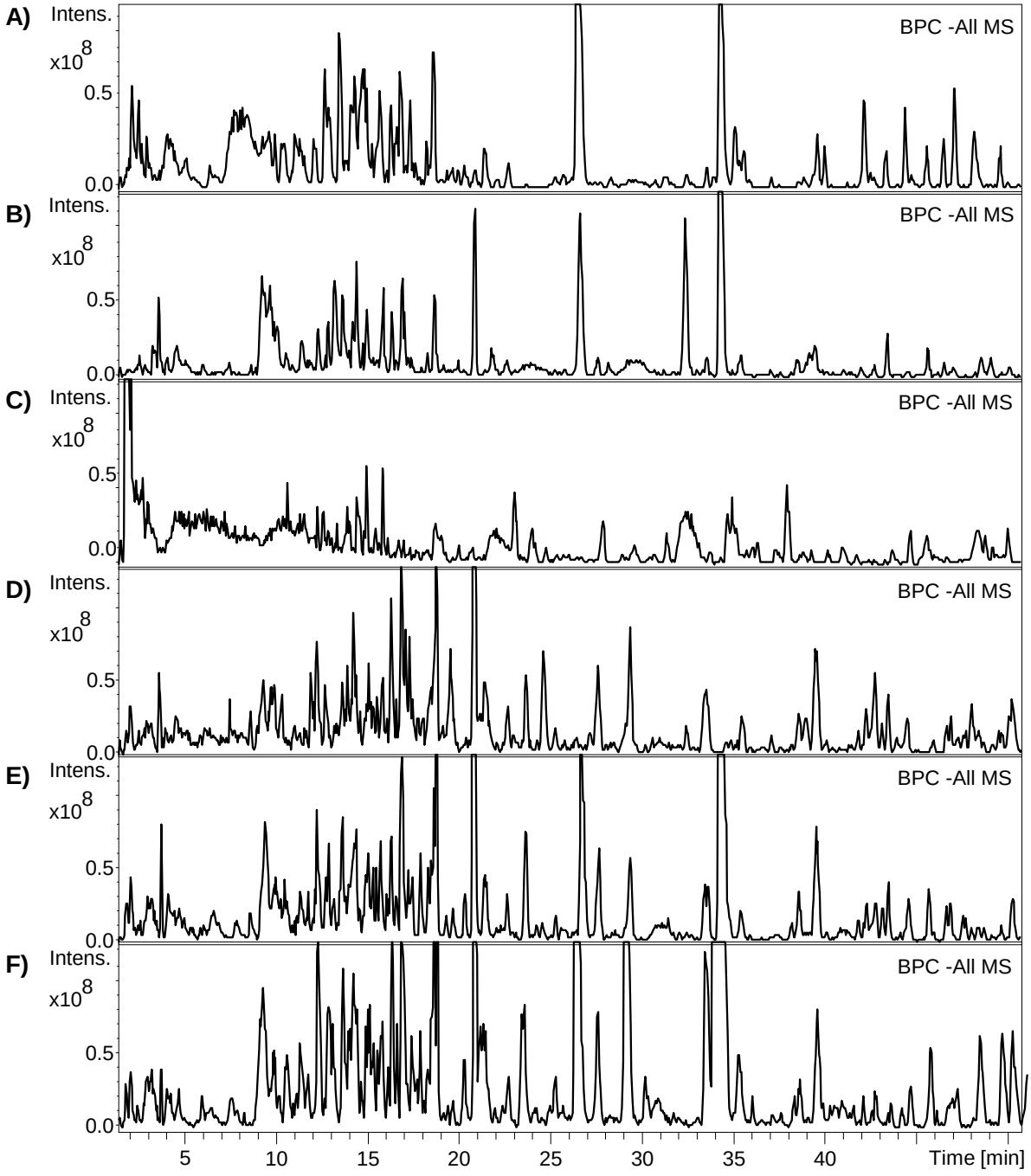


Figure S1. HPLC-MS^n fingerprints (BPC = base peak chromatograms) of *M. perennis* extracts. **A**) Aqueous extract (AE). **B**) Lactobacteria inoculated fermentation (LBF, *L. plantarum* + *P. pentosaceus*). **C**) Whey. **D - F**) Whey inoculated fermentations (WF 1 - 3).

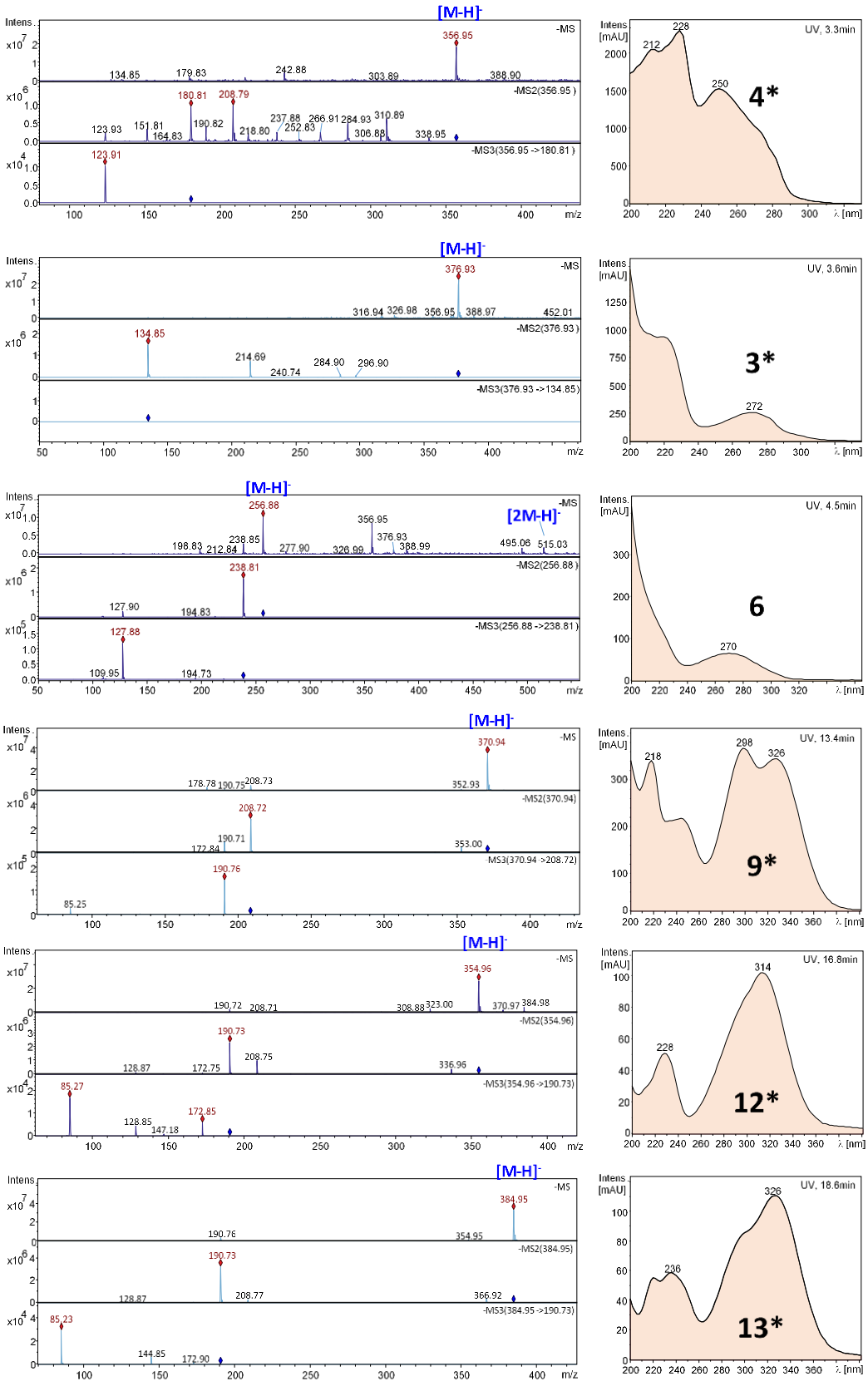


Figure S2A. Selection of MS^n(ESIneg) mass spectra (left) and UV spectra (right) of individual peaks, detected in the HPLC-DAD-MS^n(ESI^-) chromatograms of the none-fermented (AE) and fermented extracts (LBF, WF) of *M. perennis* (see Fig. S1 and Table S1).

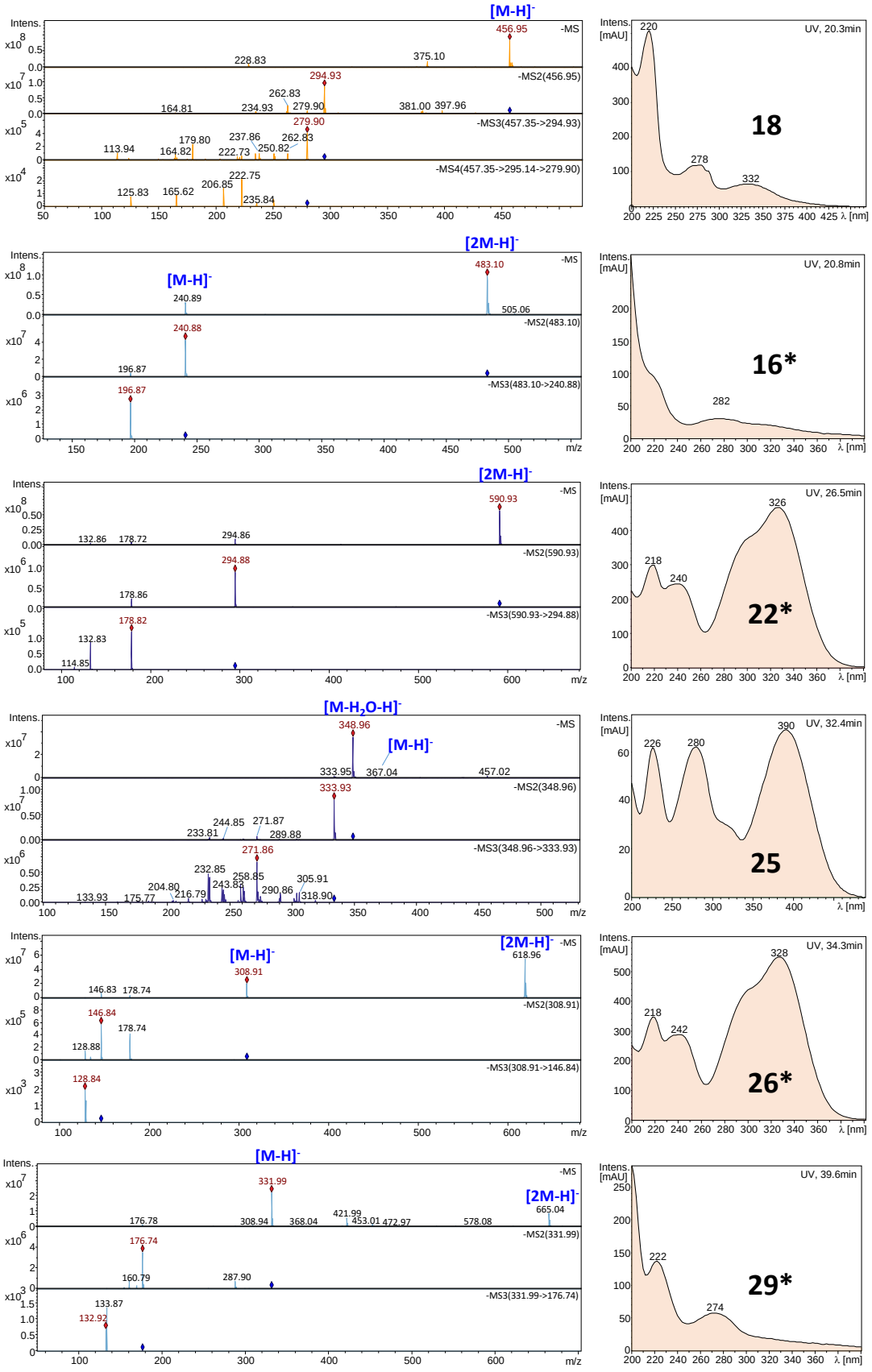


Figure S2B. (continuation). Selection of MSn(ESIneg) mass spectra (left) and UV spectra (right) of individual peaks, detected in the HPLC-DAD-$MS^n(ESI^-)$ chromatograms of the none-fermented (AE) and fermented extracts (LBF, WF) of *M. perennis* (see Fig. S1 and Table S1).

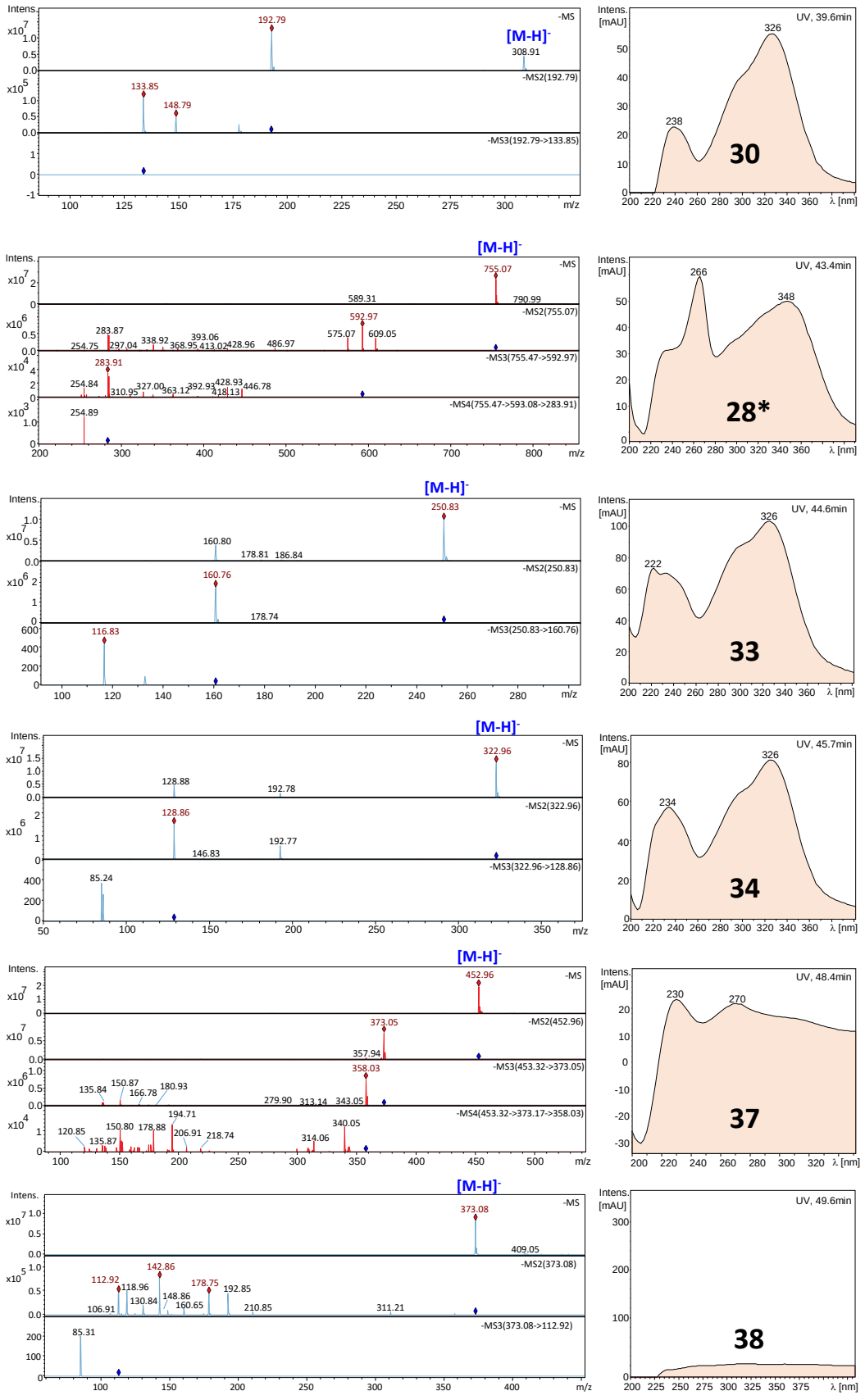


Figure S2C. (continuation). Selection of MSn(ESIneg) mass spectra (left) and UV spectra (right) of individual peaks, detected in the HPLC-DAD-MS^n(ESI$^-$) chromatograms of the none-fermented (AE) and fermented extracts (LBF, WF) of *M. perennis* (see Fig. S1 and Table S1).

Table S1. Tentative assignment of polyphenolic constituents (depsides and flavonoids) in the water extract and lactic acid fermented extract, obtained from herbal parts of *M. perennis*, according HPLC-DAD-ESI(negative)-MS^n data.

Peak No.	Constituent	t_R [min]	λ_{max} (HPLC-DAD) [nm]	Mass spectrometric data			Water extract	Fermented extracts	Literature reference*
				MS^1 [*m/z*]	MS^2 [*m/z*]	MS^3 [*m/z*]			
1	hexose oligomer	2.1	212, sh 256	669	341, 327, 283, 236	179, 161, 143, 131	V		
2	sugar oligomer	2.5	230	815, 487, 367, 327, 283, 265, 251, 236	207		V		
3*	phenylacetic acid hexoside phosphate[c)]	2.9, 3.6	208, sh 256/ 220, 272	377[a)]	297, 285, 241, 215, 135		V		
4*	phenyl lactic acid-glucarate[c)]	3.1*, 4.2, 7.8	212, 228, 250, sh 270*	357[a)]	311, 285, 238, 209, 191, 181, 152, 124	124		V	
5	unidentified	4.1-4.5	sh 218, 264	611, 397, 309	294, 279, 263, 249	279, 263, 250	V		
6	glutamic acid-diketopiperazine[c)]	4.5	270	515[b)], 257[a)], 239	239	128		V	
7	unidentified	5.1	sh 216, 268	611[b)]	593, 482, 338, 306[a)], 288, 272, 254,	288, 272, 254, 210, 179, 160	V		
8*	unidentified isomers	7.5 – 9.6	208, 270	371[a)], 309, 293, 279	294, 279, 263	279, 278, 263, 250	V		
9*	caffeoyl glucarate isomers	8.5, 9.3, 10.3, 10.4, 11.0, 11.4, 11.5, 12.7, 13.0, 13.4*, 14.3, 15.0	sh 214, sh 298, 326	371[a)], 209	209, 191	191, 85	V	V	[31]

Peak No.	Constituent	t_R [min]	λ_{max} (HPLC-DAD) [nm]	Mass spectrometric data			Water extract	Fermented extracts	Literature reference*
				MS^1 [*m/z*]	MS^2 [*m/z*]	MS^3 [*m/z*]			
10	unidentified N-containing compound	9.7-10.2	210, 238, 350	184[a)]	113, 80			V	
11	undefined N-containing glutaric acid derivative	9.9	254, sh 270	565[b)], 371, 309, 282	282[a)]	150, 133	V		
12*	*p*-coumaroyl glucarate isomers	12.2, 13.8, 13.9, 14.2, 15.1, 15.2, 15.5, 16.1, 16.3, 16.8*, 17.9	228, 314*	355[a)], 323, 291, 208, 191	337, 209, 191, 173, 147, 129	173, 129, 85	V	V	[31]
13*	Feruloyl glucarate isomers	14.1, 15.7, 16.5, 17.1, 17.3, 18.2, 18.6*, 19.1, 20.3, 21.0	220, 236, *sh* 300, 326	385[a)], 355,191	367, 209, 191, 173, 129	129, 85	V	V	[31]
14	undefined caffeic acid derivative	14.7, 14.8	314, sh 290, 222	517, 499[a)]	467, 336, 321, 291	321, 291	V		
15*	undefined N-containing dihydro-*p*-coumaroyl malic acid adduct	17.5, 18.3	220, 272, sh 286	466[a)]	350	300, 288, 274, 261, 256, 246, 217, 189, 133		V	
16*	5-oxo-L-prolyl-L-leucine (isomers)[d)]	18.8, 20.8*	Sh 218, 282, sh314	483[b)], 385, 241[a)]	241	197		V	[35,36]
17	caffeic acid	19.6	218, 234, sh 300, 322	179[a)]	136			V	
18	dihydro-*p*-coumaroyl 2-hydroxyglutaric acids adduct[c)]	20.3	220, 278, sh 288, 332	457[a)], 385	295, 280, 263, 235	280, 263, 238, 180, 165, 114		V	

Peak No.	Constituent	t_R [min]	λ_{max} (HPLC-DAD) [nm]	Mass spectrometric data			Water extract	Fermented extracts	Literature reference*
				MS^1 [*m/z*]	MS^2 [*m/z*]	MS^3 [*m/z*]			
19	12-hydroxy-jasmonate sulfate [d)]	21.3		305[a)]	225, 165, 97	181	V	V	[34]
20*	undefined N-containing caffeoyl 2-hydroxyglutaric acid adduct,	21.4*, 23.6	Sh 216, 288, sh 312	480[a)]	350	300, 288, 274, 256, 246, 231, 189		V	
21	unidentified N-containing compound	22.6	222, 274, 318	471[a)]	381	249, 161	V	V	
22*	*cis*-phaseolic acid-isomer	25.7	322	295[a)], 179, 133,	179, 133		V		[31]
22*	*trans*-phaseolic acid isomer	26.5	218, 240, sh 304, 326	591[b)],	295[a)], 179	179, 133	V	V	[31]
23	2-hydroxyglutaroyl ketoglutaric acid adduct[c)]	27.6	300	551[b)], 275	275[a)]	147, 127, 109		V	
24	Undefined flavonoid C-di-glycoside	29.2	216, 270, 330	593[a)]	503, 473, 383, 353	325, 297		V	
25	alkaloid artefact (hermidin dimer)[c), d)]	32.4	390, 280, 226	367[a)], 349	334, 272, 234	306, 291, 272, 259, 244, 233, 217, 205, 176, 134	V		[29]
26	*trans*-mercurialis acid	34.3	218, 242, sh 304, 328	619[b)], 309[a)], 147, 129	179, 147, 129	129	V	V	[31]
27	undefined caffeic acid derivative	35.1	324	391[a)]	179, 161, 143, 119	143, 131, 119, 113	V		
28*	kaempferol-rutoside-hexoside	35.6	266,sh 300, 322, 340	755[a)]	593, 447	285, 257	V		[31]

Peak No.	Constituent	t_R [min]	λ_{max} (HPLC-DAD) [nm]	Mass spectrometric data			Water extract	Fermented extracts	Literature reference*
				MS^1 [*m/z*]	MS^2 [*m/z*]	MS^3 [*m/z*]			
29*	dihydro-feruloyl histidine[c)]	38.6, 39.6*	222, 274	665[b)], 422, 332[a)]	288, 177, 161	133, 134		V	
30	Feruloyl malate	39.6	238, sh 304, 326	309[a)], 193	178, 149, 134		V		
31	quercetin-rutoside-hexoside	40.0	258, 266, sh 298, 352	771[a)]	609, 301	271, 254, 229, 179, 151	V		[31]
32	quercetin hexoside-rhamnoside (rutin)	42.1	258, sh 308, 352	609[a)]	301, 271	271, 255, 229, 211, 179, 151	V		[31]
28*	kaempferol- rutoside-hexosid	43.4	266, sh 304, 348	755[a)]	609, 593, 575, 429, 284	429, 284, 255	V	V	[31]
28*	kaempferol- rutoside-hexosid	44.4	266, sh 304, 346	755[a)]	593, 284, 239	257, 240, 230, 214, 195, 151, 123	V		[31]
33	caffeoyl glycerine aldehyde	44.6	222, sh 234, sh 302, 326	251[a)]	161	117		V	
34	feruloyl 2-hydroxy-glutararate	45.7	234, *sh* 302, 326	323[a)], 193, 129	193, 147, 129	85	V	V	[31]
35	undefined 2-hydroxyglutaric acid derivative	46.5	-	413[a)]	371, 327, 300, 256, 243, 221, 199, 186, 168, 130		V		
36	kaempferol-rutosid	47.1	266, sh 302, 346	593[a)]	285	267, 257, 229, 213, 197, 151			[31]
37	bis-dihydro-feruloyl sulfate [c), d)]	48.4	230, 270	453[a)]	373, 358	358, 151	V	V	
38	feruloyl syringate [c)]	49.6	-	373[a)]	211, 193, 179, 161, 149, 143, 131, 119, 113	85	V		

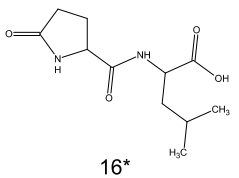
Peak No.	Constituent	t_R [min]	λ_{max} (HPLC-DAD) [nm]	Mass spectrometric data			Water extract	Fermented extracts	Literature reference*
				MS^1 [*m/z*]	MS^2 [*m/z*]	MS^3 [*m/z*]			
39	unidentified N-containing compound	49.6	230, 270	454[a)]	410, 392, 364, 348, 316, 288, 256, 221, 195, 170, 155	364, 348, 320, 288, 256, 221, 210, 195, 170, 155, 137		V	

*For references see main publication. [a)][M-H]$^-$;[b)][2M-H]$^{-}$;[c)]Tentatively assigned;[d)]Assignment based on HR-ESI-pos/negMS experiments.

HR-ESI-HPLC-MS Analyses

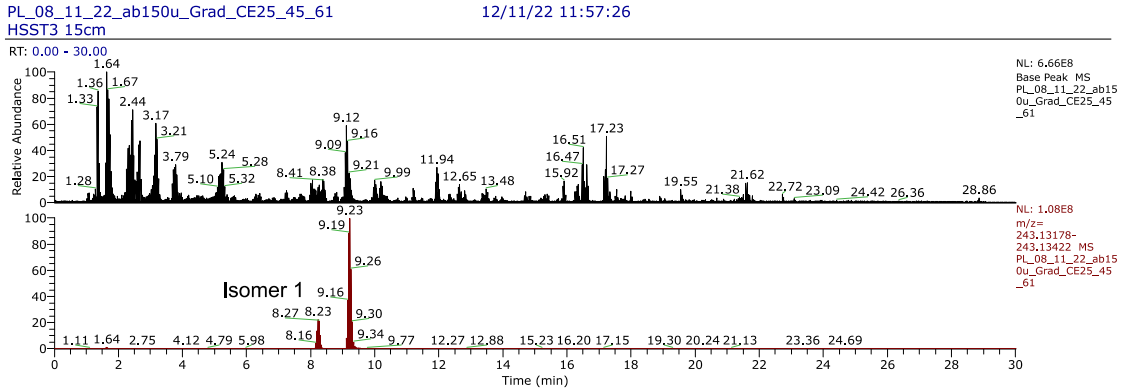
For determination of the exact molecular weights of constituent **16***, a solution of the LBF extract (5.7 mg/ml in ACN/water = 1 : 1, *v/v*) was applied to an Agilent 1290 UHPLC system (Agilent Technologies Inc., Palo Alto, USA) coupled to a QExactive Plus Orbitrap quadrupol-mass spectrometer (Thermo Fisher Scientific, Dreieich, Germany). Chromatographic separation of the analytes was performed on a ACQUITY UPLC HSS T3, C18-RP column (100 Å pore size, 1.8 µm particle size, 150 x 2.1 mm i.d., Waters Corporation, Milfort, MA , USA) at 40 °C. The mobile phase consisted of HCOOH/H_2O 0.1/99.9 (v/v; eluent A) and ACN/HCOOH 99.9/ 0.1 (v/v; eluent B). The injection volume was 3 µL, and the gradient used was as follows: 0 - 8 min, 7 - 15 % B; 8 - 13 min, 15 – 21 % B; 13 - 23 min, 21 - 65 % B; 23 - 30 min, 65 – 100 % B; 30 - 33 min, 100 % B, 33 - 37 min, 7 % B, at a flow rate of 0.4 ml/min. Full scan mass spectra (ESI, mass range *m/z* 150 – 1000) of HPLC eluates were recorded during chromatographic separation in the positive/negative ionization mode. The mass spectra were acquired in positive and negative mode with a spray voltage at 4200V/3500 V. Sheath gas was set to 60°C, aux gas 10°C, capillary temperature was 360°C and the heater temperature at 380°C. The scan range was used from 100 to 1500 m/z at a resolution of 70,000 Da. Data dependent MS/MS spectra were generated for the 5 most abundant precursor ions with a resolution of 17.500 and a stepped collision energy of 17,45,60 eV.

m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
243.13362	243.13393	-1.29	3.5	C11 H19 O4 N2
	243.13259	4.23	4.0	C9 H17 O3 N5
	243.13527	-6.79	8.5	C12 H15 N6

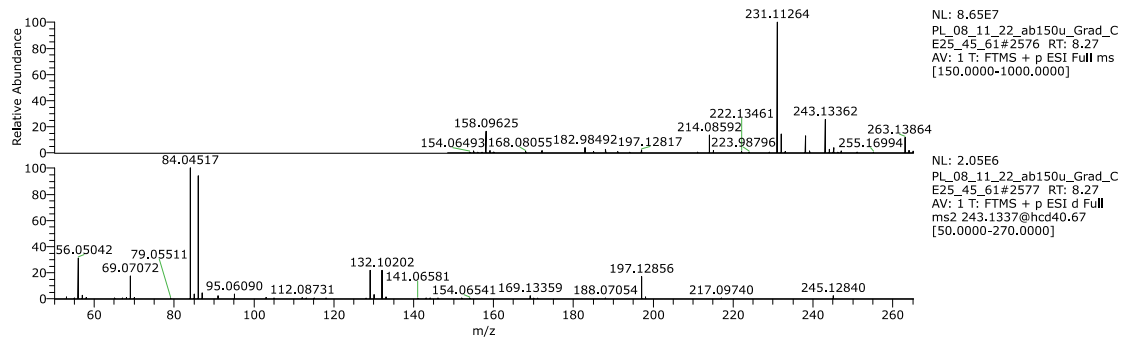


16*

Chemical Formula: C11H18N2O4
Molecular Weight: 242.12



ESI, pos - EIC 243

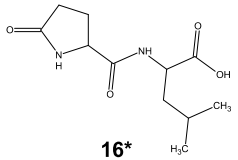


ESI, pos - full scan

ESI, pos - MS2 243

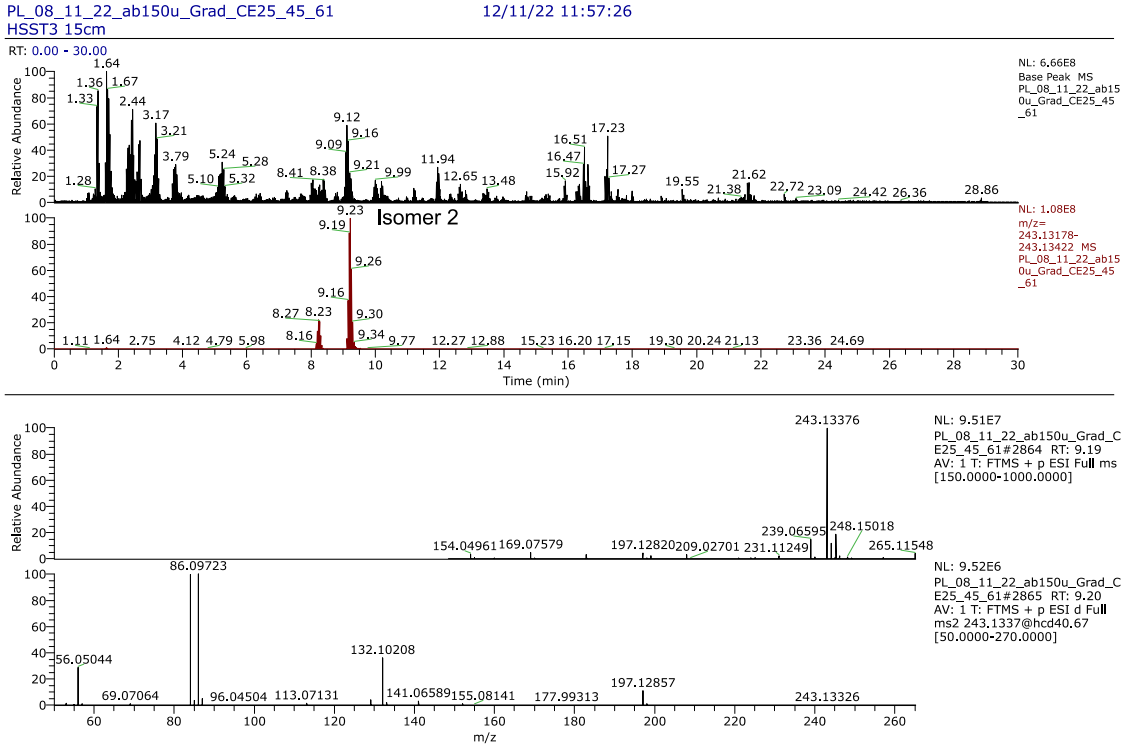
Figure S3A. Base peak chromatogram of a Lactobacteria inoculated fermentation extract (LBF) of *M. perennis* with extracted ion chromatogram (mass scan on *m/z* 243; HR-ESI-MS of the peak (t_R 8.2 min) in the positive mode, with calculated masses and proposed molecular formula for metabolite **16*** (isomer 1).

m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
243.13376	243.13393	-0.71	3.5	C11 H19 O4 N2
	243.13259	4.81	4.0	C9 H17 O3 N5
	243.13527	-6.21	8.5	C12 H15 N6



16*

Chemical Formula: C11H18N2O4
Molecular Weight: 242.16



ESI, pos - EIC 243

ESI, pos - full scan

ESI, pos - MS2 243

Figure S3B. Base peak chromatogram of a Lactobacteria inoculated fermentation extract (LBF) of *M. perennis* with extracted ion chromatogram (mass scan on *m/z* 243; HR-ESI-MS of the peak (t_R 9.2 min) in the positive mode, with calculated masses and proposed molecular formula for metabolite **16*** (isomer 2).

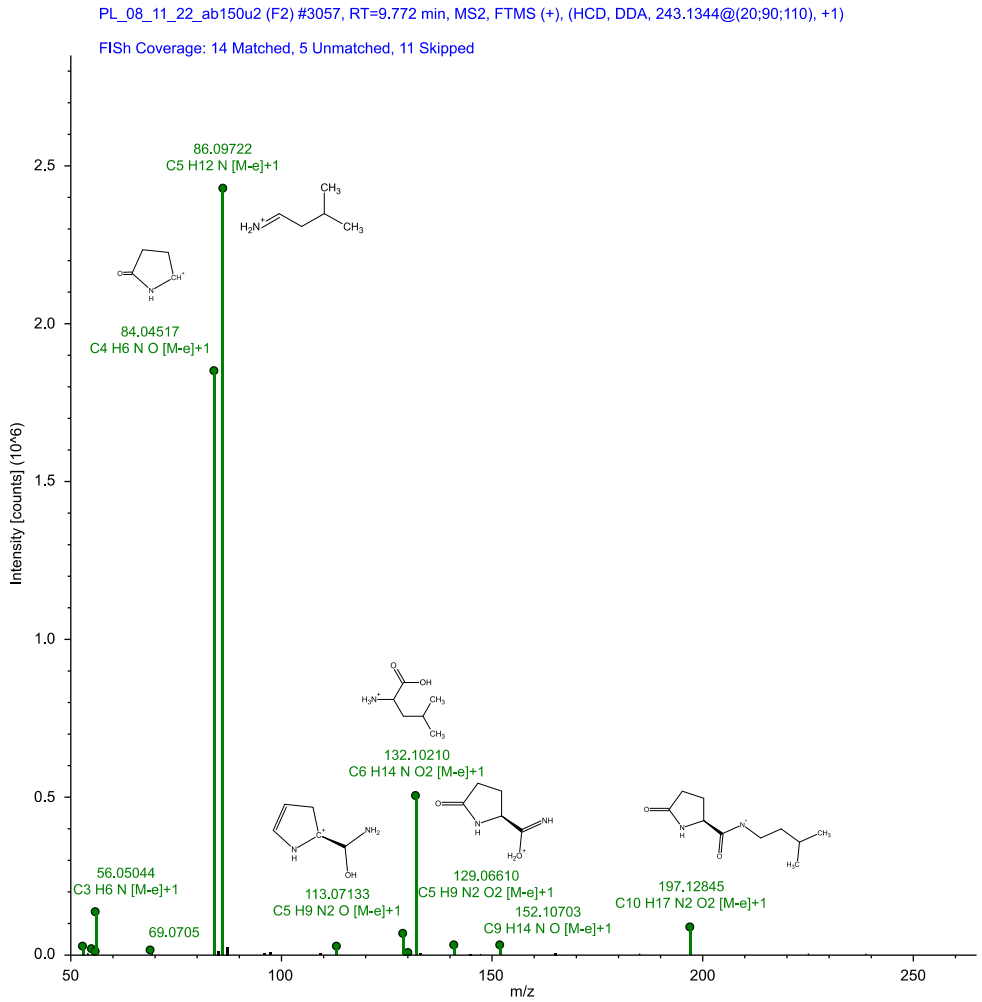
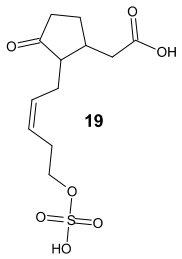


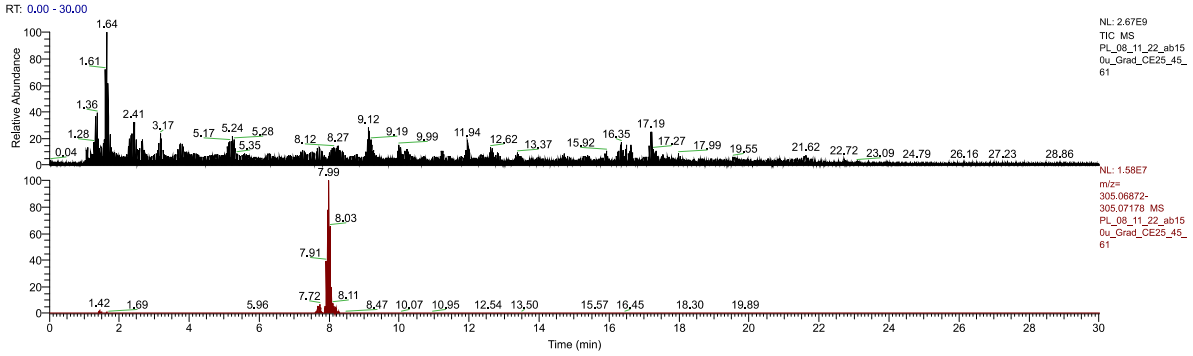
Figure S3C. Structure annotation from FISh scoring node on MS^2 spectrum of **16***.The fragmentation was simulated with the *Compound Discoverer software*, Version 3.3 of Thermo Scientific.

Elemental composition search on mass 305.07053

m/z	Theo. Mass	Delta (ppm)	RDB equiv.	Composition
305.07053	305.07005	1.58	4.5	C_{12} H_{17} O_7 S
	305.07255	-6.62	0.5	C_8 H_{17} O_{12}
	305.06668	12.63	9.5	C_{15} H_{13} O_7

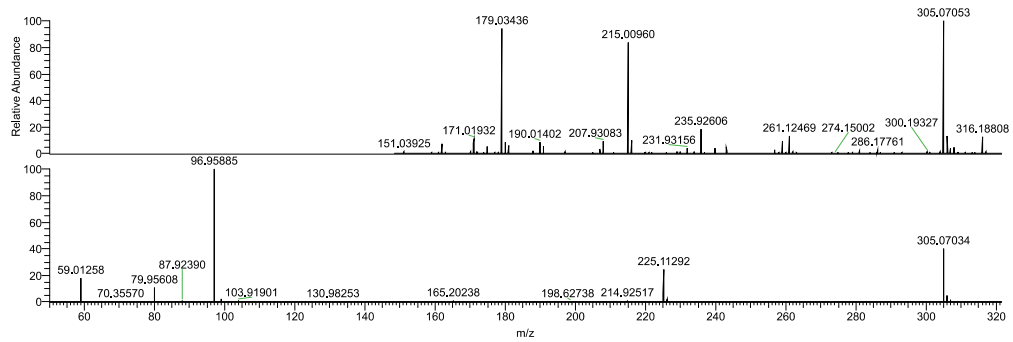


Chemical Formula: C12H18O7S
Molecular Weight: 306.07



ESI, neg - EIC 305

ESI, neg - fulls scan



ESI, neg - MS2 305

Figure S3D. Base peak chromatogram of a Lactobacteria inoculated fermentation extract (LBF) of *M. perennis* with extracted ion chromatogram (mass scan on *m/z* 305; HR-ESI-MS of the peak (t_R 8.0 min) in the negative mode, with calculated masses and proposed molecular formula for metabolite **19**.

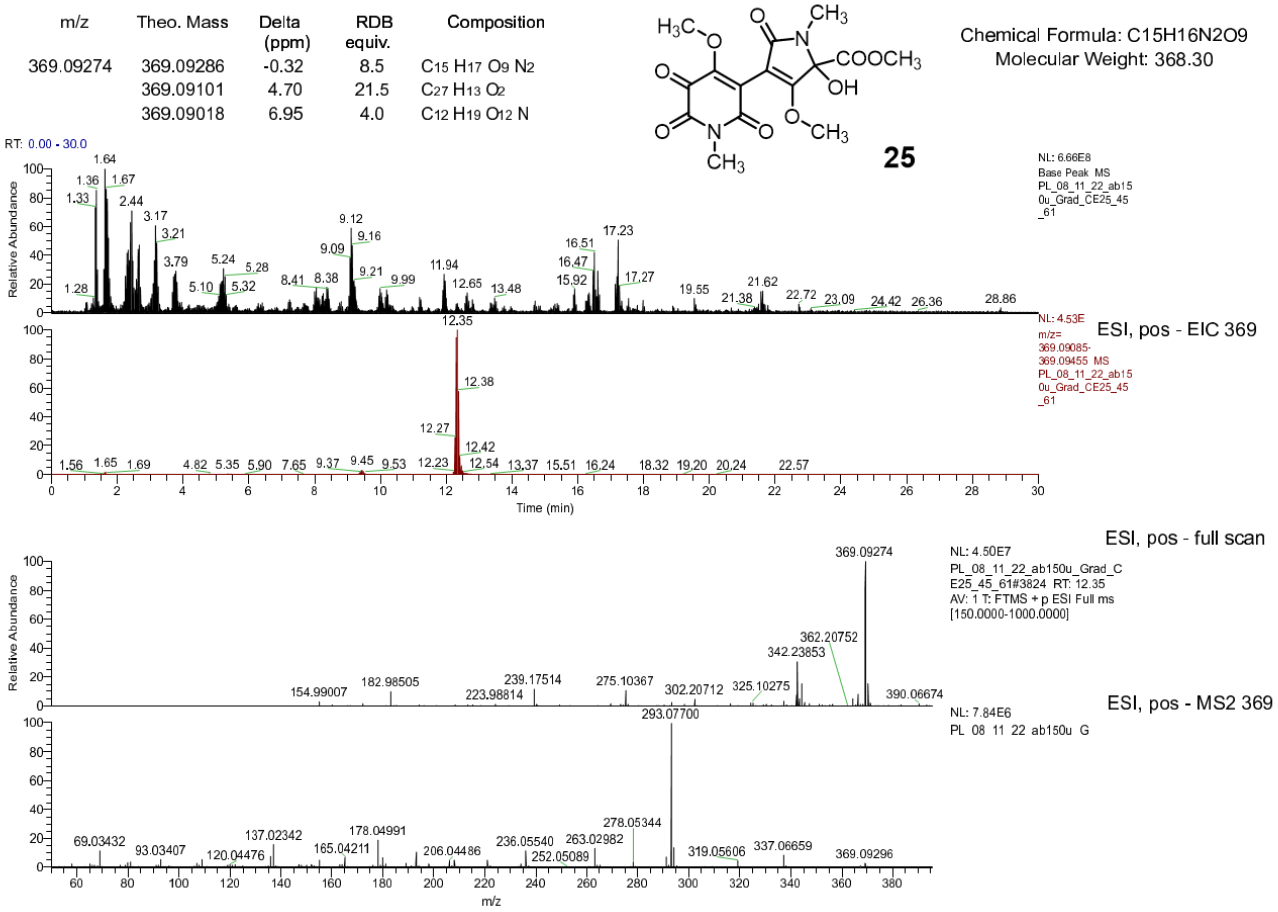


Figure S3E. Base peak chromatogram of a Lactobacteria inoculated fermentation extract (LBF) of *M. perennis* with extracted ion chromatogram (mass scan on *m/z* 369; HR-ESI-MS of the peak (t_R 12.3 min) in the positive mode, with calculated masses and proposed molecular formula for metabolite **25**.

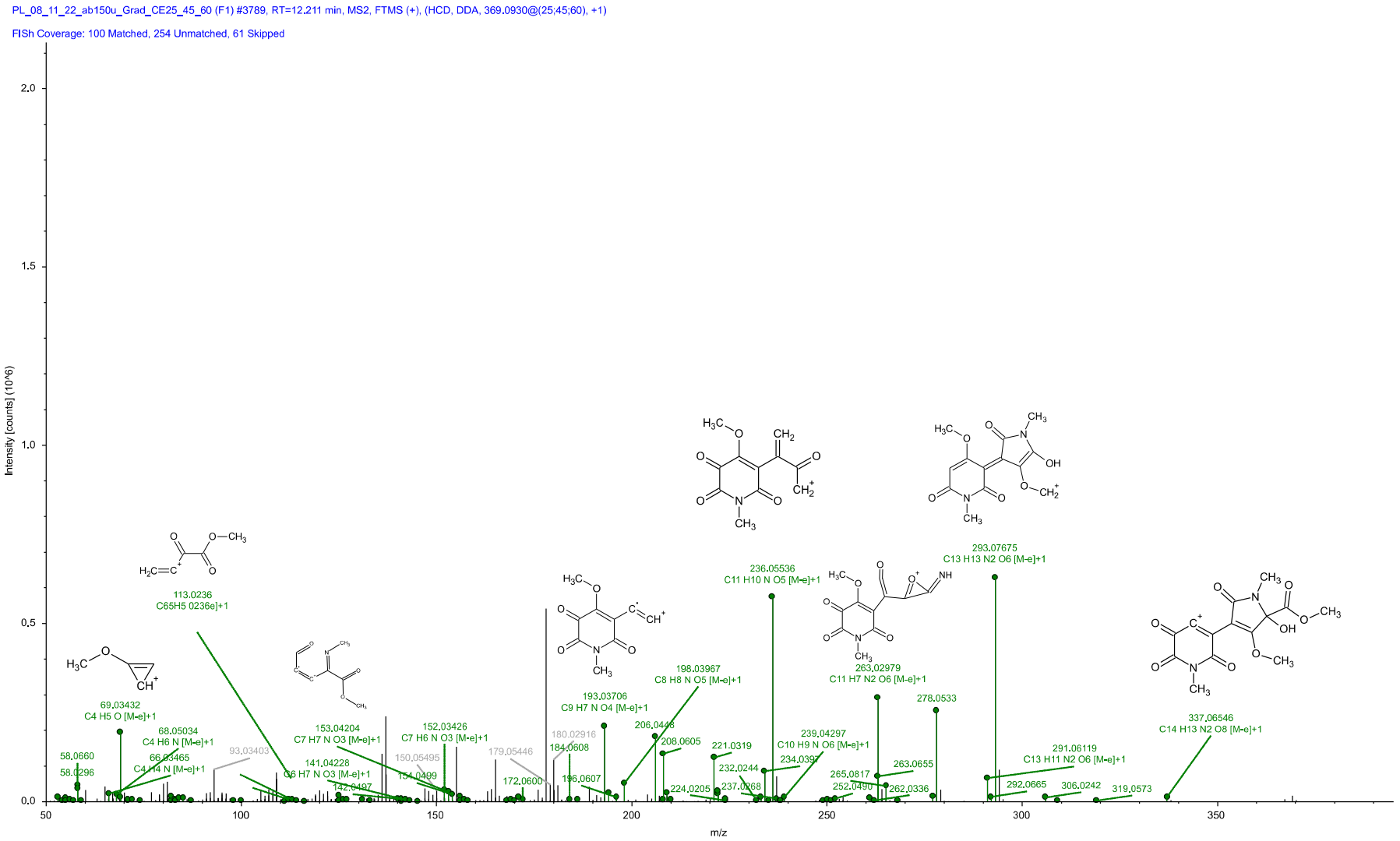


Figure S3F. Structure annotation from FISh scoring node on MS^2 spectrum of **25**. The fragmentation was simulated with the *Compound Discoverer software*, Version 3.3 of Thermo Scientific.

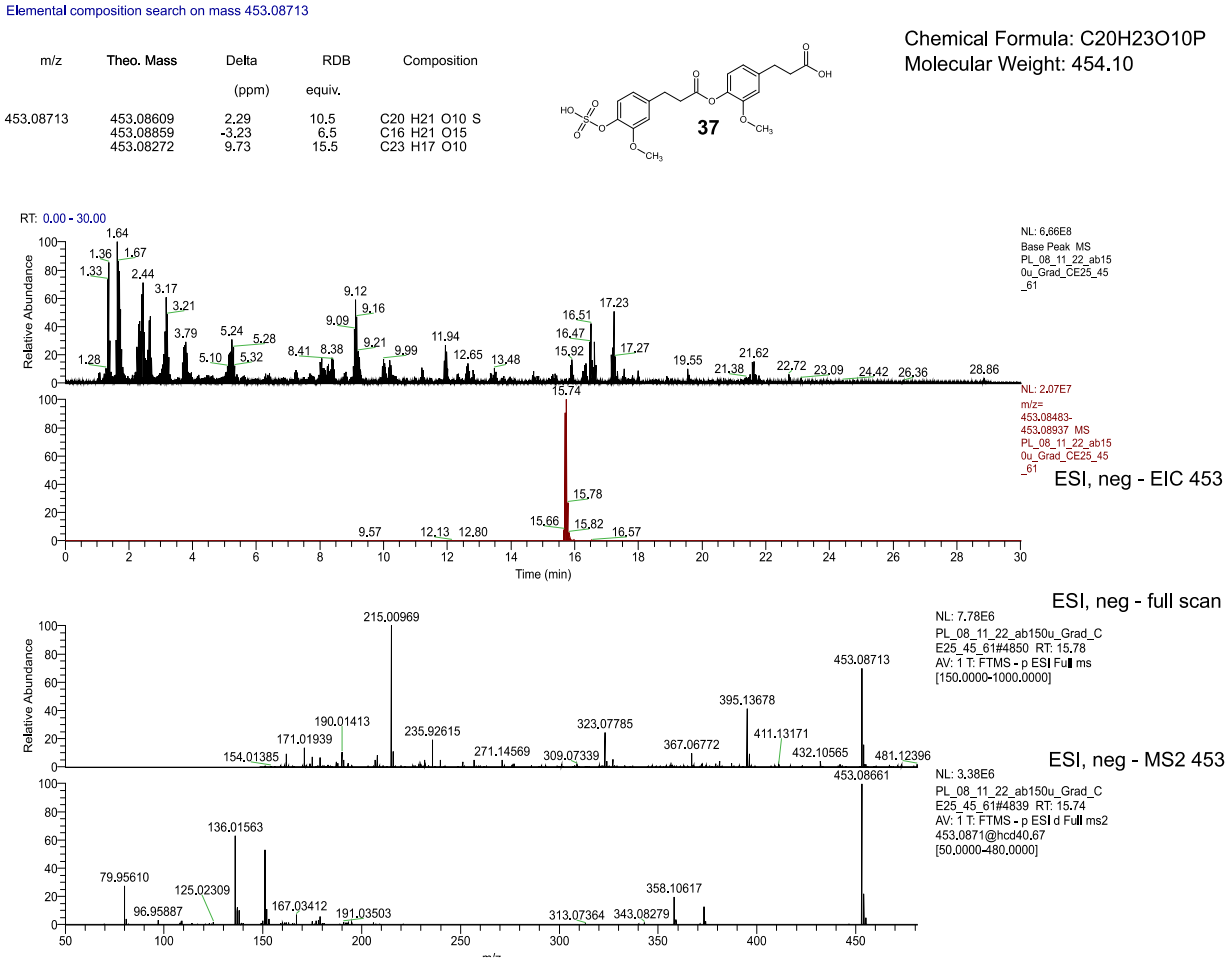


Figure S3G. Base peak chromatogram of a Lactobacteria inoculated fermentation extract (LBF) of *M. perennis* with extracted ion chromatogram (mass scan on *m/z* 453; HR-ESI-MS of the peak (t_R 15.7 min) in the negative mode, with calculated masses and proposed molecular formula for metabolite **37**.

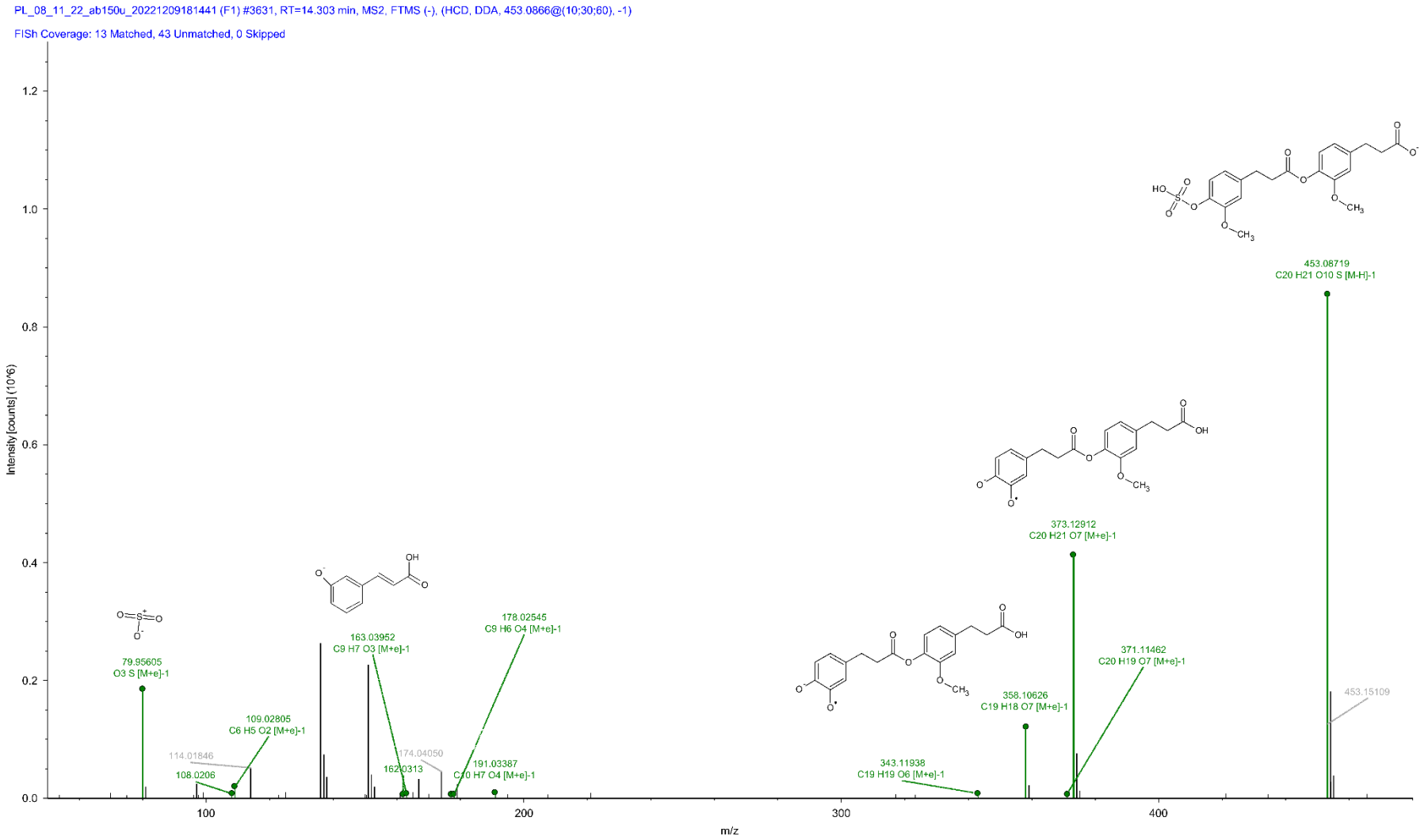


Figure S3H. Structure annotation from FISh scoring node on MS^2 spectrum of **37**. The fragmentation was simulated with the *Compound Discoverer software*, Version 3.3 of Thermo Scientific.

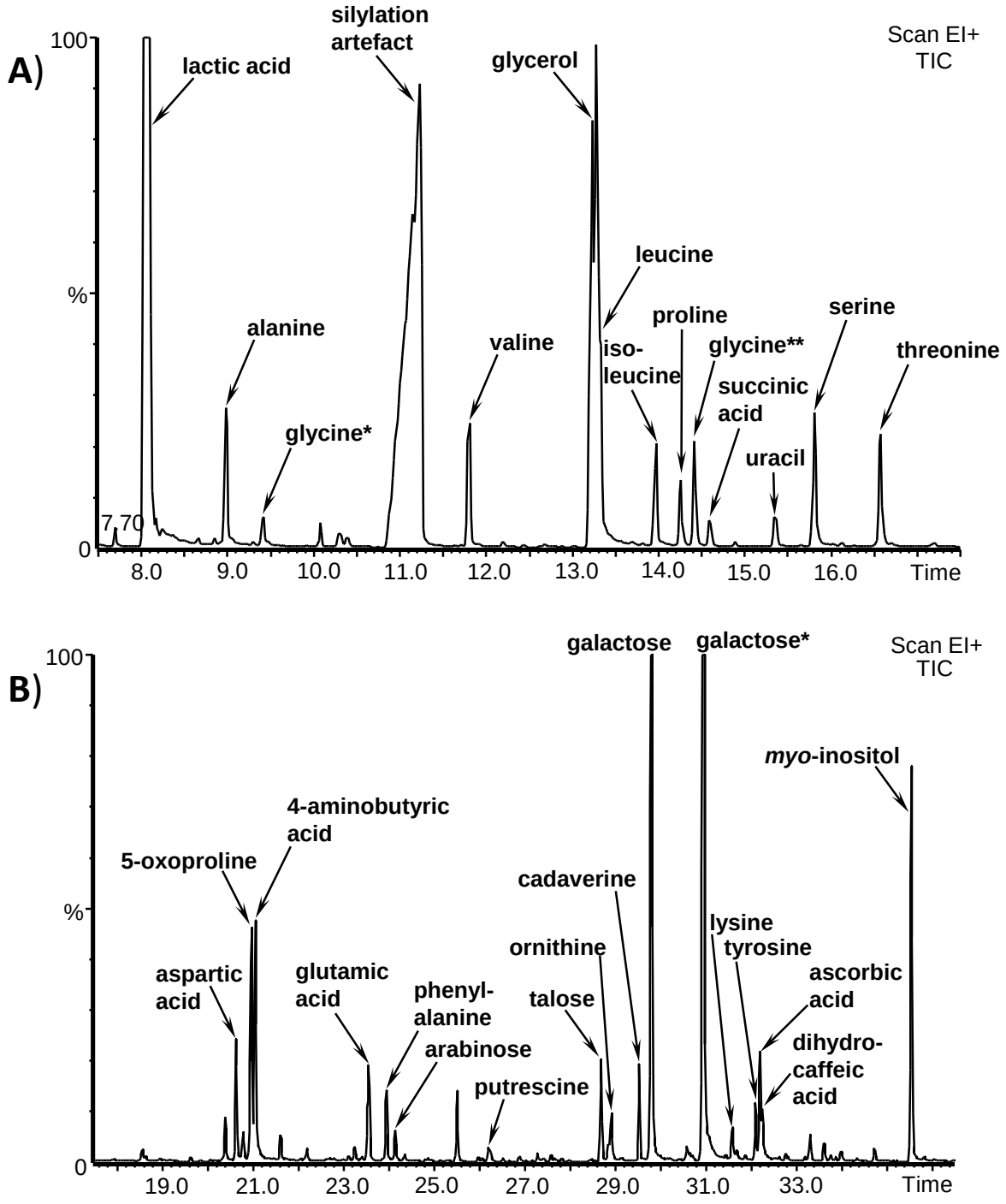


Figure S4. GC-MS total ion chromatogram sections of a WF extract, obtained after a HAB procedure, showing low molecular constituents (TMS derivatization). *A)* Section at t_R 7.5 – 17.5 min, the asterisks marks the two glycine TMS derivatives at t_R 9.4 and 14.4 min (* two and ** three TMS units, respectively). *B)* Section at t_R 17.5 – 36.5 min. Constituents were tendentially identified by comparison of the respective mass spectra with the NIST database.

Viability Assay

THP-1 NFκB-eGFP reporter cells (500 000 cells/mL) were incubated for 24 h with medium (unstim.), dexamethasone (10-5 M; Sigma Aldrich), or test substances at various concentrations (1, 3, 10, 30, 100, 300, 1000 µg/mL). Cells were washed with PBS and resuspended in 100 µL WST medium (RPMI 1640 medium without phenol red (Fischer Scientific) supplemented with 10% heat-inactivated fetal calf serum (Bioconcept), 2 mM L-glutamine (Sigma Aldrich), 100 U/ml penicillin (Sigma Aldrich), and 100 U/ml streptomycin (Sigma Aldrich)) supplemented with 1:10 WST-1 (Sigma Aldrich). Cells were incubated for 120 additional minutes and the colorimetric measurement was performed on a microplate reader (Tecan Infinite M200).

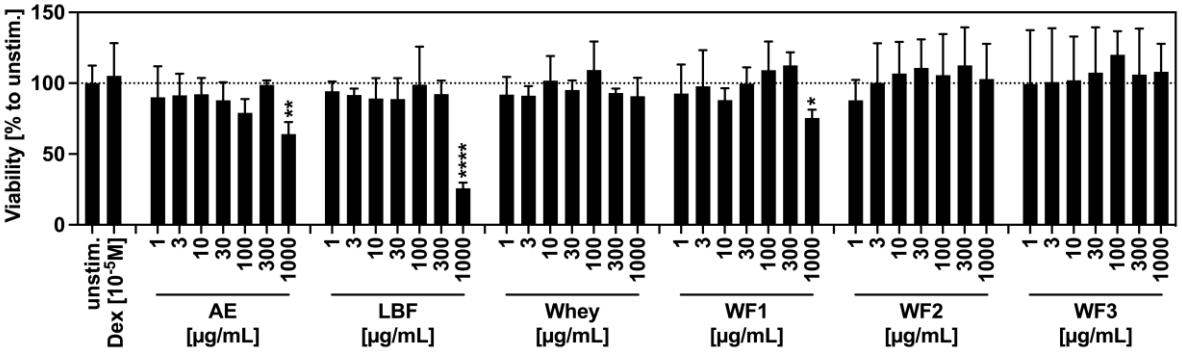


Figure S5. Effects of test substances on cell viability of THP-1 NFκB reporter cells determined by WST assay. THP-1 NFκB-eGFP cells incubated for 24 hours with medium (unstim.), dexamethasone (Dex; 10^{-5} M), or extracts. The percentage of metabolically active cells was compared and normalized to the unstimulated control and presented as mean ± standard deviation. n = 3; *p < 0.05, **p < 0.01, ***p < 0.001, ****p < 0.0001.

Determination of Evaporation Residues (Dry Weight) of Liquid Extracts

Porcelain crucibles (volume: 35 ml) were heated at 105 ^{o}C, equilibrated to room temperature in a desiccator and weighed at a precisicion balance to constant tara weight. Then, aliquots of liquid samples (5.00 ml each) were transferred into crucibles, heated 1 h at 80 ^{o}C and thereafter 2 h at 105 ^{o}C. After cool down the netto weight was determined (brutto – tara weight). Cytokine concentrations (Fig.XX) were calculated on dry weights.

Endotoxin (LAL Limulus) Assay

The endotoxin (pyrogen) content was analyzed according to manufactures protocol (Charles River Endosafe Charleston, SC, USA). In brief, on a 96 well plate the test samples (diluted 1 : 100), endotoxin standard, negative control (water) or spiked control (sample + 0,5 I.E./mL endotoxin) were pipetted into each well. Then, 100 µL amoebocytes lysate (diluted with water according manufactures protocol, Charles River) were added and thermostated at 37 oC in the ELISA reader, wereby the optical density was recorded at at 340 nm over 53.3 min, until the precipitation (coagulation) was complete. Concentrations were calculated from reaction times at 0.5 extinction units from the Michaelis-Menten-curve. The calibration range was between 0.005 and 5 EU/mL with an r-value of -0.9998 and a recovery of 120%.

Table S2. Chemical and physical parameters of tested samples.

Sample	Type	pH value	dry matter content [g/ml]	Lactic acid conc. [g/l], (SEM)	Endotoxin content [EU/ml]
AE	H_2O-extract	6.54	0.00899	-0,052 (± 0,026)	126.8
LBF (7 d)	fermentation with starter culture [a] *(L. plantarum + P. pentosaceus)*	3.89	0.01095	3,446 (± 0,089)	42.3
whey	whey	3.99	0.07054	9,779 (± 0,368)	< 0.5
WF1 (180 d)	whey fermentation[b]	3.97	0.04783	14,613 (± 0,052)	5.0
WF 2 (180 d)	whey fermentation[b]	3.99	0.05520	15,338 (± 0,026)	12.6
WF3 (180 d)	whey fermentation[b]	3.91	0.05168	14,66 (± 0,078)	58.7

[a] Fermentation time 7d; [b] fermentation time 180 d.