

LC-MS/MS STUDIES ON THE FRUIT EXTRACTS OF *MORINDA CITRIFOLIA* L (NONI)

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ABSTRACT

Introduction: *Morinda citrifolia* L (Noni) has been extensive history of medicinal uses among the traditional therapeutic action in 2000 years ago. It's belongs to Rubiaceae family and commonly known as Indian Mulberry. Commercially Noni fruit is functional and widely distributed in throughout Andaman, Pacific islands and Indian coastal areas. Noni has reported broad spectrum of Pharmacological activity like anti-bacterial, anti-fungal, anti-hepatoprotective, anti-tumor, anti-tubercular, wound healing, immunological and anti-viral activity. The Noni fruit containing enriched secondary metabolites like Anthroquinones, Flavonoids, alkaloids, amino acids, vitamins and glycosides. **Objective:** The present study is carried out to prepare extracts from Noni fruit by using different solvents such as Pet. Ether,

Acetone, Ethyl acetate, Ethanol and Methanol. Continues to analyse preliminary phytochemical screening and identify the bioactive phytoconstituents in Noni fruit extracts by LC-MS/MS method. **Methodology:** The air dried Noni fruit powder was subjected to hot continues extraction by using Soxhlet apparatus with range of non-polar to polar solvents such as Pet. Ether (MCF-Pet. Et), Acetone (MCF-Ac), ethyl acetate (MCF-EtoAc), ethanol (MCF-Et) and methanol (MCF-Me). Preliminary Phytochemical analysis and identification of active constituents confirmed by modern Liquid Chromatography-mass spectrometry (LC-MS/MS) technique. **Results:** The crude extracts obtained from the *Morinda citrifolia* fruit with different solvents subjected to successive extraction. The preliminary phytochemical analysis of different solvent extracts of Noni shows all common secondary metabolites. The presences of bioactive constituents were confirmed by LC-MS/MS technique and test

samples are compared with reference standard compounds. We are reporting first time in presence of Rutin, Quercetin, Kaempferol, Scopoletin and Rubiadin 1-methyl ether in ethanol (MCF-Et) and methanol (MCF-Me) extracts. **Conclusion:** Phytochemical studies showed that Noni fruit confined a wide spectrum of secondary metabolites such as Carbohydrates, Alkaloids, cardiac glycosides; flavonoids were found in MCF-EtoAc, MCF-Et and MCF-Me extracts, where sterols and proteins are found in MCF-Pet. Et and MCF-Ac extracts. This study intensely supports the use of *M. Citrifolia* (Noni) constituent's Rutin, Kaempferol and Quercetin possess as an anti-viral activity and Immune-enhancing properties.

KEYWORDS: *Morinda citrifolia*, phytochemical, LC-MS/MS, Rutin, Quercetin, Kaempferol, Scopoletin, Rubiadin 1-methyl ether.

INTRODUCTION

Natural products have inspired many developments in organic chemistry, leading to advances in synthetic methodologies and to the possibility of making analogues of the original lead compound with improved pharmacological or pharmaceutical properties. The unlimited wealth of the plant kingdom has become a target for research institute for new lead compounds and drug discovery of new drugs. India is virtually a store globe of the herbs where a large variety of herbs can be grown.^[19]

Morinda citrifolia is technically an evergreen shrub or bush, which can grow to heights of fifteen to twenty feet. It has rigid, coarse branches which bear dark, oval, glossy leaves. Small white fragrant flowers bloom out of cluster-like pods which bear creamy-white colored fruit. The fruit is fleshy and gel-like when ripened, resembling a small bread fruit. The Noni plant containing broad spectrum pharmacological activities including anti-inflammatory, astringent, emollient, laxative, sedative, hypotensive (lowers blood pressure), blood purifier.^[18,19]

Noni has various chemical constituents it has an impressive array of terpene compounds, three of which L. Asperuloside and glucose have been identified by their acetyl derivatives. Both caproic and caprylic acids have been isolated from Noni fruit extracts.^[2] A number of Kaempferol and Quercetin based flavonol glycosides from the leaves of *Thevetia peruviana* have exhibited an appreciable HIV-1 reverse transcriptase-associated RNA-dependent DNA polymerase (RDDP) inhibitory activity with IC₅₀ values of 20–43 μM; Quercetin derivatives being more active than Kaempferol.^[6,13,17] Quercetin 3-O-[(6-O-feruloyl)-β-D-

glucopyranosyl-(1→2)-β-D-galactopyranoside] and quercetin 3-O-[(6-O-sinapoyl)-β-D-glucopyranosyl-(1, 2) and D-glucopyranosyl-(1, 2) also inhibited HIV-1 integrase with IC₅₀ values of 5 and 7 μM, respectively.^[17] Alkaloids exhibit a wide range of pharmacological and biological activities in the human body.^[3] They are nitrogen containing organic compounds which can react with acids to form salts and which are the basis of many medicines.^[3] The previous studies of this plant has confirmed the two new secondary metabolites of glycosides (2E, 4E, 7Z)-deca-2,4,7-trienoate-2-O-β-D-glucopyranosyl-β-D-glucopyranoside and amyl-1-O-β-D-apio-furanosyl-1,6-O-β-D-glucopyranoside and Scopoletin respectively.^[10,12]

The main objectives of the present study were to analyse preliminary phytochemical screening and confirm the presence of bioactive constituents by LC-MS/MS method from extracts of *Morinda citrifolia* L. fruit.

MATERIALS & METHODS

Plant material: The fruit of *M. citrifolia* L was collected from Noni Research cum Demonstration Centre, Wadakkencherry (Thrissur, Kerala, India). Noni fruits were authenticated and the voucher specimen (MCF-Fruit-01) was preserved in the Department of Pharmaceutical Chemistry, Nova College of Pharmaceutical Education and Research, Ibrahimpatnam, Andhra Pradesh, India.

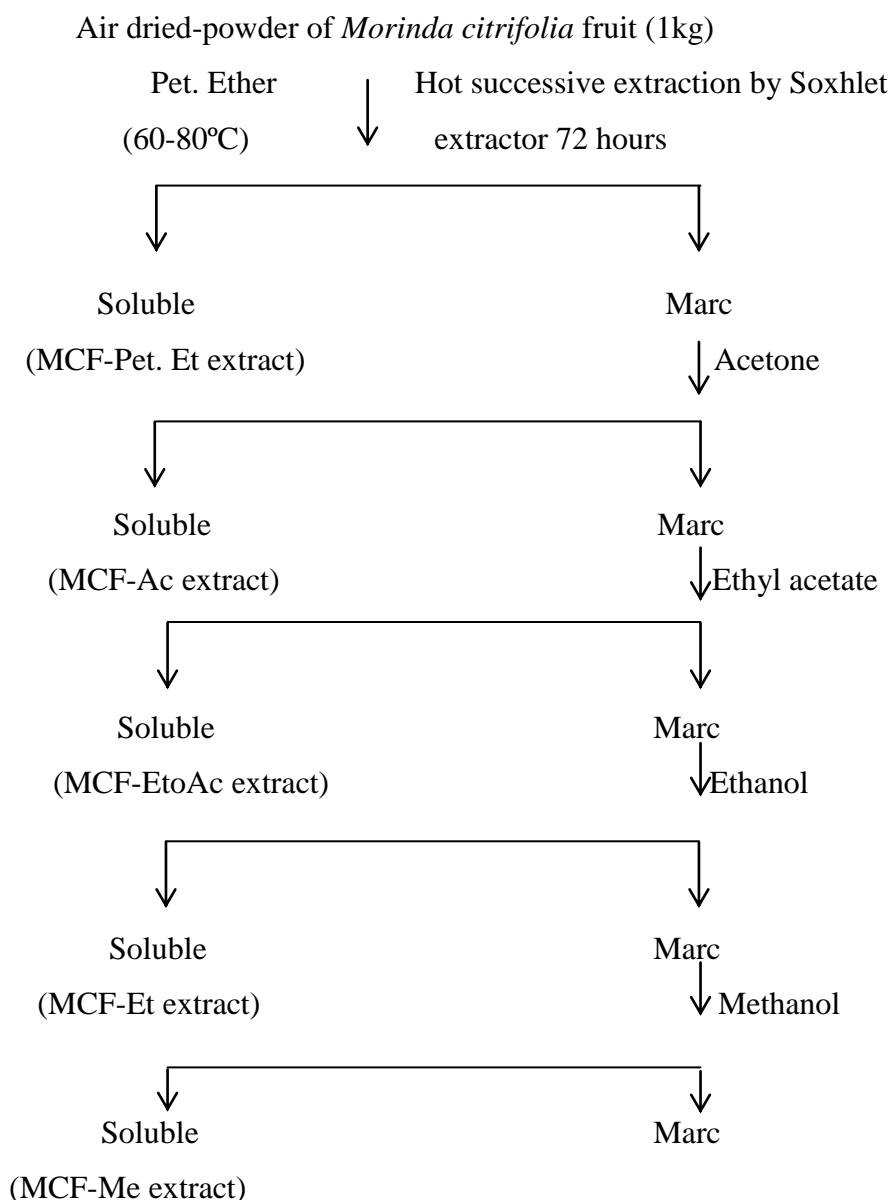


Morinda citrifolia L. (Noni) fruit

Chemicals and solvents: All chemicals and reagents were procured from Millipore and Sigma-Aldrich on analytical reagent grade. HPLC grade Acetonitrile and methanol were purchased from J.T. Baker Inc. Phillipsburg, NJ, USA). The standard substances of Rutin and Quercetin were purchased from Sigma-Aldrich chemie (Steinheim, Germany). The different extractive solvents LR grade was procured from Chemwin chemicals, Kochi, Kerala.

Preparation of extracts: The Fresh fruits of *M. citrifolia* were washed with running water and cut into small pieces, shade dried at room temperature and then grounded. 1kg of dried Noni powder was subjected to hot continuous successive extraction in Soxhlet extractor with Petroleum ether, Acetone, Ethyl Acetate, Ethanol and Methanol. The average time period for each solvent extraction is 72 hours at $60^{\circ}\text{C} \pm 5^{\circ}\text{C}$. The insoluble part of plant material was filtered through Whatmann filter paper (No. 1) and the solvents were removed under reduced pressure by using rotary evaporator. The yield of each extract was Petroleum ether – 20g (MCF-Pet. Et), Acetone-25g (MCF-Ac), Ethyl acetate- 40g (MCF-EtoAc), Ethanol- 80g (MCF-Et) and Methanol-120g (MCF-Me).

Flow chart of successive extraction



Phytochemical analysis^[7, 16]**Test for Carbohydrates**

- **Molish test**

2-3 ml of each extracts, few drops of alpha naphthol solution in alcohol were added and it was shaking well. Then concentrated H₂SO₄ was added through the sides of the test tube and violet ring is formed at the junction of two liquid.

- **Fehling's test**

1ml Fehling's A and 1ml Fehling's B solutions were mixed and it was boiled for 1 min. then equal volume of extracts was added. It was heated on a boiling water bath for 5-10 mints, brick red precipitate was formed.

- **Benedict's test**

Equal volume of Benedict's reagent and each extracts was mixed in a separate test tube. It was heated in a boiling water bath for 5mints, orange colour precipitate was observed.

- **Barfoed's test**

Equal volume of Barfoed's reagents and extracts were mixed and it was heated for 1-2 mins on a boiling water bath and then it was cooled. Red colour was observed.

Test for Proteins

- **Biuret test**

3 ml of each extracts, 4% NaOH solution and few drops of 1% CuSO₄ solution were added; violet or pink color was observed.

- **Millon's test**

3 ml of each extracts was mixed with 5ml millon's reagent, white colour precipitate was observed.

- **Xanthoprotein test**

3 ml of each extracts was mixed with 1 ml concentrated HNO₃ and then NH₄OH solution added, yellow colour precipitate was not formed.

Test for Amino Acids

- **Ninhydrin test**

3 ml of each extracts was heated with few drops of 5% Ninhydrin solution in a boiling water bath for 10 min and purple or bluish colour changes was observed.

Test for Steroids

- **Salkowski's test**

2 ml of each extracts, 2 ml of chloroform and 2 ml of concentrated H_2SO_4 were added and it was shaking well and chloroform layer appears red and acid layer appears greenish yellow.

- **Liebermann Burchard reaction**

2 ml of each extracts was mixed with chloroform. To this solution 1-2 ml acetic anhydride was taken and 2 drops of concentrated H_2SO_4 was added from the sides of test tube and first red, then blue and finally green colour was observed.

Test for Saponin Glycosides

- **Foam test**

2 – 3 ml of each extract was taken in water in test tubes and shake vigorously, stable foam forming was observed.

Test for Glycosides**Test for Cardiac Glycosides**

- **Legal's test**

2ml of each extracts, 1 ml pyridine and 1 ml sodium nitro prusside were added and pink to red colour were observed.

- **Keller-killiani test**

2 ml of each extracts, 3 ml of glacial acetic acid and 1 drop of 5% ferric chloride were added. This solution was carefully transferred to the surface of 2 ml concentrated H_2SO_4 and reddish brown color appears at junction of the two liquid layers and upper layer appears bluish green.

Test for Anthroquinones Glycosides

- **Borntrager's test**

3 ml of ethanolic extract, dilute H_2SO_4 was added and it was boiled and filtered. To the cold filtrate, equal volumes of benzene or chloroform were added and shaking well. The organic

solvent layer was separated and ammonia was added. The ammonical layer shows pink colour.

Test for Phenolic Compounds

- **Ferric chloride test**

2-3 ml of each extracts, few drops of 5% w/w ferric chloride solution were added and deep blue-black colour was observed.

Test for Flavonoids

- **Shinoda's test**

2 ml of each extracts, 5 ml of 95% ethanol was added then few drops of concentrated HCl and 0.5 gm of magnesium turnings were added and pink color observed.

Test for Alkaloids

Each extracts diluted with mother solvent and evaporated separately. To the residue, dilute HCl were added and it was shaking well and filtered. With the filtrate, the following tests were performed.

- **Dragendorff's test**

2-3 ml of filtrate, few drops of Dragendorff's reagent (Potassium bismuth iodide) was added and reddish brown precipitate was observed.

- **Mayer's test**

2-3 ml of the filtrate, few drops of Mayer's reagent (Potassium mercuric iodide) was added and the cream colored precipitate was observed.

- **Hager's test**

2-3 ml of the filtrate Hager's reagent (saturated solution of picric acid) was added and yellow color precipitate was observed.

- **Wagner's test**

2-3 ml of the filtrate few drops of Wagner's reagent (Solution of potassium iodide) was added and reddish brown precipitate was observed.

LC-MS/MS analysis: Liquid chromatography mass spectroscopy analysis was performed by using API-2000 Applied Biosystem mass spectrometer (Canada) interface with ESI

(Electrospray ionization) source coupled with HPLC system (Shimadzu, Kyoto, Japan) consisting of a binary LC 20A series, gradient pump with solvent degasser, auto sampler (SIL-HTc) and a column oven. Separation was achieved reverse phase column (Hiber 250x4.6 mm, Pure sphere STAR RP C18, 5 μ particle size, Merck, Germany) using linear gradient elution with a mobile phase A consisted of 0.1% formic acid in water and mobile phase B was Acetonitrile (95:5% v/v) under isocratic condition was kept at 0.5 mL/min. The column oven temperature was set to 40°C and the auto sampler was maintained at 20°C and the injection volume was 10 μ L. The After injection of 10 μ L, separation was achieved using a gradient program starting with 95% mobile phase A and 5% mobile phase B for 0.5min, changing to 50% mobile phase A within 8.5min. This gradient was held constant for 4.6min and kept constant again for 3min. Finally, mobile phase B was increased to 75% within 0.5min and kept constant for 11.5min till the end of the run. The total run time was 20min at a flow rate of 0.3ml/min¹.

Samples: For this qualitative analysis study, MCF-Et, MCF-Me and standards Rutin, Quercetin was subjected to LC-MS/MS Applied Biosystem API 2000 series, Canada. Primary stock solution of Rutin and Quercetin standard were separately prepared in methanol to achieve the desired concentration of 0.5mg/mL. Working standards solution was prepared by serial dilution of primary stock solution using methanol. MCF-Et and MCF-Me extracts stock solution was prepared in methanol with concentration 10 mg/mL. All the samples prepared were filtered through a 0.45 nylon filter (Spincotech, India) and were transferred to auto sampler vial for LCMS/MS qualitative analysis. The concentration of each constituent was expressed in μ g/mg. Mobile phase pump-A is (0.1 % formic acid in water) and pump-B is (Acetonitrile), Run time was set to 20 min with a ramp rate of 2°C per min up to 190°C and with a hold at 50°C for 5 min. Injection volume was 1 μ L. The carrier gas was used as Nitrogen 50psi pressure and 0.3ml/min¹.

Identification of compounds was achieved by comparing their multiple reaction monitoring (MRM) retention times with those of standards Rutin (4.02) and Quercetin (6.93). Electro Spray Ionization source (ESI) was performed in the negative ion mode. For both Dwell time was chosen to be 20min. The test was carried out by injecting 10 μ L of mixture of standard solution of Rutin and Quercetin (0.5mg/ml) in six times. More ever the combination of test sample and reference standards with LC-MS/MS represents a powerful and sensitive procedure for generating a complete profile of test samples¹.

RESULTS AND DISCUSSION

An overview of the present Preliminary phytochemical screening of Noni fruit extracts exposed the presence of several bioactive secondary metabolites and the results were summarized in Table No. 1. The different solvent extracts of *Morinda citrifolia* L. are MCF-Pet. Et, MCF-Ac, MCF-EtoAc, MCF-Et and MCF-Me extracts. The preliminary phytochemical analysis of *Morinda citrifolia* shows the presence of all major phytoconstituents such as carbohydrates, cardiac glycosides, phenolic compounds, flavonoids, and alkaloids. In some of phytosterols and amino acids were presented in MCF-Pet. Et & Acetone extracts in moderate amount.

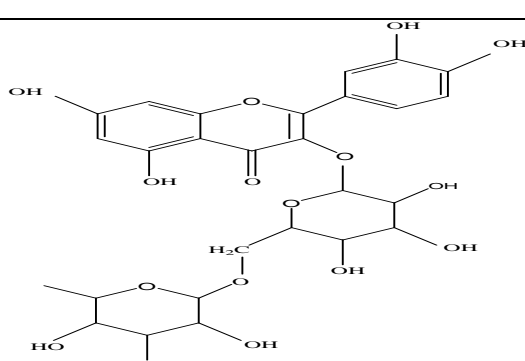
The previous studies of this plant confirming the contains of Ascorpic acid⁹, Asperulosidic acid^[11], Asperuloside tetra-acetate^[18], Caproic acid^[4], Caprylic acid^[8,15], Ethyl caprylate^[4,19] Ethyl caproate^[4], Hexanoic acid^[4], Octanoic acid^[5], Rubiadin 1-methyl ether^[20] and Quercetin 3-*O*- α -L-rhamanopyranosyl- (1,6)- β -D- glucopyranoside.^[5,19] Kaempferol and Quercetin based flavonol glycosides from the leaves of *Thevetia peruviana* have exhibited an appreciable HIV-1 reverse transcriptase-associated RNA-dependent DNA polymerase (RDDP) inhibitory activity with IC₅₀ values of 20–43 μ M; Quercetin derivatives being more active than Kaempferol.^[6,13,17] Scopoletin compound isolated from Noni fruit and molecule structure was confirmed by NMR and GC-MS.^[12,14] The MCF-Et and MCF-Me extracts were further studied to explore by LC-MS/MS and confirmed the presence bioactive constituents by mass spectrum. The retention time (RT) of the standards compounds were confirmed by MRM mode on parent product ion Rutin (4.02 & 3.97) and Quercetin (6.93) results are showed in Fig. 1, 2, 3 & 4. Both the extracts of mass spectrum shown in Fig. 5 & 6 and individual compounds mass confirmed with mass bank database and clearly showed the protonated molecular ion $[M-H]^-$ peak of Rutin was observed at m/z 609.10, Quercetin 303, Scopoletin 192.01, Kaempferol 286.23 Rubiadin 1-methyl ether 268.86 respectively, results chemical structure are shown in Table No.2.

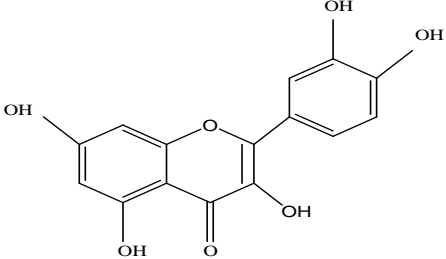
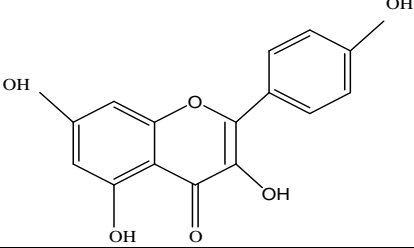
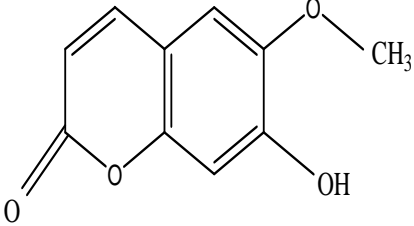
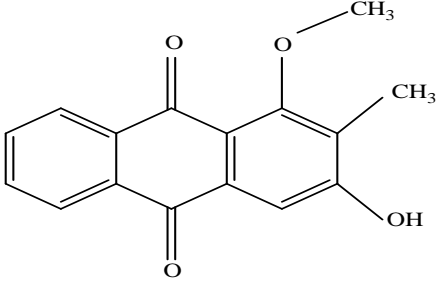
Table No.1 Phytochemical analysis of Noni Fruit extracts:

Plant constituents test / reagents used	MCF-Pet. Et	MCF-Ac	MCF-EtoAc	MCF-Et	MCF-MeOH
1. Test for Carbohydrates					
Molisch's Reagent Test	-	-	-	+	+
Fehling's test	-	-	-	+	+
Benedict's test	-	-	-	+	+
Barfoad's test	-	-	-	+	+
2. Test for Proteins & Amino acids					
Biuret Test	-	+	+	+	-
Millon's test	-	+	+	+	-
Xanthoprotein test	-	+	+	+	-
Ninhydrine test	-	+	+	+	-
3. Test for Phytosterols					
Salkowski's Test	+	+	+	+	+
Liebermann – Burchard Reaction Test	+	+	+	+	+
4. Test for Saponin					
Foam Test	-	-	-	+	+
5. Test for Glycosides					
Legal's Test	-	-	+	+	+
Keller killani Test	-	-	+	+	+
Borntrager's Test	-	-	+	+	+
6. Test for Phenolic Compounds					
Ferric Chloride Solution Test	-	-	+	+	+
7. Test for Flavonoids					
Shinoda's Test	-	-	+	+	+
8. Test for Alkaloids					
Dragendorff's Reagent Test	-	-	+	+	+
Mayer's Reagent Test	-	-	+	+	+
Hager's Reagent Test	-	-	+	+	+
Wagner's Reagent test	-	-	+	+	+

+ Positive, - Negative

Table No. 2 Identification of chemical constituents from Noni fruit extracts by LC-MS/MS

S. No.	Chemical constituents name	Chemical constituents molecular weight	Chemical structure
1.	Rutin	610.52	

2.	Quercetin	302.23	
3.	Kaempferol	286.83	
4.	Scopoletin	192.81	
5.	Rubiadin 1-methyl ether	268.86	

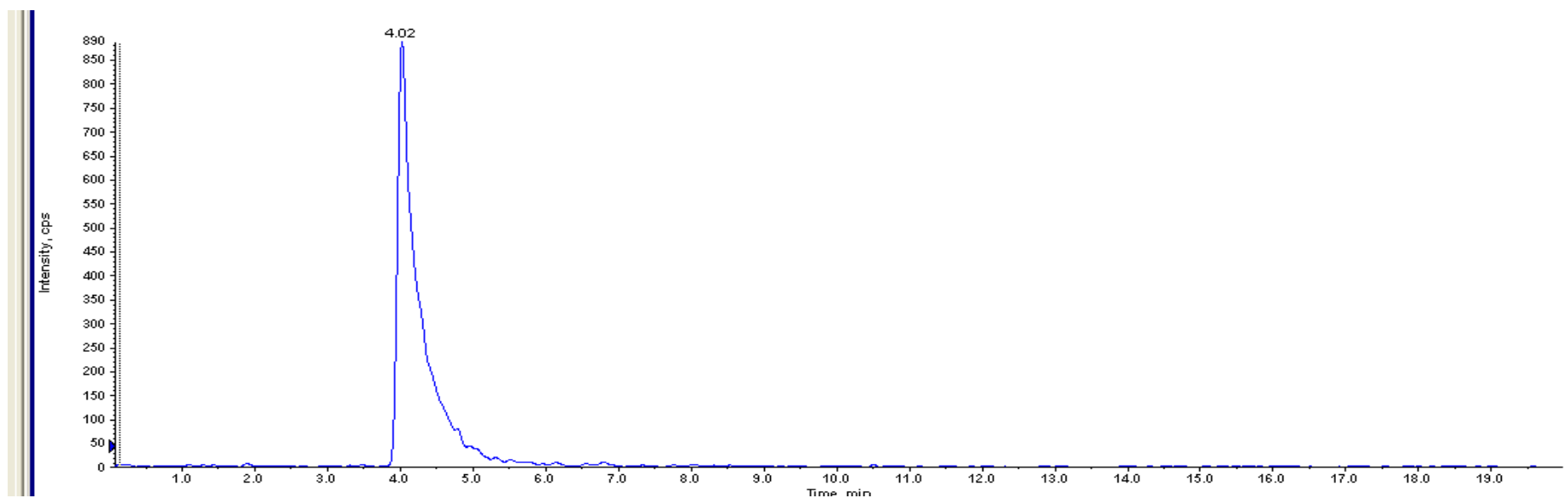


Fig. 1 – MCF-Et Rutin (MRM)

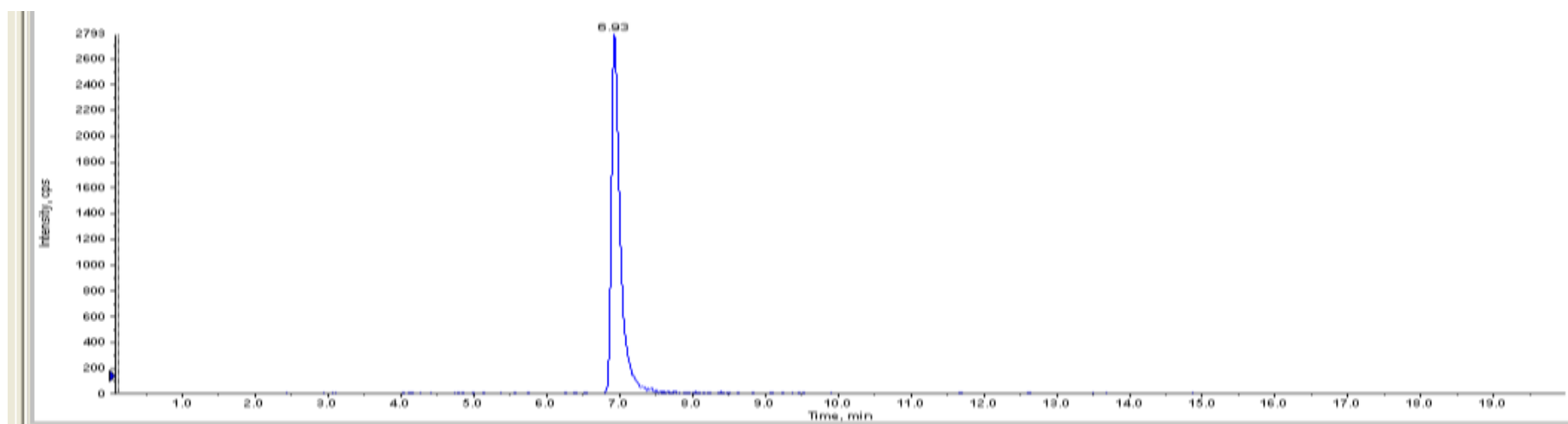


Fig. 2 – MCF-Et Quercetin (MRM)

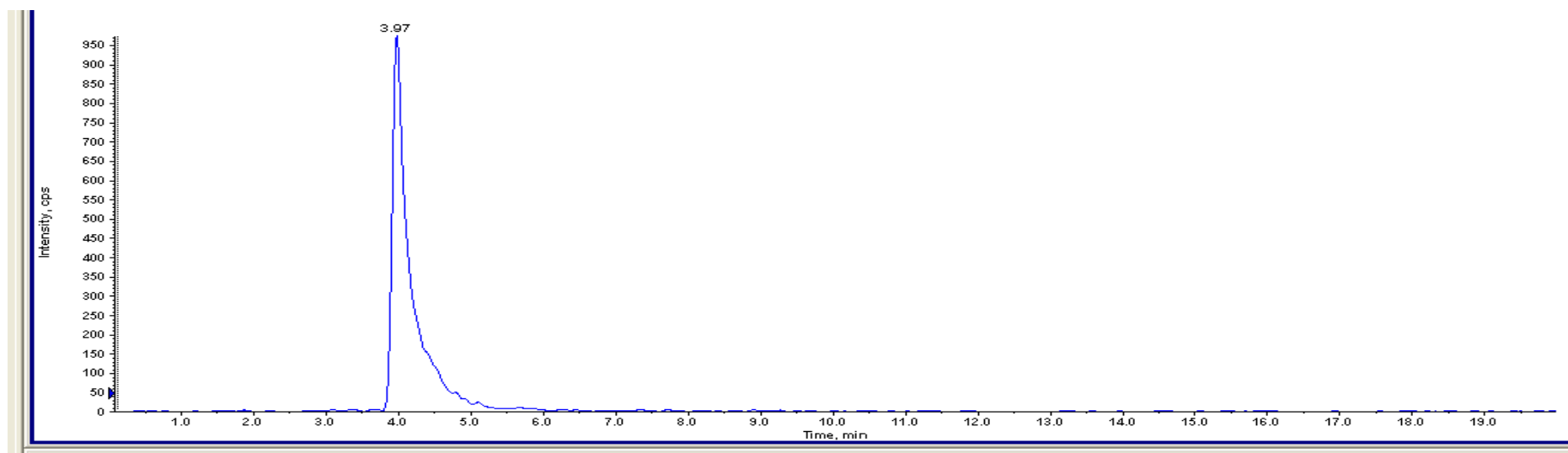


Fig. 3- MCF-Me Rutin (MRM)

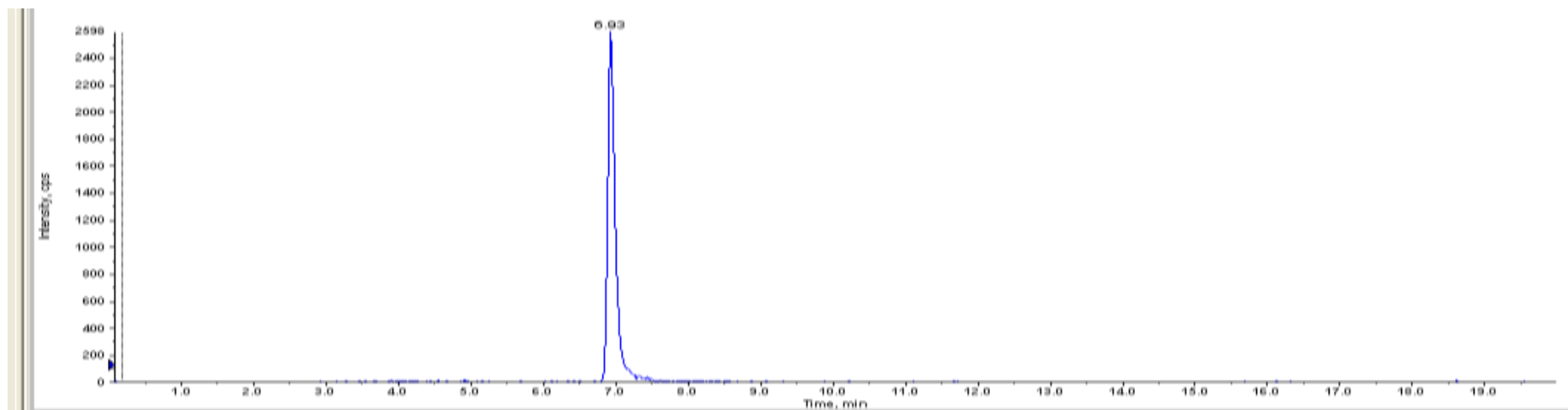


Fig. 4 – MCF-Me Quercetin (MRM)

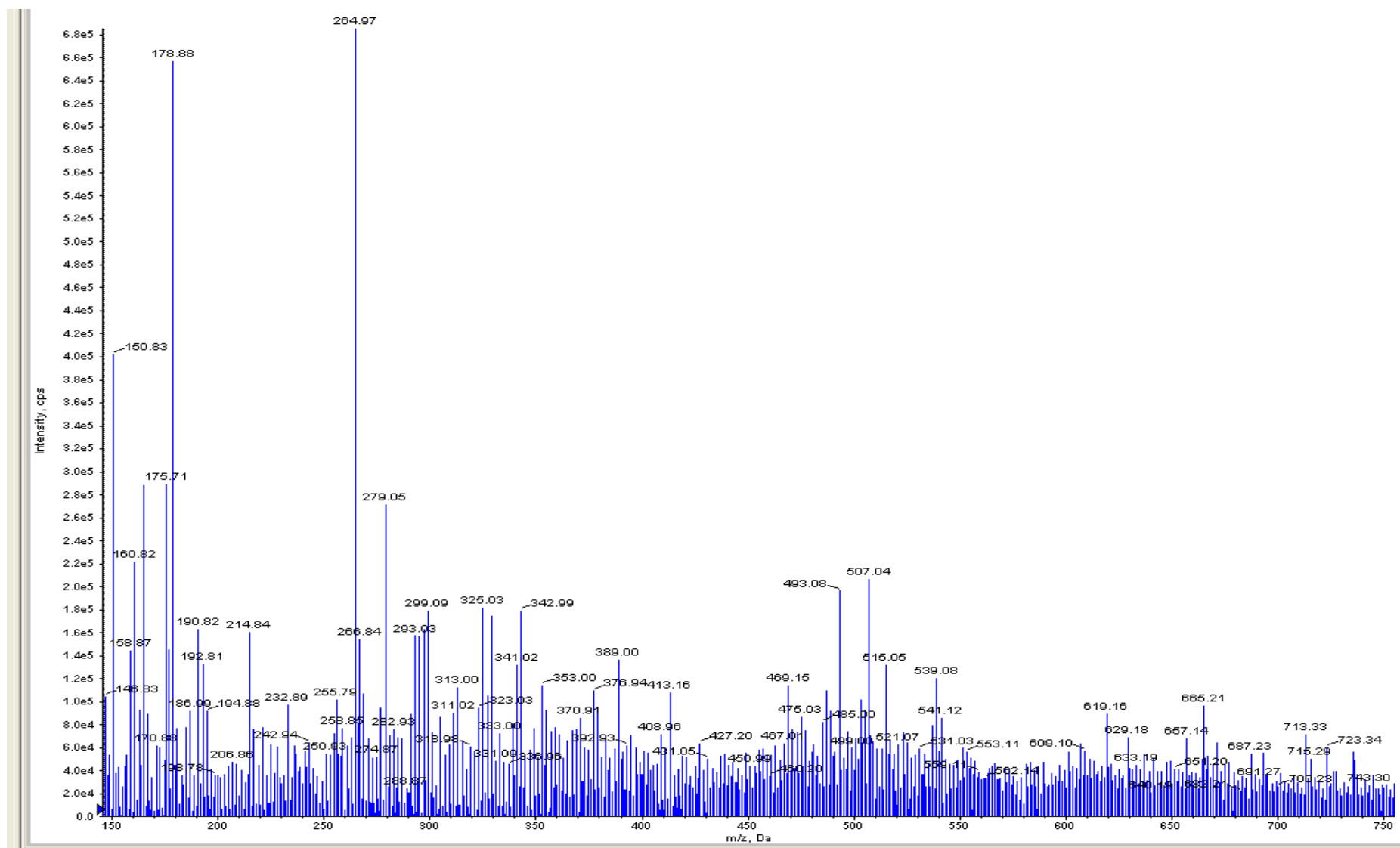


Fig. 5- Total mass spectrum (-Q1) of MCF-Et extract

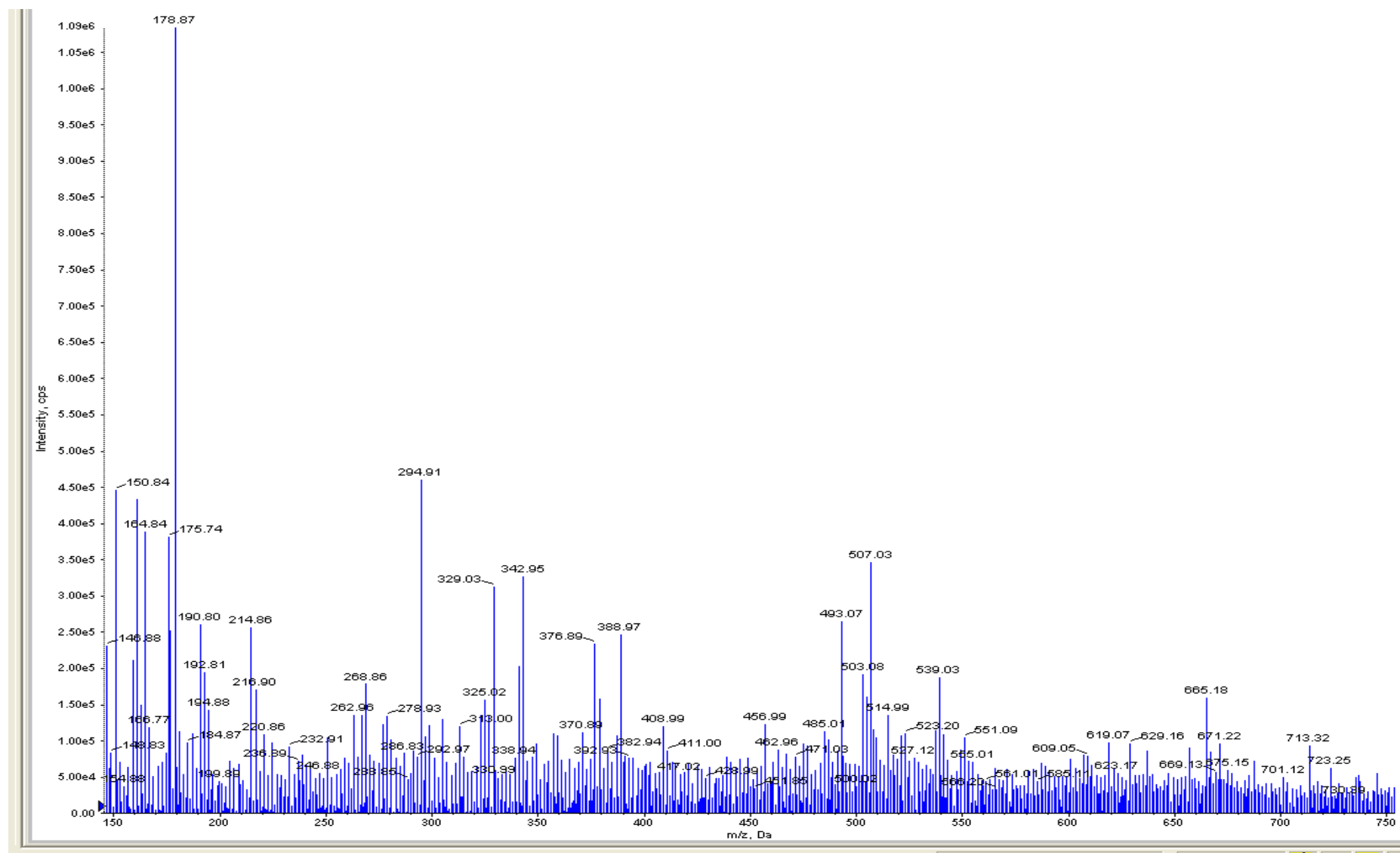


Fig. 6- Total mass spectrum (-Q1) of MCF-Me extract

CONCLUSION

The Preliminary phytochemical studies and the knowledge of the bioactive chemical constituents of Noni fruit are appropriate to realise the important medicinal drugs and their preparations. Therefore, the phytochemical exploration of *Morinda citrifolia* fruit in the present study reveals that the presence of various prospective phytochemical constituents which may be useful for pharmaceutical industries and could be used as an effective food supplements. However, LC-MS/MS mass spectrum of MCF-Et and MCF-Me extracts showed the presence of bioactive compounds and total mass of the each constituents are exactly matching with mass bank database including Rutin, Quercetin, Kaempferol, Scopoletin and Rubiadin 1-methyl ether, so further studies are needed to separate and purify the bioactive chemical constituents of this plant (*Morinda citrifolia*) for new active marker based pharmaceutical formulation.

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