Supplementary Material

Anti-Alzheimer chemical constituents of *Morus macroura* Miq.: Chemical profiling, *in silico*, and *in vitro* investigations

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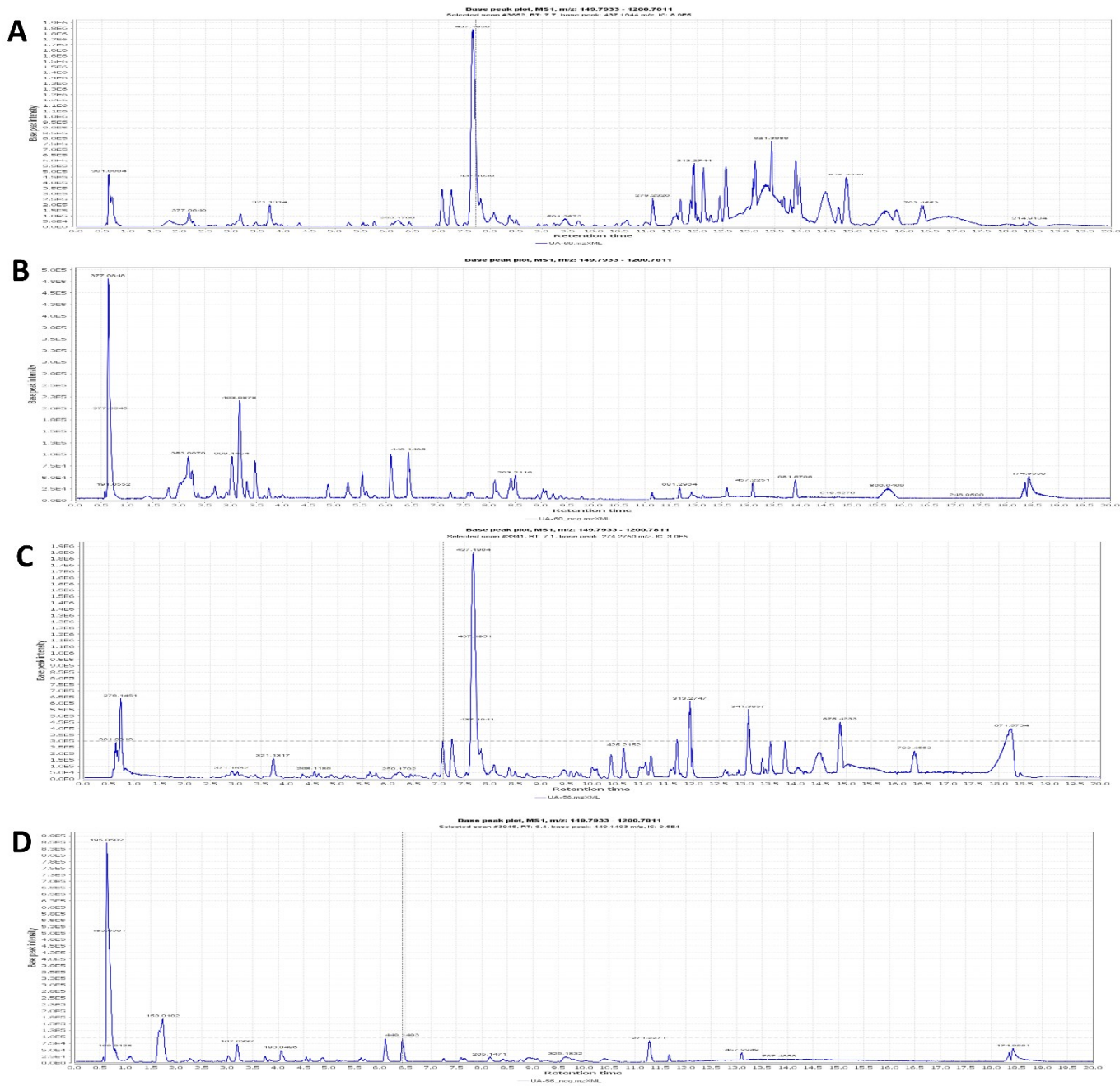usama.ramadan@mu.edu.eg, Tel: +2-86-2347759, +20 86-2369075

Figure S1. LC-HRESIMS base peak intensity (positive and negative modes) chromatograms of MLE (A and B) and MFE (C and D), respectively.

Table S1. The abbreviations and names of 82 protein targets related to Alzheimer's disease.

No.	Target	Full name
1	APP	Beta amyloid A4 (resveratrol and ferulic acid and Chrysin)
2	MAOA	Monoamine oxidase A (Resveratrol and chrysin)
3	MAOB	Monoamine oxidase B (Ferulic acid and chrysin)
4	ACHE	Acetylcholinesterase
5	BCHE	Butyrylcholinesterase
6	PIK3CB	PI3-kinase p110-beta subunit
7	PIK3CA	PI3-kinase p110-alpha subunit
8	BACE1	Beta-Secretase 1
9	BACE2	Beta secretase 2
10	HTR7	Serotonin 7 (5-HT7) receptor
11	HTR6	Serotonin 6 (5-HT6) receptor
12	MAPT	Microtubule-associated protein tau
13	CDK5	Cyclin-dependent kinase 5/CDK5 activator 1
14	PTGS2	Cyclooxygenase-2 (and resveratrol)
15	PSEN1	Presenilin 1
16	PSEN2	Presenilin 2
17	APOE	Apolipoprotein E
18	ABCA7	ATP Binding Cassette Subfamily A Member 7
19	SNCA	Synuclein Alpha
20	SORL1	Sortilin Related Receptor 1
21	ADAM10	ADAM Metallopeptidase Domain 10
22	A2M	Alpha-2-Macroglobulin
23	NOS3	Nitric Oxide Synthase 3
24	PRNP	Prion Protein
25	TREM2	Triggering Receptor Expressed On Myeloid Cells 2
26	MT-ND1	Mitochondrially Encoded NADH:Ubiquinone Oxidoreductase Core Subunit 1
27	HFE	Homeostatic Iron Regulator
28	PLAU	Plasminogen Activator, Urokinase
29	SNCB	Synuclein Beta
30	GRN	Granulin Precursor
31	MT-ND2	Mitochondrially Encoded NADH:Ubiquinone Oxidoreductase Core Subunit 2
32	UNC5C	Unc-5 Netrin Receptor C
33	TOMM40	Translocase Of Outer Mitochondrial Membrane 40
34	MPO	Myeloperoxidase
35	GSK3B	Glycogen Synthase Kinase 3 Beta
36	COMT	Catechol-O-Methyltransferase
37	PRKN	Parkin RBR E3 Ubiquitin Protein Ligase
38	CLU	Clusterin
39	HTR2A	5-Hydroxytryptamine Receptor 2A
40	LRP1	LDL Receptor Related Protein 1
		Table S1 Cont.

No.	Target	Full name
41	Serpin Family A Member 3 MIR29A	Serpin Family A Member 3 MicroRNA 29a
42	DRD3	Dopamine Receptor D3
43	MIR29B1	MicroRNA 29b-1
44	IDE	Insulin Degrading Enzyme
45	MIR107	MicroRNA 107
46	MIR146A	MicroRNA 146a
47	CHAT	Choline O-Acetyltransferase
48	CTSD	Cathepsin D
49	TNF	Tumor Necrosis Factor
50	APBB1	Amyloid Beta Precursor Protein Binding Family B Member 1
51	BDNF	Brain Derived Neurotrophic Factor
52	NCSTN	Nicastrin
53	PICALM	Phosphatidylinositol Binding Clathrin Assembly Protein
54	HSD17B10	Hydroxysteroid 17-Beta Dehydrogenase 10
55	CDK5R1	Cyclin Dependent Kinase 5 Regulatory Subunit 1
56	COL25A1	Collagen Type XXV Alpha 1 Chain
57	ACE	Angiotensin I Converting Enzyme
58	PLD3	Phospholipase D Family Member 3
59	PSENEN	Presenilin Enhancer, Gamma-Secretase Subunit
60	CASP3	Caspase 3
61	CR1	Complement C3b/C4b Receptor 1
62	IL1B	Interleukin 1 Beta
63	MME	Membrane Metalloendopeptidase
64	CALHM1	Calcium Homeostasis Modulator 1
65	IL1A	Interleukin 1 Alpha
66	TF	Transferrin
67	GAPDH	Glyceraldehyde-3-Phosphate Dehydrogenase
68	SOD1	Superoxide Dismutase 1
69	IL6	Interleukin 6
70	PTGS2	Prostaglandin-Endoperoxide Synthase 2
71	VLDLR	Very Low Density Lipoprotein Receptor
72	MAPK1	Mitogen-Activated Protein Kinase 1
73	DHCR24	24-Dehydrocholesterol Reductase
74	CAPN1	Calpain 1
75	VCP	Valosin Containing Protein
76	APLP2	Amyloid Beta Precursor Like Protein 2
77	CHRNA7	Cholinergic Receptor Nicotinic Alpha 7 Subunit
Table S1 Cont.		

No.	Target	Full name
78	NGF	Nerve Growth Factor
79	CLSTN1	Calsyntenin 1
80	OLR1	Oxidized Low Density Lipoprotein Receptor 1
81	INS	Insulin
82	NOS1	Nitric Oxide Synthase 1

Table S2. The 13 AD-related proteins targeted by the 4 key constituents of MFE and MLE (i.e. ferulic acid, resveratrol, chrysin, and moracin D).

No.	Target	Full name	Uniport ID	SWISS Target Prediction (Probability)	PharmMapper (Fit score)	Vina score kcal/mol
1	APP	Beta amyloid A4	P05067	FA (5.1%); Chr (13.5%); Res (100%)	-	-
2	MAOA	Monoamine oxidase A	P21397	Chr (27.6%); Res (100%)[#]	Chr (1.1); Res (1.5)	Res (-6.6)
3	PIK3CB	PI3-kinase p110-beta subunit	P42338	Res (100%)	-	Res (-6.4);
4	PIK3CA	PI3-kinase p110-alpha subunit	P42336	Res (100%)	Res (1.2); Chr (1.3)	Res (-6.6);
5	**MAOB***	**Monoamine oxidase B**	**P27338**	**FA (7.2%)**	**FA (2.6)**	**FA (-8.1); Chr (-7.8)**
6	**BACE1***	**Beta secretase 1**	**P56817**	**Mor (10.1%)**	**Mor (4.1); Chr (3.8)**	**Mor (-9.6); Chr (-8.4); Res (-7.5)**
7	HTR7	Serotonin 7 (5-HT7) receptor	P34969	Mor (10.2%)	-	Mor (-7.3)
8	HTR6	Serotonin 6 (5-HT6) receptor	P50406	Mor (10%)	-	-
9	**ACHE***	**Acetylcholinesterase**	**P22303**	**Chr (35%)**	**Res (2.9); Chr (4.3)**	**Res (-8.1); Chr (-9.9)**
10	BCHE	Butyrylcholinesterase	P06276	Chr (17.4%)	Res (1.3); Chr (2.2)	Res (-6.1); Chr (-7.1)
11	MAPT	Microtubule-associated protein tau	P10636	Chr (11.9%)	-	-
12	CDK5	Cyclin-dependent kinase 5/CDK5 activator 1	Q00535	Chr (100%)	Chr (4.6); Res (3.3); FA (2.4)	Chr (-9.2); Res (-8.4); FA (-7.4)
13	PTGS2	Cyclooxygenase-2	P35354	Chrysin (27.6%); Res(100%)	Chr (3.3); Res (4.5); FA (3.5)	Chr (-8.3); Res (-8.1); FA (-7.3)

FA = Ferulic acid; Chr = Chrysin; Res = Resveratrol; Mor = Moracin D.

*This protein target was selected for the in-vitro validation.

Only compounds that got 100% probability score in SWISS prediction or docking score < -6 kcal/mol were selected for the compound-protein interaction map.