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# Isolation, characterization and structural elucidation of eight known phenolic compounds from *Lycium ruthenicum Murr.*

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***Abstract***
*Lycium ruthenicum Murr. (Solanaceae family), a flowering plant commonly known as "Black Goji" is generally consumed as ethnic medicine and nutraceutical food. This study was carried out in order to ascertain the quality control bases for this herbal medicine via chemical compounds isolation and identification to confirm its traditional used. The dried fruits of L. ruthenicum were extracted with water, 60% ethanol and 95% ethanol. Column chromatography of this extract was followed by purification of different fractions, leading to the isolation of eight known compounds namely four phenolic acids (Caffeic acid (**1**), cis-p-coumaric acid (**2**), Gallic acid (**3**), trans-p-coumaric acid (**6**)) and four flavonoids (Quercetin (**4**), Rutin (**5**), Syringin (**7**) and Catechin (**8**)). Their structures were established by interpretation of their 1D NMR data experiments, comparative TLC and by comparison with data reported in the literature. These compounds were reported to have promising biological activities including antioxidant, anti-inflammatory, antidiabetic, cardio protective, antiaging, and anticancer that perfectly corroborate with the traditional use of the plant. These results offer essential information for further understanding of the biological functions of these Lycium fruits used as phytomedicines and functional food.*
***Keywords****: Lycium ruthenicum, Solanaceae, flavonoids, phenolics.*

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## I. Introduction

Herbal medicine, also known as botanical medicine is a medical discipline focused on the use of plants, usually with multiple active constituents working in synergy to exert their pharmacological actions in or on the body. Herbal medicine has long been used by several ethnic groups throughout the world to treat different diseases and to improve immune system functions. Even though it is not a licensed profession in some countries, herbal medicines (in a pharmaceutical form or as infusion) are often recommended by traditional healthcare practitioners as a way to remedy a wide variety of health conditions. However, there is limited scientific evidence to establish the safety and efficacy of most herbal products. As a country with a rich herbal resource, China is not an exception. In the past few years, the range of disease has shifted and the complex chronic diseases have become the main point[1]. The effect of Western medicine treatment is not always satisfactory and problems of the adverse drug reaction are also very prominent. Herbal medicine has therefore gained more attention and has also become popular. About 80% of people worldwide rely on herbal medicines for some aspects of their primary health care[2].

*Lycium ruthenicum* Murr. (black "Goji" ), is a nutritional food, a medicinal and edible plant which is mainly found in the salinized desert of Northwest of China [3]. It is widely used in traditional medicine. It constitutes genuine "chemical factories", producing numerous biologically active compounds, which could be certainly exploitable in phytotherapy. Its fruits are used both as food and Traditional Chinese Medicine (TCM) for the treatment of heart disease [4], menopause [4], abnormal menstruation [5], hypertension [6]; and as a principal material to prepare nutritious drinks , to fill up vital essence in the body and improve eyesight.

In the past years, a wide spectrum of secondary metabolites such as polysaccharides, and phenolic compounds have been isolated, characterized or identified/tentatively identified from the fruits of *Lycium* plants [7-9], other compounds include terpenoids [10, 11], peptides[12], sterols[13], aromatic acids and derivatives [14-16], carotenoids and their esters [17], flavonoids [6, 18], and phenolic amides [19] which have also been

isolated and characterized from the roots, leaves and fruits. Meanwhile, the antioxidant properties of the fruits of *Lycium* have been intensively studied for many years

As though the use of *L. ruthenicum* is increasing steadily, and in the course of our continuing search for secondary metabolites of biological importance from medicinal plant, we investigated the EtOAc extract of the dry fruits of *L. ruthenicum* Murr. from Tibet.In the present study, we reported the isolation and structural elucidation of nine known phenolic compounds using chemical, and spectroscopic methods in complement with data from reported literature.

## II. Materials And Methods

### 2.1. Experimental

$^1H$ (300-500 MHz) and $^{13}C$ (100 MHz) nuclear magnetic resonance (NMR) spectra were recorded on a BRUKER Avance ACF-500 spectrometer (Bruker, Wissembourg, France) equipped with a cryoplatform using $CD_3OD$, with tetramethylsilane (TMS) as the internal standard. Column chromatography was performed on Merck silica gel, (Fuji, Japan) 60 (70-230 mesh), RP-C18 (40–63 µm, Fuji, Japan) and gel permeation chromatography was performed on Sephadex LH-20 (Pharmacia, Sweden), while thin layer chromatography (TLC) was carried out on silica gel GF254 pre-coated plates (Qingdao Marine Chemical Co. Ltd., China) with detection accomplished by spraying with 50% $H_2SO_4$ followed by heating at 100°C or by visualization with an ultra-violet (UV) lamp at 254 and 365 nm. ESI-MS mass spectra were recorded on an Agilent 1100 series LC/MSD trap mass spectrophotometer.

### 2.2. Plant material

The fruits of *Lycium ruthenicum* Murr. were collected from Tibet. The botanical identity as, *Lycium ruthenicum* Murr (Solanaceae) was confirmed by Prof. Feng Feng (Institute of Chinese Medicine, Key Laboratory of Biomedical Functional Materials, China Pharmaceutical University) China. A voucher specimen (LR2015-01) was deposited at the Department of Natural Medicinal Chemistry, China Pharmaceutical University**.**

### 2.3. Extraction and isolation

The air-dried fruits of *Lycium ruthenicum* Murr. (7.9 kg) was powdered and extracted with 95% ethanol (2 h each) using a soxhlet under reflux. The extract was concentrated to dryness under reduced pressure to yield a dark crude ethanol extract (800 g). Part of the residue obtained (750 g) was suspended in water (1.5 L) and successively extracted with petroleum ether, dichloromethane, and ethyl acetate. The result was concentrated to dryness under reduced pressure to yield respectively petroleum ether (145 g), dichloromethane (85 g) and ethyl acetate (120 g) extracts.

The ethyl acetate extract (110 g), was submitted to further separation and purification. It was purified over a silica gel column and eluted with $CHCl_3$ containing increasing concentrations of MeOH (10%, 20%, 30%, 40%, 50%, 60%, 70%, 80% and 90%). On the basis of their TLC profiles, four fractions were obtained: A, B, C and D. Fraction C (12.6 g) was purified over a silica gel column and eluted with $CHCl_3$ containing increasing concentrations of MeOH (30%, 40%, 50%, 60%, 70% and 80%). On the basis of their TLC profiles six subfractions were obtained: LRCa, LRCb, LRCc, LRCd, LRCe and LRCf. Subfraction LRCa (3.2 g) was purified over a Sephadex LH-20 gel column and eluted with MeOH to yield compounds **1** and **3** (3.8 mg and 12.4 mg respectively). Compounds **4** and **9** (16.6 mg and 4.1 mg respectively) was obtained after purification of subfraction LRCc (2.4 g) over reversed-phase C18 silica gel column chromatography a with MeOH-$H_2O$ (7:3). Subfraction LRCd (118.8 mg) was purified over a sephadex LH-20 gel column chromatography with MeOH to yield compound **7** (14.5 mg). Compounds **5** (5.1 mg) was obtained after purification of subfraction LRCd (100 mg) over silica gel column chromatography with $CHCl_3$-MeOH mixture (8:2). Subfractions LRCe (23 mg) and LRCf (830 mg) were combined and purified over a silica gel column chromatography with a $CHCl_3$-MeOH mixture (9:1) to yield compounds **2, 6** and **8** (7.1 mg, 9.2 mg and 6.5 mg respectively).

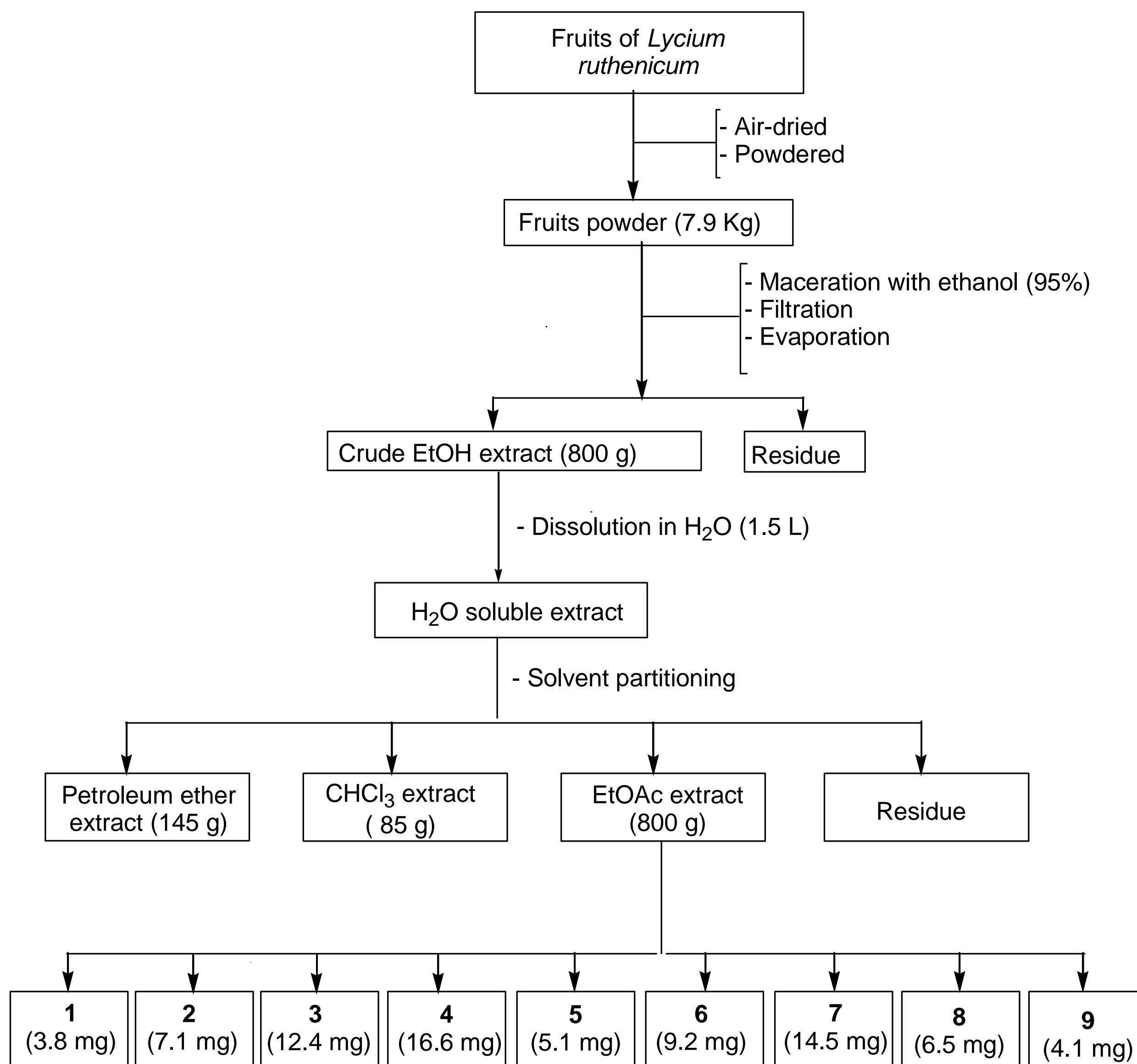



**Figure1**: Isolation procedure of secondary metabolites from fruits of *Lycium ruthenicum*

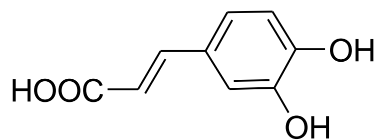
## III. Results and discussion

### 3.1. Structural identifications

#### 3.1.1. Structural identification of compound 1

Compound **1** was obtained as a yellow powder. Its ESI-MS spectrum (**fig. 2**) exhibited a pseudo-molecular ion peak at *m/z* 178.02 $[M - H]^-$ indicating the molecular formula $C_9H_7O_4$. Results of 5% $FeCl_3$ / MeOH reaction was blue, suggesting that the compound contains phenolic hydroxyl groups. The $^1$H-NMR spectrum (**fig. 3**) displayed a signal at $\delta_H$ 9.44 (2H, s) indicating the presence of 2 active (2-bromo-2-hydroxyethyl) Phenolic hydroxyl, two signals at δ H 6.16 (1H, d, J = 15.9 Hz) and δ H 7.41 (1H, d, J = 15.9 Hz), typical of a pair of trans olefinic protons, with additional signals for aromatic proton at δ H 6.75 (1H, d, J = 8.1 Hz), 6.96 (1H, d, J = 8.2 Hz) and 7.02 (1H, s).

comparison of the $^1$H data of **1** with those of related compounds[20] , together with The physicochemical properties and comparative TLC supported structure **1** for caffeic acid (CA). Its structure is shown below:




**(1)**

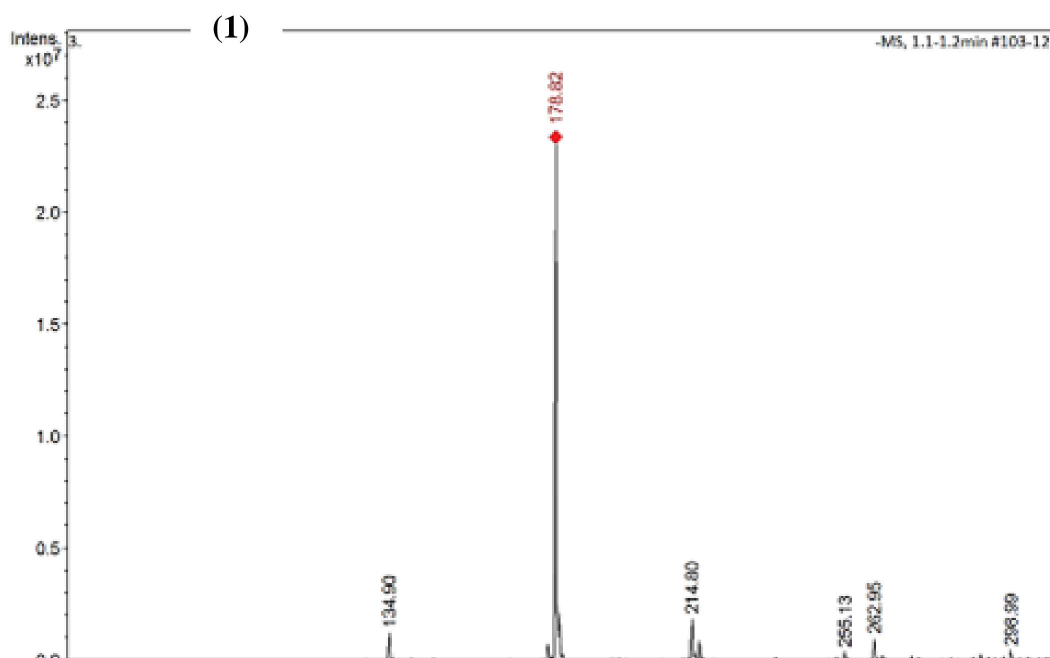



**Figure 2:** ESI-MS spectrum of compound 1

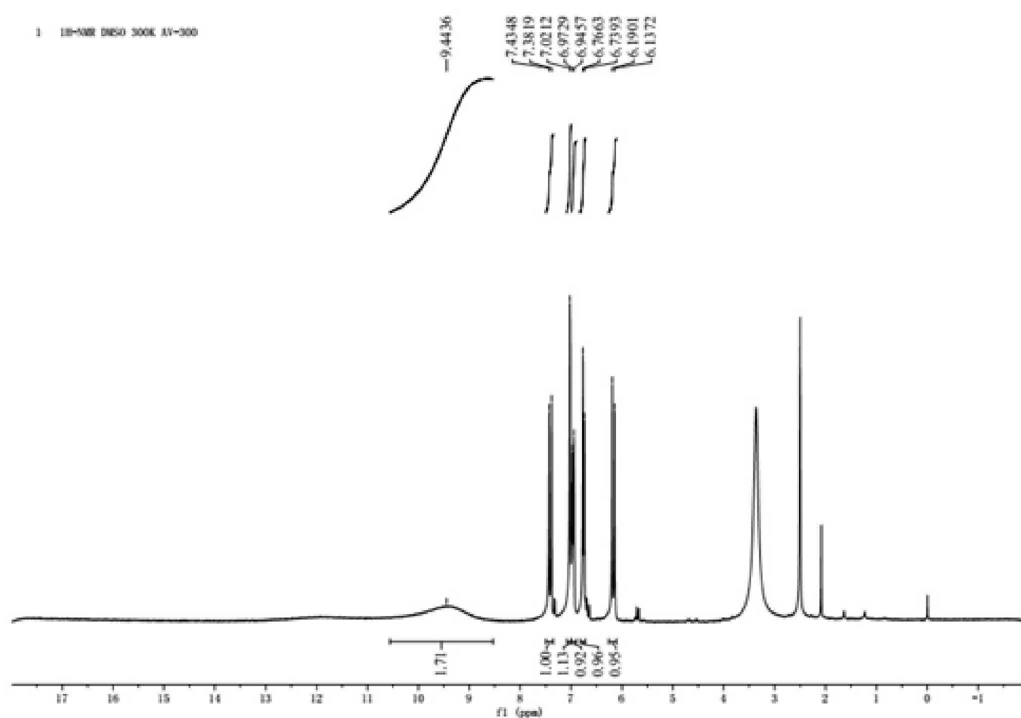
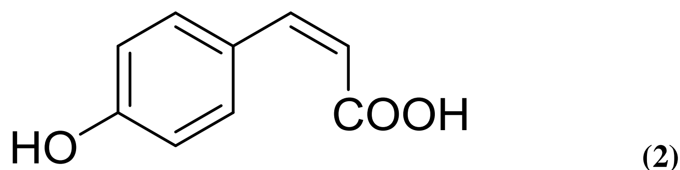



**Figure 3:** $^{1}$H-NMR spectrum of compound 1 (300 MHz, DMSO-$d_6$)

**3.1.2. Structural identification of compound 2.**

Compound **2** was obtained as a white powder, soluble in methanol. It gave a negative Molish reaction. Characteristic test with 1% vanillin - concentrated sulfuric acid reaction gave blue-purple color, and sprayed $FeCl_3$ was purple. All these indicating phenolic hydroxyl. ESI-MS spectrum (**fig.4**) revealed a quasimolecular signal at *m/ z*: 163.0 $[M-H]^-$.$^{1}$H-NMR (300 MHz, DMSO-$d_6$) (**fig. 5**) showed signals for two hydroxyl hydrogens

at δH 11.98 (1H, s) δH 9.94 (1 H, s), four aromatic hydrogens at δ H 7.43 (2H, d, J = 6.1 Hz), 6.72 (2H, s), and two ethylenic protons at δ H 7.43 (1H, s), 6.21 (1H, d, J = 10.1 Hz). The coupling constant of 10.1Hz confirmed the *cis* geometry [21]. The physicochemical properties and spectral data of the compounds were compared with those reported in the literature [22]. The compound was identified as *cis*-*p*-coumaric acid (**2**), a phenolic acid of the hydroxycinnamic acid family. The structure of compound **2** is shown below:




**(2)**

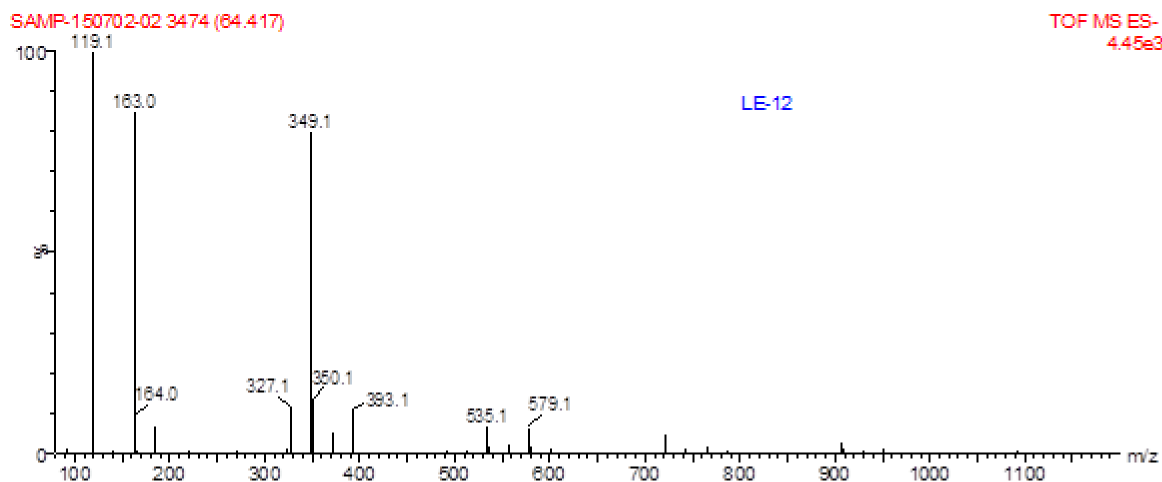



**Figure4**: ESI-MS spectrum of compound 2

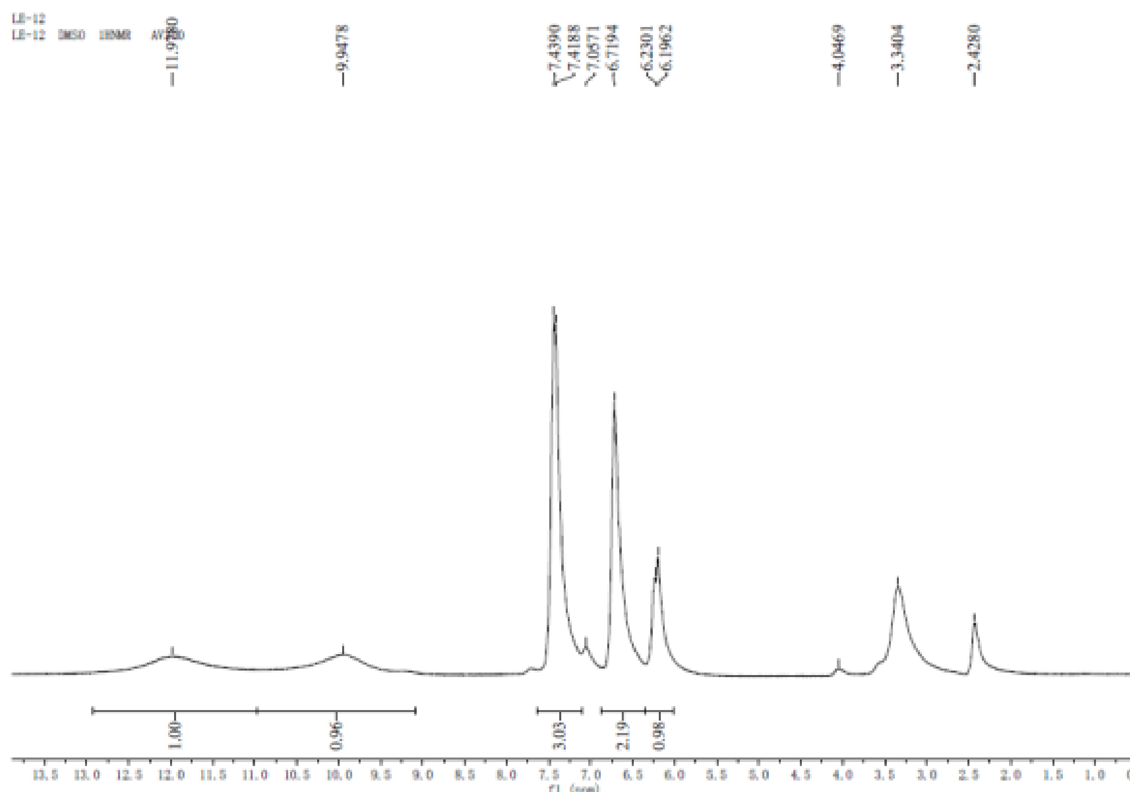



**Figure5**: $^{1}$H-NMR spectrum of compound 2 (300 MHz, DMSO-$d_6$)

**3.1.3. Structure identification of compound 3**.

Compound **3** was obtained as Light yellow crystals, soluble in methanol, DMSO, and insoluble in chloroform. UV light revealed no fluorescence at 365 nm. 1% vanillin - concentrated sulfuric acid lead to a tan color, 5% $FeCl_3$ / MeOH solution test was blue, suggesting that the structure of the compound presents phenolic hydroxyl.

ESI-MS (**fig. 6**) negative ion mode revealed a pseudo-molecular ion peak at $m$ / $z$: 168.77 $[MH]^-$. Analysis on the $^1$H-NMR spectrum (500 MHz, DMSO-$d_6$) (**fig. 7**) displayed phenolic hydroxyl groups at δ H12.11 (2H, s), and 8.80 (1H, s), aromatic hydrogens at δH 6.90 (2H, s), suggesting the presence of tetra substituted benzene ring, and symmetrical structure.

The physico-chemical properties and $^1$H-NMR spectra data of compound **3** were basically the same as those reported [23] and comparative TLC. Therefore, compound **3** was identified as gallic acid. Its structure is shown below:

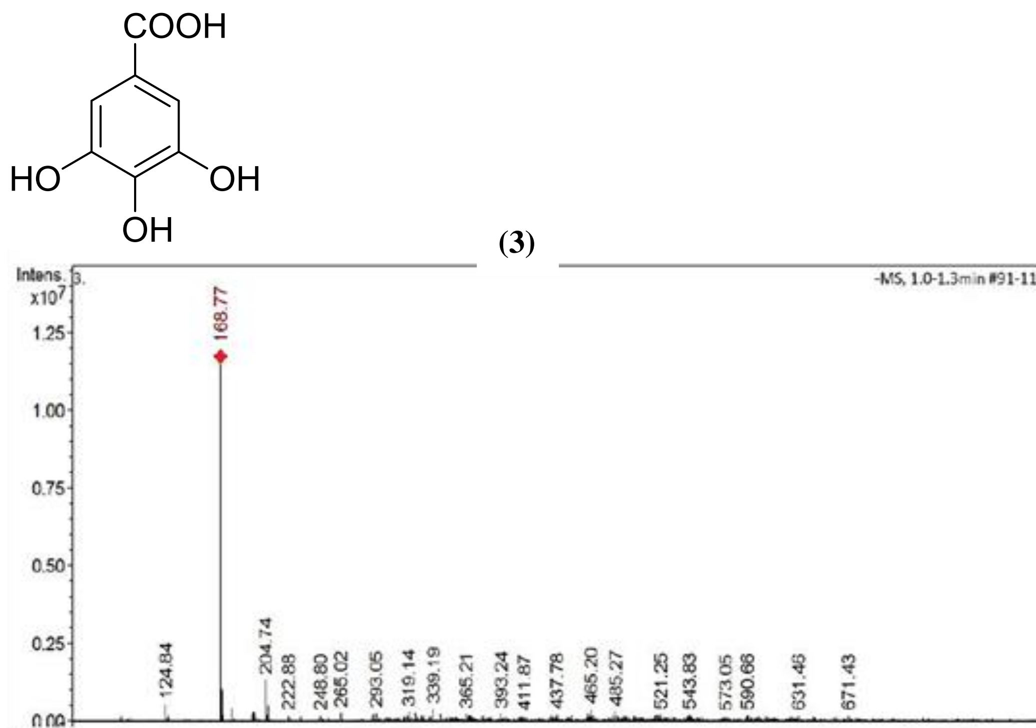



**Figure 6:** ESI-MS spectrum of compound 3

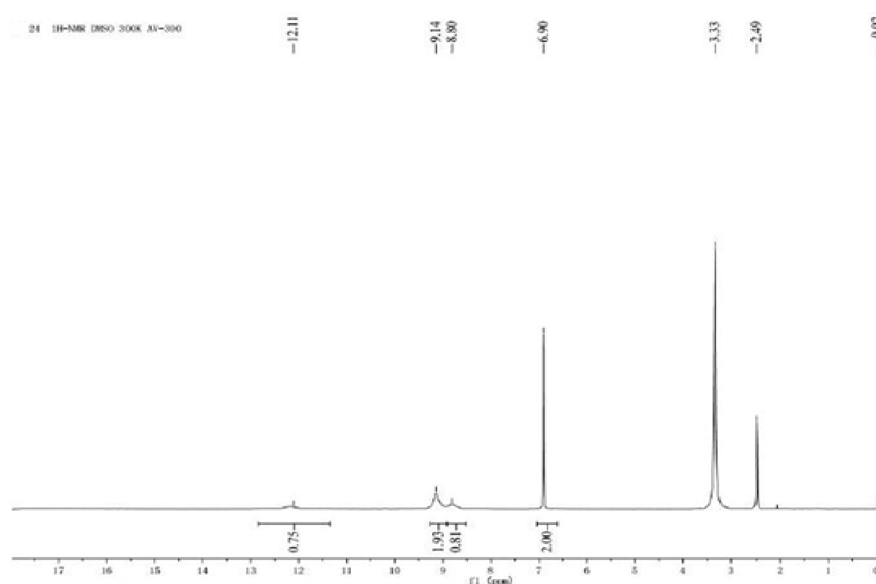



**Figure7:** $^1$H-NMR spectrum of compound 3 (500 MHz, DMSO-$d_6$)

**3.1.4. Structural identification of compound 4**

Compound **4** was obtained as a Yellow powder, soluble in methanol. UV irradiation at 365 nm exhibited a yellow fluorescence. Molish test reaction was negative, and $FeCl_3$ solution reaction was green, indicating that the compound is a flavonoid.

$^1$H-NMR (300 MHz, $C_5D_5N$) spectrum (fig. 8) displayed a set of signals typical of flavonol flavonoid at δ H 7.67 (1H, d, J = 1.4 Hz), 7.54 (1H, dd, J = 8.2, 1.4 Hz), 6.88 (1H, d, J = 8.2 Hz), δH 12.48 (1H, s), δ H 6.40 (1H, s), 6.18 (1H, s).

The physicochemical properties and $^1$H-NMR data of the compounds together with a comparative TLC, were compared with those reported in the literature[24]. The compound was identified as quercetin. Its structure is shown below:

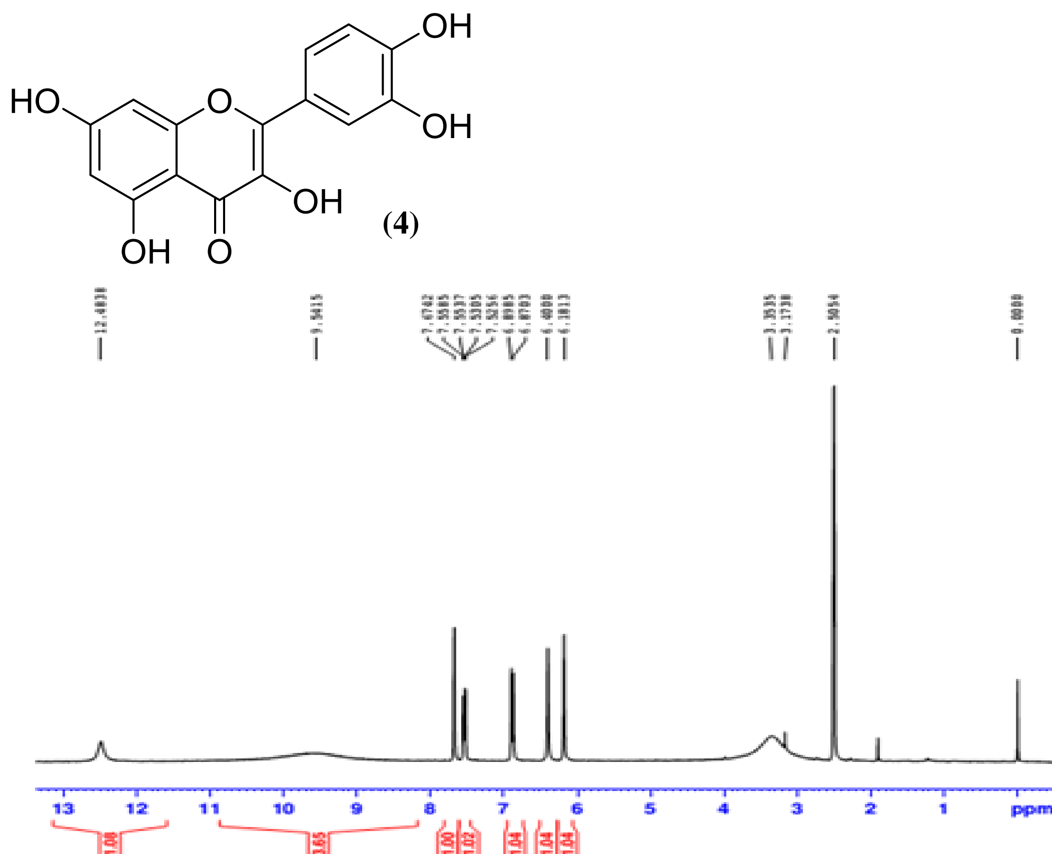



**Figure 8:** $^1$H-NMR spectrum of compound 4 (300 MHz, $C_5D_5N$)

**3.1.5. Structural identification of compound 5**

Compound **5** was obtained as a Yellow powder, soluble in methanol. UV irradiation at 365 nm revealed a dark purple fluorescence. It gave a positive Molish test reaction and $FeCl_3$ solution reaction was green, suggesting that the compound might be a flavonoid glycoside.

Positive ion ESI-MS revealed a quasimolecular ion $[M + H]^+$ at $m/z$: 611. $^1$H-NMR spectra (300 MHz, $CD_3COCD_3$) (fig.9) displayed a set of signals typical of a flavonoid and showed almost similar chemical shifts to those of compound **5** apart from additional signals for a glucose-rhamnose moiety at δ H 5.31 (1H, d, J = 7.5 Hz), 4.50 (1H, J = 3.0 Hz), δH 1.06 (3H, d). On the of above data in addition with physico-chemical characteristic tests, comparative TLC and reported literature, compound **5** was identified as rutin[23]. Its structure as shown below:

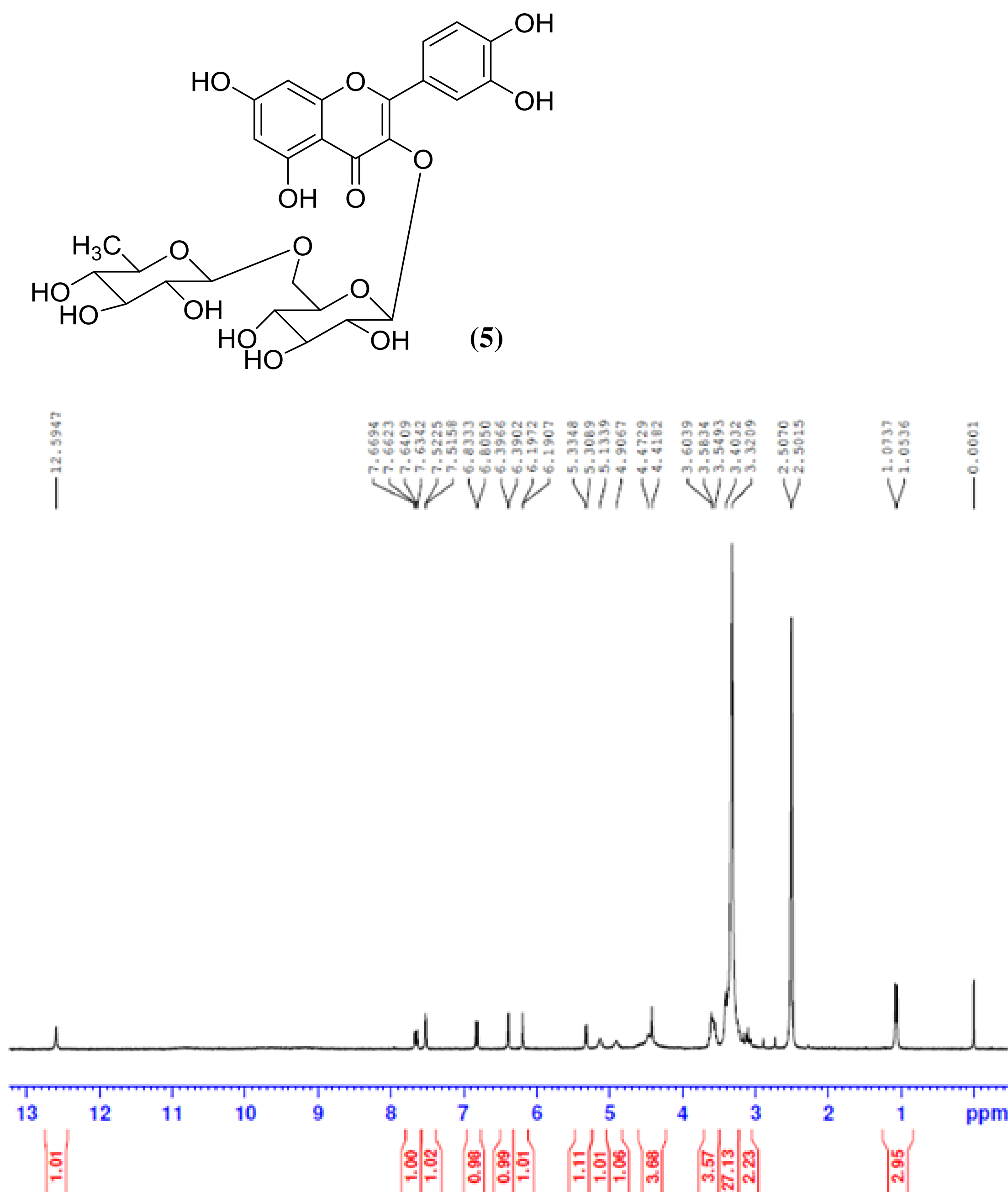


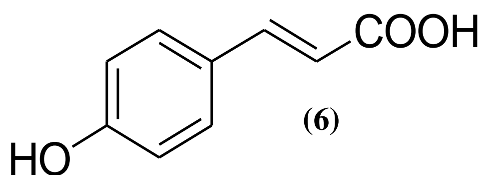

**Figure 9:** $^{1}$H-NMR spectrum of compound 5 (300 MHz,$CD_3COCD_3$)

**3.1.6. Structural identification of compound 6**

Compound 6 was identified as a White powder, soluble in methanol. It gave a negative Molish test. 1% vanillin - concentrated sulfuric acid test was blue-purple, sprayed $FeCl_3$ was purple, indicating the presence of phenolic hydroxyl.

Negative ion ESI-MS (fig. 10) revealed a pseudomolecular ion at *m / z*: 163.1 $[M-H]^-$ .$^{1}$H-NMR spectra (400 MHz, $CD_3OD$) showed signals of a pair of trans-olefinic hydrogens at δH 7.71(1H, dJ = 15.9 Hz), δH 6.51(1H, dJ = 15.9 Hz) (fig. 11), para-substituted aromatic hydrogen signals at δH 7.44 (2H, d, J = 8.6 Hz), 6.80 (2H, d, J = 8.6 Hz). The coupling constant at 16Hz clearly showed *trans* geometry. $^{13}$C-NMR (100 MHz, $CD_3OD$) (fg. 12) displayed seven carbon signals for nine carbon atoms including a carboxyl carbon signal at δC 171.0, a phenolic hydroxyl carbon at δC 161.1, δC 116.8 and hydroxy adjacent to the two aromatic carbon signal, aromatic carbon signals at δC 131.1 and δC 127.2, and trans-carbon signals δC 146.7 and 115.6

The physicochemical properties and spectral data of the compounds were compared using comparative TLC. The compound was identified as *trans-p*-coumaric acid. Its structure is shown below:



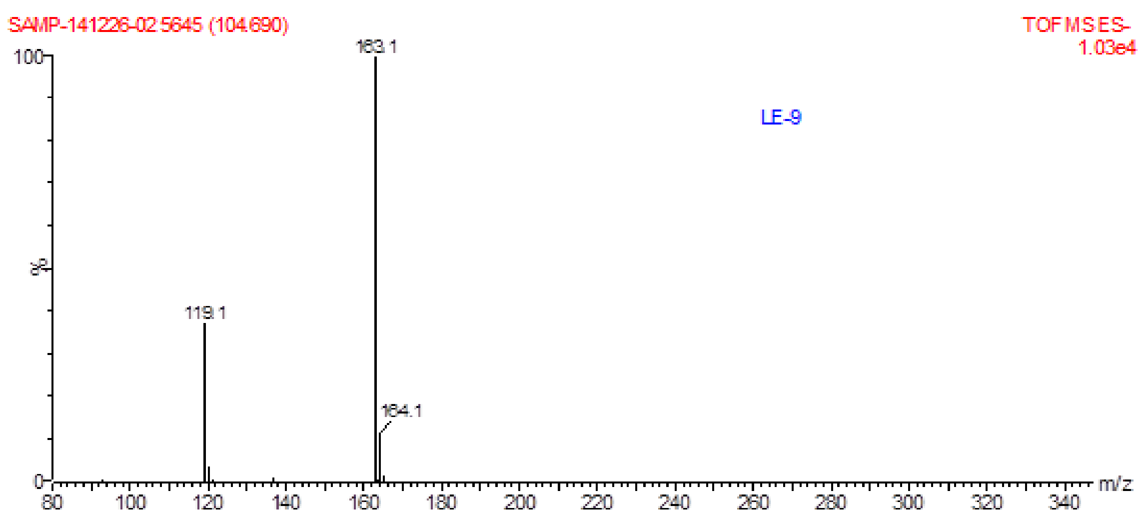




**Figure 10:** ESI-MS spectrum of compound 6

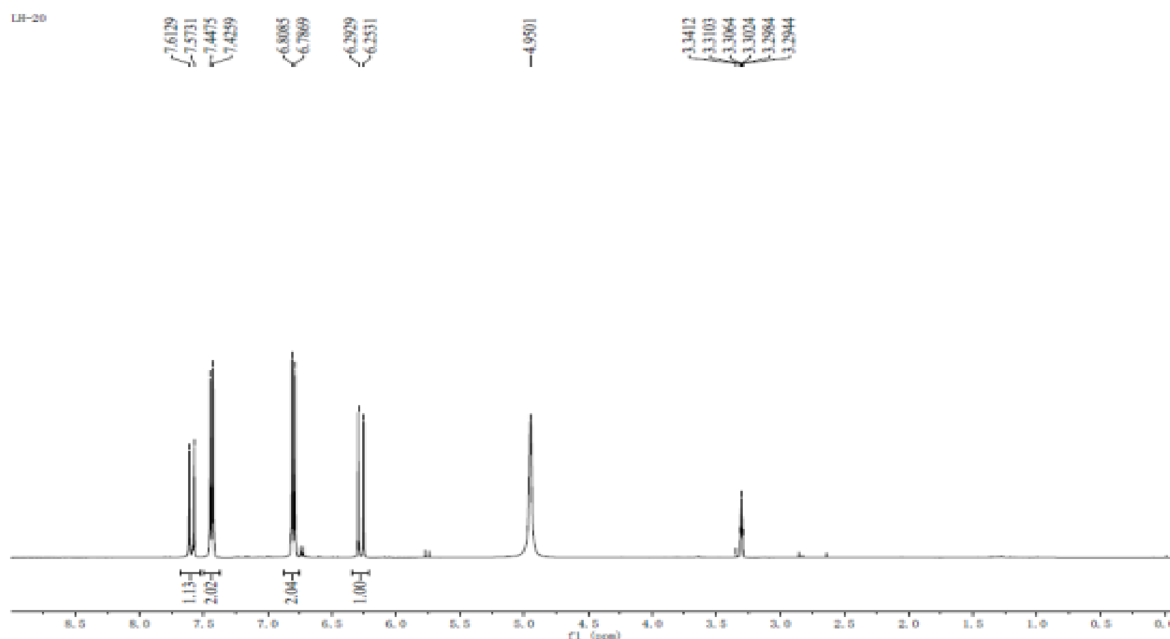



**Figure 11:** $^{1}$H-NMR spectrum of compound 6 (400 MHz, DMSO-$d_6$)

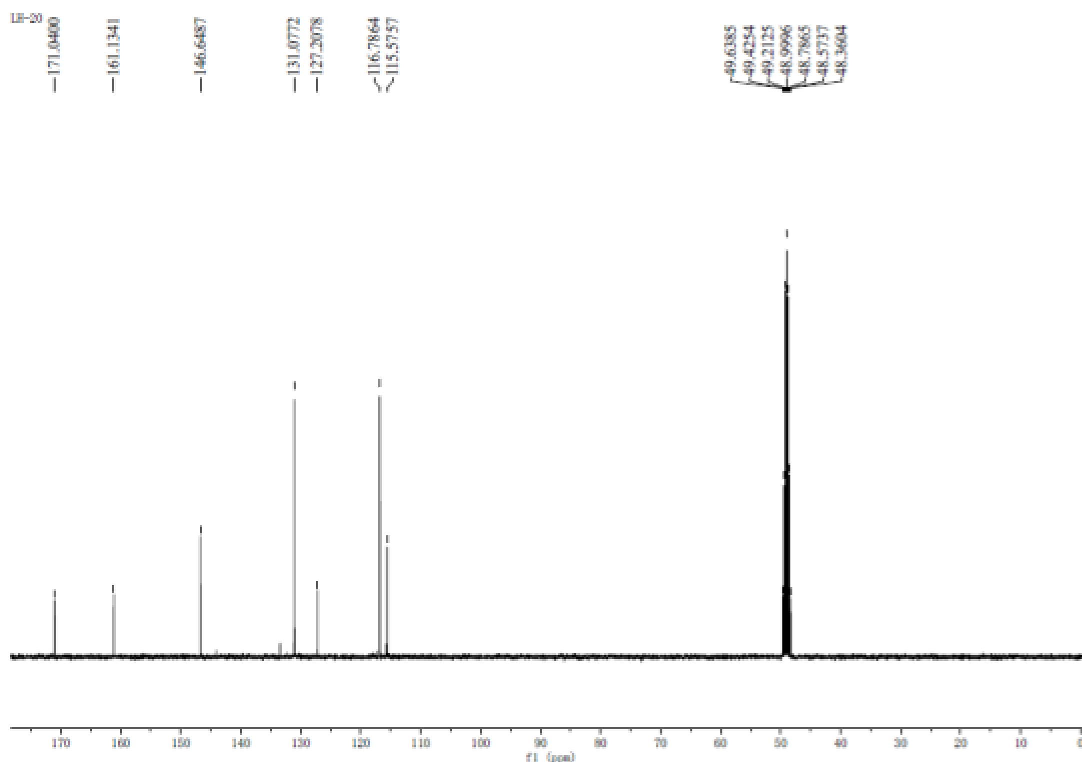


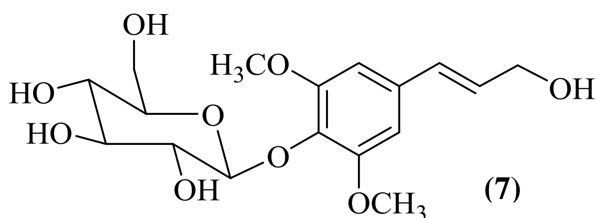

**Figure 12:** $^{13}$C-NMR spectrum of compound 6 (100 MHz, DMSO-$d_6$)

**3.1.7. Structural identification of compound 7**

Compound 7 was obtained as White crystals soluble in methanol. It gave s positive Molish test. and 1% vanillin - concentrated sulfuric acid heating reaction was blue, suggesting that the compound is glycoside.

Positive ion ESI-MS (fig. 13) exhibited a pseudomolecular ion peak at *m / z*: 390.08 $[M + NH4]^+$.$^{1}$H-NMR (300 MHz, $C_5D_5N$) spectrum (fig. 14) showed chemically and magnetically equivalent Aromatic proton signals at $\delta$H 6.90 (2H, s), suggesting that benzene ring has four substituents. trans-ene hydrogen signals were observed at $\delta$H 6.90 (1H, d, J = 15.8 Hz) and $\delta$ H 6.63 (1H, dt, J = 15.8, 5.0 Hz), two protons signals relative to aliphatic hydroxyl at $\delta$H 4.61 (2H, d, J = 4.3 Hz), two methoxy groups signals at $\delta$H 3.78 (6H, s), and sugar moiety signals at H 5.80 (1H, d, J = 5.1 Hz), $\delta$H 3.96-4.44 (6H).

The physicochemical properties and $^{1}$H-NMR spectra data of the compound were compared with those of syringin reported in the literature [25, 26]. The compound was identified as syringin. Its structure as shown below:



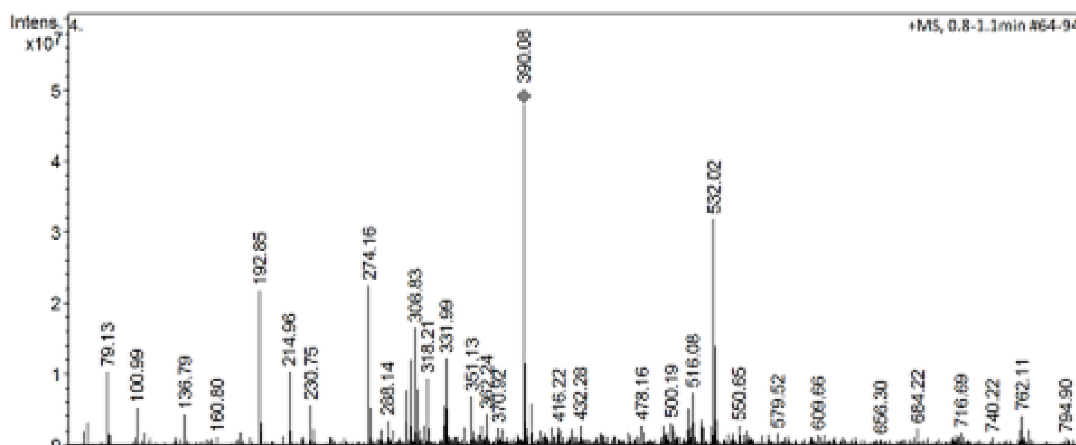




**Figure 13:** ESI-MS spectrum of compound 7

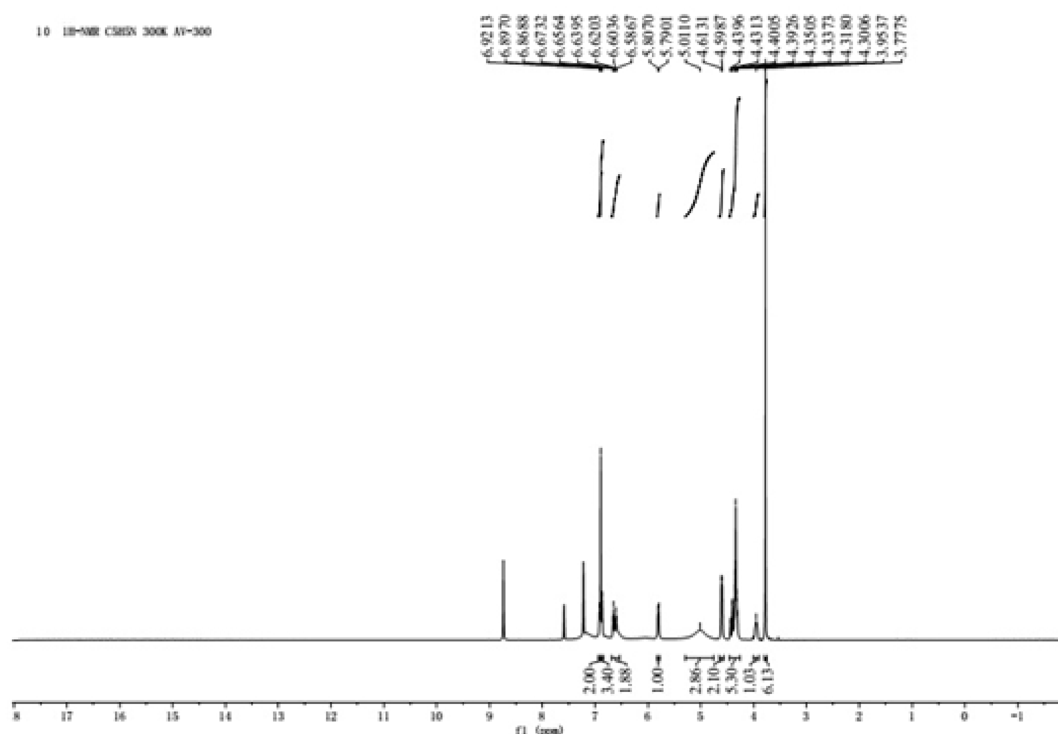


**Figure 14:** $^{1}$H-NMR spectrum of compound 7 (300 MHz, $CDCl_3$)

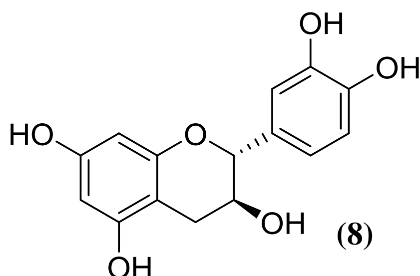
**3.1.8 Structural Characterization of Compound 8**

Compound 8 was obtained as white cluster of crystals, soluble in methanol, DMSO, insoluble in chloroform and petroleum ether. 1% vanillin - concentrated sulfuric acid was bright red. 5% $FeCl_3$ / MeOH solution was blue, suggesting the presence of phenolic hydroxyl.

Positive ion ESI-MS (fig. 15) exhibited a pseudomolecular ion peak at *m / z*: 291.04 $[M + H]^+$, indicating a molecular weight of 290.$^{1}$H-NMR spectra (500 MHz, DMSO-$d_6$) (fig.16) showed 4 phenolic hydroxyl signals at δ H 9.11 (1H, s), 8.89 (1H, s), 8.80 (1H, s), 8.75 (1H, s), two signals at δH 2.66 (1H, dd, J =

16.0, 5.2 Hz), δH 2.36 (1H, dd, J = 16.0, 8.0 Hz) characteristic of 4β and 4α catechin hydrogen signals, hydrogens signals at 6-position and 8-position at δ H 5.69 (1H, s), δH 5.89 (1H, s), 6- and 5-position hydrogen signals of the B ring at δH 6.59 (1H, d, J = 8.0 Hz), δH 6.69 (1H, d, J = 8.0 Hz), and hydrogen signal of the B-ring at the 2-position at δH 6.72 (1H, s).

Spectral data of the compound were consistent with those reported in the literature[27] for catechin, its structure is shown below:



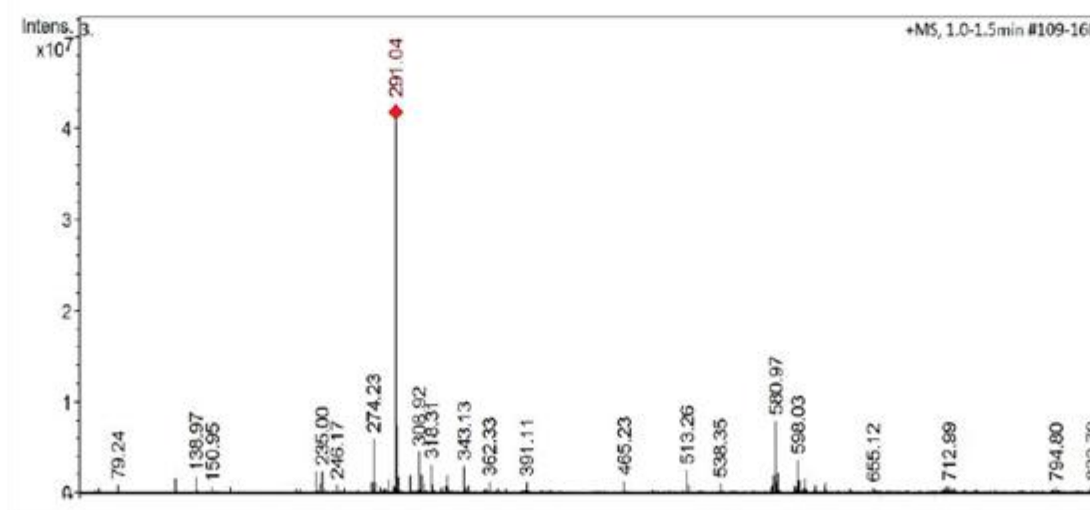




**Figure 15**: ESI-MS spectrum of compound 8

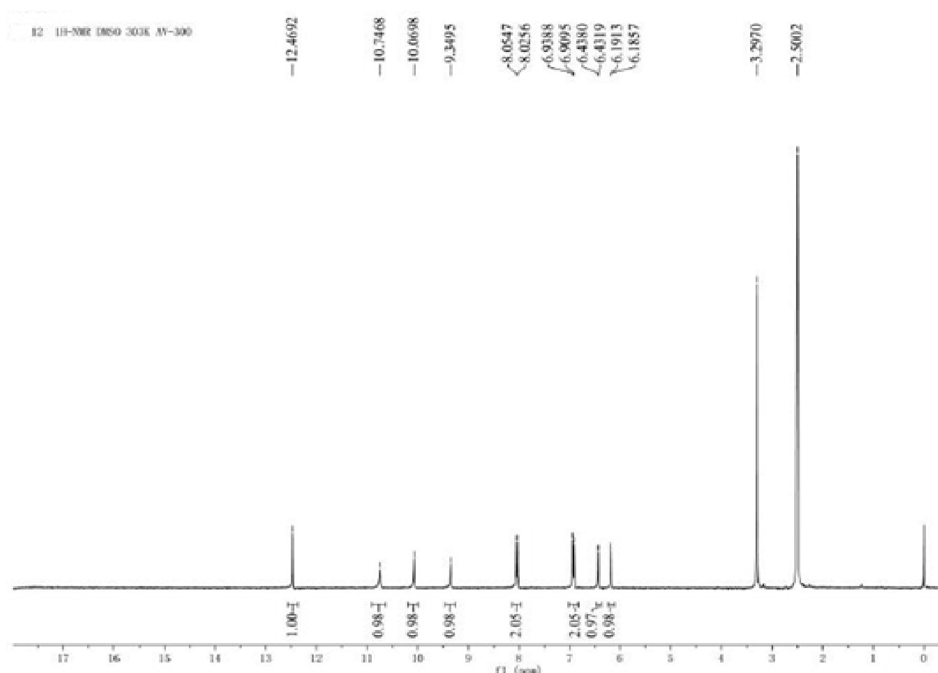



**Figure 16**: $^{1}$H-NMR spectrum of compound 8 (500 MHz, DMSO-$d_6$)

### 3.3. Antioxidant and related activities of isolated compounds

Evidence from multiple studies previously showed that the different compounds isolated in this study exert multiple important pharmacological activities. The table 1 below summarizes their antioxidant and related activities.

**Table 1**. Overview of antioxidant and related activities of isolated compounds

| Chemical compounds | Biological activity | Dosage/minimal active concentration and observed effect | Reference |
|---|---|---|---|
| **Caffeic acid** | Antioxidant and prooxidant | Against AAPH-induced damage in splenic lymphocytes and lipid peroxidation in mouse liver microsomes. | [28, 29] |
| | Antiinflammatory | Against lipopolysaccharide (LPS) treated macrophages and HCl/EtOH-induced gastritis | [30] |
| **cis-p-coumaric acid and trans-p-coumaric acid** | Antioxidant | IC50 of 6.65 μM for DPPH Radical scavenging activity, 1234.1 μM for chelating activity of Fe2+, and 51.5 μM for the cytochrome c reduction | [31] |
| | Anti-cancer | 100 mg/kg body weight in Male albino rats activated apoptosis both in *vitro* and *in vivo* models of colon cancer | [32] |
| | Antiinflammatory | 8-days-Administration of 100 mg/kg body weight in rats normalyses physical and biochemical inflammatory parameters | [33] |
| **Gallic acid** | Antioxidant | IC50 of 6.9 μM for DPPH Radical scavenging activity | [34] |
| | cytotoxic and antitumor | modulates oantioxidant/pro-oxidant balance, control the reactive oxygen species (ROS)-induced carcinogenesis, induce the cell cycle arrest, autophagy, and apoptosis | [35] |
| **Quercetin** | Antioxidant | IC50 of 6.9 μM for DPPH Radical scavenging activity | [34] |
| | Inhibition of osteoclastic bone resorption | 01 to 100 mM on rabbits osteoclasts | [36] |
| | Anti-inflammatory | 01to 100 mM on experimental rats with induced arthritis | [37]<br>[38] |
| | Anti-inflammatory | dose-dependent protection of mouse neurona cells against inflammation | [39] |
| **Rutin** | Anti-atherosclerosis | 1000 mg/kg body weight in Atherosclerosis-prone mutant mice | [40] |
| | Antioxidant activity | - | |
| | Anti-inflammatory | 1000 mg/kg body weight per day against Experimental arthritis induced in rats | [38] |
| **Syringin** | Antioxidant and neuroprotective | 20 μM improves cell viability of neuroblastoma cells | [41] |
| | antidiabetic | 30 days-oral administration of 50 mg/kg per day to diabetic rats normalized the level of blood glucous, insulin, hemoglobin levels, Plasma protein, blood urea, serum creatinine and uric acid | [42] |
| | anti-inflammatory, anti-nociceptive | 20/30 mg/kg/day presented significant anti-inflammatory, anti-nociceptive effects in rats | [43] |
| **Catechin** | Anti-atherosclerosis, Antioxidant activity and Anti-inflammatory | 2000 mg/kg diet in atherosclerosis-prone mutant mice<br>10 mg/kg day for 2 weeks for Adriamycin-induced cardiotoxicity in rats | [44] |

*AAPH : 2,20-azobis-amidinopropane dihydrochloride*
*DPPH: 2,2-diphényl 1-picrylhydrazyle*

## IV. Conclusion

In conclusion, we investigated the Phytochemical study of *L. ruthenicum.* Murr. eight compounds including Caffeic acid, *cis-p*-coumaric acid, Protocatechuic acid, Gallic acid, Quercetin, Rutin, *trans-p*-coumaric acid, Syringin, and Catechin were isolated, purified and identified in *L. ruthenicum* Murr. dry fruits using phytochemical techiniques. Based on chromatographic data (NMR, $^{13}$C, $^{1}$H), physiochemical techniques, standards available in laboratory, and characteristic tests the structure of these compounds were identified and compared with reported literature. Compounds isolated were previously reported to have efficient biological activities. Our results suggest that *Lycium ruthenicum* is rich in phenolic compounds. Current evidence confirms the pharmacological and therapeutic interventions of gallic acid in multiple health complications, hence LRM

could be labeled as a functional food, ingredient or supplement in the formulation of food products for the population under oxidative stress.

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