

FTICR/MS Analysis of *Micromeria Fruticosa* and *Teucrium Polium* Growing in Lebanon

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ABSTRACT

Micromeria fruticosa and *Teucrium polium* are *Lamiaceae* plants found throughout the Mediterranean, including Lebanon. Aerial parts of both plants were taken from a rocky mountain in Lebanon's Bekaa region and alcoholic extraction and chromatographic separation were performed. Fourier transform ion cyclotron resonance mass spectrometry (FTICR-MS) was used to examine crude extracts of both plants A and B, as well as their fractions. The mass spectra of both plants revealed great chemical complexity with a total of 6352 ions (peaks) for crude extract of plant A and 5147 ions (peaks) for extract B. The majority of chemicals found in both plants are condensed aromatics, particularly polyphenols which could explain the previously documented anticancer effects of both plants.

Key words: *Micromeria*, *Teucrium* chromatographic analysis, FTICR-MS.

INTRODUCTION

Plants are considered as significant source of natural bioactive substances with a wide range of applications in pharmaceutical, food, and cosmetic industries and have been used in traditional medicine since ancient times.¹ Herbal medicine is used by 78 percent of the world's population (in Latin America and Asia) and has been shown to have few negative side effects.² However, the use of natural products has several drawbacks, the most significant of which are the limited availability of the compounds and their minute quantities, which is not usually sufficient for commercial extraction.³

Plants of family *Lamiaceae*, such as those in the genera *Micromeria* and *Teucrium*, are widely distributed in the Mediterranean region including Lebanon.^{4,5} They have long been used to treat a variety of maladies, including migraines, gastrointestinal disorders, upper respiratory tract infections, and several cardiovascular diseases.⁶ Both *Micromeria* and *Teucrium* are reported as an important source of flavonoid, terpenoid, and phenolic substances responsible for the extensive range of medicinal applications for their antioxidant and anticancer effects.⁶

As an essential aspect of genomics research, Metabolomics aims to gain a comprehensive understanding of metabolic networks by analyzing a wide range of known and novel metabolites found in living organisms simultaneously. The first stage of metabolomics was built up to allow for reliable analyses of known metabolites by comparing them to previously identified compounds. The majority of these metabolomics systems were based on mass spectrometry (MS) technologies, which enabled by a mix of diverse ionization processes and a range of separation methods, including Liquid Chromatography, Gas Chromatography, Capillary electrophoresis, and Fourier-transform ion cyclotron resonance MS (FT-ICR/MS) for metabolite identification and quantification, and

nuclear magnetic resonance (NMR) spectroscopy for structural elucidation and relative quantification.⁷

When presenting metabolomics data, finding an acceptable visual approach for representing complicated chemical mixtures can be difficult.⁸ FT-ICR/MS for metabolite identification and quantification by plotting the H:C ratio versus the O:C ratio for each compound in the mixture.⁹ VK diagrams have traditionally been used to visualize petrochemical mixtures, for example, where compound identities were determined using well-defined GC-MS spectral libraries.⁸ With the introduction of robust and widely accessible high-resolution mass spectrometry (HRMS), VK diagrams are becoming more widely used.^{10,11} This is because HRMS data can be used to determine elemental compositions for a large fraction of chemicals in a mixture and the possibility to derive the ratios needed for VK diagram generation. In addition, the plots can demonstrate information about the nature of the chemicals in the mixture.^{8,11,12}

VK diagrams offer several advantages compared to other commonly used visualization formats HRMS data, such as 3 Dimension intensity plots, and base peak chromatograms. VK diagrams can provide information about the chemical classes of the compounds present and the number of compounds in a sample more accurately. This data is also independent of any chromatographic method, making this technique particularly useful for comparing data across time, columns, instruments, and/or laboratories.¹³

Researchers Kew and coworkers developed visualization tools-van Krevelen for FTICR MS instrumentation used in conjunction with other high-resolution instruments to analyze a particular form of MS data.¹³ Among a variety of MS technologies, FT-ICR/MS provides the best resolution performance and ultra-high-mass to charge ratio (*m/z*) accuracy of each analyte present in a compound mixture, including plant metabolomics that can be identified

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without chromatographic separation stages.^{7,14} These qualities enable the attribution of suspected metabolite formulae purely based on accurate mass, via matching with computed masses for a particular chemical sequence of compounds, in conjunction with metabolomic database search by accurate mass.¹⁴ To avoid errors caused by referring to previously published hypothetical compound class maps and the use of axes that exclude a large amount of the observed data, the researchers devised a new method. A prompt-driven, open-access package of scripts to generate VK diagrams called Open Van Krevelen which produced an empirically derived density map of where seven classes of metabolites are most likely to be depicted within the diagram space. This method produced a better map with longer axes and more distinct metabolite groups, leading to wider VK diagrams as a metabolomics data visualization tool.¹³ In conclusion, ultrahigh-resolution MS technologies offer accurate molecular weight information, which in turn can be used to predict the elemental compositions (molecular formulas) of metabolites as clues for their structural elucidation.⁷ Previously,⁶ we found that the crude extracts of *Micromeria fruticosa* and *Teucrium polium*, as well as some of their fractions, exhibit significant anticancer activity. This activity motivated us to use this advanced technique to investigate the chemical classes and active ingredients in crude extracts of both plants and their fractions that are responsible for these findings.

EXPERIMENTAL PART

Plant material

Micromeria fruticosa and *Teucrium polium* aerial parts were taken in July 2017 from a rocky mountain in the Lebanese Bekaa valley (1300m above sea level) during their full flowering phase. Dr. Ali Chakas a botanist from the Lebanese University, Faculty of Science) authenticated the plants. Both plant samples processed as described before⁶ Chromatographic separation.

As fully described in our previous study, crude extracts of *Micromeria fruticosa* (extract A) and *Toucrium polium* (extract B) were separated using column chromatography, followed by chromatographic isolation of their fractions via elution using mixtures of different organic solvents, yielding 22 fractions for A and 43 fractions for B.⁶

Instrument

Analyses were performed on a SolarixXR instrument with a 9.4 T actively shielded superconducting magnet and a dynamically harmonized cell (Bruker Daltonics, Bremen, Germany). The mass spectrometer is equipped with a Varian Nano-electrospray online source (Varian Nano ESI ON, Bruker Daltonics, Bremen, Germany). FT-ICR MS has been invented by Pr Alan G. Marshall and Pr Melvin B. Comisarow in 1974. Compared to all the mass spectrometers currently available, FT-ICR MS is the most powerful. They offer mass resolving power and mass accuracy up to 100 times higher than any other commercially available mass spectrometry technique. Alternatively, viewed only as a separation device, ultra-high-resolution FT-ICR MS offers more than 100 times higher peak capacity than the most effective wet chemical separation methods, making it possible to analyze complex mixtures with no prior chromatography. The only characteristic for better mass spectrometers may be found in the scanning speed (100 Hz versus 10 Hz for the FT-ICR MS at 100,000 resolutions).

ANALYSIS

Method

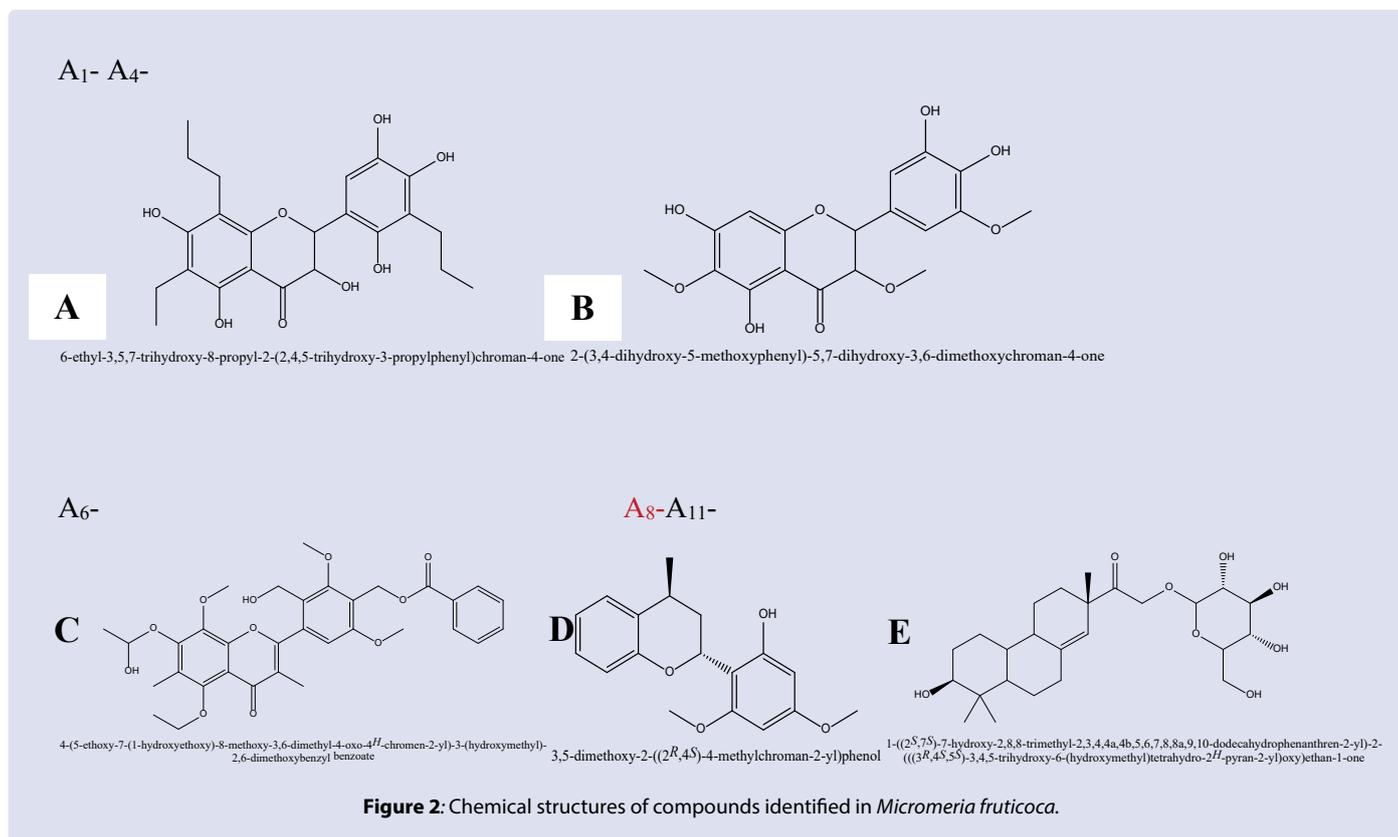
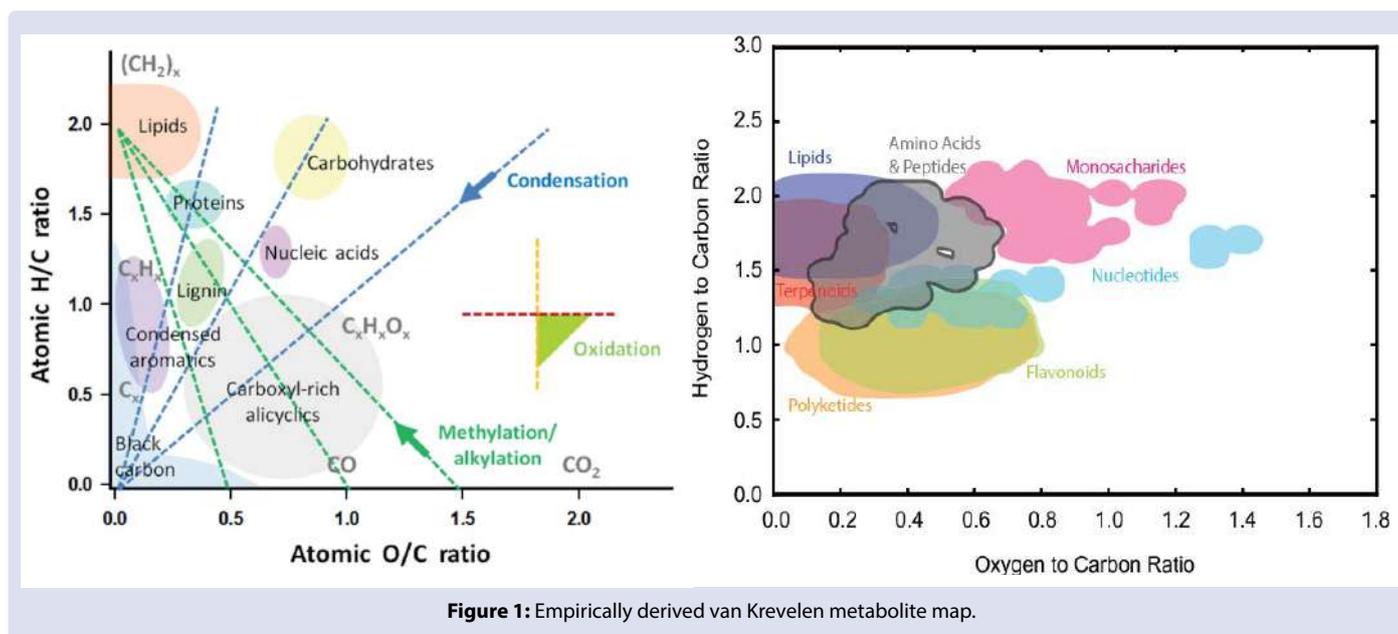
For all experiment parts of the total extract of both plants and their separated fractions, FT-ICR mass spectra were acquired in positive ion mode. Samples were diluted in acetonitrile (10 mg/mL). The obtained solutions were further diluted to 100 ng/ μ L in acetonitrile. Mixture solutions of sample and formic acid at a ratio of 10:1 (sample/formic

acid, v/v) were introduced in the spectrometer by direct infusion using a Cole-Parmer single-syringe infusion pump (Cole-Parmer[®], Vernon Hills, USA) at a rate of 10 μ L/min through a 250 μ L Hamilton syringe (51 mm, Gastight). The syringe is connected to a capillary line (100 μ m ID, 360 μ m OD) equipped with a SilicaTipTM needle (10 \pm 1 μ m, PicoTipTM Emitter, New Objective, Woburn, MA, USA) to which a potential of 1.3 kV was applied. The front and back trapping potentials were set at 1.5 V with a skimmer 1 voltage at 20 V. Spectra were acquired using broadband detection, 8 M data points, 300 scans accumulation for a better signal-to-noise ratio with a mass range between m/z 144 to 1500. The transient time consisted of 4.20 s, resulting in a resolution of 1,000,000 at m/z 400 in the magnitude mode. Ions were accumulated in the hex pole during 0.05 s. Instrument calibration was achieved using an external calibrant (Sodium trifluoroacetate TFA, 0.01 mg/mL in H₂O/MeOH 50/50 v/v) with a linear calibration. Following the acquisition, spectra were internally calibrated in the Data Analysis software version 5.0 (Bruker Daltonics, Bremen, Germany) using a calibration list of assigned signals limiting the mass error to under 100 ppb. Mass spectra treatment was done using a modified python script originating from the FTMS Visualization software (also known as i-van Krevelen) in which masse to formula assignment is based on the Kendrick mass defect and z* approach formulae assignment. The attributed compounds were classed according to the number of CH₂, instauration, and oxygen atoms in the molecule. Van Krevelen diagrams were generated, and the corresponding families of molecules present in each sample were identified relying on the empirically derived van Krevelen metabolite map. Map displays the areas of highest point density for seven major classes of metabolites: lipids, terpenes, polyketides, monosaccharides, nucleotides, flavonoids, amino acids, and peptides (Figure 1). The x-axis represents the oxygen to carbon ratio, and the y-axis the hydrogen to carbon ratio. Overlap between groups results from the parameters used by the software but more fundamentally arises from the fact that it is not simply the molecular formula of a molecule that dictates its classification but its structure. As molecules with different structures can have similar or even identical molecular formulas, compound classes overlap.

RESULTS AND DISCUSSION

Analysis of the metabolic profiles of both plants and their fractions identified a total of 6352 ions (peaks) of the whole extract of *Micromeria fruticosa* (Extract A) (Figure 2) in the positively ionized mode. Metabolite formulas were assigned to the detected masses to provide insight into metabolite diversity and elemental ratios. The H/C ratio was plotted against the O/C ratio in the Van Krevelen plot (Figure 3).

The mass spectrum of sample A showed high chemical complexity. Van Krevlen plots revealed the presence of high concentrations of aromatics as well as the presence of some lipids. The highest density of formulas contains atomic H/C ratios in extract A between 1 and 1.5. This high ratio reflects the absence of highly saturated molecules and also indicates the presence of compounds with short carbon chains. The low O/C ratios between 0.4 and 0.6 (Figure 3) show the absence of highly oxygenated compounds. This vicinity corresponds particularly to linear hydrocarbons and condensed aromatics mainly polyphenols which is probably accountable for its significant anticancer effect confirmed in our previous study against MCF7 and A549 cancer cell with IC₅₀ 28.52 and 26.47 μ g/ml respectively. Many phenolic compounds, predominantly flavonol compounds, epicatechin derivatives of molecular formula C₂₃H₂₆O₈ (Figures 6 and 7), and eriodictiol derivatives of molecular formula C₁₈H₁₆O₈ (Figures 8 and 9) have been identified in fractions A1 and A4. Flavone compound of molecular formula (C₃₃H₃₆O₁₁) in fraction A6 (Figures 10 and 11), flavonoid taxicatigenin derivatives of molecular formula C₁₈H₂₀O₄ of fraction A8 (Figures 12 and 13), in addition to the identification of two other phenolic compounds of chemical formulae C₂₆H₄₂O₈ (Figure 14),



and $C_{24}H_{18}O_3$ (Figures 16 and 17) in fractions A11 and A15 respectively, these two compounds, besides being unsaturated, their richness in carboxylic and hydroxylic groups that possess antioxidant features, may stand behind their anticancer activity that has been demonstrated in our previous study.⁶

On the other hand, 5147 ions (peaks) were identified in the positive ionization mode for the total extract of *Teucrium polium* plant (extract B) (Figures 17 and 18). Also, the mass spectroscopy of sample B showed high chemical complexity. The highest density formula contains H/C ratios between 1.5 and 2. This high ratio reflects the absence of highly

saturated molecules and also indicates the presence of compounds with short carbon chains, while the low O/C ratios between 0 and 0.5 demonstrate the absence of highly oxygenated compounds and represent the area of lipids and terpenoids (Figure 18). The compound database revealed that the lipid class was the most prevalent within the major metabolic classes, accounting for 73% of the total detected metabolome. The Van Krevelen plot of elemental data, calculated from the ultra-high resolution mass spectrum (FTICR) for the different fractions of extract B, provides a qualitative visual description of the nature of many compounds and their chemical formulas. Mainly the flavanone, chrome-4-one derivative of chemical formula $C_{24}H_{18}O_3$ in

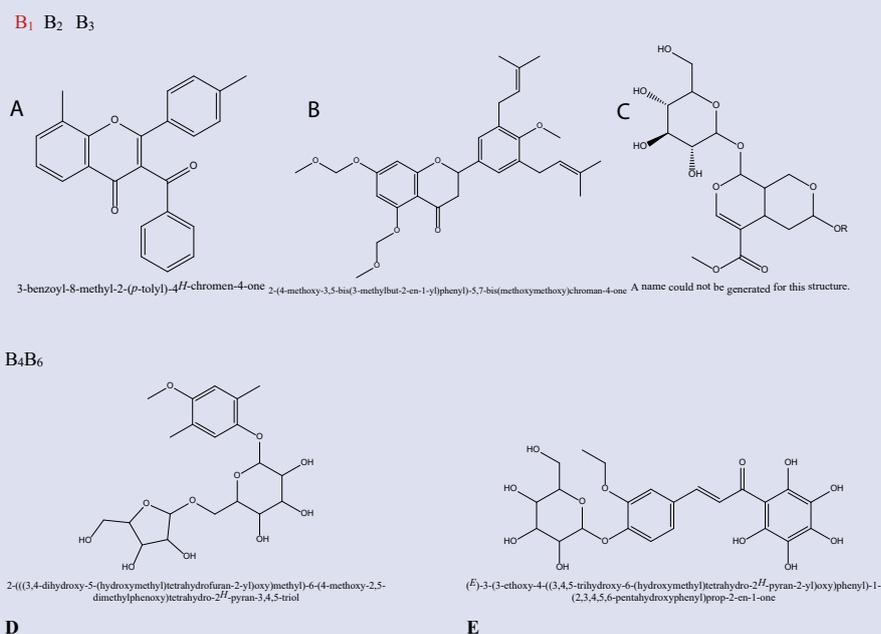


Figure 3: Chemical structures of compounds identified in *Teucrium polium*.

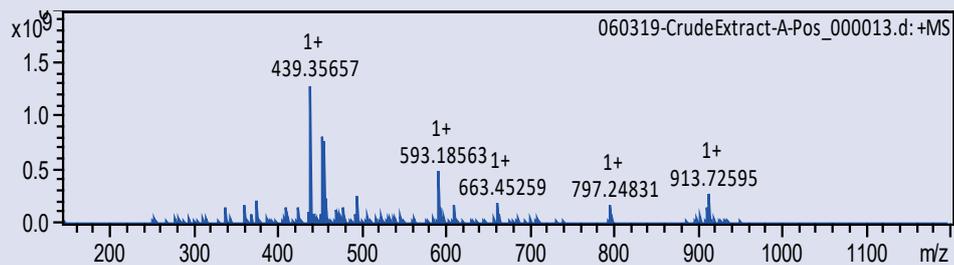


Figure 4: FTICR mass spectrum for the total extract A.

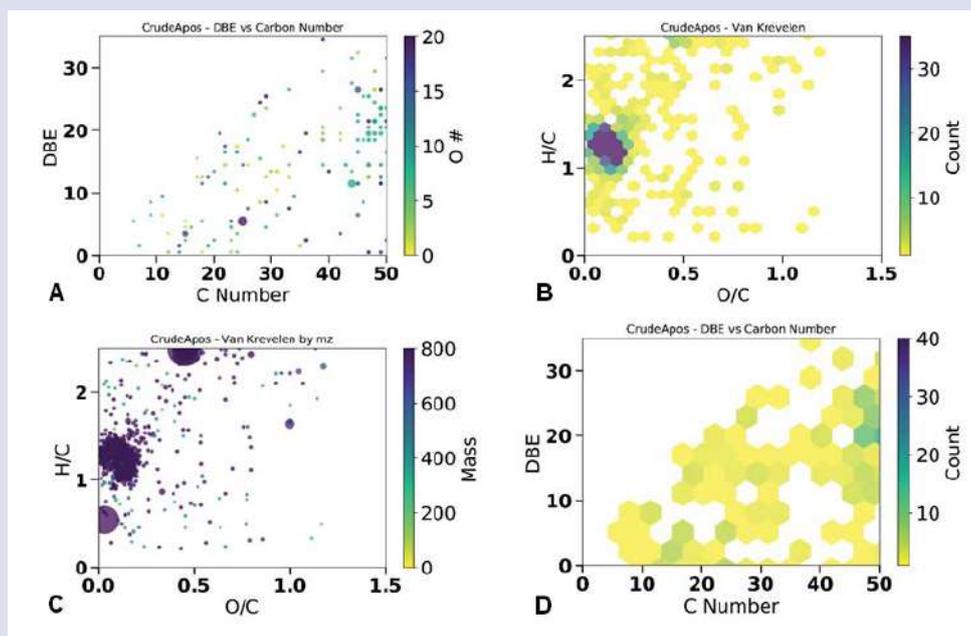


Figure 5: Van Krevelen plot for elemental data calculated from the ultrahigh resolution mass spectrum (FTICR) for the total extract A.

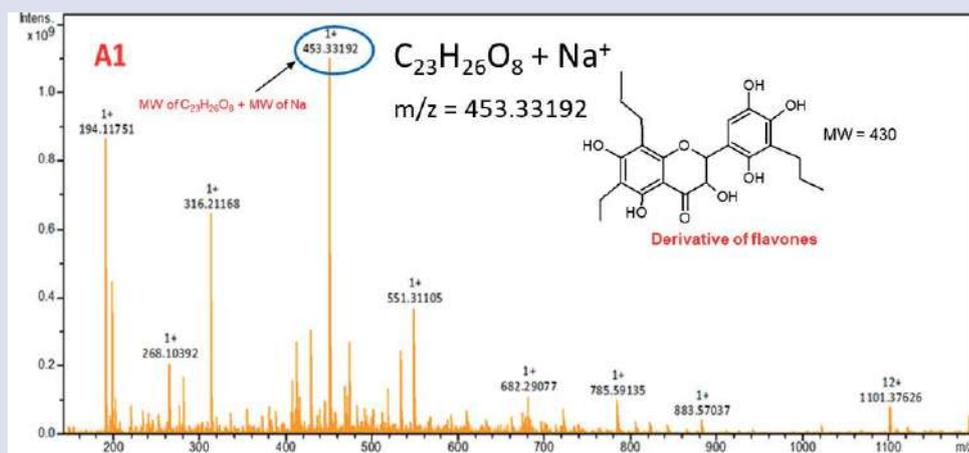


Figure 6: FTICR mass spectrum for the compound A1: Flavanonol (3= Hydroxyflavone). $C_{23}H_{26}O_8$ (6-ethyl-3,5,7-trihydroxy-8-propyl-2-(2,4,5-trihydroxy-3 propylphenyl)chroman-4-one). Epicatechin derivative.

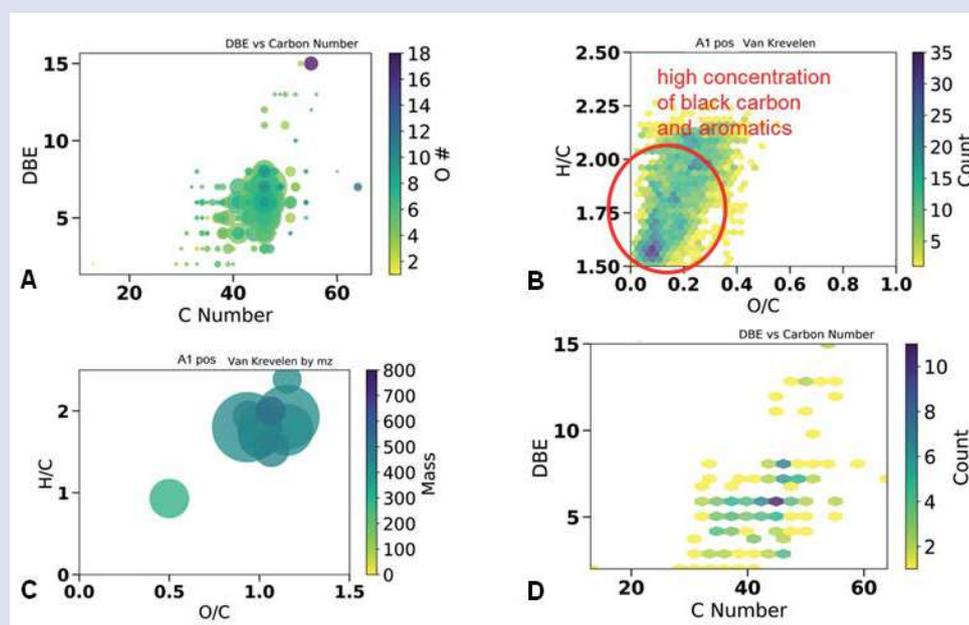


Figure 7: Van Krevelen plot for elemental data calculated from the ultrahigh resolution mass spectrum (FTICR) for the sample named A1; $C_{23}H_{26}O_8$.

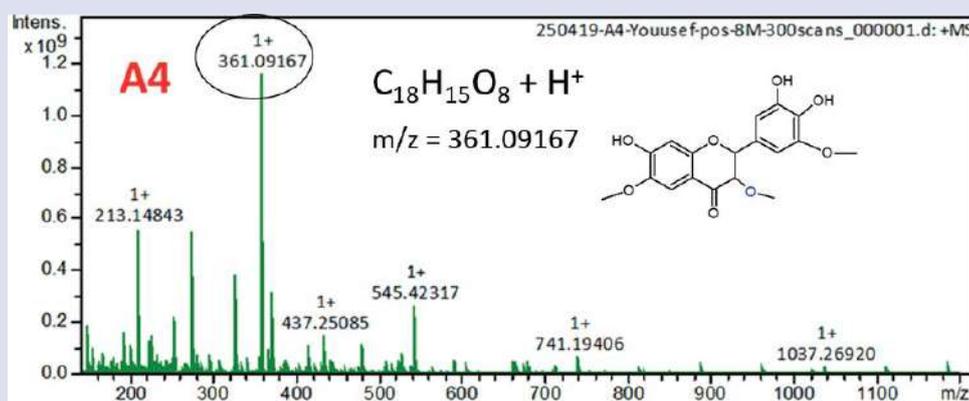


Figure 8: FTICR mass spectrum for the compound $C_{18}H_{15}O_8$. From sample A4.2-(3,4-dihydroxy-5-methoxyphenyl)-7-hydroxy-3,6-dimethoxychroman-4-one. Derivative of Flavanonols (dihydroquercetin).

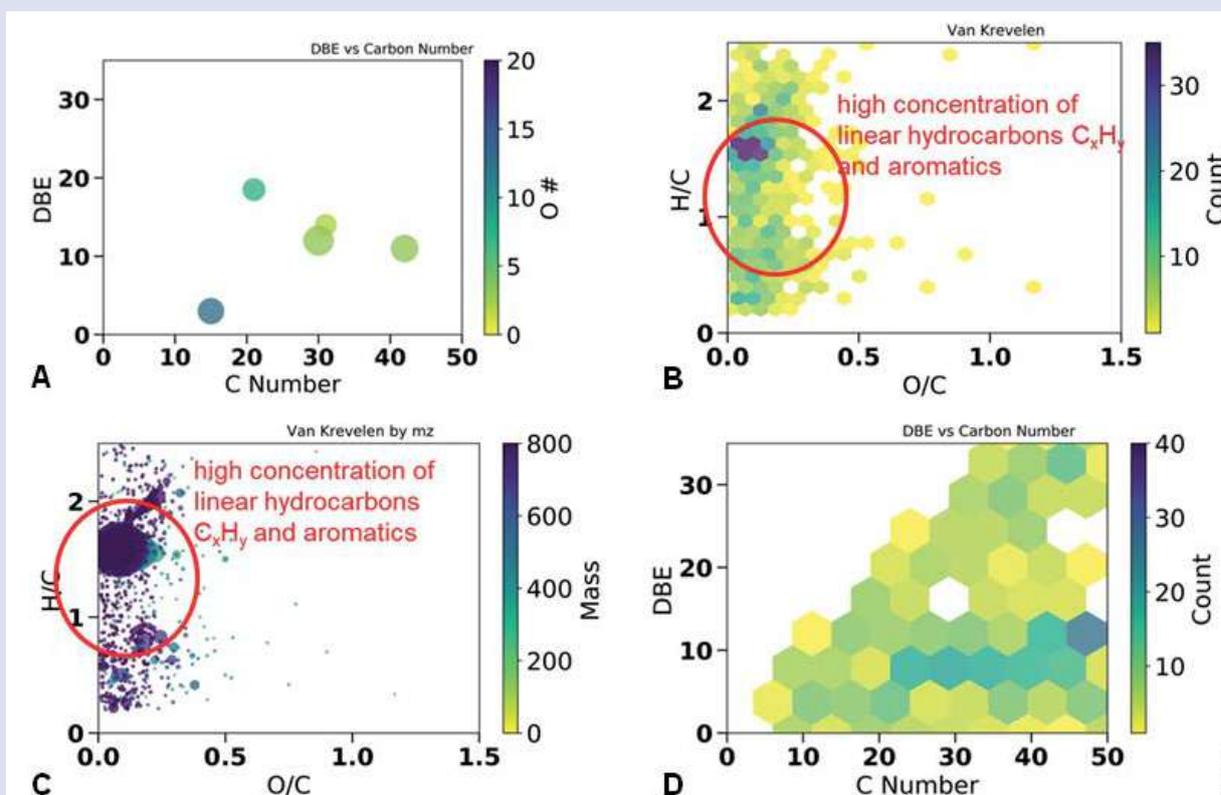


Figure 9: Van Krevelen plot for elemental data calculated from the ultrahigh resolution mass spectrum (FTICR) for the sample named A4.

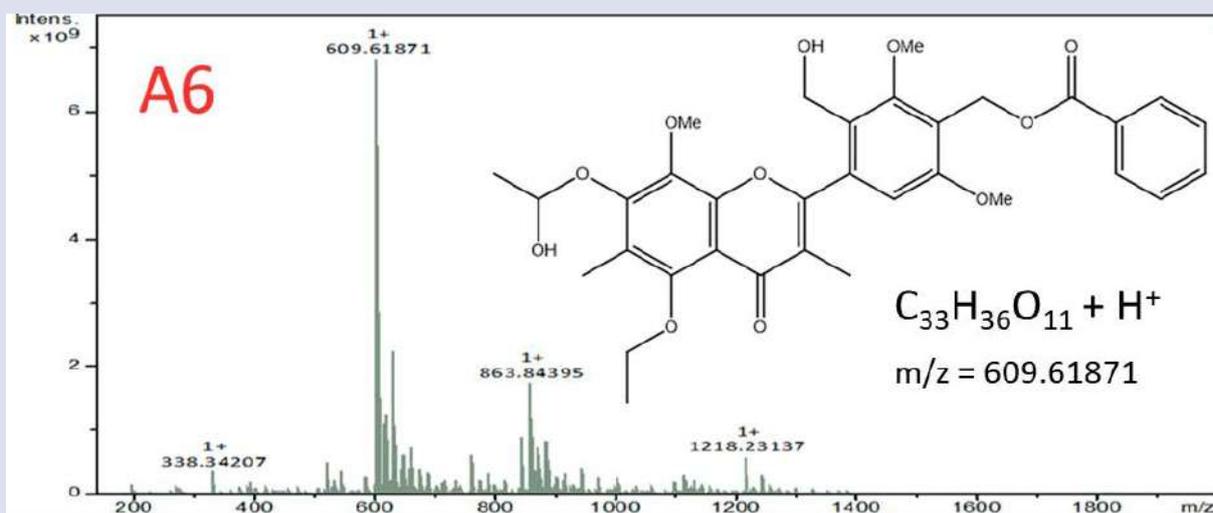


Figure 10: FTICR mass spectrum for the compound $C_{33}H_{36}O_{11}$. From sample named A6. :4-(5-ethoxy-7-(1-hydroxyethoxy)-8-methoxy-3,6-dimethyl-4-oxo-4H-chromen-2-yl)-3-(hydroxymethyl)-2,6-dimethoxybenzyl benzoate. 7-methylsudachitin derivative.

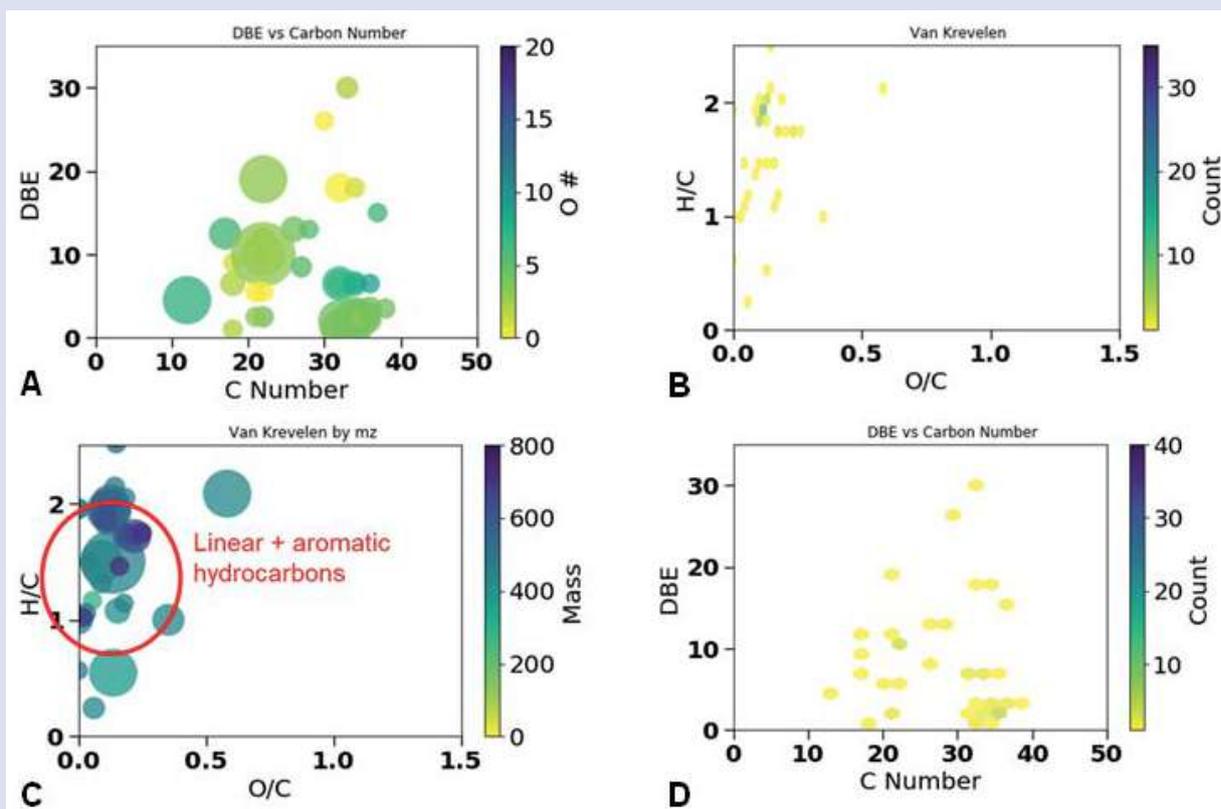


Figure 11: Van Krevelen plot for elemental data calculated from the ultrahigh resolution mass spectrum (FTICR) for the sample named A6.

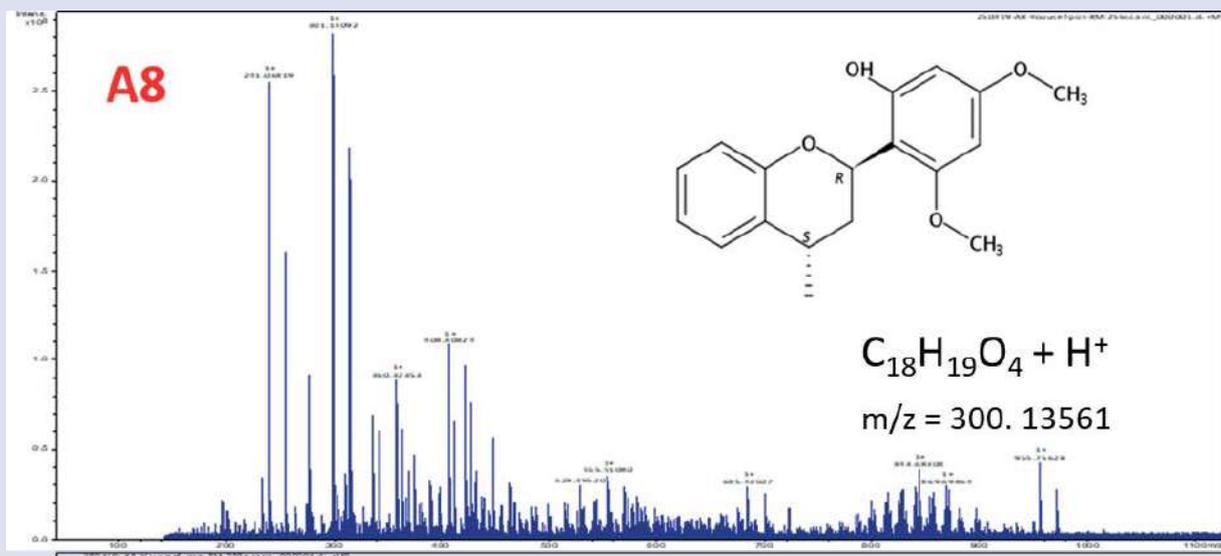


Figure 12: FTICR mass spectrum for the compound $C_{18}H_{19}O_4$. From sample named A8. 3,5-dimethoxy-2-((2R,4S)-4-methylchroman-2-yl)phenol.

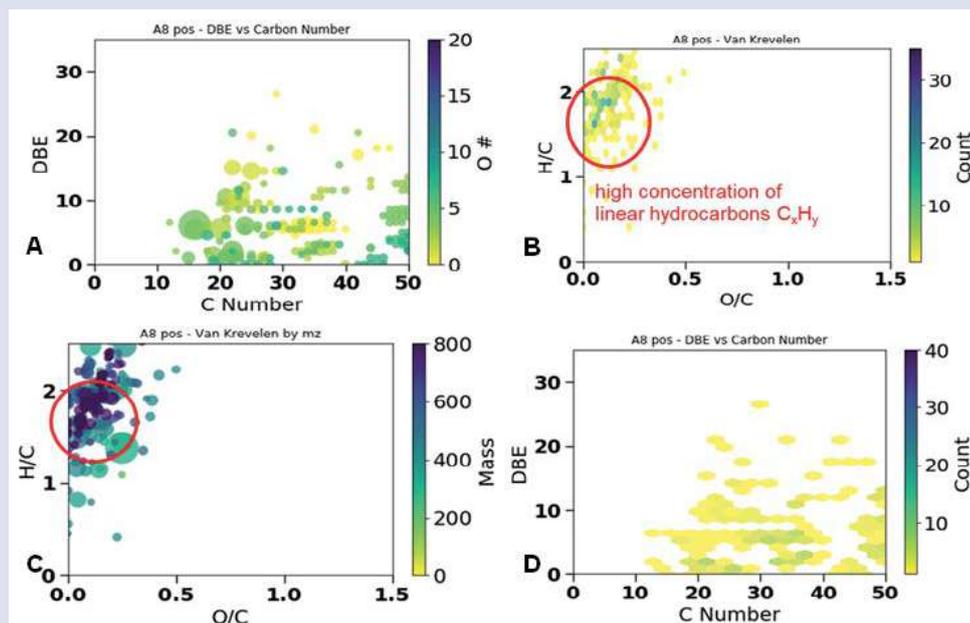


Figure 13: Van Krevelen plot for elemental data calculated from the ultrahigh resolution mass spectrum (FTICR) for the sample named A8.

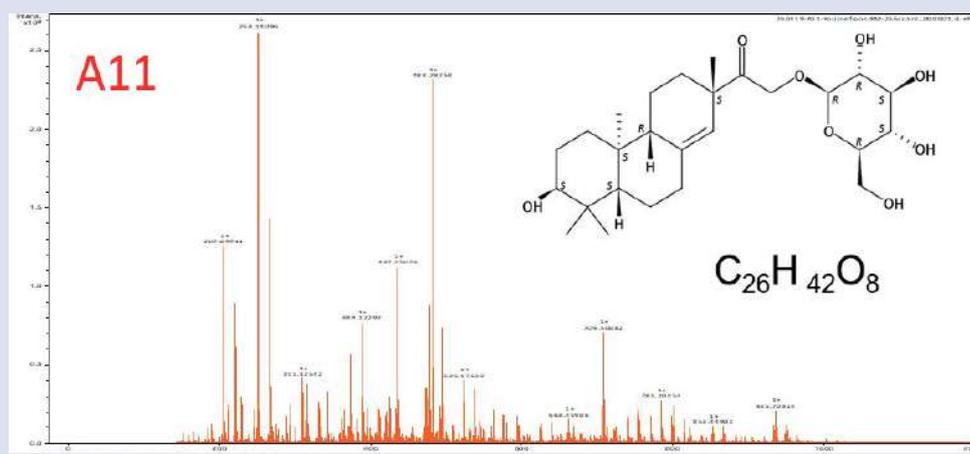


Figure 14: FTICR mass spectrum for the compound $C_{26}H_{42}O_8$. From sample named A11. phenolic acid derivative.

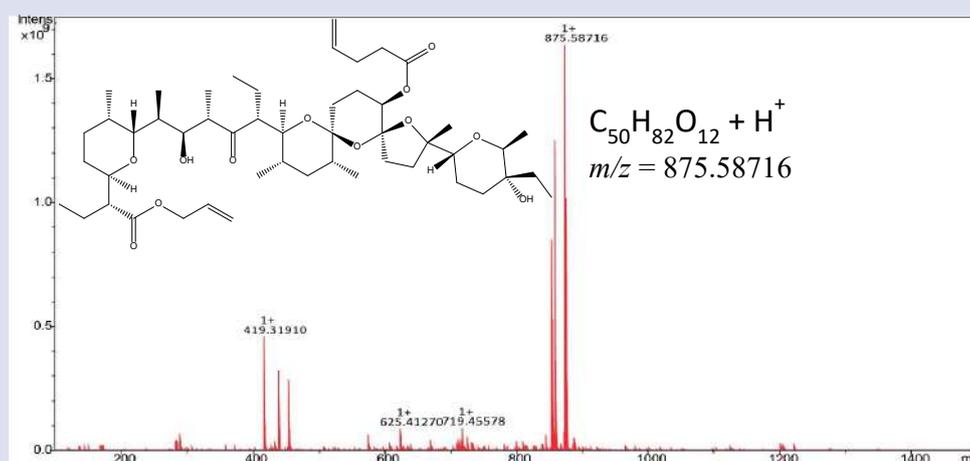


Figure 15: FTICR mass spectrum for the compound $C_{50}H_{82}O_{12}$. From sample named A15.

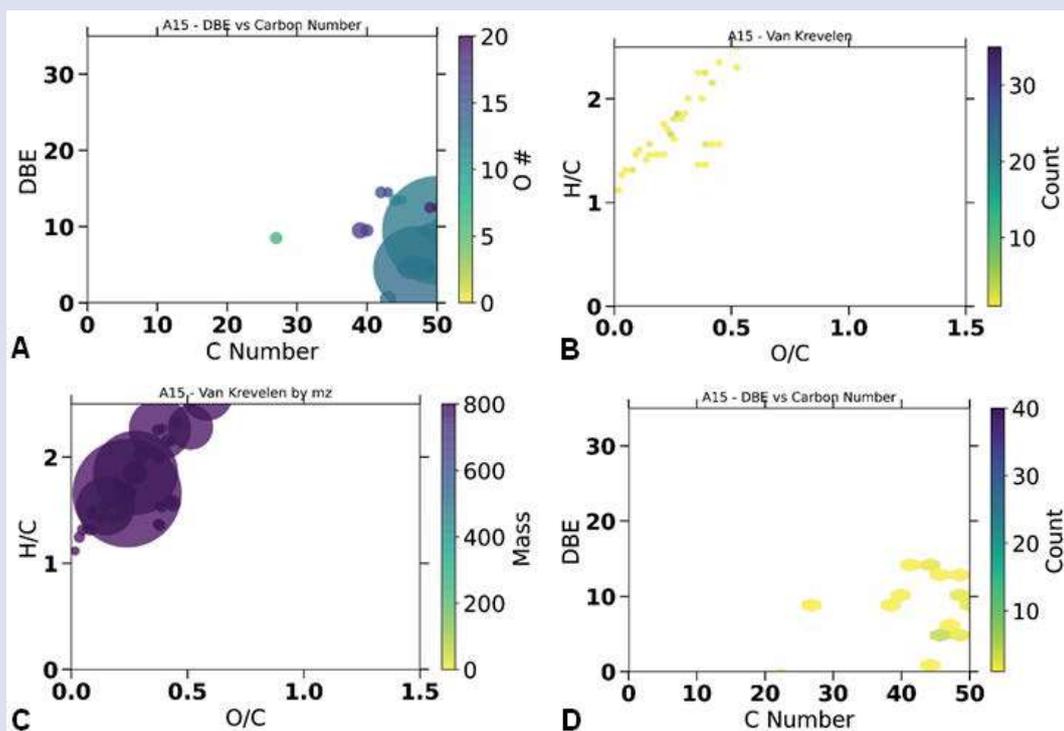


Figure 16: Van Krevelen plot for elemental data calculated from the ultrahigh resolution mass spectrum (FTICR) for the sample named A15.

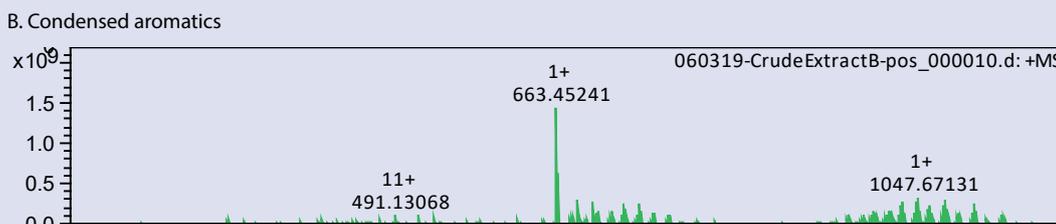


Figure 17: FTICR mass spectrum for the total extract B.

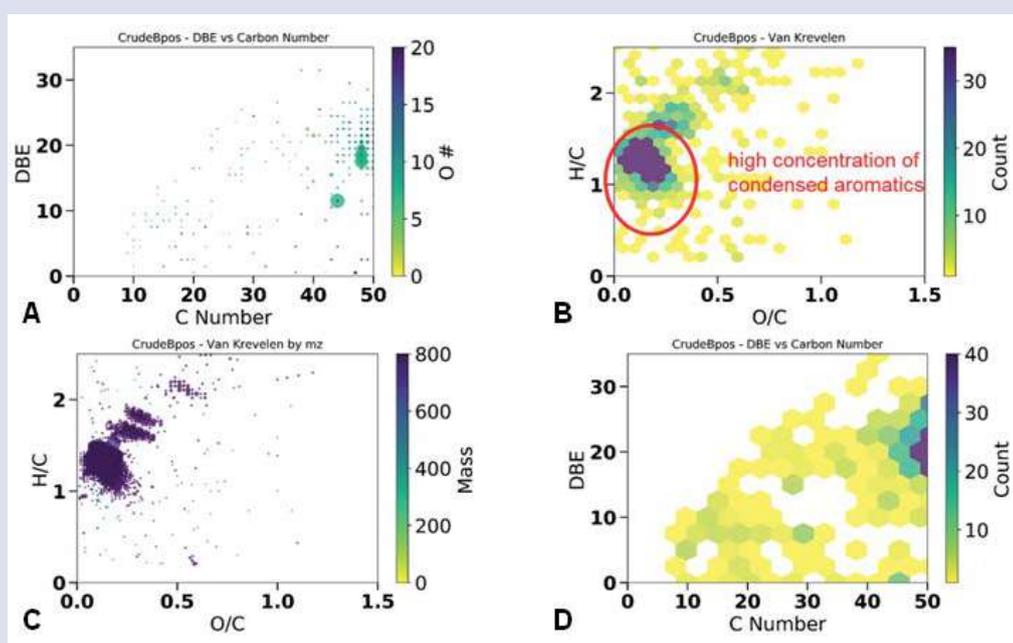


Figure 18: Van Krevelen plot for elemental data calculated from the ultrahigh resolution mass spectrum (FTICR) for the total extract B.

B1: Flavanone derivative

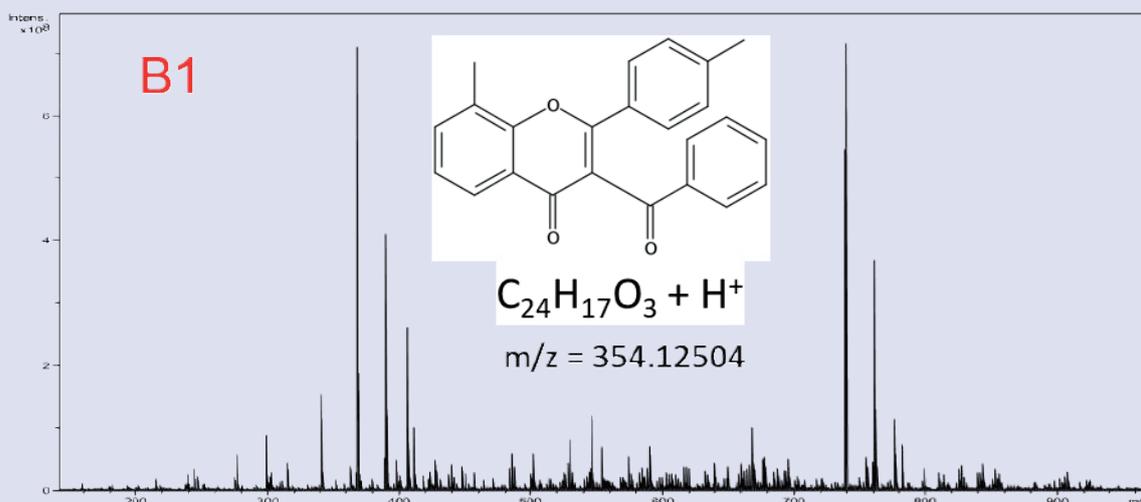


Figure 19: FTICR mass spectrum for the compound $C_{24}H_{18}O_3$. From sample named B1. 3-benzoyl-8-methyl-2-(p-tolyl)-4H-chromen-4-one. methyl-2-(p-tolyl)-4H-chromen-4-one.

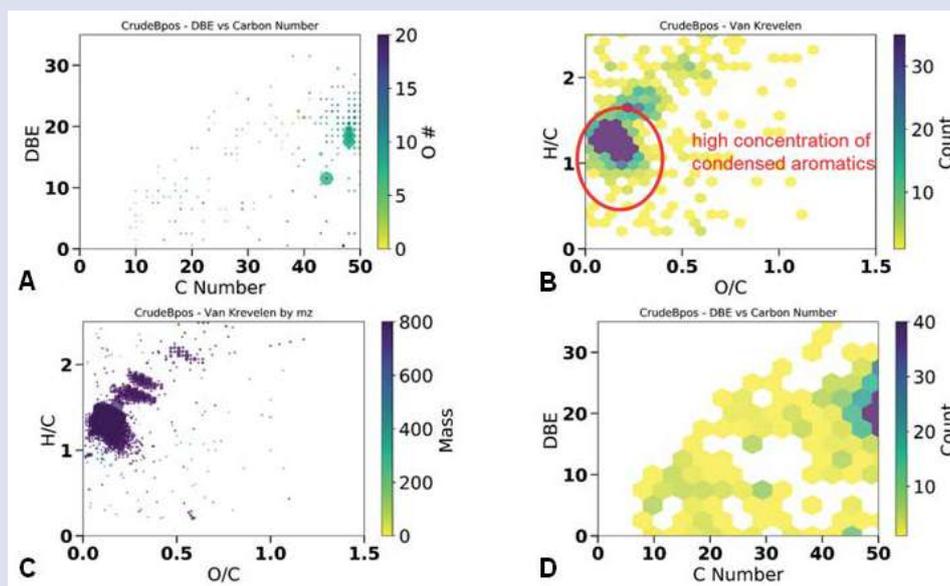


Figure 20: Van Krevelen plot for elemental data calculated from the ultrahigh-resolution mass spectrum (FTICR) for the sample named B1.

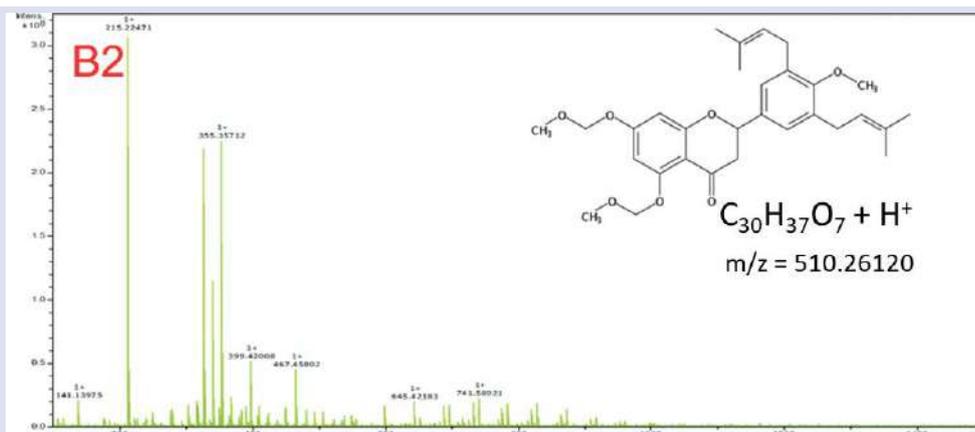


Figure 21: FTICR mass spectrum for the compound $C_{30}H_{38}O_7$. From sample named B2. 2-(4-methoxy-3,5-bis(3-methylbut-2-en-1-yl)phenyl)-5,7-bis(methoxymethoxy)chroman-4-one.

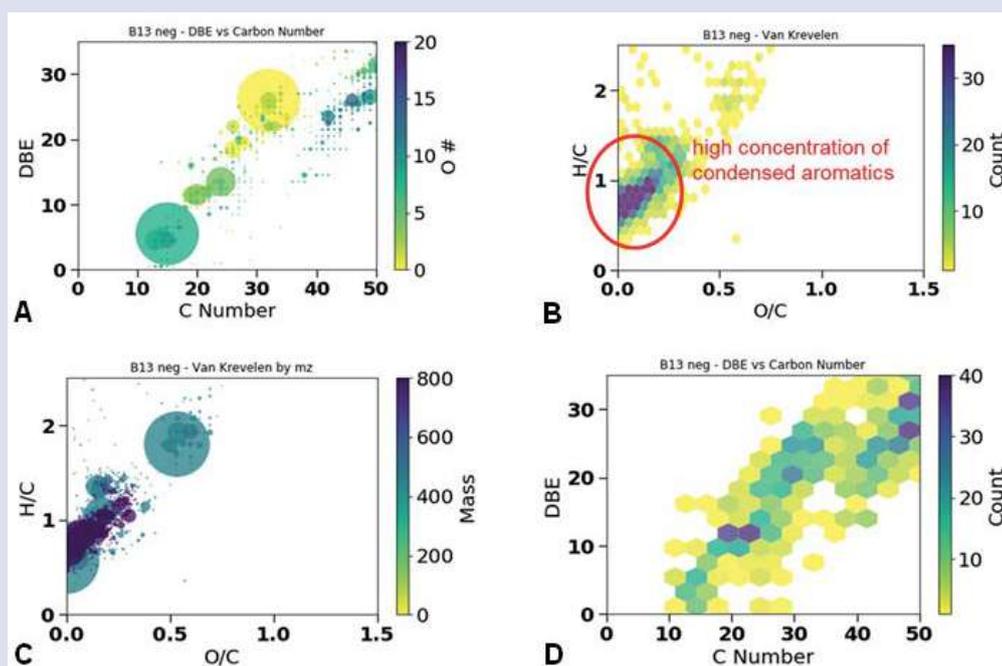


Figure 22: Van Krevelen plot for elemental data calculated from the ultrahigh resolution mass spectrum (FTICR) for the sample named B2.

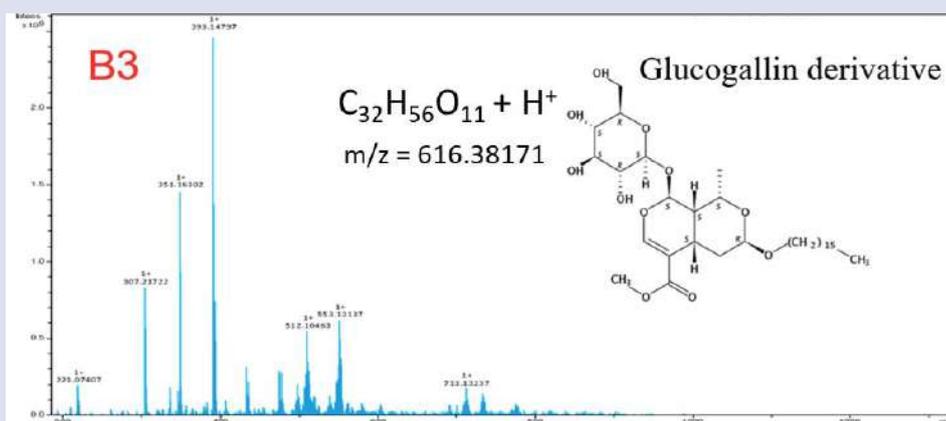


Figure 23: FTICR mass spectrum for the compound $C_{32}H_{56}O_{11}$. From sample named B3 methyl (3R,4aS,8S,8aS)-3-(hexadecyloxy)-8-(((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl)tetrahydro-2H-pyran-2-yl)oxy)-4,4a,8,8a-tetrahydro-1H,3H-pyrano[3,4-c]pyran-5-carboxylate.

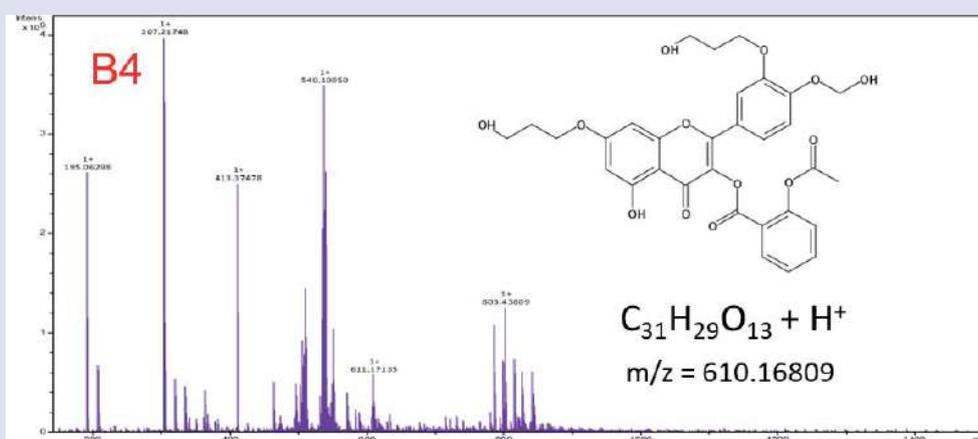


Figure 24: FTICR mass spectrum for the compound $C_{31}H_{29}O_{13}$. :5-hydroxy-2-(4-(hydroxymethoxy)-3-(3-hydroxypropoxy)phenyl)-7-(3-hydroxypropoxy)-4-oxo-4H-chromen-3-yl 2-acetoxybenzoate(querctin derivative).

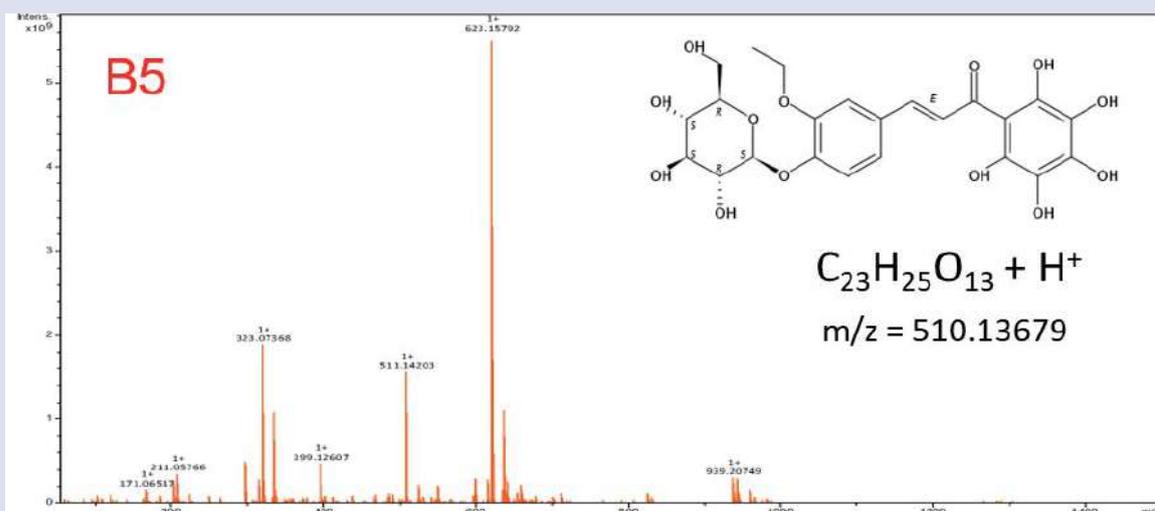


Figure 25: FTICR mass spectrum for the compound $C_{23}H_{26}O_{13}$. From sample named B5. (E)-3-(3-ethoxy-4-(((2S,3R,4S,5S,6R)-3,4,5-trihydroxy-6-(hydroxymethyl) tetrahydro-2H-pyran-2-yl)oxy)phenyl)-1-(2,3,4,5,6-pentahydroxyphenyl)prop-2-en-1-one. Ferulic acid derivative.

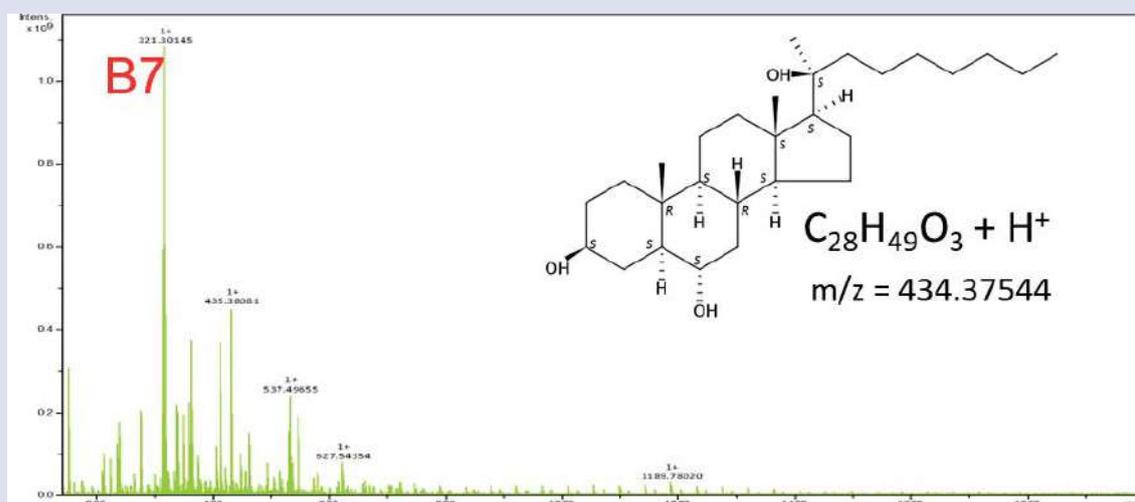


Figure 26: FTICR mass spectrum for the compound $C_{19}H_{18}O_7$. From sample named B6. 2-(4-ethoxy-3-methoxyphenyl)-3,5-dihydroxy-7-methoxy-4H-chromen-4-one(Isorhamnetin derivative).

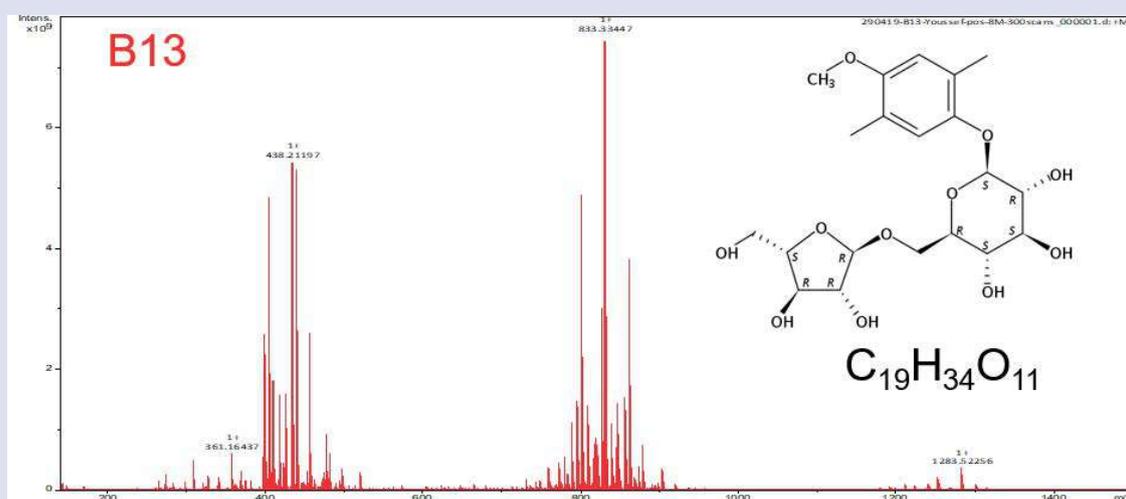


Figure 27: FTICR mass spectrum for the compound $C_{28}H_{50}O_3$. From sample named B7. (3S, 5S,6S,8R,10R,13S,14S,17S)-17-((S)-2-hydroxynonan-2-yl)-10,13-dimethylhexadecahydro-1H-cyclopenta[a]phenanthrene-3,6-diol(Nervosan derivative).

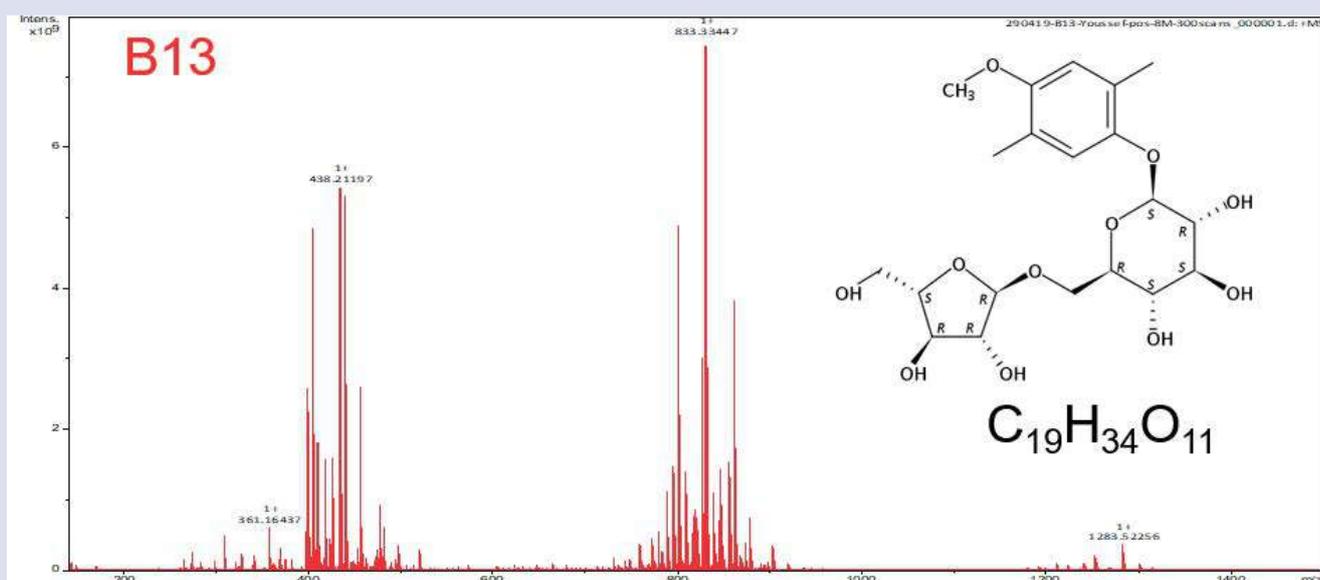


Figure 28: FTICR mass spectrum for the compound $C_{19}H_{34}O_{11}$. From sample named B13phenolic acid (Tachioside derivative).

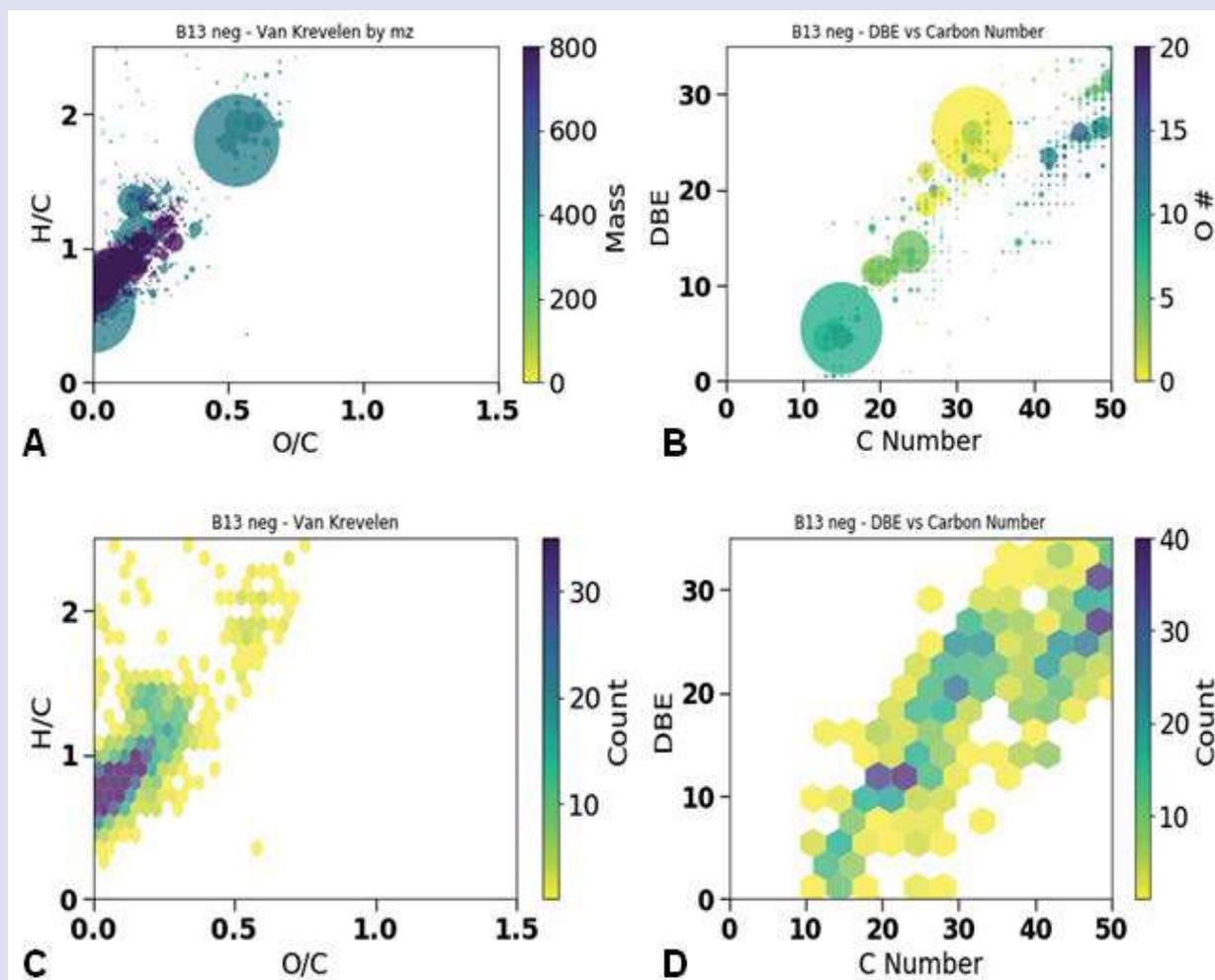


Figure 29: The Van Krevelen plot for elemental data calculated from the ultrahigh resolution mass spectrum (FTICR) for the sample named B13.

fraction B1 (Figures 19 and 20). This class of compounds possesses anticancer activity as demonstrated in previous studies.^{15,16} Also, the flavanone compound sakuranetin derivative of molecular formula $C_{30}H_{38}O_7$ detected in fraction B2 (Figures 21 and 22), it is well known that poly oxygenated unsaturated compounds, which are the properties that this compound has, have antioxidant effects that may stand behind its interesting anticancer property against A549 cell line with IC_{50} lower than $30\mu\text{g/ml}$.⁶ This is consistent with the previous studies that reported the anticancer properties of Sakuranetin.¹⁷⁻¹⁹

Many other compounds, gallo tannin of molecular formula $C_{32}H_{56}O_{11}$, quercetin derivative) $C_{31}H_{30}O_{13}$, Dihydrochalcon derivative $C_{23}H_{26}O_{13}$, 3-Hydroxyflavone isorhamnetin $C_{19}H_{18}O_7$, nervosa derivative $C_{28}H_{50}O_3$ and tachioside derivative $C_{28}H_{50}O_3$ identified in fractions B3(Figure 23), B4(Figure 24), B5(Figure 25), B6(Figure 26), B7(Figure 27) and B13 (Figures 28 and 29) respectively. In our previous study, fractions B5 and B13 showed cytotoxic activity. This activity might be due to the high percentage of hydroxyl groups in both compounds and being highly unsaturated. This finding is in agreement with previous publications that conform the anticancer activity of both dihydrochalcon and phenolic glycoside compounds.^{15,20-22}

CONCLUSION

The Fourier transform ion cyclotron resonance mass spectrometry (FTICR MS) instrumentation provides the best resolution performance and ultra-high-mass to charge ratio (m/z) accuracy of each analyte present in a complex mixture without the need for chromatographic separation. It also offers metabolite identification, quantification as well as accurate molecular weight information. The mass spectra of both *Micromeria fruticosa* and *Teucrium polium* showed high chemical complexities and revealed the presence of many classes of metabolites including lipids and flavonoids that possess antioxidant activities that might be responsible for the previously demonstrated significant anticancer activity against MCF7 and A549 cancer cell lines. More studies are needed to see whether a particular compound in each plant is responsible for the anticancer effect, or the synergistic effect of the compounds present in the plants lie behind it.

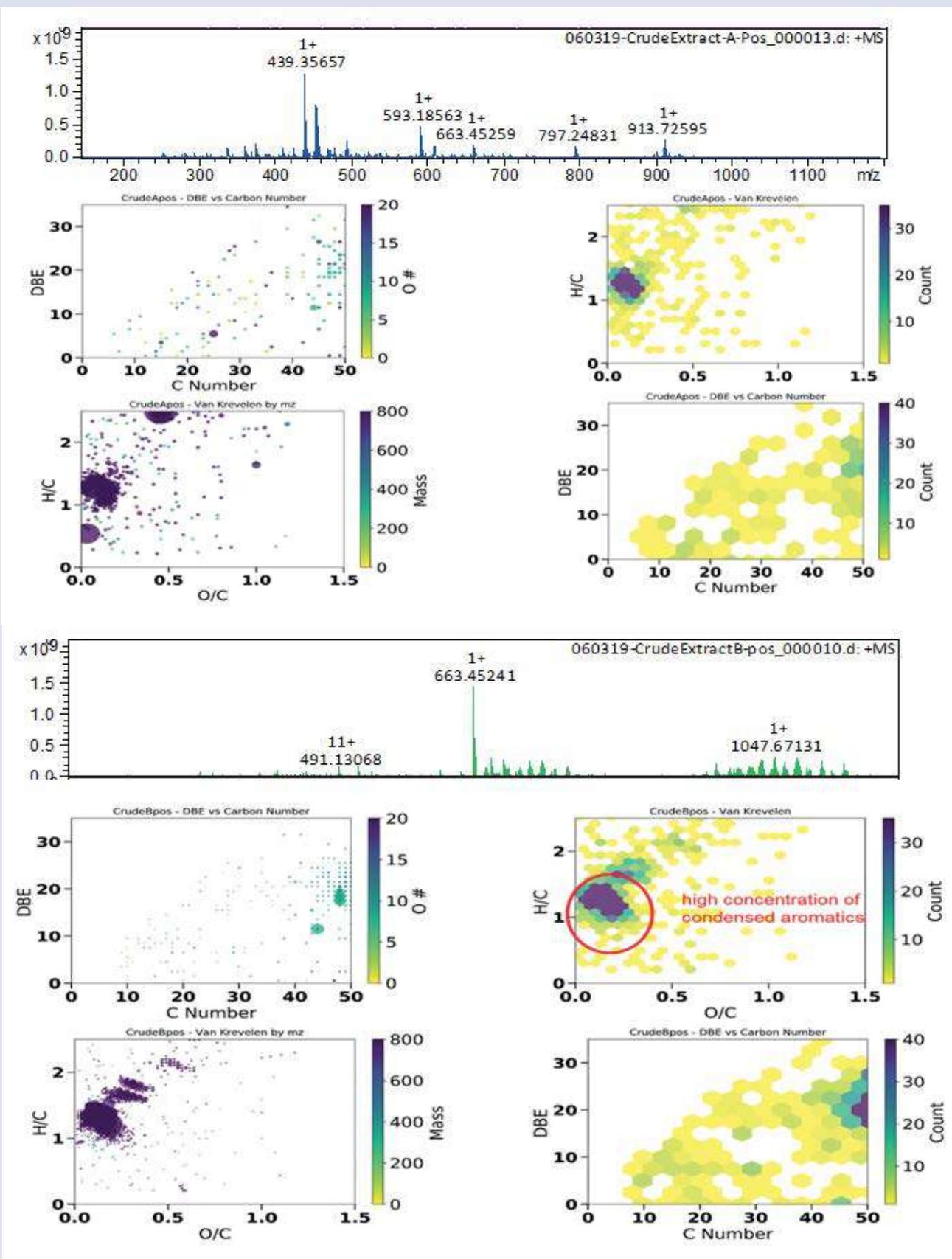
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GRAPHICAL ABSTRACT



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