoflavone (**1**) [14], (7*R*,8*S*)-3,5′-dimethoxy-4′,7-epoxy-8,3′-neolignane-5,9,9′-triol (**2**) [15], (7*R*,8*S*)-dihydrodehydrodiconiferyl alcohol 9′-O-β-D-glucopyranoside (**3**) [16], lupeol (**4**) [17], arjunglucoside I (**5**) [18], stigmasterol (**6**) [19], 3β-hydroxy-7α-methoxy-24β-ethyl-cholest-5-ene (**7**) [20], 4-hydroxy-5-(9′-oxo-8′-pyrrolidinyl)-benzoic acid (**8**) [21], 1-pyrrolidineacetic methyl ester (**9**) [22], 2-hydroxyquinoline-4-carboxyic acid (**11**) [23], pumilaside A (**12**) [1], 3,4-dihydroxy-cyclohexanecarboxylic acid-methyl ester (**13**) [24], 1-methyl ester, butanedioic acid (**14**) [25], 1,1-cyclopropanediacetic acid,1-methyl ester (**15**) [26], cyclopropaneacetic acid, 2-(methoxycarbonyl) (**16**) [27].

3.2 Antioxidant Activity

In the present study, the DPPH assay was implemented to evaluate the antioxidant capacities of compounds **1**–**17**. The results were summarized in Fig. 4, compounds **3** exhibited noteworthy DPPH radical scavenging activity with the IC_{50} values (30.41±1.13 μM). Compounds **17** displayed moderate DPPH free radical scavenging activity, compared to ascorbic acid (29.97±1.12 μM). The IC_{50} values of other compounds more than 400 μM and were considered feeble activities. The DPPH methanol solution, a dark violet solution with main absorption at 510 nm, become discolored with the presence of the radical scavenger in the reactive system as the odd electron of nitrogen was paired in the DPPH. As we known, the

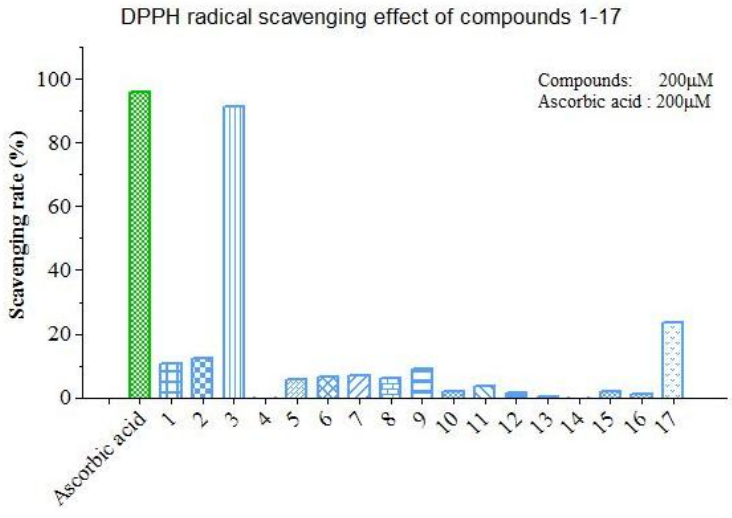

Fig. 4. Antioxidant actives of compounds 1-17

*Test concentrations ranged from 12.5 to 200 μM. The IC_{50} values of compound 3 (30.41 ±1.13 μM). Ascorbic acid was implement as positive control. **p < 0.01 vs the positive control. *p < 0.05 vs the positive control*

Table 1. ^{13}C NMR (101 MHz) data of compounds 1-8 in DMSO-d_6

NO.	δ_C (ppm)							
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**
1	164.1	132.6	132.6	38.2	46.1	37.4	38.0	125.9
2	102.6	110.3	110.3	27.0	67.5	29.9	32.8	130.0
3	182.1	147.6	147.6	76.8	77.7	71.9	71.5	116.5
4	160.5	146.3	146.3	38.2	42.5	42.5	43.7	156.9
5	98.8	115.3	115.4	54.8	46.1	140.9	147.6	121.7
6	161.8	118.5	118.6	17.6	17.4	121.9	121.2	129.6
7	103.9	86.8	86.9	33.7	30.3	32.0	74.1	166.7
8	154.5	53.3	53.3	40.3	40.8	32.0	37.8	174.4
9	103.6	63.1	63.1	49.8	47.1	50.3	43.9	30.6
10	121.4	135.1	134.7	36.6	37.4	36.7	38.3	18.4
11	127.8	116.5	112.6	20.3	23.4	21.1	21.6	48.9
12	115.8	129.1	143.4	24.5	121.6	39.9	40.0	
13	161.0	145.6	145.6	37.4	137.8	42.4	42.7	
14	116.1	143.4	129.1	42.2	41.4	56.9	49.8	
15	128.2	112.4	116.6	26.9	31.6	24.5	24.9	
16	163.8	31.5	31.5	35.0	27.5	28.4	29.0	
17	103.0	34.7	31.3	42.4	45.9	56.2	56.6	
18	181.7	60.3	67.9	47.7	43.2	12.1	12.1	
19	161.4	55.7	55.7	47.3	81.0	19.6	18.9	
20	98.6	55.6	55.8	149.9	33.9	40.6	36.8	
21	163.7			29.2	27.1	21.2	19.5	
22	94.0			38.4	31.8	138.5	34.6	
23	157.4			27.9	63.7	129.4	26.6	
24	103.7			15.5	13.7	51.4	46.4	
25	120.0			15.8	16.7	31.8	29.9	
26	127.8			15.6	16.8	20.0	20.4	
27	121.0			14.1	24.9	18.9	19.6	
28	159.5			17.8	175.3	25.5	23.8	
29	116.1			109.3	27.5	12.2	12.5	
30	131.4			18.9	25.6		56.6	
1'			103.1		94.1			
2'			73.6		72.4			
3'			76.8		76.7			
4'			70.1		69.6			
5'			76.9		75.6			
6'			61.2		60.7			

hydrogen donating ability of antioxidant take responsibility for DPPH radical scavenging effects [28], and hydroxyl function, as a potential hydrogen contributor, was primary factor for the radical scavenging capacities of compound **3**. Generally, the presence of free radicals could damage the cells of organisms, which may take responsibility for a series of health issues. However, antioxidants, especially natural antioxidant products, could produce benefit to health. The previous literature [29] suggested that a great deal of lignans with different chemical structural exhibited variant antioxidant activities, both the number and the location of hydroxyl as well as glycosides were the main characteristic of lignans for the overall scavenging abilities against DPPH radicals. Above those, also explained why the antioxidant effects of compound **3** stranger than **2**. The antioxidant effects of compounds **3** displayed that flavonoids compounds could not be the only element for the high antioxidant activity in lychee seeds.

Table 2. ^{13}C NMR (101 MHz) data of compounds 8-17 in DMSO-d_6

NO.	δ_C (ppm)								
	9	**10**	**11**	**12**	**13**	**14**	**15**	**16**	**17**
1		137.3		77.9	36.3	173.3	51.2	51.3	174.9
2	174.5	129.0	161.1	28.0	33.8	28.7	172.9	172.2	38.0
3	29.8	128.2	123.3	39.9	67.8	28.5	33.0	19.3	63.3
4	17.5	126.6	141.3	71.3	70.1	172.5	11.0	17.1	23.8
5	47.1	128.2	115.8	49.9	27.6	51.3	10.9	13.9	29.3
6	49.2	129.0	115.8	76.8	26.2		10.2	36.3	28.9
7	169.3	36.7	122.3	40.4	175.9		33.3	174.7	29.0
8	51.8	53.6	130.9	22.6	51.5		174.1		29.2
9		172.2	126.1	35.5					29.4
10		51.8	139.4	41.2					25.6
11		169.3	166.8	24.7					32.6
12		22.2		23.1					60.9
13				22.4					18.7
14				13.9					103.1
15				23.6					73.1
16				98.3					76.8
17				74.3					70.3
18				77.0					76.7
19				70.4					61.6
20				76.9					
21				61.4					

4. CONCLUSION

In this present study, seventeen compounds were isolated from the *Litchi chinensis* Sonn. and their structures were further established by the spectroscopic analysis and comparison with literatures. Among them, compounds **1** ,**3**, **5**, **7**, **8**, **9**, **10**, **11**, **13**, **15**, **16** were detected from lychee seed for the first time. The antioxidant capacities of all isolated compounds were assessed by DPPH assay. Compounds **3** and **17** showed potential DPPH radical scavenging abilities. These results suggested that other types of compounds could also contribute to the prominent antioxidant activity in lychee seed, not just flavonoids derivatives and phenolic acid. Moreover, with more and more fresh phenolics have been used in functional foods, extensive investigation about other type of phenolics and multifunctional bioactivity ingredients in lychee seed is required for the potential utilization of this seed resource as a natural product in the development of dietary supplement and medicine.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

ACKNOWLEDGEMENTS

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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