

**Table A.** Predicted upstream regulators upon epicatechin supplementation ( $\Delta$  epicatechin).

Upstream Regulator	Molecule Type	Predicted Activation State	Activation z-score	P-value of Overlap
NFkB (complex)	complex	Inhibited	-5.38	<0.01
PDGF BB	complex	Inhibited	-5.18	<0.01
TNF	cytokine	Inhibited	-5.03	<0.01
EGF	growth factor	Inhibited	-4.59	0.01
IL1B	cytokine	Inhibited	-4.35	<0.01
NUPR1	transcription regulator	Inhibited	-4.35	<0.01
EGFR	Kinase	Inhibited	-4.25	<0.01
TGFB1	growth factor	Inhibited	-4.17	<0.01
F2	peptidase	Inhibited	-4.14	0.01
Cg	complex	Inhibited	-3.98	<0.01
TLR4	transmembrane receptor	Inhibited	-3.96	<0.01
STAT3	transcription regulator	Inhibited	-3.81	<0.01
IL6	cytokine	Inhibited	-3.67	0.01
IL17A	cytokine	Inhibited	-3.52	<0.01
IGF1	growth factor	Inhibited	-3.47	0.04
ERBB2	Kinase	Inhibited	-3.47	<0.01
CSF3	cytokine	Inhibited	-3.43	<0.01
RELA	transcription regulator	Inhibited	-3.34	<0.01
IFNG	Cytokine	Inhibited	-3.33	<0.01
MAP2K1	Kinase	Inhibited	-3.27	0.02
CSF2	cytokine	Inhibited	-3.19	<0.01
MYD88	Other	Inhibited	-3.19	<0.01
SP1	transcription regulator	Inhibited	-3.19	<0.01
IL5	cytokine	Inhibited	-3.18	<0.01
IL1A	cytokine	Inhibited	-3.18	0.04
CREM	transcription regulator	Inhibited	-3.15	0.03
HMGB1	transcription regulator	Inhibited	-3.08	<0.01
ADIPOQ	Other	Inhibited	-3.05	0.02
SYVN1	transporter	Inhibited	-3.05	0.02
NRG1	Other	Inhibited	-2.98	<0.01
TLR7	transmembrane receptor	Inhibited	-2.95	0.04
	ligand-dependent nuclear			
PGR	receptor	Inhibited	-2.84	0.04
CSF1	cytokine	Inhibited	-2.82	<0.01
EDN1	cytokine	Inhibited	-2.81	0.01
FOXO1	transcription regulator	Inhibited	-2.81	<0.01
FOXL2	transcription regulator	Inhibited	-2.81	<0.01
Creb	Group	Inhibited	-2.78	0.01
EIF2AK2	Kinase	Inhibited	-2.76	0.01
CAMP	Other	Inhibited	-2.75	<0.01
TICAM1	Other	Inhibited	-2.75	<0.01
IKBKB	Kinase	Inhibited	-2.66	<0.01

EGR1	transcription regulator	Inhibited	-2.65	0.01
TGM2	enzyme	Inhibited	-2.64	<0.01
TREM1	transmembrane receptor	Inhibited	-2.61	<0.01
IKBKG	Kinase	Inhibited	-2.61	<0.01
NOD2	Other	Inhibited	-2.60	0.02
TNFSF13B	cytokine	Inhibited	-2.59	0.01
Fibrinogen	complex	Inhibited	-2.57	<0.01
PI3K (complex)	complex	Inhibited	-2.50	<0.01
LDL	complex	Inhibited	-2.48	<0.01
TNFSF11	cytokine	Inhibited	-2.46	<0.01
ECSIT	transcription regulator	Inhibited	-2.45	<0.01
AGT	growth factor	Inhibited	-2.45	0.04
CHUK	kinase	Inhibited	-2.44	<0.01
IFNGR1	transmembrane receptor	Inhibited	-2.43	0.01
TRADD	other	Inhibited	-2.43	<0.01
IL32	cytokine	Inhibited	-2.42	0.03
ID3	transcription regulator	Inhibited	-2.40	<0.01
TLR5	transmembrane receptor	Inhibited	-2.39	0.01
PLAUR	transmembrane receptor	Inhibited	-2.38	0.01
CCL2	cytokine	Inhibited	-2.37	<0.01
C5	cytokine	Inhibited	-2.35	<0.01
JUN	transcription regulator	Inhibited	-2.34	0.01
TGFA	growth factor	Inhibited	-2.34	0.01
CD5	transmembrane receptor	Inhibited	-2.33	<0.01
P38 MAPK	group	Inhibited	-2.32	0.02
IRF8	transcription regulator	Inhibited	-2.29	<0.01
FOS	transcription regulator	Inhibited	-2.24	<0.01
BTC	growth factor	Inhibited	-2.24	<0.01
CFB	peptidase	Inhibited	-2.22	<0.01
IL13	cytokine	Inhibited	-2.22	0.01
NCR2	transmembrane receptor	Inhibited	-2.21	<0.01
CCL5	cytokine	Inhibited	-2.21	<0.01
Growth hormone	group	Inhibited	-2.21	<0.01
Pro-inflam.Cytokine	group	Inhibited	-2.20	0.03
JUND	transcription regulator	Inhibited	-2.19	<0.01
ITGA5	transmembrane receptor	Inhibited	-2.18	0.02
S100A4	other	Inhibited	-2.17	0.01
EIF4E	translation regulator	Inhibited	-2.14	0.01
RETN	other	Inhibited	-2.10	<0.01
Vegf	group	Inhibited	-2.09	0.01
ERK1/2	group	Inhibited	-2.09	<0.01
MAPK14	kinase	Inhibited	-2.05	<0.01
CEBPD	transcription regulator	Inhibited	-2.04	0.04
LGALS3	other	Activated	2.01	0.03
FLT1	kinase	Activated	2.12	0.03
miR-155-5p	mature microRNA	Activated	2.17	<0.01

miR-27a-3p	mature microRNA	Activated	2.22	0.04
SOX7	transcription regulator	Activated	2.24	0.02
IL1RN	cytokine	Activated	2.38	0.02
miR-34a-5p	mature microRNA	Activated	2.43	0.04
miR-124-3p	mature microRNA	Activated	2.54	0.02
Alpha catenin	group	Activated	2.55	<0.01
GFI1	transcription regulator	Activated	2.65	0.02
GPX1	enzyme	Activated	2.80	<0.01
DUSP1	phosphatase	Activated	2.88	<0.01
ESR1	ligand-dependent nuclear receptor	Activated	3.92	<0.01

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Upstream regulators were considered predicted if two-sided *P* value <0.05 and activation z-score > 2 or < -2. Upstream regulators classified as chemicals/drugs were excluded.

**Table B.** Predicted upstream regulators upon placebo supplementation ( $\Delta$  placebo).

Upstream Regulator	Molecule Type	Predicted Activation State	Activation z-score	p-value of overlap
ERBB3	kinase	Inhibited	-2.22	0.03
CD24	other	Activated	2.00	0.02

Upstream regulators were considered predicted if two-sided *P* value <0.05 and activation z-score > 2 or < -2. Upstream regulators classified as chemicals/drugs were excluded.

**Table C.** Genes of which expression changes showed significant correlation with changes in FMD after the epicatechin or placebo intervention

Gene	Epicatechin		Placebo	
	<i>r</i>	<i>P</i> -value	<i>r</i>	<i>P</i> -value
<i>RRAGA</i>	0.52	0.01	-0.08	NS
<i>VPS29</i>	0.48	0.02	0.24	NS
<i>RPL9</i>	-0.46	0.02	-0.07	NS
<i>FBXO39</i>	-0.45	0.03	-0.20	NS
<i>LOC100128288</i>	-0.45	0.03	-0.30	NS
<i>ARID1B</i>	-0.44	0.03	-0.10	NS
<i>SLC25A35</i>	-0.43	0.04	0.25	NS
<i>SUMO1</i>	0.43	0.04	0.32	NS
<i>ST8SIA1</i>	0.42	0.04	-0.31	NS
<i>USP51</i>	0.42	0.04	0.16	NS
<i>HRK</i>	0.23	NS	0.56	0.00
<i>ARHGAP10</i>	-0.07	NS	-0.47	0.01
<i>FKBP9</i>	-0.08	NS	0.45	0.02
<i>FAM149B1</i>	-0.22	NS	0.45	0.02
<i>EEPD1</i>	0.13	NS	0.44	0.02
<i>GFI1</i>	-0.23	NS	-0.42	0.03
<i>CCDC149</i>	-0.09	NS	0.42	0.03
<i>MAGOH</i>	-0.17	NS	0.41	0.03
<i>NFIA</i>	-0.04	NS	0.41	0.03
<i>SLITRK4</i>	-0.01	NS	0.39	0.04
<i>C2orf48</i>	-0.04	NS	0.39	0.04
<i>CD180</i>	0.08	NS	0.38	0.04
<i>NAMPT</i>	0.00	NS	0.38	0.04
<i>BIK</i>	0.24	NS	0.38	0.05
<i>OR10G4</i>	-0.06	NS	-0.38	0.05

Pearson Correlation was performed on signal-to-log ratios (SLR). Correlations were performed on 234 genes significantly regulated by epicatechin supplementation compared to the placebo. Depicted correlations were significant in the epicatechin (*n*=24) or placebo (*n*=28) intervention. NS: not significant.

**Table D.** Genes of which expression changes showed significant correlation with changes in insulin after the epicatechin or placebo intervention

Gene	Epicatechin		Placebo	
	<i>r</i>	<i>P</i> -value	<i>r</i>	<i>P</i> -value
<i>JMJD6</i>	0.44	0.01	0.11	NS
<i>PLXNA1</i>	-0.42	0.02	0.00	NS
<i>MT1M</i>	0.39	0.03	-0.19	NS
<i>LINC00910</i>	-0.39	0.03	-0.09	NS
<i>MUT</i>	0.39	0.03	0.15	NS
<i>LRCH4</i>	-0.38	0.03	-0.28	NS
<i>ARMC5</i>	-0.38	0.03	-0.07	NS
<i>EGLN3</i>	0.38	0.03	-0.14	NS
<i>CNFN</i>	-0.38	0.03	-0.27	NS
<i>DCK</i>	0.38	0.03	0.25	NS
<i>MYPOP</i>	-0.37	0.04	0.22	NS
<i>CES4A</i>	0.37	0.04	0.07	NS
<i>FOXQ1</i>	-0.37	0.04	-0.09	NS
<i>OR10G4</i>	-0.37	0.04	-0.25	NS
<i>AGXT</i>	-0.36	0.04	0.02	NS
<i>PLXND1</i>	-0.36	0.04	-0.05	NS
<i>KRBA1</i>	0.36	0.04	-0.16	NS
<i>MIER3</i>	0.14	NS	0.46	0.01
<i>MAN2C1</i>	-0.27	NS	-0.46	0.01
<i>RAE1</i>	0.13	NS	0.42	0.02
<i>PQLC2</i>	0.03	NS	-0.41	0.02
<i>SHISA7</i>	-0.11	NS	-0.41	0.02
<i>BNIP1</i>	-0.10	NS	0.37	0.04

Pearson Correlation was performed on signal-to-log ratios (SLR). Correlations were performed on 234 genes significantly regulated by epicatechin supplementation compared to the placebo. Depicted correlations were significant in the epicatechin or placebo ( $n=32$ ) intervention. NS: not significant.