# Beyond $\alpha$-glucosidase and $\alpha$-amylase inhibition: integrated *in vitro* and multi-scale *in silico* insights into the antidiabetic and antioxidant mechanisms of *Oxalis corniculata* L. aerial parts

Thi-Van-Anh Nguyen [1], Duong Quang Quy [1,2], Nguyen Thanh Tung [3], Nguyen Thu Huyen [1], Pham Le Minh [1], Nguyen T. Minh Huyen [1], Tue-Tam Ho [3], Nguyen Thi Thu Ha [4], Gerardo M. Casanola-Martin [2], Bakhtiyor Rasulev [2] and Hai Pham-The [1,*]

[1] University of Science and Technology of Hanoi (USTH), Vietnam Academy of Science and Technology, 18-Hoang Quoc Viet, Nghia Do, Hanoi 10000, Vietnam
[2] Department of Coatings and Polymeric Materials, North Dakota State University, Fargo, ND 58102, USA
[3] Hanoi University of Pharmacy, 13-15 Le Thanh Tong, Cua Nam, Hanoi 10000, Vietnam
[4] Institute of Chemistry (ICH), Vietnam Academy of Science and Technology, 18-Hoang Quoc Viet, Nghia Do, Hanoi 10000, Vietnam

* Correspondence: hpham.phd@gmail.com (H.P-T)

## Supplementary materials:

**Table S1**. Inhibitory activity of *O. corniculata* extracts and fractions against $\alpha$-glucosidase and $\alpha$-amylase.

| Sample | $\alpha$-Glucosidase $IC_{50}$ (mg/mL) | $\alpha$-Amylase $IC_{50}$ (mg/mL) |
|---|---|---|
| EtOH extract | 0.135 ± 0.003 | 0.021 ± 0.003 |
| n-Hex fraction | 0.225 ± 0.003 | 0.062 ± 0.004 |
| DCM fraction | 0.260 ± 0.002 | 0.081 ± 0.002 |
| EtOAc fraction | 0.097 ± 0.004 | 0.015 ± 0.001 |
| AqExt fraction | 0.114 ± 0.002 | 0.032 ± 0.005 |
| Acarbose | 0.397 ± 0.003 | 0.013 ± 0.003 |

*Data are presented as mean ± SD (n = 3).*

**Table S2**. Antioxidant activity of *O. corniculata* extracts and fractions evaluated by DPPH and ABTS assays.

| Sample | DPPH $IC_{50}$ (mg/mL) | ABTS $IC_{50}$ (mg/mL) |
|---|---|---|
| EtOH extract | 0.0265 ± 0.003 | 0.0390 ± 0.004 |
| n-Hex fraction | 0.0659 ± 0.004 | 0.0656 ± 0.005 |
| DCM fraction | 0.0509 ± 0.005 | 0.0495 ± 0.005 |
| EtOAc fraction | 0.0249 ± 0.005 | 0.0202 ± 0.004 |
| AqExt fraction | 0.0357 ± 0.004 | 0.0330 ± 0.005 |
| Ascorbic acid | 0.0075 ± 0.003 | |
| Trolox | | 0.0075 ± 0.003 |

*Data are presented as mean ± SD (n = 3).*

**Table S3**. List of 113 compounds identified from *Oxalis corniculata* L. based on literature review and screening results for drug-likeness and oral bioavailability

| No. | Compound | TCMSP | | SwissADME | |
|---|---|---|---|---|---|
| | | OB (%) | DL | GI | "yes" DL |
| 1 | Stearic acid | 17.83 | 0.14 | High | 1 |
| 2 | *p*-Hydroxybenzoic acid | 30.15 | 0.03 | High | 3 |
| 3 | Vanillic acid | 35.47 | 0.04 | High | 4 |
| 4 | Syringic acid | 47.78 | 0.06 | High | 4 |
| 5 | Isoorientin | 23.3 | 0.76 | Low | 0 |
| 6 | Isovitexin | 31.29 | 0.72 | Low | 2 |
| 7 | Swertisin | 5.75 | 0.75 | Low | 2 |
| 8 | Acacetin | 34.97 | 0.24 | High | 5 |
| 9 | Apigenin 7,4'-dimethyl ether | 27.12 | 0.27 | High | 5 |
| 10 | Dillenetin | 21.33 | 0.34 | High | 5 |
| 11 | Corniculatin A | - | - | Low | 0 |
| 12 | Oxalic acid | 29.68 | 0.01 | High | 3 |
| 13 | Beta-sitosterol | 36.91 | 0.75 | Low | 2 |
| 14 | Betulin | 15.48 | 0.78 | Low | 2 |
| 15 | 3,5,2'-Trihydroxy-7,5'-dimethoxyflavone | - | - | High | 5 |
| 16 | Apigenin | 23.06 | 0.21 | High | 5 |
| 17 | Gallic acid | 31.69 | 0.04 | High | 3 |
| 18 | Harmine | 56.8 | 0.13 | High | 5 |
| 19 | Harmaline | - | - | High | 5 |
| 20 | 2-heptadecyl-5-methoxy-phenol | - | - | Low | 1 |
| 21 | Phlorizin | 2.88 | 0.6 | Low | 2 |
| 22 | Bilirubin | - | - | Low | 0 |
| 23 | Embelin | 37.72 | 0.18 | High | 4 |
| 24 | Quercitrin | 4.04 | 0.74 | Low | 1 |
| 25 | Parthenin | 23.18 | 0.19 | High | 5 |
| 26 | Petunidin | - | - | High | 5 |
| 27 | Octanal | 19.07 | 0.01 | High | 4 |
| 28 | Lecanoric acid | - | - | High | 5 |
| 29 | Sphinganine | - | - | High | 3 |
| 30 | Ophiobolin A | - | - | High | 5 |
| 31 | Phytosphingosine | - | - | High | 3 |
| 32 | *N*-acetylsphinganine | - | - | High | 3 |
| 33 | 1-Linolenoyl lysolecithin | - | - | High | 3 |
| 34 | (+)-Larixol | - | - | High | 3 |
| 35 | Sebacic acid | 16.23 | 0.05 | High | 5 |
| 36 | Malvidin | - | - | High | 5 |
| 37 | Docosanedioic acid | 16.2 | 0.36 | Low | 1 |
| 38 | Apigetrin | 9.68 | 0.74 | Low | 2 |
| 39 | Rhapontin | - | - | Low | 2 |
| 40 | oleic acid | 33.13 | 0.14 | High | 1 |
| 41 | linoleic acid | 41.9 | 0.14 | High | 1 |
| 42 | linolenic acid | 45.01 | 0.15 | High | 1 |
| 43 | 4'-O-Methylvitexin | - | - | Low | 2 |
| 44 | 4'-OMeiso vitexin | - | - | Low | 2 |
| 45 | 3',4'-diOMe orientin | - | - | Low | 1 |
| 46 | 5-hydroxy-7,8-dimethoxyflavone | 44.09 | 0.25 | High | 5 |

| | | | | | |
|---|---|---|---|---|---|
| 47 | 5-O-Desmethylnobiletin | - | - | High | 5 |
| 48 | 5-hydroxy-3,6,7,4'-tetramethoxyflavone | 8.2 | 0.4 | High | 5 |
| 49 | 4',5-hydroxy-3,6,7-trimethoxyflavone | 24.96 | 0.36 | High | 5 |
| 50 | 3,3',5-trihydroxy-4'-methoxyflavone 7-O-β-D-glucopyranoside | - | - | Low | 1 |
| 51 | Tridecane | 17.89 | 0.03 | Low | 4 |
| 52 | Tetradecane | 15.94 | 0.04 | Low | 2 |
| 53 | Hexadecane | 12.32 | 0.06 | Low | 1 |
| 54 | Heptadecane | 8.64 | 0.07 | Low | 1 |
| 55 | Pentatriacontane | 7.97 | 0.42 | Low | 1 |
| 56 | 1-Octene | 39.25 | 0.01 | Low | 3 |
| 57 | 1-Dodecene | 17.74 | 0.02 | Low | 4 |
| 58 | 4-Tetradecene | - | - | Low | 4 |
| 59 | 1-Nonadecene | 5.23 | 0.11 | Low | 1 |
| 60 | 1-Docosene | 16.74 | 0.18 | Low | 1 |
| 61 | Linalyl anthranilate | - | - | High | 5 |
| 62 | ethyl N-(heptan-4-ylideneamino)carbamate | - | - | High | 5 |
| 63 | Palmitic acid | 19.3 | 0.1 | High | 3 |
| 64 | 1-Hexacosanol | 10.95 | 0.35 | Low | 1 |
| 65 | *E*-14-Hexadecenal | 30.25 | 0.08 | High | 3 |
| 66 | *E*-15-Heptadecenal | - | - | High | 2 |
| 67 | *p*-Coumaroyl hexose | 9.8 | 0.26 | Low | 3 |
| 68 | Sinapic acid | 64.15 | 0.08 | High | 5 |
| 69 | *p*-Coumaric acid | 43.29 | 0.04 | High | 4 |
| 70 | Caffeic acid | 25.76 | 0.05 | High | 4 |
| 71 | Kaempferol-3-(*p*-coumaroyldiglucoside)-7-glucoside | - | - | Low | 0 |
| 72 | Chlorogenic acid | 11.93 | 0.33 | Low | 1 |
| 73 | Kaempferol 3-glucuronide | - | - | Low | 1 |
| 74 | Vitexin 6''-O-malonyl 2''-O-xyloside | - | - | Low | 0 |
| 75 | Isorhamnetin-3-caffeoyl-7-glucoside | - | - | Low | 0 |
| 76 | Quercetin-3-(caffeoyldiglucoside)-7-glucoside | - | - | Low | 0 |
| 77 | Kaempferol 3-sophorotrioside | - | - | Low | 0 |
| 78 | Eschweilenol C | - | - | Low | 1 |
| 79 | Phytofluene | - | - | Low | 1 |
| 80 | Pheophorbide B | - | - | Low | 1 |
| 81 | Violaxanthin | 17.68 | 0.51 | Low | 1 |
| 82 | Pheophytin B | - | - | Low | 1 |
| 83 | Hydroxy-pheophytin B | - | - | Low | 1 |
| 84 | All-E-neoxanthin | 28.01 | 0.51 | Low | 1 |
| 85 | (10S)-Hydroxypheophytin A | - | - | Low | 0 |
| 86 | Hydroxy-pheophytin A' | - | - | Low | 1 |
| 87 | Pheophytin A | - | - | Low | 0 |
| 88 | All-E-lutein | 22.59 | 0.55 | Low | 0 |
| 89 | 9-*cis*-Lutein | - | - | Low | 0 |
| 90 | Chlorophyll B | - | - | Low | 1 |
| 91 | 13-Hydroxy-chlorophyll B | - | - | Low | 0 |
| 92 | Chlorophyl B' | - | - | Low | 1 |
| 93 | Chlorophyl A | - | - | Low | 0 |
| 94 | Eburicoic acid | 38.7 | 0.81 | Low | 2 |
| 95 | 24-methylenecholest-4-ene-3β,6β-diol | - | - | High | 2 |

| | | | | | |
|---|---|---|---|---|---|
| 96 | Trametenolic acid | - | - | Low | 2 |
| 97 | Vitexin 2''-O-beta-D-glucoside | - | - | Low | 0 |
| 98 | Tartaric acid | - | - | Low | 3 |
| 99 | Citric acid | 56.22 | 0.05 | Low | 2 |
| 100 | Ascorbic acid | 13.34 | 0.04 | High | 3 |
| 101 | Maltose | 1.8 | 0.24 | Low | 0 |
| 102 | α-D-glucopyranoside, O-α-*D*-glucopyranosyl-(1-3)-α-D-fructofuranosyl | - | - | Low | 0 |
| 103 | Squalene | 33.55 | 0.42 | High | 1 |
| 104 | α-Tocopherol | 14.26 | 0.55 | Low | 1 |
| 105 | Limonene dioxide | - | - | High | 4 |
| 106 | Tectorigenin | 28.41 | 0.27 | High | 5 |
| 107 | Irigenin | 1.95 | 0.41 | High | 5 |
| 108 | Iristectorigenin A | 63.36 | 0.34 | High | 5 |
| 109 | Lespedin | 7.97 | 0.79 | Low | 0 |
| 110 | Rotenone | - | - | High | 5 |
| 111 | 2-Pentylfuran | 54.59 | 0.02 | High | 3 |
| 112 | Pyruvic acid | 54.46 | 0.01 | High | 3 |
| 113 | Malic acid | - | - | High | 3 |

*"-" : No data available.*

**Table S4.** List of gene IDs of 956 common targets

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ABCB1 | ABCB11 | ABCC1 | ABCC4 | ABCC9 | ABCG2 | ACACA | ACACB |
| ACAT1 | ACE | ACE2 | ACLY | ACP1 | ACR | ACVR2B | ACHE |
| ADA | ADAM17 | ADH1B | ADH1C | ADORA1 | ADORA2B | ADORA3 | ADRA1A |
| ADRA1B | ADRA1D | ADRA2A | ADRA2B | ADRA2C | ADRB1 | ADRB2 | ADRB3 |
| AGPAT2 | AGTR1 | AGXT2 | AHR | AHSA1 | AKR1A1 | AKR1B1 | AKR1B10 |
| AKR1C2 | AKT1 | AKT2 | ALB | ALDH1A2 | ALDH2 | ALK | ALOX12 |
| ALOX15 | ALOX5 | ALOX5AP | ALPL | AMPD1 | AMY1A | ANPEP | AOC3 |
| APC | APOB | APP | AR | ARG1 | ATIC | ATP12A | ATP2A1 |
| ATP4A | AVPR2 | BACE1 | BACE2 | BAD | BAX | BCAT1 | BCL2 |
| BCL2A1 | BCL2L1 | BCHE | BDKRB2 | BHMT | BIRC2 | BMP4 | BRAF |
| BRD2 | BRD4 | BRD9 | BRS3 | CA2 | CA4 | CA5A | CACNA1C |
| CACNA1D | CALM1 | CAMK1D | CAMK2A | CAMK2G | CAMKK2 | CAPN1 | CAPN2 |
| CASP1 | CASP3 | CASP7 | CASP8 | CASP9 | CASR | CAT | CBR1 |
| CBS | CCKAR | CCKBR | CCL16 | CCND1 | CCND2 | CCND3 | CCR1 |
| CCR2 | CCR5 | CD38 | CD4 | CD40LG | CD81 | CDC42 | CDK11A |
| CDK2 | CDK4 | CDK5 | CDK6 | CDK9 | CDKN1A | CDKN1B | CDKN1C |
| CDKN2A | CEL | CELA1 | CES1 | CETP | CFD | CFLAR | CFTR |
| CISD1 | CLK2 | CNR1 | CNR2 | COL1A1 | COMT | CPA1 | CPT1A |
| CPT1B | CPT2 | CREB1 | CREBBP | CRHR1 | CRHR2 | CSNK2A1 | CTNNB1 |
| CTSB | CTSC | CTSD | CTSH | CTSL | CTSS | CTRB1 | CXCL12 |
| CXCR1 | CXCR3 | CXCR4 | CYCS | CYP11B2 | CYP17A1 | CYP19A1 | CYP1A1 |
| CYP1A2 | CYP1B1 | CYP24A1 | CYP27B1 | CYP2A6 | CYP2C19 | CYP2C8 | CYP2C9 |
| CYP2D6 | CYP3A4 | CHEK2 | CHRM3 | CHRNA4 | CHRNB4 | CHUK | DAPK2 |
| DBH | DGAT1 | DHCR7 | DMPK | DNTT | DPP4 | DPP9 | DRD1 |
| DRD2 | DRD3 | DRD4 | DRD5 | DYRK1A | DYRK1B | DYRK3 | EBP |
| ECE1 | EDNRA | EDNRB | EGFR | EIF2AK2 | EIF2AK3 | EIF2AK4 | ELANE |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| ELAVL1 | ENGASE | EP300 | EPAS1 | EPHA4 | EPHB1 | EPHB2 | EPHX1 |
| EPHX2 | ERBB2 | ERG | ERN1 | ESR1 | ESR2 | ESRRA | ESRRB |
| ESRRG | F12 | F2 | F2R | F2RL3 | F3 | F7 | F9 |
| FAAH | FABP1 | FABP2 | FABP3 | FABP4 | FABP5 | FADS1 | FAP |
| FASLG | FASN | FBP1 | FEN1 | FFAR1 | FFAR4 | FGF1 | FGF2 |
| FGFR1 | FGFR2 | FLT1 | FOLH1 | FOS | FTO | G6PC | G6PC1 |
| G6PD | GAA | GABRA2 | GABRA4 | GABRG2 | GANAB | GANC | GAPDH |
| GC | GCG | GCGR | GCK | GFAP | GFER | GHSR | GLA |
| GLB1 | GLI2 | GLO1 | GLS | GLUL | GNAO1 | GOT1 | GOT2 |
| GPBAR1 | GPR119 | GPR35 | GPR39 | GPR55 | GPT | GRK2 | GSK3A |
| GSK3B | GSR | GSTA1 | GSTK1 | GSTM1 | GSTP1 | GUSB | GYS1 |
| GIP | HCAR2 | HDAC3 | HDAC4 | HDAC7 | HDAC9 | HGF | HIF1A |
| HLA-A | HMGB1 | HMGCR | HMOX1 | HNF4A | HPGDS | HPSE | HRAS |
| HSD11B1 | HSD11B2 | HSD17B3 | HSP90AA1 | HSP90B1 | HSPA1A | HSPA8 | HSPD1 |
| HTR1A | HTR1B | HTR1D | HTR2A | HTR2B | HTR2C | HTR3B | HTR4 |
| HTR7 | IARS1 | ICAM1 | IFNG | IGF1R | IGF2 | IGF2R | IGFBP1 |
| IGFBP2 | IGFBP3 | IGFBP4 | IGFBP5 | IKBKB | IKBKE | IL10 | IL13 |
| IL1B | IL2 | IL4 | IL6 | ILK | INS | INSR | IRAK4 |
| ITGA2B | ITGB2 | ITGB3 | ITGB6 | JAK1 | JAK2 | JUN | KCNB1 |
| KCND3 | KCNJ1 | KCNJ11 | KCNJ3 | KCNJ5 | KCNJ6 | KCNK3 | KCNMA1 |
| KCNQ1 | KDM1A | KDR | KIF11 | KISS1R | KLF5 | KLK1 | KLK5 |
| LDHA | LDLR | LIMK1 | LIPA | LIPE | LIPG | LNPEP | LOXL2 |
| LPAR1 | LPAR2 | LPAR3 | LRP6 | LTF | LY96 | LYPLA1 | LYZ |
| MAK | MALT1 | MAOA | MAOB | MAP2K1 | MAP2K7 | MAP3K1 | MAP3K8 |
| MAP4K5 | MAPK1 | MAPK10 | MAPK14 | MAPK3 | MAPK7 | MAPK8 | MAPK9 |
| MAPT | MAX | MB | MC4R | MC5R | MDH2 | MDM2 | ME1 |
| MET | METAP2 | MGAM | MGAT2 | MGLL | MIF | MME | MMP1 |
| MMP12 | MMP13 | MMP14 | MMP2 | MMP26 | MMP3 | MMP7 | MMP8 |
| MMP9 | MPI | MPO | MRGPRX1 | MS4A2 | MT-ND1 | MT-ND2 | MT-ND3 |
| MT-ND4 | MT-ND5 | MTNR1A | MTNR1B | MTOR | MTTP | MTR | MYLK |
| NAMPT | NCOA1 | NDUFA12 | NDUFB6 | NDUFS4 | NEK2 | NFE2L2 | NFKB1 |
| NFKBIA | NISCH | NLRP3 | NNMT | NOD1 | NOD2 | NOS1 | NOS2 |
| NOS3 | NOX4 | NPC1 | NPC1L1 | NPEPPS | NPY1R | NPY2R | NPY5R |
| NQO1 | NR0B2 | NR1H2 | NR1H3 | NR1H4 | NR1I2 | NR1I3 | NR3C1 |
| NR3C2 | NR4A1 | NR4A2 | NSD2 | NTRK1 | NTRK2 | NGFR | OGA |
| OPRM1 | OXCT1 | OXER1 | P2RX3 | P2RX7 | P2RY1 | P2RY12 | P4HB |
| PADI1 | PADI4 | PAK1 | PAM | PARP1 | PASK | PCSK7 | PCYT1A |
| PDE2A | PDE3A | PDE3B | PDE4B | PDE4D | PDE5A | PDGFRB | PDHB |
| PDK4 | PEPD | PER2 | PFKFB3 | PGC | PGF | PGR | PIK3C2G |
| PIK3CA | PIK3CB | PIK3CD | PIK3CG | PIK3R1 | PIM3 | PIN1 | PKLR |
| PKM | PKN2 | PLA2G10 | PLA2G1B | PLA2G2A | PLA2G4A | PLA2G6 | PLA2G7 |
| PLAT | PLAUR | PLCG1 | PLD1 | PLG | PLK1 | PON1 | PPARA |
| PPARD | PPARG | PPIA | PPP2CA | PREP | PRKAA2 | PRKAB1 | PRKCA |
| PRKCB | PRKCD | PRKCE | PRKCI | PRKCQ | PRKCZ | PRKD1 | PRMT1 |
| PSEN1 | PSMD3 | PTAFR | PTEN | PTER | PTGDR2 | PTGER3 | PTGES2 |
| PTGS1 | PTGS2 | PTK2B | PTPN1 | PTPN11 | PTPN2 | PTPN22 | PTPN5 |
| PTPN6 | PTPRB | PTPRC | PTPRF | PTPRS | PYGM | RAC1 | RAF1 |
| RAMP1 | RARB | RBP4 | RELA | REN | RHO | RHOA | RIPK2 |
| ROCK1 | RORA | RORB | RORC | RPS6KA2 | RPS6KA3 | RPS6KB1 | RXRA |
| RXRB | RXRG | SCD | SCN2A | SCNN1A | SDHA | SELE | SELL |
| SELP | SERPINA6 | SERPINE1 | SHBG | SHH | SI | SIGMAR1 | SIRT1 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| SIRT2 | SIRT3 | SIRT5 | SLC10A2 | SLC16A1 | SLC16A7 | SLC18A2 | SLC22A1 |
| SLC22A12 | SLC22A2 | SLC22A3 | SLC22A6 | SLC22A8 | SLC25A20 | SLC2A2 | SLC2A3 |
| SLC2A4 | SLC47A1 | SLC5A1 | SLC5A2 | SLC5A4 | SLC5A5 | SLC6A2 | SLC6A4 |
| SLC8A1 | SLC9A1 | SMAD3 | SNCA | SOAT1 | SPHK1 | SPHK2 | SRC |
| SRD5A1 | SRD5A2 | SREBF2 | SSTR2 | SSTR4 | ST3GAL3 | ST6GAL1 | STAT1 |
| STAT3 | STK33 | STK4 | STS | SUCLA2 | SYK | TAAR1 | TACR3 |
| TAS1R3 | TCF4 | TEK | TEP1 | TERT | TF | TGFB1 | TGFBR1 |
| TGFBR2 | TGM2 | TIMP3 | TKFC | TKT | TLR1 | TLR2 | TLR4 |
| TLR9 | TNF | TNFRSF1A | TNKS2 | TNNT2 | TOP1 | TOP2A | TP53 |
| TPO | TSPO | TTR | TYK2 | TYMP | TH | TRPA1 | TRPM2 |
| TRPM5 | TRPV1 | UGCG | UGT2B7 | UTS2R | VCAM1 | VDR | VEGFA |
| XDH | YWHAG | ABL1 | ADAM10 | ADH5 | ADORA2A | AHCY | AKR1C1 |
| AKR1C3 | ALDH1A1 | ALDH3A1 | ALDH5A1 | ALDH9A1 | ALKBH3 | AMPD3 | APEX1 |
| ASAH1 | ATF1 | ATG4B | ATR | AURKB | BCL2L2 | BRPF1 | BTK |
| C3AR1 | C5AR1 | CA3 | CAMK2D | CASP2 | CASP6 | CCNA2 | CCNB1 |
| CCR3 | CDC25A | CDC25C | CDK1 | CES2 | CRYAB | CTSG | CTSV |
| CTH | CXCR2 | CYP26A1 | CHAT | CHEK1 | CHKA | CHRNA7 | CHRNB2 |
| DAO | DAPK1 | DDO | DHCR24 | DHFR | DHODH | DNMT3B | DUSP3 |
| EEF1A1 | EEF1A2 | EGLN1 | EGLN3 | EIF6 | EPHA3 | ERCC1 | ERCC5 |
| EZH2 | F10 | FLT3 | FYN | GATM | GLUD1 | GLUD2 | GNAI1 |
| GNB1 | GNG2 | GRIN1 | GRIN2A | GRIN2B | GRM5 | GSTM2 | GSTO1 |
| HAO1 | HCK | HCRTR1 | HDAC1 | HDAC10 | HDAC11 | HDAC2 | HDAC5 |
| HDAC6 | HDAC8 | HIF1AN | HRH2 | HRH4 | HSD17B2 | HSF1 | HSP90AB1 |
| HTT | ICMT | IDH1 | IDH2 | IDO1 | IKBKG | ITGA4 | ITGAL |
| ITGAV | ITGB1 | ITGB5 | KCNA3 | KCNA5 | KCNE1 | KCNK9 | KCNH2 |
| KCNH3 | KIT | KMO | LCK | LDHB | LIG1 | LRRK2 | LTB4R |
| LYN | MAP2 | MAP3K14 | MAP3K7 | MAPK15 | MAPKAPK2 | MCL1 | MDH1 |
| MDM4 | ME2 | ME3 | MECP2 | MGMT | MGST1 | MITF | MPEG1 |
| MPG | MT-ND4L | MT-ND6 | NDUFA1 | NDUFA10 | NDUFA11 | NDUFA13 | NDUFA2 |
| NDUFA3 | NDUFA4 | NDUFA4L2 | NDUFA5 | NDUFA6 | NDUFA7 | NDUFA8 | NDUFA9 |
| NDUFAB1 | NDUFAF1 | NDUFAF2 | NDUFAF3 | NDUFAF4 | NDUFB1 | NDUFB10 | NDUFB11 |
| NDUFB2 | NDUFB3 | NDUFB4 | NDUFB5 | NDUFB7 | NDUFB8 | NDUFB9 | NDUFC1 |
| NDUFC2 | NDUFS1 | NDUFS2 | NDUFS3 | NDUFS5 | NDUFS6 | NDUFS7 | NDUFS8 |
| NDUFV1 | NDUFV2 | NDUFV3 | NFS1 | NLRP1 | NQO2 | NTSR1 | OAT |
| ODC1 | OPRK1 | PABPC1 | PARP2 | PDE4A | PDGFRA | PDK1 | PDK3 |
| PGD | PGK1 | PIM1 | PIM2 | PLAU | PLCG2 | POLB | POLH |
| POLI | POLL | PRKACA | PRKAG1 | PRKCG | PRKDC | PSEN2 | PSMB5 |
| PTGES | PTK2 | PTPN12 | QDPR | RAD51 | RARA | RB1 | RIPK1 |
| RPA1 | RPS6KA1 | RPS6KB2 | RUNX1T1 | SCN5A | SHMT2 | SLC16A4 | SLC1A1 |
| SLC37A4 | SLC6A12 | SLC6A3 | SLC7A11 | SMPD2 | SOAT2 | SQLE | ST14 |
| STK3 | TACR1 | TBXA2R | TDP1 | TLR8 | TNNI3 | TOP2B | TYR |
| TYRP1 | TRPM8 | TRPV4 | UBE2D3 | UQCRB | USP10 | VAV1 | VCP |
| WEE1 | XIAP | XPO1 | YARS1 | | | | |

**Table S5**. List of 86 hub proteins in the protein–protein interaction (PPI) network.

| No. | Gene ID | DC | EC | LAC | BC | CC | NC |
|---|---|---|---|---|---|---|---|
| 1 | SRC | 120 | 0.173 | 30.617 | 2780.278 | 0.670 | 84.263 |
| 2 | AKT1 | 114 | 0.169 | 29.719 | 2012.759 | 0.660 | 74.475 |
| 3 | TP53 | 113 | 0.147 | 26.549 | 2986.067 | 0.658 | 77.059 |
| 4 | MAPK3 | 110 | 0.162 | 28.527 | 1763.745 | 0.653 | 70.305 |
| 5 | STAT3 | 104 | 0.163 | 31.250 | 1287.163 | 0.642 | 69.128 |
| 6 | HSP90AA1 | 103 | 0.143 | 24.388 | 1926.044 | 0.640 | 59.426 |
| 7 | EGFR | 101 | 0.156 | 29.307 | 1416.507 | 0.635 | 64.062 |
| 8 | MAPK1 | 97 | 0.141 | 24.887 | 1312.481 | 0.630 | 55.596 |
| 9 | HRAS | 92 | 0.142 | 27.783 | 1243.605 | 0.618 | 57.230 |
| 10 | JUN | 92 | 0.133 | 26.239 | 1463.556 | 0.622 | 55.718 |
| 11 | CTNNB1 | 91 | 0.135 | 24.593 | 1256.456 | 0.618 | 50.679 |
| 12 | PIK3R1 | 83 | 0.131 | 27.229 | 589.721 | 0.601 | 50.112 |
| 13 | TNF | 77 | 0.101 | 22.000 | 1180.272 | 0.592 | 45.675 |
| 14 | PIK3CA | 77 | 0.127 | 27.792 | 418.421 | 0.595 | 46.791 |
| 15 | EP300 | 77 | 0.098 | 21.299 | 1268.206 | 0.598 | 45.526 |
| 16 | RELA | 74 | 0.114 | 24.108 | 792.664 | 0.593 | 40.193 |
| 17 | VEGFA | 71 | 0.120 | 26.930 | 468.048 | 0.589 | 41.678 |
| 18 | MAPK8 | 69 | 0.109 | 22.000 | 611.026 | 0.583 | 34.265 |
| 19 | IL6 | 68 | 0.099 | 22.471 | 754.430 | 0.577 | 39.513 |
| 20 | CASP3 | 68 | 0.101 | 20.353 | 634.240 | 0.580 | 32.916 |
| 21 | ESR1 | 67 | 0.111 | 24.836 | 589.687 | 0.582 | 36.866 |
| 22 | RHOA | 65 | 0.105 | 22.708 | 444.180 | 0.566 | 33.032 |
| 23 | CREBBP | 65 | 0.083 | 19.538 | 820.813 | 0.580 | 36.621 |
| 24 | JAK2 | 63 | 0.100 | 20.952 | 474.324 | 0.569 | 30.276 |
| 25 | FYN | 63 | 0.102 | 24.730 | 340.619 | 0.557 | 36.399 |
| 26 | PTPN11 | 62 | 0.105 | 24.903 | 268.730 | 0.560 | 34.429 |
| 27 | GAPDH | 62 | 0.086 | 18.742 | 1114.016 | 0.573 | 30.373 |
| 28 | MAPK14 | 62 | 0.105 | 21.774 | 457.923 | 0.572 | 29.846 |
| 29 | INS | 61 | 0.095 | 19.705 | 775.899 | 0.575 | 29.010 |
| 30 | PLCG1 | 61 | 0.093 | 21.377 | 341.432 | 0.552 | 31.648 |
| 31 | PTK2 | 60 | 0.106 | 26.967 | 197.600 | 0.560 | 35.529 |
| 32 | LYN | 60 | 0.102 | 23.567 | 338.622 | 0.562 | 32.502 |
| 33 | LCK | 60 | 0.103 | 26.500 | 190.210 | 0.556 | 35.838 |
| 34 | PTEN | 58 | 0.102 | 23.172 | 367.228 | 0.565 | 29.710 |
| 35 | RAC1 | 58 | 0.096 | 23.172 | 283.446 | 0.548 | 31.495 |
| 36 | HIF1A | 57 | 0.091 | 21.895 | 496.906 | 0.569 | 30.313 |
| 37 | IL1B | 56 | 0.082 | 20.964 | 341.878 | 0.558 | 31.267 |
| 38 | STAT1 | 56 | 0.099 | 22.429 | 274.301 | 0.566 | 27.492 |
| 39 | TLR4 | 55 | 0.084 | 19.891 | 363.407 | 0.557 | 28.963 |
| 40 | PRKCA | 54 | 0.079 | 16.037 | 443.093 | 0.554 | 23.230 |
| 41 | CDC42 | 54 | 0.093 | 22.556 | 186.482 | 0.549 | 28.649 |
| 42 | NFKB1 | 53 | 0.089 | 20.491 | 227.738 | 0.558 | 25.637 |
| 43 | JAK1 | 51 | 0.084 | 18.941 | 249.231 | 0.541 | 24.251 |
| 44 | ERBB2 | 51 | 0.088 | 19.333 | 405.580 | 0.556 | 23.172 |
| 45 | CCND1 | 51 | 0.084 | 21.843 | 230.361 | 0.556 | 28.092 |
| 46 | NFKBIA | 50 | 0.084 | 20.080 | 256.667 | 0.557 | 24.646 |
| 47 | AR | 50 | 0.080 | 18.400 | 340.415 | 0.553 | 23.508 |
| 48 | CXCL12 | 49 | 0.082 | 20.776 | 199.709 | 0.543 | 26.075 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 49 | CREB1 | 47 | 0.073 | 15.872 | 296.574 | 0.550 | 20.159 |
| 50 | MTOR | 47 | 0.083 | 17.957 | 238.394 | 0.548 | 20.577 |
| 51 | HDAC1 | 47 | 0.061 | 17.362 | 330.533 | 0.539 | 23.869 |
| 52 | FOS | 46 | 0.082 | 20.304 | 170.712 | 0.553 | 23.535 |
| 53 | PPARG | 46 | 0.070 | 17.130 | 351.957 | 0.553 | 22.101 |
| 54 | IL2 | 46 | 0.084 | 21.087 | 129.354 | 0.540 | 24.100 |
| 55 | SIRT1 | 46 | 0.064 | 16.957 | 252.732 | 0.544 | 23.116 |
| 56 | MDM2 | 46 | 0.065 | 16.000 | 320.059 | 0.547 | 20.569 |
| 57 | SYK | 45 | 0.071 | 17.333 | 195.669 | 0.525 | 21.254 |
| 58 | GNB1 | 45 | 0.070 | 18.222 | 197.957 | 0.529 | 23.155 |
| 59 | AKT2 | 44 | 0.075 | 16.636 | 170.189 | 0.544 | 19.046 |
| 60 | HSP90AB1 | 44 | 0.066 | 14.682 | 237.755 | 0.540 | 19.155 |
| 61 | PRKCZ | 43 | 0.079 | 19.953 | 101.823 | 0.541 | 22.181 |
| 62 | ALB | 43 | 0.063 | 15.907 | 385.094 | 0.544 | 20.794 |
| 63 | RAF1 | 43 | 0.075 | 16.930 | 134.798 | 0.533 | 19.019 |
| 64 | PRKCD | 43 | 0.075 | 17.767 | 154.294 | 0.535 | 20.323 |
| 65 | CXCR4 | 42 | 0.069 | 17.952 | 238.592 | 0.529 | 20.944 |
| 66 | CDKN1A | 42 | 0.065 | 17.714 | 168.676 | 0.543 | 21.724 |
| 67 | BCL2L1 | 41 | 0.070 | 16.439 | 149.983 | 0.544 | 19.440 |
| 68 | NR3C1 | 41 | 0.070 | 17.220 | 128.060 | 0.545 | 19.724 |
| 69 | MAP2K1 | 40 | 0.069 | 15.350 | 144.834 | 0.539 | 17.305 |
| 70 | SMAD3 | 40 | 0.058 | 14.000 | 221.471 | 0.535 | 17.007 |
| 71 | FGF2 | 40 | 0.066 | 17.550 | 114.204 | 0.533 | 20.449 |
| 72 | CD4 | 40 | 0.059 | 16.100 | 191.018 | 0.519 | 19.123 |
| 73 | ITGB1 | 39 | 0.066 | 17.077 | 100.371 | 0.519 | 18.877 |
| 74 | MMP9 | 39 | 0.064 | 17.590 | 185.780 | 0.538 | 21.232 |
| 75 | TLR2 | 39 | 0.056 | 15.077 | 147.910 | 0.525 | 18.419 |
| 76 | PDGFRB | 39 | 0.070 | 18.564 | 100.730 | 0.518 | 20.484 |
| 77 | ABL1 | 39 | 0.060 | 13.846 | 212.860 | 0.535 | 16.342 |
| 78 | RPS6KB1 | 38 | 0.066 | 14.947 | 116.395 | 0.538 | 16.167 |
| 79 | GNAI1 | 38 | 0.067 | 18.526 | 99.782 | 0.526 | 21.179 |
| 80 | CDK2 | 38 | 0.055 | 16.579 | 159.312 | 0.535 | 20.126 |
| 81 | IKBKB | 37 | 0.061 | 15.514 | 98.554 | 0.537 | 17.491 |
| 82 | RB1 | 37 | 0.058 | 16.919 | 108.502 | 0.529 | 19.417 |
| 83 | TGFB1 | 36 | 0.058 | 14.000 | 142.951 | 0.532 | 16.400 |
| 84 | CASP8 | 35 | 0.059 | 14.629 | 99.100 | 0.534 | 16.436 |
| 85 | ITGAV | 34 | 0.055 | 14.000 | 110.426 | 0.516 | 15.820 |
| 86 | PPP2CA | 34 | 0.059 | 14.588 | 104.873 | 0.527 | 16.036 |

**Table S6**. Cartesian coordinates of MOL01 optimized using DFT calculations.

| No. | Atom | Coordinates (Å) | | |
|---|---|---|---|---|
| | | X | Y | Z |
| 1 | O1 | 3.4739 | -0.7052 | -0.8454 |
| 2 | O2 | 3.0040 | 1.8624 | 1.7818 |
| 3 | O3 | 5.6097 | 0.8850 | 2.3169 |
| 4 | O4 | 6.9716 | -0.1605 | 0.0481 |
| 5 | O5 | 5.0936 | -3.0219 | -1.1382 |
| 6 | O6 | 0.9008 | 2.3969 | -0.9352 |
| 7 | O7 | 1.6450 | -2.1106 | 0.4952 |
| 8 | O8 | -2.7587 | -0.5212 | 0.1093 |
| 9 | O9 | -1.5395 | 3.1686 | -1.1601 |
| 10 | O10 | -8.9997 | -1.3249 | 0.5168 |
| 11 | C11 | 3.4627 | 0.6628 | 1.1659 |
| 12 | C12 | 4.9771 | 0.8081 | 1.0419 |
| 13 | C13 | 2.8389 | 0.4443 | -0.2359 |
| 14 | C14 | 5.5900 | -0.3805 | 0.3061 |
| 15 | C15 | 4.8928 | -0.5690 | -1.0459 |
| 16 | C16 | 1.3499 | 0.1871 | -0.1889 |
| 17 | C17 | 5.3643 | -1.7992 | -1.8172 |
| 18 | C18 | 0.4435 | 1.2024 | -0.5278 |
| 19 | C19 | 0.8259 | -1.0701 | 0.2059 |
| 20 | C20 | -0.9602 | 0.9896 | -0.4305 |
| 21 | C21 | -0.5489 | -1.3029 | 0.3175 |
| 22 | C22 | -1.4154 | -0.2662 | 0.0016 |
| 23 | C23 | -1.9126 | 2.0341 | -0.7681 |
| 24 | C24 | -3.6817 | 0.4366 | -0.1965 |
| 25 | C25 | -3.3049 | 1.6792 | -0.6111 |
| 26 | C26 | -5.0601 | -0.0393 | -0.0105 |
| 27 | C27 | -6.1510 | 0.6514 | -0.5749 |
| 28 | C28 | -5.3251 | -1.1989 | 0.7389 |
| 29 | C29 | -7.4544 | 0.2124 | -0.3895 |
| 30 | C30 | -6.6295 | -1.6460 | 0.9307 |
| 31 | C31 | -7.6998 | -0.9403 | 0.3689 |
| 32 | H32 | 3.2375 | -0.2033 | 1.8050 |
| 33 | H33 | 5.1889 | 1.7236 | 0.4669 |
| 34 | H34 | 3.0302 | 1.3333 | -0.8481 |
| 35 | H35 | 5.4531 | -1.2902 | 0.9079 |
| 36 | H36 | 5.0822 | 0.3191 | -1.6691 |
| 37 | H37 | 6.4490 | -1.7356 | -1.9318 |
| 38 | H38 | 4.9049 | -1.7932 | -2.8141 |
| 39 | H39 | 2.0494 | 1.8089 | 1.9259 |
| 40 | H40 | 5.2113 | 1.6222 | 2.8012 |
| 41 | H41 | 7.3894 | 0.0748 | 0.8891 |
| 42 | H42 | -0.9153 | -2.2770 | 0.6164 |
| 43 | H43 | 4.1678 | -3.2563 | -1.2795 |
| 44 | H44 | 0.0928 | 2.9631 | -1.1235 |
| 45 | H45 | 2.5351 | -1.9045 | 0.1417 |

| | | | | |
|---|---|---|---|---|
| 46 | H46 | -4.0445 | 2.4411 | -0.8184 |
| 47 | H47 | -5.9817 | 1.5330 | -1.1836 |
| 48 | H48 | -4.5040 | -1.7512 | 1.1804 |
| 49 | H49 | -8.2918 | 0.7415 | -0.8313 |
| 50 | H50 | -6.8139 | -2.5418 | 1.5191 |
| 51 | H51 | -9.0552 | -2.1302 | 1.0487 |

**Table S7**. Cartesian coordinates of MOL02 optimized using DFT calculations.

| No. | Atom | Coordinates (Å) | | |
|---|---|---|---|---|
| | | X | Y | Z |
| 1 | O1 | -0.3736 | 0.5978 | -0.0656 |
| 2 | O2 | -4.6307 | -1.6206 | 0.1129 |
| 3 | O3 | -2.4032 | -2.9450 | 0.1536 |
| 4 | O4 | -4.3262 | 3.1422 | -0.1321 |
| 5 | O5 | 5.9203 | 0.0806 | -0.0791 |
| 6 | C6 | -2.4751 | -0.5802 | 0.0270 |
| 7 | C7 | -1.7457 | 0.6195 | -0.0428 |
| 8 | C8 | 0.3113 | -0.5811 | -0.0071 |
| 9 | C9 | 1.7676 | -0.3812 | -0.0320 |
| 10 | C10 | -1.7810 | -1.8558 | 0.0870 |
| 11 | C11 | -0.3371 | -1.7771 | 0.0761 |
| 12 | C12 | -3.8956 | -0.5023 | 0.0443 |
| 13 | C13 | -2.3540 | 1.8672 | -0.0966 |
| 14 | C14 | -3.7526 | 1.9059 | -0.0783 |
| 15 | C15 | -4.5275 | 0.7404 | -0.0089 |
| 16 | C16 | 2.6450 | -1.4495 | -0.3140 |
| 17 | C17 | 2.3263 | 0.8795 | 0.2281 |
| 18 | C18 | 4.0176 | -1.2649 | -0.3210 |
| 19 | C19 | 3.7076 | 1.0776 | 0.2260 |
| 20 | C20 | 4.5630 | 0.0020 | -0.0480 |
| 21 | C21 | 6.5423 | 1.3364 | 0.1814 |
| 22 | H22 | 0.2181 | -2.7023 | 0.1551 |
| 23 | H23 | -1.7725 | 2.7785 | -0.1540 |
| 24 | H24 | -5.6125 | 0.7816 | 0.0050 |
| 25 | H25 | 2.2504 | -2.4321 | -0.5490 |
| 26 | H26 | 1.6745 | 1.7181 | 0.4435 |
| 27 | H27 | 4.6918 | -2.0846 | -0.5453 |
| 28 | H28 | 4.0992 | 2.0649 | 0.4387 |
| 29 | H29 | -3.9857 | -2.3847 | 0.1440 |
| 30 | H30 | -5.2893 | 3.0621 | -0.1165 |
| 31 | H31 | 6.3065 | 1.6942 | 1.1907 |
| 32 | H32 | 6.2413 | 2.0892 | -0.5570 |
| 33 | H33 | 7.6145 | 1.1567 | 0.1009 |

**Table S8**. Cartesian coordinates of MOL05 optimized using DFT calculations.

| No. | Atom | Coordinates (Å) | | |
|---|---|---|---|---|
| | | X | Y | Z |
| 1 | O1 | 0.5855 | -0.3027 | 0.0127 |
| 2 | O2 | -1.2767 | -2.2802 | 0.0411 |
| 3 | O3 | -4.0127 | -1.5650 | 0.1244 |
| 4 | O4 | -2.8809 | 3.0388 | 0.0373 |
| 5 | O5 | -0.3556 | 3.6741 | -0.0401 |
| 6 | C6 | -1.1042 | 1.4247 | 0.0113 |
| 7 | C7 | -0.7334 | 0.0677 | 0.0208 |
| 8 | C8 | -1.6771 | -0.9643 | 0.0556 |
| 9 | C9 | 1.5713 | 0.6351 | -0.0384 |
| 10 | C10 | -2.4861 | 1.7553 | 0.0411 |
| 11 | C11 | -0.0729 | 2.4530 | -0.0302 |
| 12 | C12 | -3.0390 | -0.6031 | 0.0593 |
| 13 | C13 | 1.2903 | 1.9666 | -0.0700 |
| 14 | C14 | -3.4394 | 0.7369 | 0.0632 |
| 15 | C15 | 2.9151 | 0.0274 | -0.0709 |
| 16 | C16 | 4.0538 | 0.7808 | 0.2670 |
| 17 | C17 | 3.0758 | -1.3182 | -0.4474 |
| 18 | C18 | 5.3221 | 0.2062 | 0.2144 |
| 19 | C19 | 4.3480 | -1.8878 | -0.4993 |
| 20 | C20 | 5.4746 | -1.1294 | -0.1714 |
| 21 | C21 | -1.2092 | -2.8951 | 1.3393 |
| 22 | C22 | -4.1446 | -2.4101 | -1.0332 |
| 23 | H23 | 2.0847 | 2.6975 | -0.1447 |
| 24 | H24 | -4.4956 | 0.9796 | 0.0785 |
| 25 | H25 | 3.9493 | 1.8108 | 0.5911 |
| 26 | H26 | 2.2036 | -1.9080 | -0.7056 |
| 27 | H27 | 6.1910 | 0.7991 | 0.4833 |
| 28 | H28 | 4.4582 | -2.9257 | -0.7991 |
| 29 | H29 | -2.0547 | 3.5947 | 0.0092 |
| 30 | H30 | 6.4639 | -1.5755 | -0.2111 |
| 31 | H31 | -2.1884 | -2.8755 | 1.8296 |
| 32 | H32 | -0.4672 | -2.3899 | 1.9684 |
| 33 | H33 | -0.9012 | -3.9286 | 1.1700 |
| 34 | H34 | -4.4306 | -1.8108 | -1.9057 |
| 35 | H35 | -4.9443 | -3.1135 | -0.7966 |
| 36 | H36 | -3.2158 | -2.9497 | -1.2362 |

**Table S9**. Cartesian coordinates of MOL08 optimized using DFT calculations.

| No. | Atom | Coordinates (Å) | | |
|---|---|---|---|---|
| | | X | Y | Z |
| 1 | O1 | 1.1812 | -2.4732 | -0.3481 |
| 2 | O2 | 5.0937 | 1.4176 | -0.0783 |
| 3 | O3 | 2.3569 | 2.1654 | 0.1548 |
| 4 | O4 | -0.0840 | 1.3842 | 0.1903 |
| 5 | O5 | 5.7165 | -1.1469 | -0.4086 |
| 6 | O6 | -4.7699 | 1.4582 | -1.1512 |
| 7 | O7 | -6.2645 | -0.2761 | 0.4028 |
| 8 | C8 | 1.7023 | -0.1402 | -0.0717 |
| 9 | C9 | -0.6452 | -0.9304 | -0.0391 |
| 10 | C10 | 2.1151 | -1.4729 | -0.2620 |
| 11 | C11 | 0.2932 | 0.1975 | 0.0361 |
| 12 | C12 | -2.1088 | -0.7458 | 0.1131 |
| 13 | C13 | 2.7017 | 0.8768 | 0.0002 |
| 14 | C14 | 4.0481 | 0.5194 | -0.0872 |
| 15 | C15 | 3.4490 | -1.8418 | -0.3794 |
| 16 | C16 | -0.1311 | -2.1719 | -0.2436 |
| 17 | C17 | 4.4063 | -0.8307 | -0.2913 |
| 18 | C18 | -2.7805 | 0.3041 | -0.5371 |
| 19 | C19 | -2.8625 | -1.6283 | 0.9011 |
| 20 | C20 | -4.1600 | 0.4604 | -0.4311 |
| 21 | C21 | -4.2464 | -1.4833 | 1.0108 |
| 22 | C22 | -4.9070 | -0.4510 | 0.3424 |
| 23 | C23 | 5.2190 | 2.2551 | 1.0892 |
| 24 | C24 | -5.3601 | 2.5174 | -0.3836 |
| 25 | H25 | 3.7389 | -2.8730 | -0.5369 |
| 26 | H26 | -0.7399 | -3.0614 | -0.3534 |
| 27 | H27 | -2.2367 | 1.0187 | -1.1425 |
| 28 | H28 | -2.3686 | -2.4218 | 1.4539 |
| 29 | H29 | -4.8174 | -2.1761 | 1.6256 |
| 30 | H30 | 1.3559 | 2.1803 | 0.2012 |
| 31 | H31 | 6.2143 | -0.3111 | -0.3644 |
| 32 | H32 | 4.3690 | 2.9352 | 1.1665 |
| 33 | H33 | 5.2918 | 1.6392 | 1.9933 |
| 34 | H34 | 6.1426 | 2.8191 | 0.9498 |
| 35 | H35 | -6.6585 | -0.9734 | 0.9432 |
| 36 | H36 | -5.7626 | 3.2245 | -1.1111 |
| 37 | H37 | -6.1676 | 2.1440 | 0.2531 |
| 38 | H38 | -4.5985 | 3.0159 | 0.2288 |

**Table S10**. Cartesian coordinates of MOL17 optimized using DFT calculations.

| No. | Atom | Coordinates (Å) | | |
|---|---|---|---|---|
| | | X | Y | Z |
| 1 | O1 | -0.0391 | -0.6850 | 0.0531 |
| 2 | O2 | -4.1368 | 1.8191 | -0.0864 |
| 3 | O3 | -1.8239 | 2.9896 | -0.1375 |
| 4 | O4 | -4.1548 | -2.9545 | 0.1358 |
| 5 | O5 | 6.2426 | -0.7548 | -0.0317 |
| 6 | C6 | -2.0564 | 0.6343 | -0.0199 |
| 7 | C7 | -1.4101 | -0.6129 | 0.0395 |
| 8 | C8 | 0.7226 | 0.4449 | -0.0059 |
| 9 | C9 | 2.1628 | 0.1467 | 0.0066 |
| 10 | C10 | -1.2779 | 1.8600 | -0.0797 |
| 11 | C11 | 0.1577 | 1.6827 | -0.0810 |
| 12 | C12 | -3.4791 | 0.6531 | -0.0276 |
| 13 | C13 | -2.1013 | -1.8164 | 0.0923 |
| 14 | C14 | -3.4995 | -1.7599 | 0.0834 |
| 15 | C15 | -4.1936 | -0.5439 | 0.0245 |
| 16 | C16 | 3.1049 | 1.1401 | 0.3255 |
| 17 | C17 | 2.6360 | -1.1428 | -0.3055 |
| 18 | C18 | 4.4684 | 0.8649 | 0.3171 |
| 19 | C19 | 3.9963 | -1.4265 | -0.3167 |
| 20 | C20 | 4.9197 | -0.4213 | -0.0069 |
| 21 | H21 | 0.7748 | 2.5675 | -0.1647 |
| 22 | H22 | -1.5825 | -2.7653 | 0.1419 |
| 23 | H23 | -5.2790 | -0.5109 | 0.0178 |
| 24 | H24 | 2.7764 | 2.1360 | 0.6025 |
| 25 | H25 | 1.9279 | -1.9260 | -0.5496 |
| 26 | H26 | 5.1803 | 1.6459 | 0.5740 |
| 27 | H27 | 4.3594 | -2.4183 | -0.5645 |
| 28 | H28 | -3.4417 | 2.5375 | -0.1191 |
| 29 | H29 | -5.1106 | -2.8103 | 0.1267 |
| 30 | H30 | 6.7876 | 0.0111 | 0.1937 |

**Table S11**. Cartesian coordinates of MOL38 optimized using DFT calculations.

| No. | Atom | Coordinates (Å) | | |
|---|---|---|---|---|
| | | X | Y | Z |
| 1 | O1 | -0.2415 | -0.7681 | -0.0701 |
| 2 | O2 | 5.2679 | -0.2185 | -0.0299 |
| 3 | O3 | 4.0420 | -2.7376 | -0.1221 |
| 4 | O4 | 3.6540 | 2.0421 | 0.0161 |
| 5 | O5 | 1.2631 | 3.0235 | 0.0134 |
| 6 | O6 | -6.4134 | -1.6507 | -0.0070 |
| 7 | C7 | 1.6694 | 0.6896 | -0.0166 |
| 8 | C8 | 1.1147 | -0.5985 | -0.0462 |
| 9 | C9 | -1.1050 | 0.2897 | -0.0240 |
| 10 | C10 | -2.5053 | -0.1594 | -0.0300 |
| 11 | C11 | 3.0854 | 0.8246 | -0.0103 |
| 12 | C12 | 0.8022 | 1.8539 | 0.0031 |
| 13 | C13 | 1.9040 | -1.7429 | -0.0548 |
| 14 | C14 | -0.6291 | 1.5803 | 0.0233 |
| 15 | C15 | 3.8991 | -0.3176 | -0.0483 |
| 16 | C16 | 3.2942 | -1.5958 | -0.0511 |
| 17 | C17 | -2.8182 | -1.4663 | 0.4084 |
| 18 | C18 | -3.5593 | 0.6523 | -0.4835 |
| 19 | C19 | -4.1236 | -1.9300 | 0.4088 |
| 20 | C20 | -5.1670 | -1.1048 | -0.0433 |
| 21 | C21 | -4.8760 | 0.1896 | -0.4943 |
| 22 | C22 | 5.8683 | 0.3410 | -1.2110 |
| 23 | C23 | 4.9419 | -3.0013 | 0.9693 |
| 24 | C24 | -7.5172 | -0.8729 | -0.4618 |
| 25 | H25 | 1.4632 | -2.7319 | -0.0753 |
| 26 | H26 | -2.0250 | -2.1177 | 0.7561 |
| 27 | H27 | -3.3491 | 1.6522 | -0.8382 |
| 28 | H28 | -5.6579 | 0.8438 | -0.8604 |
| 29 | H29 | 2.9035 | 2.7014 | 0.0194 |
| 30 | H30 | 6.9459 | 0.3061 | -1.0414 |
| 31 | H31 | 5.5496 | 1.3762 | -1.3577 |
| 32 | H32 | 5.6146 | -0.2635 | -2.0899 |
| 33 | H33 | 4.3762 | -3.1141 | 1.9022 |
| 34 | H34 | 5.6839 | -2.2070 | 1.0716 |
| 35 | H35 | 5.4300 | -3.9457 | 0.7239 |
| 36 | H36 | -7.4042 | -0.6025 | -1.5185 |
| 37 | H37 | -7.6384 | 0.0359 | 0.1400 |
| 38 | H38 | -8.3953 | -1.5078 | -0.3413 |
| 39 | H39 | -4.3624 | -2.9304 | 0.7544 |
| 40 | O40 | -1.5112 | 2.6258 | 0.0122 |
| 41 | C41 | -1.4732 | 3.5019 | 1.1563 |
| 42 | H42 | -0.5042 | 3.9987 | 1.2299 |
| 43 | H43 | -2.2617 | 4.2373 | 0.9882 |
| 44 | H44 | -1.6873 | 2.9368 | 2.0715 |

**Table S12**. Cartesian coordinates of gallic acid optimized using DFT calculations.

| No. | Atom | Coordinates (Å) | | |
|---|---|---|---|---|
| | | X | Y | Z |
| 1 | O1 | -3.0829 | -0.1217 | 0.0001 |
| 2 | O2 | -1.8699 | 2.2959 | 0.0000 |
| 3 | O3 | -1.6446 | -2.4314 | 0.0000 |
| 4 | O4 | 3.1602 | -1.0855 | 0.0000 |
| 5 | O5 | 3.1764 | 1.1660 | -0.0001 |
| 6 | C6 | 1.0632 | 0.0316 | 0.0000 |
| 7 | C7 | -1.7178 | -0.0361 | 0.0000 |
| 8 | C8 | -1.0464 | 1.1919 | 0.0000 |
| 9 | C9 | -0.9926 | -1.2340 | 0.0000 |
| 10 | C10 | 0.3411 | 1.2362 | 0.0000 |
| 11 | C11 | 0.4007 | -1.2034 | 0.0000 |
| 12 | C12 | 2.5427 | 0.1249 | -0.0001 |
| 13 | H13 | 0.8794 | 2.1788 | 0.0000 |
| 14 | H14 | 0.9521 | -2.1350 | -0.0001 |
| 15 | H15 | -3.4575 | 0.7723 | 0.0001 |
| 16 | H16 | -1.3487 | 3.1089 | 0.0001 |
| 17 | H17 | -2.6004 | -2.2702 | 0.0000 |
| 18 | H18 | 4.1154 | -0.9085 | 0.0001 |

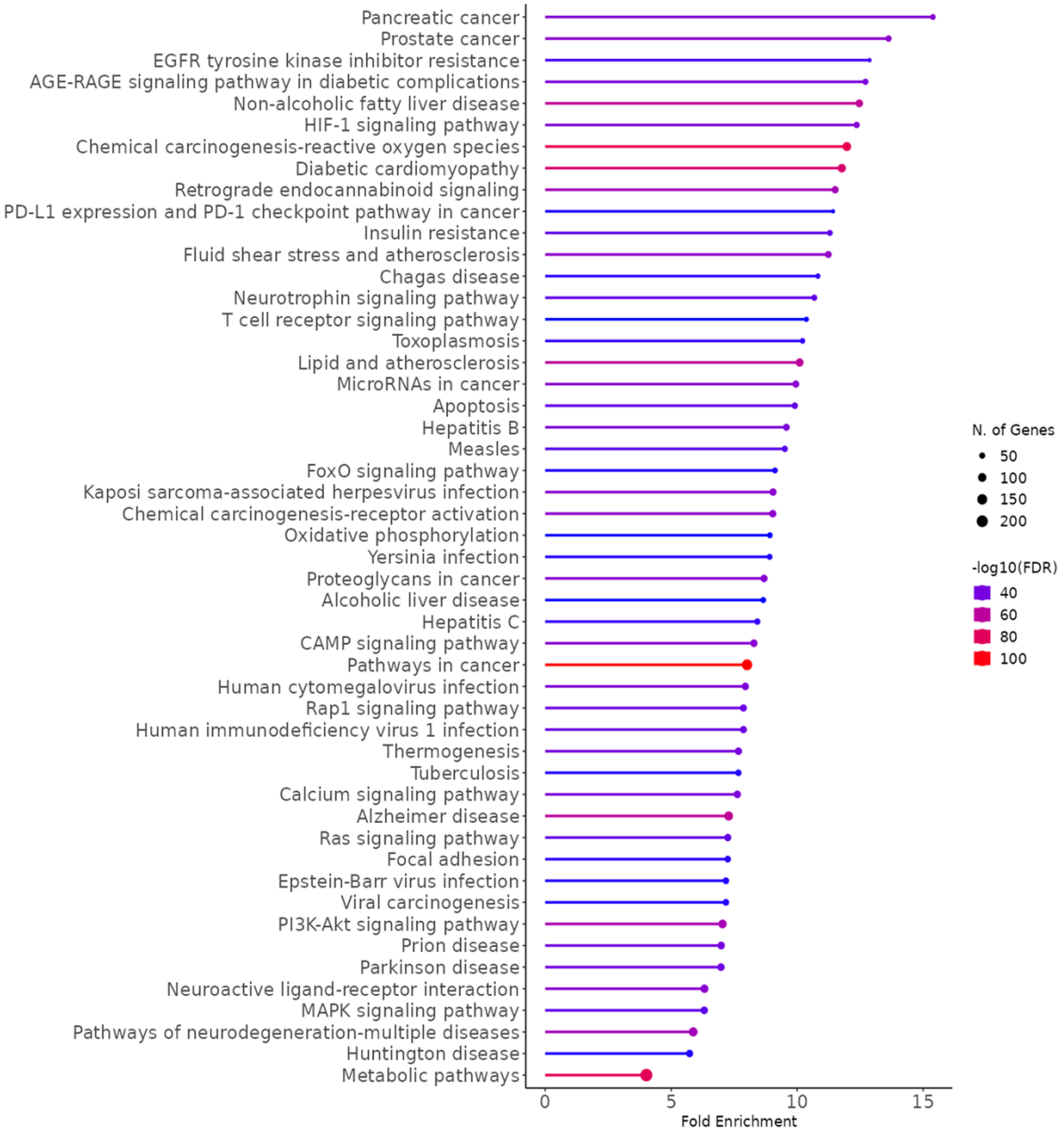



**Figure S1**. KEGG pathway enrichment analysis of the identified targets

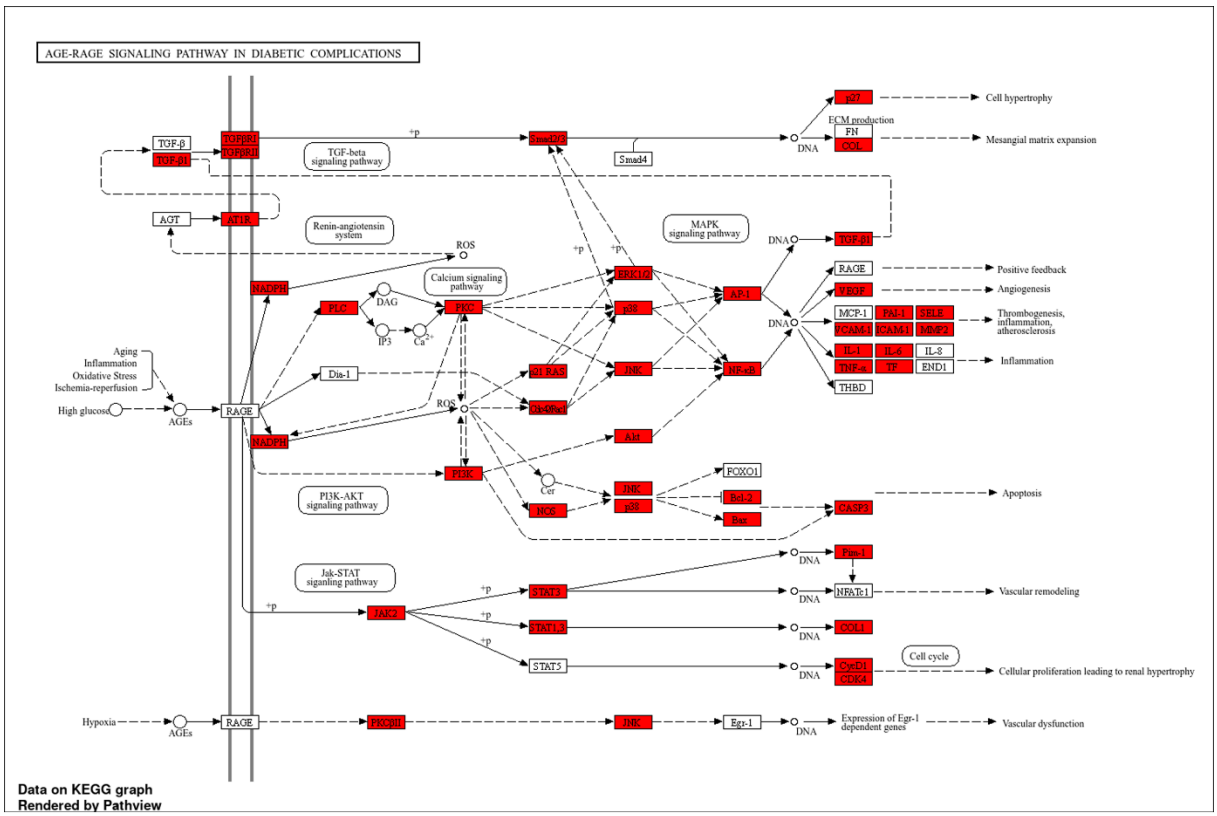



**Figure S2.** AGE–RAGE signaling pathway in diabetic complications identified by KEGG pathway analysis. The targets of *O. corniculata* L. compounds are marked in red.

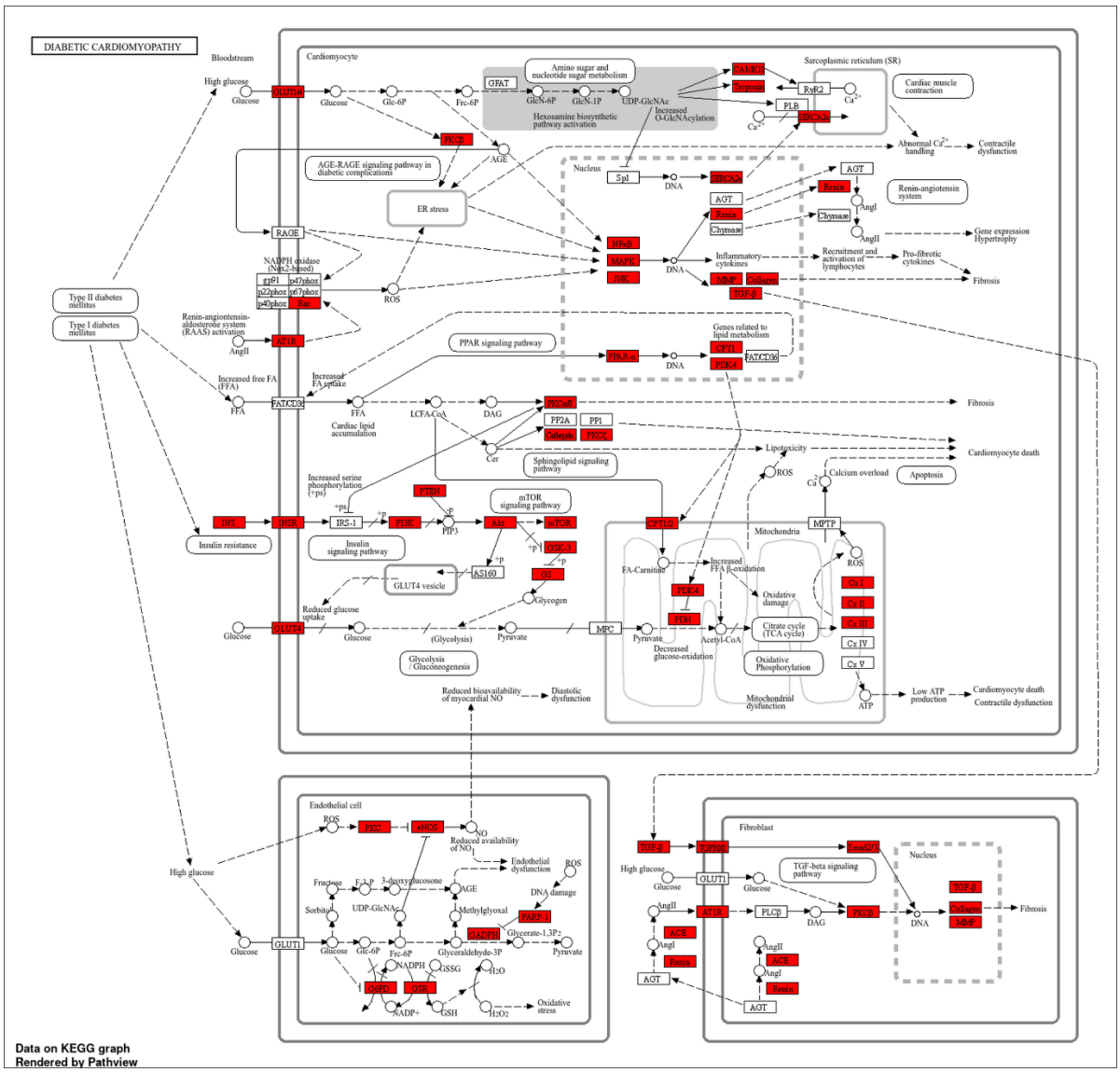



Figure S3. Cardiomyopathy pathway in diabetic complications identified by KEGG pathway analysis. The targets of *O. corniculata* L. compounds are marked in red.

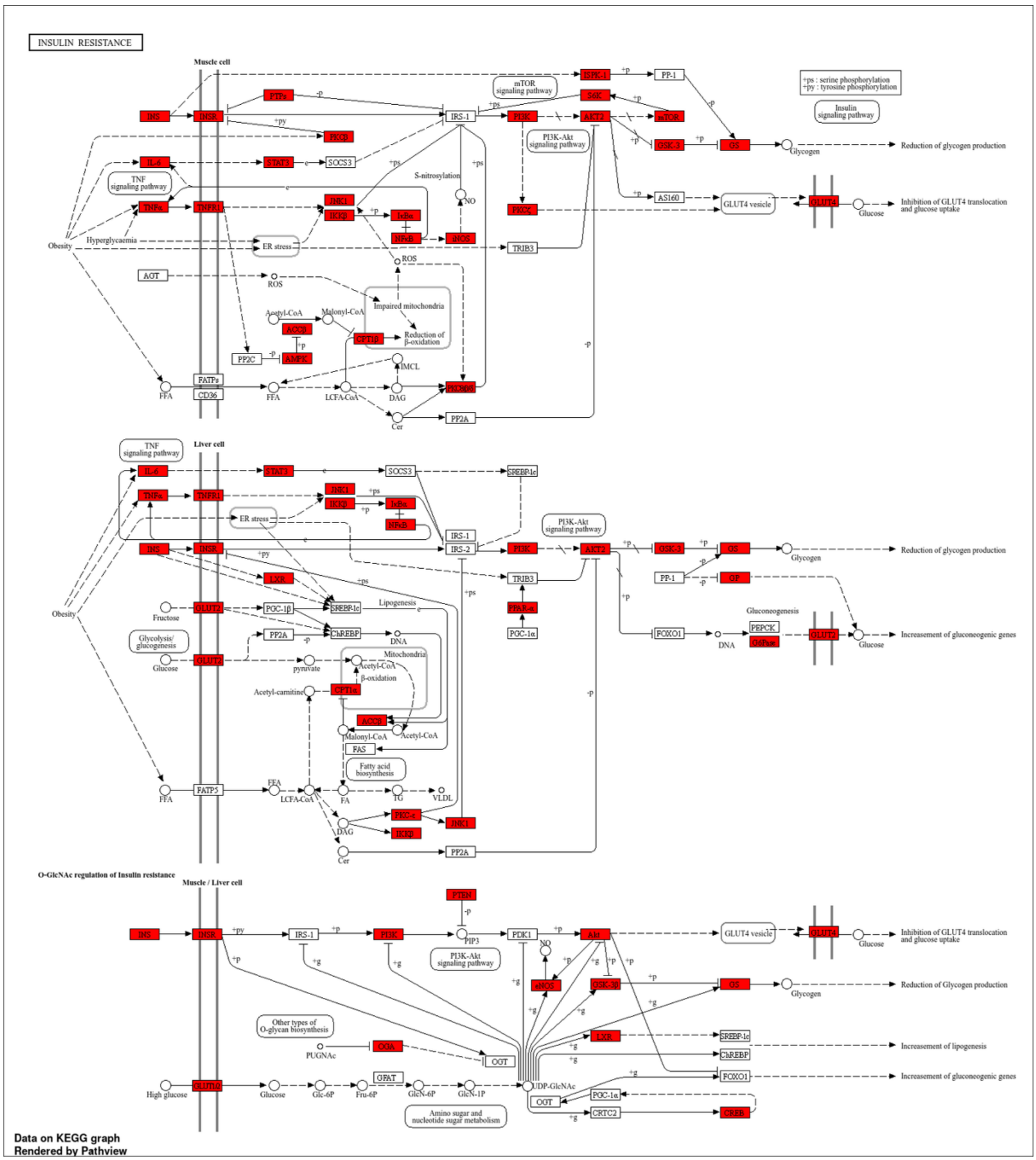



**Figure S4.** KEGG insulin resistance pathway. Protein targets of compounds derived from *O. corniculata* L. are highlighted in red.

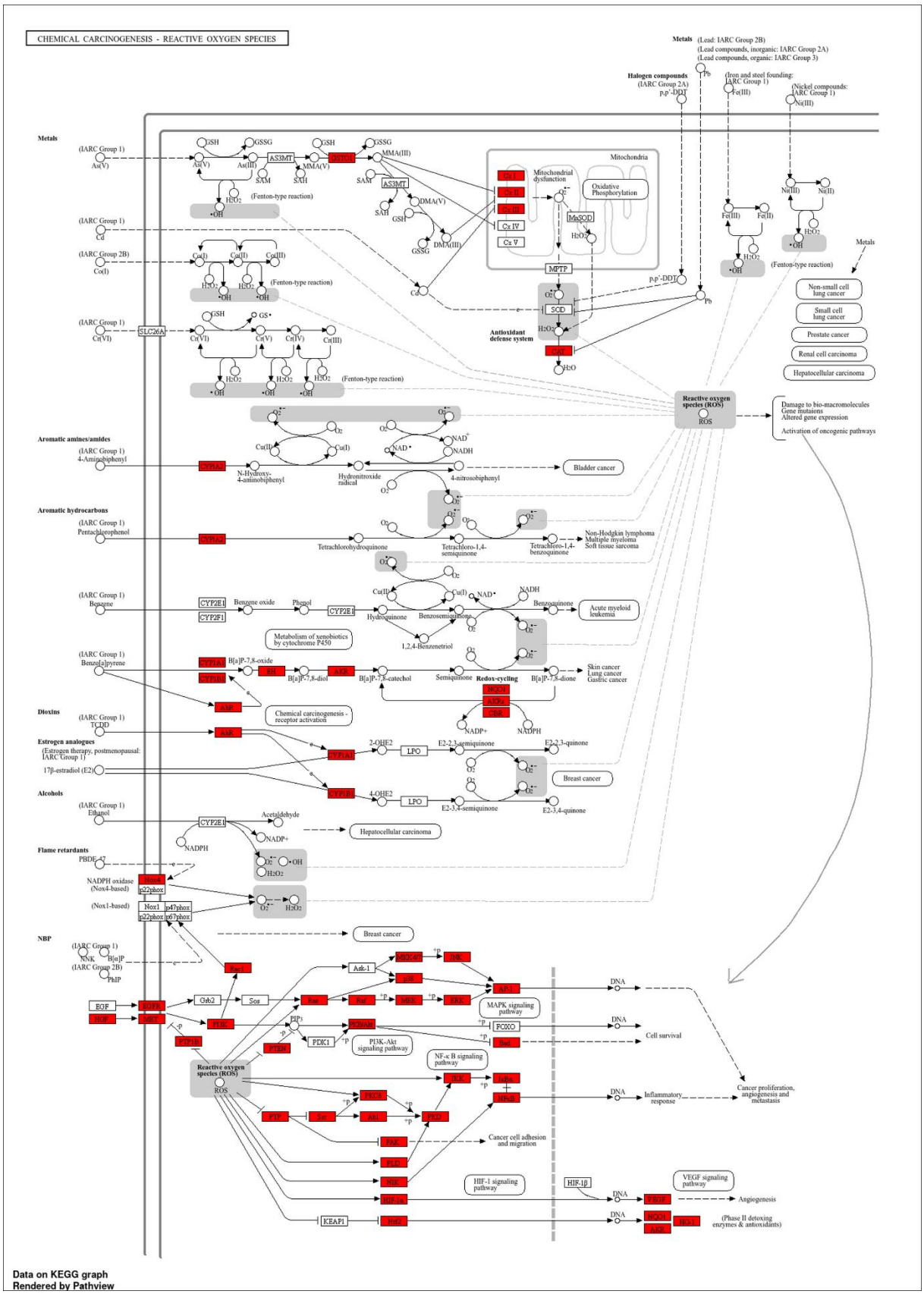



**Figure S5.** Chemical carcinogenesis – reactive oxygen species (ROS) pathway identified by KEGG analysis. Protein targets of compounds derived from *O. corniculata* L. are highlighted in red.