



**Fig. 1.** Weekly food intake of beagles during the period of study with different extract supplementations (CE, GTE, GSE), control fed ad libitum (C) and caloric-restricted (CR). Values are the means of 4 dogs. Significance of the differences between groups (two-way ANOVA): effect of time  $p < 0.0001$  and effect of treatment  $p < 0.005$ .

**Table 4.** Gene expression changes in leukocytes of dogs with CE intake. Fold changes between 0 and 90 days are expressed in log<sub>2</sub> and fold diff (CE/C) indicates the difference between CE and C fold changes. P-values of both analyses are shown in the right column of the values. Only genes with fold diff ≥ 0.3 are shown.\* predicted genes.

ENSEMBL ID	GENE	Fold diff (CE/C)	P-value	Fold change (0/90d)	P-value	GENE FUNCTION
<i>DOWN - REGULATED</i>						
ENSCAFG00000013214	* Glucose regulated protein. 58kDa (GRP 58) (ERp57) (PDIA3)	-1.55	0.0013	-0.49	0.0004	Antigen processing and presentation
ENSCAFG00000003029	Interleukin-8 precursor (IL-8)	-0.59	0.0030	-0.33	0.0010	Inflammatory response
ENSCAFG00000014175	* Integrin alpha-4 precursor (VLA-4) (CD49d)	-0.54	0.0015	-0.29	0.0001	Leukocyte adhesion
ENSCAFG00000014251	* DEAD-box protein 3 (Helicase-like protein 2) (HLP2)	-0.54	0.0040	-0.24	0.0006	RNA processing
ENSCAFG00000009532	K-Ras protein	-0.49	0.0002	-0.35	0.0000	Cell growth
ENSCAFG00000009058	Topoisomerase I	-0.46	0.0013	-0.29	0.0000	DNA topology
ENSCAFG00000006153	* B-cell translocation gene 1 protein (BTG-1 protein)	-0.44	0.0001	-0.14	0.0019	Antiproliferative. apoptosis
ENSCAFG00000020196	* 78 kDa glucose-regulated protein precursor (GRP 78)	-0.37	0.0064	-0.13	0.0089	Antigen processing and presentation
ENSCAFG00000015421	* Mitogen-activated protein kinase 1 (ERK-2)	-0.30	0.0022	-0.25	0.0000	Signal transduction
<i>UP - REGULATED</i>						
ENSCAFG00000019138	Mitogen-activated protein kinase kinase 2 (MAP2K2)	0.49	0.0085	0.21	0.0096	Signalling pathway
ENSCAFG00000018285	* Kinesin 2 60/70kDa isoform 1	0.43	0.0016	0.16	0.0187	Organelles transport
ENSCAFG00000007034	* Yamaguchi sarcoma viral (v-yes-1) oncogene homolog	0.43	0.0078	-0.07	0.0389	Protein tyrosine kinase activity
ENSCAFG00000005223	Rab GDP dissociation inhibitor beta (Rab GDI beta) (GDI-2)	0.42	0.0087	0.25	0.0007	Inhibits GDP dissociation from Rab
ENSCAFG00000007350	* C19orf13 protein/alpha synuclein binding protein	0.40	0.0002	0.17	0.0000	Presynaptic protein
ENSCAFG00000008647	* Transketolase (TK)	0.40	0.0013	-0.06	0.0149	Links pentose phosphate-glycolytic pathway
ENSCAFG00000014749	* Annexin VII isoform 2	0.38	0.0071	-0.08	0.0367	Exocytosis
ENSCAFG00000004201	* Sodium-dep broad specificity neutral aa transporter (SLC1A5)	0.35	0.0042	0.10	0.0289	Aminoacid transport
ENSCAFG00000018670	* Phosphoglucomutase 1 (Glucose phosphomutase 1) (PGM 1)	0.34	0.0006	-0.06	0.0132	Glucose metabolism
ENSCAFG00000012916	* Calgizzarin (S100 calcium-binding protein A11) (S100C protein)	0.33	0.0028	0.07	0.0019	Calcium binding protein

**Table 5.** Gene expression changes in leukocytes of dogs with GTE intake. Fold changes between 0 and 90 days are expressed in log<sub>2</sub> and fold diff (GTE/C) indicates the difference between GTE and C fold changes. P-values of both analyses are shown in the right column of the values. Only genes with fold diff ≥ 0.3 are shown.\* predicted genes.

ENSEMBL ID	GENE	Fold diff (GTE/C)	P-value	Fold change (0/90d)	P-value	GENE FUNCTION
<i>DOWN - REGULATED</i>						
ENSCAFG00000005947	* Zinc finger protein 268 (Zinc finger protein HZF3)	-0.33	0.0093	-0.23	0.0014	Transcriptional regulation
ENSCAFG00000019100	* Hypothetical protein FLJ20152	-0.32	0.0030	0.17	0.0003	Unknown
<i>UP - REGULATED</i>						
ENSCAFG00000018824	* Flotillin-2 (Reggie-1) (REG-1)	0.52	0.0033	0.27	0.0000	Epidermis development
ENSCAFG00000001579	Guanine nucleotide binding protein (G protein) (GNAQ)	0.42	0.0042	0.31	0.0000	Signalling transduction
ENSCAFG00000015213	* Signal transducer and activator of transcription 3 isoform 2 (STAT3)	0.40	0.0066	0.18	0.0003	Transcription activation
ENSCAFG00000017622	* Protein kinase C, beta type (PKC-B)	0.34	0.0016	0.17	0.0000	Signal transduction

**Table 6.** Gene expression changes in leukocytes of dogs with GSE intake. Fold changes between 0 and 90 days are expressed in log<sub>2</sub> and fold diff (GSE/C) indicates the difference between GSE and C fold changes. P-values of both analyses are shown in the right column of the values. Only genes with fold diff ≥ 0.3 are shown.\* predicted genes.

ENSEMBL ID	GENE	Fold diff (GSE/C)	P-value	Fold change (0/90d)	P-value	GENE FUNCTION
<i>UP - REGULATED</i>						
ENSCAFG00000008647	* Transketolase (TK)	0.40	0.0017	-0.06	0.0496	Pentose pathway
ENSCAFG00000014749	* Annexin VII isoform 2	0.39	0.0039	-0.07	0.0278	Exocytosis
ENSCAFG00000007350	* C19orf13 protein	0.33	0.0003	0.10	0.0002	Presynaptic protein
ENSCAFG00000018670	* Phosphoglucomutase 1 (Glucose phosphomutase 1) (PGM 1)	0.30	0.0095	-0.10	0.0439	Glucose metabolism

**Table 7.** Gene expression changes in leukocytes of dogs with CR intake. Fold changes between 0 and 90 days are expressed in log<sub>2</sub> and fold diff (CR/C) indicates the difference between CR and C fold changes. P-values of both analyses are shown in the right column of the values. Only genes with fold diff ≥ 0.3 are shown.\* predicted genes.

ENSEMBL ID	GENE	Fold diff (CR/C)	P-value	Fold change (0/90d)	P-value	GENE FUNCTION
<i><b>DOWN - REGULATED</b></i>						
ENSCAFG00000013214	* Glucose regulated protein. 58kDa (GRP 58) (Erp57) (PDIA3)	-1.73	0.0053	-0.64	0.0235	Antigen processing and presentation
ENSCAFG00000014175	* Integrin alpha-4 precursor (VLA-4) (CD49d)	-0.51	0.0067	-0.26	0.0031	Leukocyte adhesion
ENSCAFG00000000634	* Small nuclear ribonucleoprotein polypeptide D2 (SNRPD2)	-0.49	0.0070	-0.31	0.0001	Ribonucleoprotein
ENSCAFG00000000670	GTP-binding nuclear protein Ran (GTPase Ran) (RAN)	-0.49	0.0080	-0.39	0.0001	Chromatin condensation and cell cycle
ENSCAFG00000017648	* ATP synthase alpha subunit (ATP5A1)	-0.43	0.0044	-0.27	0.0008	ATP synthesis
ENSCAFG00000000418	Ubiquitin-protein ligase E3 Mdm2 (p53-binding protein Mdm2) (MDM2)	-0.41	0.0009	-0.32	0.0000	Antiapoptosis
ENSCAFG00000012277	* Cytochrome c oxidase subunit VIIc (COX7C)	-0.37	0.0037	-0.29	0.0000	Respiratory chain
ENSCAFG00000015340	* Adenosine kinase isoform b (ADK)	-0.36	0.0025	-0.30	0.0000	Phosphorylation of nucleosides
ENSCAFG00000006545	* SLC25A3 protein	-0.35	0.0020	-0.17	0.0002	Phosphate transport
ENSCAFG00000003507	* Mitochondrial ribosomal protein L32 (MRPL32)	-0.34	0.0046	-0.28	0.0000	Transcription
ENSCAFG00000018324	* THO complex subunit 1 (THOC1) (Nuclear matrix protein p84)	-0.32	0.0014	-0.22	0.0000	Growth induction. apoptosis and DNA repair
ENSCAFG00000017798	* Transcription factor-like protein MRGX (MORF4L2)	-0.30	0.0016	-0.21	0.0000	Unknown
<i><b>UP - REGULATED</b></i>						
ENSCAFG00000007034	* Yamaguchi sarcoma viral (v-yes-1) oncogene homolog	0.72	0.0057	0.22	0.0418	Unknown
ENSCAFG00000013904	B-cell CLL/lymphoma 6 (zinc finger protein 51) (BCL6)	0.70	0.0043	0.40	0.0005	Transcriptional repressor
ENSCAFG00000009795	Na <sup>+</sup> /K <sup>+</sup> transporting ATPase alpha-1 chain precursor (ATP1A1)	0.51	0.0021	0.27	0.0000	Na/K transport
ENSCAFG00000015213	* Signal transducer and activator of transcription 3 isoform 2 (STAT3)	0.39	0.0097	0.17	0.0002	Transcription activator
ENSCAFG00000019363	* Vacuolar ATP synthase 16 kDa proteolipid subunit (ATP6VOC)	0.38	0.0071	0.17	0.0050	ATP synthesis
ENSCAFG00000002180	* Semaphorin 4D (CD100) (SEMA4D)	0.35	0.0028	0.12	0.0019	Immune system