Electronic Supplementary Material (ESI) for Food & Function.

Supplementary Data

Table S1 Basal diet formulation and nutrient levels[1]

Dietary ingredient	Content (%)
Corn	62.7
Soybean meal	26.3
Limestone	8.5
DL-Methionine	0.1
Calcium hydrogen phosphate	1.0
50% Choline chloride	0.1
NaCl	0.3
Vitamin and trace mineral premix[2]	1.0
Total	100
Nutrient levels (analyzed)	
Metabolic energy, MJ/kg	11.09
Crude protein, %	16.61
Calcium, %	3.5
Available phosphorus, %	0.35
Methionine, %	0.35
Lysine, %	0.85

[1]Values are expressed on an air-dry basis.

[2]Premix provided per kilogram of diet: vitamin A, 7,715 IU; vitamin D_3, 2,755 IU; vitamin E, 8.8 IU; vitamin K, 2.2 mg; vitamin B_{12}, 0.01 mg; menadione, 0.18 mg; riboflavin, 4.41 mg; pantothenic acid, 5.51 mg; niacin, 19.8 mg; folic acid, 0.28 mg; pyridoxine, 0.55 mg; manganese, 50 mg; iron, 25 mg; copper, 2.5 mg; zinc, 50 mg; iodine, 1.0 mg; and selenium, 0.15 mg.

Supplementary Data

Table S2 Primers used for the quantitative polymerase chain reaction

Genes	GenBank ID	Primers sequence (5’ to 3’)	Products (bp)
RUNX2	NM_204128.1	F: GATTACAGACCCCAGGCAGG	75
		R: TGGCTCAAGTAGGACGGGTA	
OPG	NM_001033641.1	F: GTTCCTACTCGTTCCACACC	115
		R: GCTCTTGTGAACTGTGCCTTTG	
RANKL	NM_001083361.1	F: AGGAGAAATAAGCCCGAGAA	108
		R: TTTGTTATGATGCCAGGATGTA	
β-actin	NM_205518.1	F: CACGATCATGTTTGAGACCTT	100
		R: CATCACAATACCAGTGGTACG	

RUNX2: runt related transcription factor 2; OPG: TNF receptor superfamily member 11b; RANKL: tumor necrosis factor superfamily member 11.

Supplementary Data

Table S3 Differential metabolites in untargeted metabolomics positive ion mode

No.	Metabolites	Mode	Mean (Control)	Mean (+ICA2.0)	VIP score	Fold change +ICA2.0/Control	*P* value
1	Acetyl-DL-Valine	ESI+	0.1584	0.2939	2.268	1.856	6.62E-05
2	Icariin	ESI+	0.0026	0.1354	2.264	52.531	2.13E-02
3	Uridine	ESI+	0.0192	0.0443	2.192	2.309	5.62E-06
4	Uracil	ESI+	0.0729	0.1863	2.133	2.554	3.91E-05
5	4-Hydroxy-6-methylpyran-2-one	ESI+	0.0604	0.0230	2.116	0.380	1.20E-04
6	Quinone	ESI+	0.0476	0.0327	2.098	0.687	1.27E-04
7	Docosatetraenoyl Ethanolamide	ESI+	0.0098	0.0001	2.062	0.010	2.01E-02
8	5-Methoxytryptamine	ESI+	0.0059	0.0024	2.055	0.401	8.32E-03
9	Ala-Phe	ESI+	0.0604	0.3253	2.015	5.383	2.55E-03
10	Cholic acid	ESI+	0.0038	0.0086	1.976	2.265	1.88E-03
11	N2,N2-Dimethylguanosine	ESI+	0.0416	0.0655	1.931	1.574	1.35E-03
12	L-Proline	ESI+	11.6971	7.6088	1.930	0.650	7.54E-03
13	Trigonelline	ESI+	1.6425	0.4109	1.878	0.250	4.95E-02
14	Phenylacetic acid	ESI+	0.0481	0.0555	1.862	1.153	2.46E-03
15	N-Palmitoylsphingosine	ESI+	0.0119	0.0188	1.857	1.581	1.61E-03
16	His-Pro	ESI+	0.1358	0.0349	1.857	0.257	4.39E-02
17	Zolmitriptan	ESI+	0.0257	0.0114	1.843	0.444	5.01E-03
18	2-Methylbutyroylcarnitine	ESI+	0.3656	0.1755	1.843	0.480	4.31E-03
19	2-Methylguanosine	ESI+	0.0338	0.0530	1.825	1.571	2.20E-03
20	Larixinic Acid	ESI+	0.0643	0.0438	1.790	0.681	6.43E-03
21	Stearoylcarnitine	ESI+	0.0712	0.2403	1.781	3.375	4.26E-02
22	His-Val	ESI+	0.0113	0.0065	1.778	0.578	2.57E-02
23	LysoPC(18:0)	ESI+	6.0633	9.9752	1.757	1.645	2.79E-03
24	Pro-Asn	ESI+	0.0628	0.0359	1.746	0.572	1.26E-02
25	L-Arabinose	ESI+	0.1318	0.2324	1.745	1.763	2.12E-03

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No.	Metabolites	Mode	Mean (Control)	Mean (+ICA2.0)	VIP score	Fold change +ICA2.0/Control	*P* value
26	Cuminaldehyde	ESI+	0.0228	0.0118	1.736	0.517	1.23E-02
27	L-Glutamate	ESI+	0.2247	0.2541	1.733	1.131	5.20E-03
28	S-Adenosyl-L-homocysteine	ESI+	0.0124	0.0099	1.732	0.800	6.45E-03
29	Lunarine	ESI+	0.0109	0.0039	1.721	0.359	4.79E-02
30	Creatinine	ESI+	0.7796	1.0172	1.720	1.305	2.44E-02
31	Norharmane	ESI+	0.1164	0.0490	1.711	0.421	3.91E-02
32	Acetohydroxamic acid	ESI+	0.0316	0.0478	1.710	1.512	7.30E-03
33	Guanosine	ESI+	0.0137	0.0234	1.706	1.716	1.49E-02
34	Nateglinide	ESI+	0.0122	0.0216	1.701	1.765	1.87E-02
35	Inosine	ESI+	0.0602	0.0995	1.695	1.653	1.29E-02
36	Corticosterone	ESI+	0.0142	0.0262	1.686	1.841	1.28E-02
37	LysoPC(18:1(9Z))	ESI+	6.1091	10.8967	1.658	1.784	5.99E-03
38	Clofibrate	ESI+	0.0320	0.0539	1.649	1.687	1.83E-02
39	Pro-Gln	ESI+	0.0089	0.0047	1.648	0.521	1.79E-02
40	Thr-Glu	ESI+	0.0095	0.0068	1.648	0.715	1.52E-02
41	Lys-Pro	ESI+	0.0143	0.0315	1.645	2.198	2.83E-02
42	DL-O-tyrosine	ESI+	0.0067	0.0023	1.620	0.342	2.14E-02
43	Ala-Met	ESI+	0.1329	0.1842	1.616	1.386	1.69E-02
44	7-Methylxanthine	ESI+	0.1594	0.1331	1.615	0.835	1.25E-02
45	Cytidine	ESI+	0.0513	0.0789	1.611	1.539	1.48E-02
46	Gly-Val	ESI+	0.0422	0.0523	1.603	1.240	1.41E-02
47	sn-Glycerol 3-phosphoethanolamine	ESI+	0.0127	0.0160	1.576	1.260	1.14E-02
48	PC(18:1(9Z)e/2:0)	ESI+	0.0420	0.0765	1.573	1.819	1.83E-02
49	Propionylglycine	ESI+	0.2631	0.1154	1.559	0.439	1.79E-02
50	Cyanidin 3-glucoside cation	ESI+	0.0061	0.0084	1.559	1.369	1.71E-02
51	Dopamine	ESI+	0.2484	0.2923	1.550	1.177	2.43E-02
52	LysoPC(0:0/18:0)	ESI+	0.1434	0.2567	1.536	1.791	6.95E-03

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No.	Metabolites	Mode	Mean (Control)	Mean (+ICA2.0)	VIP score	Fold change +ICA2.0/Control	*P* value
53	3-Ureidopropionate	ESI+	0.0226	0.0175	1.530	0.773	2.63E-02
54	Harmane	ESI+	0.0154	0.0080	1.515	0.518	3.12E-02
55	LysoPC(14:0)	ESI+	0.1126	0.1973	1.513	1.753	1.75E-02
56	gamma-Aminobutryic acid	ESI+	0.1604	0.1033	1.508	0.644	3.09E-02
57	5-Methylcytosine	ESI+	0.0881	0.0626	1.506	0.710	3.08E-02
58	PC(18:0/18:1(9Z))	ESI+	14.6525	24.7732	1.487	1.691	5.27E-03
59	Hypoxanthine	ESI+	10.7358	14.9075	1.482	1.389	3.22E-02
60	L-Pyroglutamic acid	ESI+	0.0216	0.0317	1.465	1.467	2.96E-02
61	Naproxen	ESI+	0.0109	0.0067	1.460	0.610	3.32E-02
62	Nitrobenzene	ESI+	0.0224	0.0280	1.456	1.247	3.67E-02
63	Taurine	ESI+	1.3812	1.8210	1.455	1.318	4.95E-02
64	LysoPE(20:3/0:0)	ESI+	0.0543	0.0762	1.451	1.402	2.77E-02
65	L-Alanine	ESI+	0.0265	0.0224	1.446	0.846	3.56E-02
66	Triflupromazine	ESI+	0.0309	0.0267	1.444	0.862	2.88E-02
67	(+-)5,6-DHET	ESI+	0.0293	0.0401	1.433	1.369	2.33E-02
68	Pyridoxamine (PM)	ESI+	0.0708	0.0812	1.417	1.146	4.81E-02
69	N6-Methyl-L-lysine	ESI+	0.0767	0.0603	1.414	0.786	4.29E-02
70	Betaine	ESI+	0.2324	0.2619	1.407	1.127	2.75E-02
71	Diaminopimelic acid	ESI+	0.0115	0.0196	1.403	1.701	4.25E-02
72	Fexofenadine	ESI+	0.2251	0.3732	1.388	1.658	4.02E-02
73	DAG(18:0/20:4)	ESI+	0.0062	0.0086	1.382	1.382	4.99E-02
74	Famciclovir	ESI+	0.0279	0.0380	1.382	1.361	4.16E-02
75	His-Tyr	ESI+	0.4520	0.3050	1.370	0.675	4.57E-02
76	(3-Carboxypropyl)trimethylammonium cation	ESI+	1.1599	1.3571	1.342	1.170	4.64E-02
77	His-Ile	ESI+	0.0221	0.0362	1.321	1.636	4.45E-02
78	(+-)-Mevalonolactone	ESI+	0.0226	0.0048	1.207	0.213	4.18E-02
79	His-Met	ESI+	0.0104	0.0068	1.132	0.655	4.64E-02

Supplementary Data

Differences between control and +ICA2.0 groups were examined by the Student's t-test and variable importance in the projection. Metabolites with a variable importance projection value greater than 1.0 and a *P*-value less than 0.05 were selected as differential metabolites. VIP, variable importance projection; ICA, icariin; Control, base diet; +ICA2.0, base diet supplemented with 2.0 g/kg ICA.

Supplementary Data

Table S4 Differential metabolites in untargeted metabolomics negative ion mode

No.	Metabolites	Mode	Mean (Control)	Mean (+ICA2.0)	VIP score	Fold change +ICA2.0/Control	*P* value
1	Ribitol	ESI-	0.2537	0.1048	1.986	0.413	5.98E-04
2	Zonisamide	ESI-	0.9287	0.0581	1.978	0.063	1.97E-02
3	Hydroxyacetone	ESI-	2.1614	0.1235	1.972	0.057	7.77E-03
4	L-homocysteic acid	ESI-	2.3948	0.2097	1.871	0.088	1.35E-02
5	S-Methyl-5'-thioadenosine	ESI-	0.0413	0.1002	1.855	2.424	2.07E-04
6	N-Acetyl-D-Glucosamine 6-Phosphate	ESI-	0.2642	0.5644	1.844	2.136	3.45E-05
7	Dimethyl 4,4-o-Phenylene-Bis	ESI-	0.1742	0.0568	1.835	0.326	8.85E-05
8	Myristoleic acid	ESI-	2.2708	6.3700	1.816	2.805	2.00E-02
9	Topiramate	ESI-	0.0844	0.0447	1.799	0.529	1.39E-03
10	3-Hydroxycapric acid	ESI-	0.1663	0.4272	1.774	2.569	1.82E-02
11	Acetylvalerenolic acid	ESI-	0.1146	0.0315	1.772	0.275	8.86E-03
12	2,3-Dihydroxy-3-methylbutyric acid	ESI-	0.6108	0.1403	1.771	0.230	1.42E-02
13	Myristic acid	ESI-	9.6223	16.6212	1.768	1.727	3.48E-03
14	L-Pipecolic acid	ESI-	0.0854	0.0352	1.767	0.412	8.62E-03
15	L-Proline	ESI-	2.5317	1.3664	1.746	0.540	6.41E-03
16	Nitrendipine	ESI-	0.0360	0.0208	1.743	0.579	9.54E-03
17	Erucic acid	ESI-	0.1643	0.3867	1.731	2.354	7.13E-03
18	D-Arabinono-1,4-lactone	ESI-	0.1702	0.2295	1.726	1.348	1.95E-03
19	LysoPC(18:0)	ESI-	0.2867	0.4764	1.723	1.662	2.42E-03
20	Cytidine	ESI-	0.1550	0.2477	1.714	1.599	2.32E-03
21	Uridine	ESI-	0.0451	0.0684	1.704	1.514	1.01E-03
22	N1-Methyl-2-pyridone-5-carboxamide	ESI-	0.1123	0.0462	1.685	0.411	2.22E-03
23	Hydroxyisocaproic acid	ESI-	4.5254	2.3731	1.674	0.524	1.00E-02
24	L-Histidine	ESI-	0.6924	0.4928	1.664	0.712	4.81E-03
25	cis-9-Palmitoleic acid	ESI-	39.0923	85.8137	1.662	2.195	1.88E-02

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No.	Metabolites	Mode	Median (Control)	Median (+ICA2.0)	VIP score	Fold change +ICA2.0/Control	*P* value
26	16-Hydroxypalmitic acid	ESI-	1.5007	4.2991	1.653	2.865	4.40E-02
27	alpha-N-Acetyl-L-glutamine	ESI-	0.4736	0.3097	1.651	0.654	5.01E-03
28	6-Hydroxynicotinic acid	ESI-	0.1603	0.3591	1.643	2.240	9.72E-03
29	Deoxycholic acid	ESI-	0.4089	1.0162	1.625	2.485	1.39E-02
30	Docosapentaenoic acid	ESI-	23.6950	48.7656	1.624	2.058	1.49E-02
31	N-Acetylmannosamine	ESI-	0.1184	0.0871	1.615	0.735	2.06E-03
32	Guanosine	ESI-	0.0318	0.0560	1.615	1.762	8.12E-03
33	Dihomo-gamma-Linolenic Acid	ESI-	6.7345	11.2198	1.613	1.666	1.69E-02
34	3-Hydroxydodecanoic acid	ESI-	0.1535	0.2735	1.610	1.781	7.42E-03
35	2-Methyl-3-hydroxybutyric acid	ESI-	0.2758	0.1870	1.599	0.678	2.29E-03
36	Glycerol 3-phosphate	ESI-	0.0726	0.0876	1.595	1.207	3.99E-03
37	Adrenic Acid	ESI-	7.8758	16.9633	1.588	2.154	4.23E-02
38	Propylene glycol	ESI-	0.1500	0.0802	1.580	0.535	3.41E-03
39	Allocystathionine	ESI-	0.0791	0.0518	1.580	0.655	1.89E-02
40	N-Acetyl-D-glucosamine	ESI-	0.0684	0.0403	1.571	0.589	3.12E-02
41	Palmitic acid	ESI-	341.4321	476.5599	1.570	1.396	1.10E-02
42	Dioxybenzone	ESI-	0.0359	0.0433	1.570	1.207	7.23E-03
43	Isopimaric acid	ESI-	1.0296	1.4168	1.539	1.376	7.60E-03
44	Phenol	ESI-	3.1277	1.1417	1.536	0.365	7.74E-04
45	Magnolol	ESI-	0.1759	0.0598	1.529	0.340	2.29E-02
46	Heptadecanoic acid	ESI-	1.6100	2.2500	1.499	1.397	1.35E-02
47	DL-3-Phenyllactic acid	ESI-	5.5375	1.5600	1.493	0.282	2.20E-02
48	Cortisol	ESI-	0.1346	0.2149	1.488	1.596	3.76E-02
49	Cholic acid	ESI-	0.0142	0.0287	1.484	2.024	4.23E-02
50	Ramipril	ESI-	0.5391	1.3101	1.482	2.430	9.84E-03
51	Taurocholate	ESI-	4.7400	2.2847	1.477	0.482	8.41E-03
52	2-keto-D-Gluconic acid	ESI-	0.4608	0.2205	1.475	0.479	2.60E-02

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No.	Metabolites	Mode	Median (Control)	Median (+ICA2.0)	VIP score	Fold change +ICA2.0/Control	*P* value
53	N-Acetyl-L-alanine	ESI-	0.0391	0.0282	1.462	0.720	2.83E-02
54	L-Serine	ESI-	0.8222	0.6887	1.457	0.838	2.66E-02
55	Phosphorylcholine	ESI-	0.0297	0.0409	1.456	1.374	4.21E-02
56	Mesaconic acid	ESI-	0.6083	0.3509	1.455	0.577	2.10E-02
57	L-Pyroglutamic acid	ESI-	0.3765	0.4248	1.454	1.128	1.04E-02
58	Urocanic acid	ESI-	0.1237	0.0999	1.437	0.807	1.89E-02
59	3-Acetyl-11-keto-beta-boswellic acid	ESI-	0.1971	0.0901	1.433	0.457	4.21E-02
60	5,2'-O-dimethyluridine	ESI-	0.0817	0.1038	1.429	1.270	1.34E-02
61	L-Leucine	ESI-	6.9137	5.0868	1.423	0.736	1.41E-02
62	Sucrose	ESI-	0.2762	0.1099	1.417	0.398	4.14E-02
63	Acetohydroxamic acid	ESI-	0.0460	0.0287	1.413	0.624	1.74E-02
64	Inosine	ESI-	0.2232	0.3381	1.409	1.515	2.62E-02
65	Quinate	ESI-	0.0916	0.0563	1.408	0.615	2.45E-02
66	L-Threonine	ESI-	2.2626	0.8545	1.406	0.378	2.27E-02
67	Dodecanoic acid	ESI-	1.5242	2.2929	1.404	1.504	4.08E-02
68	Hypoxanthine	ESI-	3.9333	5.1916	1.381	1.320	3.56E-02
69	.beta.-Estradiol 3,17-disulfate	ESI-	0.0799	0.0401	1.376	0.502	1.26E-02
70	Docosahexaenoic acid	ESI-	41.4485	65.5954	1.375	1.583	4.52E-02
71	Phenylbutazone	ESI-	0.0299	0.0505	1.374	1.689	3.88E-02
72	D-Ribose	ESI-	0.1556	0.1390	1.373	0.894	4.99E-02
73	2-Hydroxyphenylacetic acid	ESI-	0.0621	0.0503	1.370	0.809	1.42E-02
74	fumagillin	ESI-	0.2935	0.1863	1.369	0.635	1.69E-02
75	Theobromine	ESI-	0.0255	0.0164	1.363	0.644	2.75E-02
76	Benzoic acid	ESI-	1.0493	1.2615	1.353	1.202	4.49E-02
77	Arachidonic Acid (peroxide free)	ESI-	96.5995	141.9100	1.343	1.469	3.11E-02
78	Stearic acid	ESI-	62.1902	80.6057	1.332	1.296	1.87E-02
79	4-Acetoxyphenol	ESI-	37.7270	21.0271	1.324	0.557	1.96E-02

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No.	Metabolites	Mode	Median (Control)	Median (+ICA2.0)	VIP score	Fold change +ICA2.0/Control	*P* value
80	Taurochenodeoxycholate	ESI-	4.2434	2.2634	1.317	0.533	2.67E-02
81	DL-lactate	ESI-	45.6161	38.4657	1.308	0.843	2.82E-02
82	Indoleacrylic acid	ESI-	0.0212	0.0302	1.307	1.421	3.64E-02
83	Mevalonic acid	ESI-	0.0678	0.0360	1.306	0.531	4.41E-02
84	Floxuridine	ESI-	0.0644	0.0975	1.301	1.514	3.40E-02
85	Indoleacetic acid	ESI-	0.1276	0.0777	1.296	0.609	2.07E-02
86	3-Phenylpropanoic acid	ESI-	1.3384	2.4341	1.293	1.819	2.84E-02
87	Zoxazolamine	ESI-	0.1548	0.0900	1.282	0.581	3.87E-03
88	Capric acid	ESI-	0.8499	1.2392	1.274	1.458	2.60E-02
89	3-Phosphoserine	ESI-	0.3623	0.1850	1.257	0.511	3.44E-02
90	Thymine	ESI-	2.4295	1.7484	1.239	0.720	4.17E-02
91	Zafirlukast	ESI-	0.0282	0.0121	1.233	0.431	3.94E-02

Differences between control and +ICA2.0 groups were examined by the Student's t-test and variable importance in the projection. Metabolites with a variable importance projection value greater than 1.0 and a *P*-value less than 0.05 were selected as differential metabolites. VIP, variable importance projection; ICA, icariin; Control, base diet; +ICA2.0, base diet supplemented with 2.0 g/kg ICA.

Supplementary Data

Table S5 Spearman correlation matrix between untargeted metabolomics, differential metabolites and femur/tibia bone mineral density

No.	Metabolites	correlation coefficients		*P* value	
		Femur	Tibia	Femur	Tibia
1	(+-)5,6-DHET	0.77	0.77	0.0214	0.0214
2	(+-)-Mevalonolactone	-0.45	-0.30	0.2298	0.4366
3	(3-Carboxypropyl) trimethylammonium cation	0.80	0.80	0.0138	0.0138
4	Docosahexaenoic acid	0.78	**0.90**	0.0172	0.0020
5	16-Hydroxypalmitic acid	0.75	0.65	0.0255	0.0666
6	LysoPE(20:3/0:0)	**0.82**	**0.82**	0.0108	0.0108
7	LysoPC(14:0)	0.73	**0.87**	0.0311	0.0045
8	PC(18:1(9Z)e/2:0)	0.72	**0.82**	0.0369	0.0108
9	LysoPC(18:1(9Z))	**0.83**	**0.92**	0.0083	0.0013
10	DAG(18:0/20:4)	0.60	0.53	0.0968	0.1475
11	LysoPC(0:0/18:0)	0.72	0.75	0.0369	0.0255
12	PC(18:0/18:1(9Z))	0.67	0.43	0.0589	0.2499
13	LysoPC(18:0)	0.73	**0.83**	0.0311	0.0083
14	2,3-Dihydroxy-3-methylbutyric acid	-0.63	-0.48	0.0760	0.1938
15	2-Hydroxyphenylacetic acid	-0.38	-0.28	0.3125	0.4630
16	2-keto-D-Gluconic acid	-0.50	-0.47	0.1777	0.2125
17	2-Methyl-3-hydroxybutyric acid	-0.63	-0.53	0.0760	0.1475
18	2-Methylbutyroylcarnitine	-0.57	-0.40	0.1206	0.2912
19	2-Methylguanosine	0.32	0.27	0.4101	0.4933
20	3-Acetyl-11-keto-beta-boswellic acid	**-0.92**	**-0.93**	0.0013	0.0007
21	3-Hydroxycapric acid	0.65	0.57	0.0666	0.1206
22	3-Hydroxydodecanoic acid	0.53	0.52	0.1475	0.1618
23	3-Phenylpropanoic acid	0.58	0.53	0.1080	0.1475
24	3-Phosphoserine	-0.27	-0.07	0.4933	0.8801
25	3-Ureidopropionate	**-0.82**	-0.77	0.0108	0.0214

Supplementary Data

No.	Metabolites	correlation coefficients		*P* value	
		Femur	Tibia	Femur	Tibia
26	4-Acetoxyphenol	-0.63	-0.55	0.0760	0.1328
27	4-Hydroxy-6-methylpyran-2-one	-0.57	-0.43	0.1206	0.2499
28	5,2'-O-dimethyluridine	0.30	0.18	0.4366	0.6436
29	5-Methoxytryptamine	-0.67	-0.53	0.0589	0.1475
30	5-Methylcytosine	-0.70	-0.53	0.0433	0.1475
31	6-Hydroxynicotinic acid	0.73	0.70	0.0311	0.0433
32	7-Methylxanthine	-0.58	-0.47	0.1080	0.2125
33	Docosapentaenoic acid	0.77	0.72	0.0214	0.0369
34	Acetohydroxamic acid	0.58	0.48	0.1080	0.1938
35	Acetyl-DL-Valine	0.70	0.57	0.0433	0.1206
36	Acetylvalerenolic acid	-0.70	-0.53	0.0433	0.1475
37	Adrenic Acid	**0.87**	**0.88**	0.0045	0.0031
38	Ala-Met	0.58	0.65	0.1080	0.0666
39	Ala-Phe	0.68	0.73	0.0503	0.0311
40	Allocystathionine	-0.55	-0.52	0.1328	0.1618
41	alpha-N-Acetyl-L-glutamine	-0.68	-0.60	0.0503	0.0968
42	Arachidonic Acid (peroxide free)	0.78	**0.90**	0.0172	0.0020
43	Benzoic acid	0.43	0.40	0.2499	0.2912
44	beta-Estradiol 3,17-disulfate	-0.45	-0.38	0.2298	0.3125
45	Betaine	0.80	0.80	0.0138	0.0138
46	Capric acid	0.68	0.60	0.0503	0.0968
47	Cholic acid	0.70	0.72	0.0433	0.0369
48	cis-9-Palmitoleic acid	**0.85**	0.75	0.0061	0.0255
49	Clofibrate	0.47	0.53	0.2125	0.1475
50	Corticosterone	0.35	0.30	0.3586	0.4366
51	Creatinine	0.43	0.37	0.2499	0.3363
52	Cuminaldehyde	-0.50	-0.27	0.1777	0.4933

Supplementary Data

No.	Metabolites	correlation coefficients		*P* value	
		Femur	Tibia	Femur	Tibia
53	Cyanidin 3-glucoside cation	0.43	0.35	0.2499	0.3586
54	Cytidine	0.63	0.60	0.0760	0.0968
55	D-Arabinono-1,4-lactone	0.52	0.48	0.1618	0.1938
56	Deoxycholic acid	0.62	0.67	0.0857	0.0589
57	Diaminopimelic acid	0.62	0.53	0.0857	0.1475
58	Dihomo-gamma-Linolenic Acid	**0.83**	0.73	0.0083	0.0311
59	Dimethyl 4,4-o-Phenylene-Bis	-0.68	-0.48	0.0503	0.1938
60	Dioxybenzone	**0.82**	0.78	0.0108	0.0172
61	DL-3-Phenyllactic acid	-0.70	-0.60	0.0433	0.0968
62	DL-lactate	-0.17	-0.07	0.6777	0.8801
63	DL-O-tyrosine	-0.55	-0.52	0.1328	0.1618
64	Docosatetraenoyl Ethanolamide	-0.80	-0.65	0.0138	0.0666
65	Dodecanoic acid	**0.87**	0.80	0.0045	0.0138
66	Dopamine	0.17	0.03	0.6777	0.9484
67	D-Ribose	-0.60	-0.62	0.0968	0.0857
68	Erucic acid	0.70	0.52	0.0433	0.1618
69	Famciclovir	0.43	0.42	0.2499	0.2696
70	Fexofenadine	**0.90**	**0.97**	0.0020	0.0002
71	Floxuridine	0.27	0.18	0.4933	0.6436
72	fumagillin	-0.58	-0.37	0.1080	0.3363
73	gamma-Aminobutryic acid	-0.08	0.12	0.8432	0.7756
74	Glycerol 3-phosphate	0.37	0.20	0.3363	0.6134
75	Gly-Val	**0.87**	0.80	0.0045	0.0138
76	Guanosine	0.42	0.47	0.2696	0.2125
77	Harmane	-0.40	-0.28	0.2912	0.4630
78	Heptadecanoic acid	0.65	0.48	0.0666	0.1938
79	His-Ile	0.37	0.10	0.3363	0.8100

Supplementary Data

No.	Metabolites	correlation coefficients		*P* value	
		Femur	Tibia	Femur	Tibia
80	His-Met	-0.47	-0.35	0.2125	0.3586
81	His-Pro	-0.55	-0.50	0.1328	0.1777
82	His-Tyr	-0.13	0.12	0.7435	0.7756
83	His-Val	-0.53	-0.48	0.1475	0.1938
84	Cortisol	0.73	**0.88**	0.0311	0.0031
85	Hydroxyacetone	-0.63	-0.52	0.0760	0.1618
86	Hydroxyisocaproic acid	-0.30	-0.20	0.4366	0.6134
87	Hypoxanthine	0.62	0.57	0.0857	0.1206
88	Icariin	0.73	0.67	0.0311	0.0589
89	Indoleacetic acid	-0.47	-0.42	0.2125	0.2696
90	Indoleacrylic acid	0.57	0.40	0.1206	0.2912
91	Inosine	0.57	0.53	0.1206	0.1475
92	Isopimaric acid	0.67	0.55	0.0589	0.1328
93	L-Alanine	-0.50	-0.37	0.1777	0.3363
94	L-Arabinose	0.55	0.45	0.1328	0.2298
95	Larixinic Acid	-0.50	-0.35	0.1777	0.3586
96	L-Glutamate	0.57	0.43	0.1206	0.2499
97	L-Histidine	-0.68	-0.73	0.0503	0.0311
98	L-homocysteic acid	-0.73	-0.62	0.0311	0.0857
99	L-Leucine	-0.35	-0.23	0.3586	0.5517
100	L-Pipecolic acid	-0.50	-0.38	0.1777	0.3125
101	L-Proline	-0.63	-0.53	0.0760	0.1475
102	L-Pyroglutamic acid	0.52	0.40	0.1618	0.2912
103	L-Serine	-0.57	-0.77	0.1206	0.0214
104	L-Threonine	**-0.85**	-0.77	0.0061	0.0214
105	Lunarine	-0.65	-0.47	0.0666	0.2125
106	Lys-Pro	0.70	0.72	0.0433	0.0369

Supplementary Data

No.	Metabolites	correlation coefficients		*P* value	
		Femur	Tibia	Femur	Tibia
107	Magnolol	-0.67	-0.55	0.0589	0.1328
108	Mesaconic acid	-0.58	-0.30	0.1080	0.4366
109	Mevalonic acid	-0.70	-0.47	0.0433	0.2125
110	Myristic acid	0.80	0.70	0.0138	0.0433
111	Myristoleic acid	0.73	0.72	0.0311	0.0369
112	N1-Methyl-2-pyridone-5-carboxamide	-0.77	-0.60	0.0214	0.0968
113	N2,N2-Dimethylguanosine	0.58	0.60	0.1080	0.0968
114	N6-Methyl-L-lysine	-0.30	-0.35	0.4366	0.3586
115	N-Acetyl-D-glucosamine	-0.68	-0.50	0.0503	0.1777
116	N-Acetyl-D-Glucosamine 6-Phosphate	0.63	0.52	0.0760	0.1618
117	N-Acetyl-L-alanine	-0.65	-0.45	0.0666	0.2298
118	N-Acetylmannosamine	-0.67	-0.62	0.0589	0.0857
119	Naproxen	-0.50	-0.30	0.1777	0.4366
120	Nateglinide	0.73	**0.88**	0.0311	0.0031
121	Nitrendipine	**-0.83**	-0.78	0.0083	0.0172
122	Nitrobenzene	0.48	0.50	0.1938	0.1777
123	Norharmane	-0.40	-0.18	0.2912	0.6436
124	N-Palmitoylsphingosine	0.68	0.65	0.0503	0.0666
125	Palmitic acid	**0.93**	**0.88**	0.0007	0.0031
126	Phenol	**-0.72**	-0.58	0.0369	0.1080
127	Phenylacetic acid	0.43	0.37	0.2499	0.3363
128	Phenylbutazone	0.55	0.63	0.1328	0.0760
129	Phosphorylcholine	0.78	**0.85**	0.0172	0.0061
130	Pro-Asn	-0.63	-0.45	0.0760	0.2298
131	Pro-Gln	-0.47	-0.23	0.2125	0.5517
132	Propionylglycine	-0.52	-0.47	0.1618	0.2125
133	Propylene glycol	-0.70	-0.47	0.0433	0.2125

Supplementary Data

No.	Metabolites	correlation coefficients		*P* value	
		Femur	Tibia	Femur	Tibia
134	Pyridoxamine (PM)	0.75	0.65	0.0255	0.0666
135	Quinate	-0.43	-0.50	0.2499	0.1777
136	Quinone	-0.78	-0.65	0.0172	0.0666
137	Ramipril	0.53	0.53	0.1475	0.1475
138	Ribitol	-0.75	-0.63	0.0255	0.0760
139	S-Adenosyl-L-homocysteine	-0.72	-0.55	0.0369	0.1328
140	S-Methyl-5'-thioadenosine	0.73	0.75	0.0311	0.0255
141	sn-Glycerol 3-phosphoethanolamine	0.18	0.22	0.6436	0.5809
142	Stearic acid	0.65	0.48	0.0666	0.1938
143	Stearoylcarnitine	0.72	0.73	0.0369	0.0311
144	Sucrose	-0.63	-0.40	0.0760	0.2912
145	Taurine	**0.88**	**0.83**	0.0031	0.0083
146	Taurochenodeoxycholate	-0.42	-0.32	0.2696	0.4101
147	Taurocholate	**-0.82**	-0.67	0.0108	0.0589
148	Theobromine	-0.73	-0.53	0.0311	0.1475
149	Thr-Glu	-0.72	-0.58	0.0369	0.1080
150	Thymine	-0.62	-0.53	0.0857	0.1475
151	Topiramate	-0.53	-0.50	0.1475	0.1777
152	Trifluprom azine	-0.33	-0.22	0.3853	0.5809
153	Trigonelline	-0.68	-0.60	0.0503	0.0968
154	Uracil	0.78	0.70	0.0172	0.0433
155	Uridine	**0.90**	**0.93**	0.0503	0.1618
156	Urocanic acid	-0.73	-0.68	0.0311	0.0503
157	Zafirlukast	-0.50	-0.60	0.1777	0.0968
158	Zolmitriptan	-0.80	-0.73	0.0138	0.0311
159	Zonisamide	-0.68	-0.58	0.0503	0.1080
160	Zoxazolamine	-0.60	-0.53	0.0968	0.1475

Supplementary Data

Table S6 The metabolic pathway perturbations affecting BMD induced by ICA

No.	Pathway Name	Total	Hit	P	-log(P)	Holm P	FDR	Impact
1	Taurine and hypotaurine metabolism	6	1	0.03	3.60	1.0	1.0	0.50
2	Glycerophospholipid metabolism	33	1	0.14	1.95	1.0	1.0	0.04
3	Pyrimidine metabolism	37	1	0.16	1.84	1.0	1.0	0.02
4	Biosynthesis of unsaturated fatty acids	22	1	0.10	2.33	1.0	1.0	0.00
5	Fatty acid elongation	34	1	0.15	1.92	1.0	1.0	0.00
6	Fatty acid metabolism	37	1	0.16	1.84	1.0	1.0	0.00
7	Fatty acid biosynthesis	43	1	0.18	1.70	1.0	1.0	0.00

Note: P is the original *P*-value calculated from the enrichment analysis; the total is the total number of compounds in the pathway; Hits is the actually matched number from the user-uploaded data; Holm P is the *P*-value adjusted by the Holm-Bonferroni method; FDR P is the *P*-value adjusted using false discovery rate; Impact is the pathway impact value calculated from pathway topology analysis.