

Original article

Unveiling the immunomodulatory mechanisms of pineapple metabolites: A multi-modal computational analysis using network pharmacology, molecular docking, and molecular dynamics simulation

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SUPPLEMENTARY INFORMATION

Supplementary Table 1. Results of pineapple bioactive compounds data mining from the KNApSAcK database

C_ID	CAS ID	Metabolite	Molecular formula	Molecular Weight (Da)	Species
C00000152	7400-08-0	p-Coumaric acid	C9H8O3	164.0473	<i>Ananas comosus</i>
C00001429	50-67-9	5-Hydroxytryptamine	C10H12N2O	176.095	<i>Ananas comosus</i>
C00002377	88110-66-1	Cyanidin 3,5,3'-triglucoside	C33H41O21	773.214	<i>Ananas comosus</i>
C00002378	2611-67-8	Cyanin	C27H31O16	611.1612	<i>Ananas comosus</i>
C00002743	1135-24-6	Ferulic acid	C10H10O4	194.0579	<i>Ananas comosus</i>
C00002780	501-13-3	Feruloylputrescine	C14H20N2O3	264.1474	<i>Ananas comosus</i>
C00003776	127-40-2	Lutein	C40H56O2	568.428	<i>Ananas comosus</i>
C00006688	132-37-6	Peonin	C28H33O16	625.1769	<i>Ananas comosus</i>
C00027843	91000-13-4	N,N'-Bis(4-hydroxy-3-methoxycinnamoyl)-1,4-butanediamine	C24H28N2O6	440.1947	<i>Ananas comosus</i>
C00029585	34427-61-7	7alpha-Hydroxysitosterol	C29H50O2	430.3811	<i>Ananas comosus</i>
C00030200	2061-64-5	5alpha,8alpha-Epidioxyergosta-6,22-dien-3beta-ol	C28H44O3	428.329	<i>Ananas comosus</i>
C00054014	70185-61-4	N1,N10-Diferuloylspermidine	C27H35N3O6	497.2526	<i>Ananas comosus</i>
C00054016	70208-06-9	Diferuloylspermine	C30H42N4O6	554.3104	<i>Ananas comosus</i>
C00054036	1260113-99-2	S-p-Coumarylglutathione	C19H25N3O7S	439.1413	<i>Ananas comosus</i>
C00054143	910101-38-1	1-O-Caffeoyl-3-O-feruloylglycerol	C22H22O9	430.1264	<i>Ananas comosus</i>
C00054144	125564-68-3	1-O-Caffeoyl-3-O-p-coumaroylglycerol	C21H20O8	400.1158	<i>Ananas comosus</i>
C00054145	123134-22-5	1,3-Dicaffeoylglycerol	C21H20O9	416.1107	<i>Ananas comosus</i>
C00054814	35194-30-0	9-Decen-2-one	C10H18O	154.1358	<i>Ananas comosus</i>
C00054902	199925-44-5	Anaflavoside A	C24H26O12	506.1424	<i>Ananas comosus</i>
C00054929	42369-86-8	N1,N4-Di-trans-feruloylputrescine	C24H28N2O6	440.1947	<i>Ananas comosus</i>
C00055150	871840-61-8	Anaflavoside B	C25H28O13	536.153	<i>Ananas comosus</i>
C00055151	871840-62-9	Anaflavoside C	C24H26O13	522.1373	<i>Ananas comosus</i>
C00055152	871840-63-0	Anaflavoside D	C24H26O13	522.1373	<i>Ananas comosus</i>
C00056759	1260113-98-1	S-Ferulyl-N-gamma-glutamylcysteine	C18H24N2O7S	412.1304	<i>Ananas comosus</i>

Supplementary Table 2. Results of data mining of pineapple bioactive compounds from the Dr. Duke database.

Chemicals	Plant part	Low ppm	High ppm	Standard deviation
Ascorbic-Acid	Fruit	148	4178	-0.02471
Caffeic-Acid	Fruit			
Zinc	Fruit	0.7	6	-0.73113
Magnesium	Fruit	110	1075	-0.4884
Bromelain	Fruit		800	
Beta-Carotene	Fruit	0	3	-0.145
Linalool	Fruit			
Beta-Sitosterol	Fruit		40	-0.74169
Niacin	Fruit	2	33	-0.37028
Alpha-Tocopherol	Fruit	1	7	-1.01387
Thiamin	Fruit	0	7	0.213422
Vanillin	Fruit			
Calcium	Fruit	62	1308	-0.58804
Linoleic-Acid	Fruit	840	6222	-0.26762
Serotonin	Fruit	19	60	0.921496
Pectin	Fruit	600	1600	-0.61125
Citric-Acid	Fruit	3200	86000	0.756119
Alpha-Terpineol	Fruit			
Gaba	Fruit		124	-0.82602
Gamma-Aminobutyric-Acid	Fruit		124	-0.7339
Oleic-Acid	Fruit	450	3333	-0.45506
Acetic-Acid	Fruit		0.49	-0.64296
Fiber	Fruit	3000	45000	-0.91228
Alpha-Linolenic-Acid	Fruit	620	4592	0.927072
Methionine	Fruit	110	815	-0.17673
Riboflavin	Fruit	0	3	-0.43032
Malic-Acid	Fruit	1000	4700	-0.64579
Potassium	Fruit	110	18200	0.025082
Manganese	Fruit	12	209	0.974581
Sulfur	Fruit	70	200	-0.84532
Sucrose	Fruit	59000	150000	0.316722
Arginine	Fruit	46	1333	-0.79401
Mufa	Fruit	480	3556	-0.20224
Palmitic-Acid	Fruit	190	1407	-0.34363
Copper	Fruit	1	8.8	-0.31279
Glycine	Fruit	65	1259	-0.90736
P-Aminobenzoic-Acid	Fruit	0	1	
Iodine	Fruit	0	1	-0.28537
Stigmasterol	Fruit		0	-1.1726
Pantothenic-Acid	Fruit	1	11	-0.45317
Sinapic-Acid	Fruit			
Oxalic-Acid	Fruit	50	58	-0.30315
Tyrosine	Fruit	58	889	-0.63388
Glutamic-Acid	Fruit	90	3333	-0.7708
Fructose	Fruit	6000	23000	-0.56851

Stearic-Acid	Fruit	110	815	-0.22517
Chlorine	Fruit	130	460	-0.37076
Salicylates	Fruit	10	150	0.093378
Glucose	Fruit	10000	32000	-0.55548
Phenylalanine	Fruit	40	889	-0.8451
Histidine	Fruit	48	667	-0.7331
Ethyl-Acetate	Fruit	3	120	-0.70662
Iron	Fruit	3	73	-0.23792
Acetaldehyde	Fruit	0.61	1.4	-0.70743
Starch	Fruit		19	-0.45655
Glutamine	Fruit		256	-1.30353
Phylloquinone	Fruit		0.002	-0.23269
Boron	Fruit		0.2	-0.79988
Silicon	Fruit	110	690	1.633348
Phosphorus	Fruit	60	923	-0.69647
Threonine	Fruit	78	859	-0.89735
Pufa	Fruit	1460	10815	-0.0653
Lysine	Fruit	46	1852	-0.58597
Valine	Fruit	39	1185	-0.67428
Methyl-Acetate	Fruit			
Alanine	Fruit	170	1259	-0.96233
Chavicol	Fruit		0.27	-0.93948
Isoleucine	Fruit	23	963	-0.80336
Ethyl-Acrylate	Fruit		0.77	
Aspartic-Acid	Fruit	293	4222	-0.77992
Isobutyl-Acetate	Fruit			
Acetone	Fruit			
Leucine	Fruit	24	1407	-0.78533
Palmitoleic-Acid	Fruit	30	220	-0.30522
Campesterol	Fruit		10	-0.5745
Methyl-Isovalerate	Fruit		0.6	
Phytosterols	Fruit	60	444	-0.64591
Methanol	Fruit			
Ethyl-Isobutyrate	Fruit			
Asparagine	Fruit		1251	-0.05455
Methyl-Caprylate	Fruit		0.75	
Methyl-Caproate	Fruit			
Methyl-Butyrate	Fruit			
Cystine	Fruit	20	148	-0.9214
Amyl-Caproate	Fruit			
Sodium	Fruit	10	347	-0.15105
Ethyl-Propionate	Fruit			
Ethyl-Lactate	Fruit			
Cellulose	Fruit	4300	5400	-0.60794
Ethyl-Isovalerate	Fruit		0.39	
Serine	Fruit	250	1852	-0.63232
Ethyl-Formate	Fruit			
Ethyl-Butyrate	Fruit			
N-Valerianic-Acid	Fruit			

Methyl-Beta-Hydroxyhexanoate	Fruit		0.021	
Ethyl-Beta-Methylthiopropionate	Fruit		0.09	
Propanol	Fruit			
Hexosans	Fruit	1000	1500	
Biacetyl	Fruit			
Methyl-Beta-Hydroxybutyrate	Fruit		0.006	
Ethyl-Beta-Hydroxyhexanoate	Fruit		0.03	
Proline	Fruit	31	963	-0.83578
L-Malic-Acid	Fruit			
Fat	Fruit	1000	42772	-0.31456
Methyl-N-Propyl-Ketone	Fruit			
Methyl-Beta-Acetoxyhexanoate	Fruit		0.03	
Ethyl-Beta-Acetoxyhexanoate	Fruit		0.006	
Isopropyl-Isobutyrate	Fruit			
Sfa	Fruit	320	2370	-0.32711
Isocaproic-Acid	Fruit			
Ethyl-Alcohol	Fruit		60	
Methyl-Isocaproate	Fruit		1.4	
Isobutyl-Formate	Fruit			
Methyl-Isobutyrate	Fruit			
Phosphatase	Fruit			
Acetoxyacetone	Fruit			
Gamma-Octalactone	Fruit		0.3	
Carbohydrates	Fruit	116000	938000	0.829497
Methyl-Cis-(4?)-Octenoate	Fruit		0.001	
Isobutanol	Fruit			
Esters	Fruit	1	250	
Gamma-Caprolactone	Fruit		0.12	
Ash	Fruit	2800	36000	-0.5351
Peroxidase	Fruit			
Kilocalories	Fruit	460	3770	0.166233
Gamma-Butyrolactone	Fruit			
Butyl-Formate	Fruit			
Nitrogen	Fruit	450	1150	-0.94465
Ethyl-Caprylate	Fruit			
Protein	Fruit	4000	55000	-0.73058
Dimethyl-Malonate	Fruit		0.06	
Pentosans	Fruit	3300	4300	-0.82843
Gamma-Eudesmol	Fruit			
Bromelin	Fruit			
Nitrate	Fruit	0	1200	
Propyl-Formate	Fruit			
Ethyl-Caproate	Fruit		0.77	
Indole-Acetic-Acid-Oxidase	Fruit			
Water	Fruit	812000	890000	0.519268
Delta-Octalactone	Fruit		0.3	1
Pentanol	Fruit			
Propyl-Acetate	Fruit			
Methyl-Beta-Methylthiopropionate	Fruit	0.12	1.1	

Vit-B-6	Fruit	0.9	6	-0.3708
Bromelain	Fruit			

Supplementary Table 3. Results of PASS Online analysis to determine the immunomodulatory potential of pineapple secondary metabolites.

Compound Name	PubChem ID	Bioactivities		
		Immunomodulator	Immunostimulant	Immunosuppressant
CMB	44263865	0.67	0.952	0.695
1-O-Caffeoyl-3-O-feruloylglycerol	11311691	0.276	0.293	0.441
Ascorbic acid	54670067	0.422	0.557	0.43
Caffeic acid	689043	0.222	0.218	0.379
Citric acid	311	0.218	0.303	0.284
Ferulic acid	445858	0	0	0.379
Linoleic acid	5280450	0.438	0.558	0.448
Oleic acid	445639	0.416	0.54	0.505
Palmitic Acid	985	0.419	0.504	0.451
Palmitoleic acid	445638	0.416	0.54	0.505
Pantothenic acid	6613	0.37	0.438	0.266
Serotonin	5202	0.196	0.271	0
Stearic Acid	5281	0.419	0.504	0.451
(-)-threo-isodihomocitric acid	24892803	0.277	0.38	0.292
(Hydroxyethyl)methacrylate	13360	0.209	0.382	0.341
(R)-2-hydroxystearic acid	439885	0.400	0.488	0.492
alpha-linolenic acid	5280934	0.413	0.505	0.418
2-caffeoylisocitric acid	5280552	0.223	0.175	0.216
2-Isopropylmalic acid	77	0.193	0.283	0.235
2-methylecitric acid	515	0.191	0.242	0.235
2-O-ethyl ascorbic acid	54694369	0.433	0.562	0.405
4-Coumaric acid	637542	0.225	0.237	0.401
4-Methyleneglutamic acid	96407	0.303	0.559	0.319
9,10-Dihydroxystearic acid	89377	0.514	0.616	0.524
alpha-Methylene-gamma-butyrolactone	68352	0	0.189	0.451
butyl acrylate	8846	0.340	0.388	0.388
D-(+)-Malic acid	92824	0.325	0.435	0.42
Dehydroascobic acid	440667	0.386	0.554	0.535
Ethyl vanillin isobutyrate	673160	0.192	0.324	0.339
Geranylacetone	1549778	0.237	0.512	0.590
n-Butyl lactate	8738	0.425	0.511	0.434
N-linoleoyl-4-aminobutyric acid	6438152	0.483	0.677	0.440
Spermine	1103	0.376	0.38	0.311
Succinylacetone	5312	0.483	0.677	0.44

Supplementary Table 4. The activities of prostaglandin-reductase, cyclooxygenase inhibitor, and cyclooxygenase inhibitor and substrate in pineapple secondary metabolites.

Name of Compounds	Prostaglandin-E2 9-reductase inhibitor	Prostaglandin-A1 delta-isomerase inhibitor	Cyclooxygenase 1 inhibitor	Cyclooxygenase substrate	Cyclooxygenase inhibitor	Cyclooxygenase 2 inhibitor	Cyclooxygenase 3 inhibitor	Cyclooxygenase 1 substrate
CMB	0	0	0	0	0	0	0	0
1-O-Caffeoyl-3-O-feruloylglycerol	0.268	0.268	0	0.269	0.098	0	0	0.163
Ascorbic acid	0.3	0.349	0	0.336	0	0	0	0.132
Caffeic acid	0.614	0.645	0.183	0.363	0.169	0.113	0	0.200
Citric acid	0.7	0.786	0	0.386	0	0	0	0.326
Ferulic acid	0.464	0.431	0.178	0.314	0.174	0.111	0.067	0.147
Linoleic acid	<u>0.912</u>	<u>0.878</u>	0	<u>0.715</u>	0	0	0.075	<u>0.737</u>
Oleic acid	<u>0.924</u>	<u>0.891</u>	0	<u>0.703</u>	0	0	0.086	<u>0.729</u>
Palmitic Acid	<u>0.841</u>	<u>0.921</u>	0.083	0.614	0	0	0.087	0.610
Palmitoleic acid	<u>0.924</u>	<u>0.891</u>	0	<u>0.703</u>	0	0	0.086	<u>0.729</u>
Pantothenic acid	0.516	0.491	0	0.375	0	0	0	0.324
Serotonin	0.273	0.213	0	0.222	0	0	0	0
Stearic Acid	<u>0.841</u>	<u>0.921</u>	0.083	0.614	0	0	0.087	0.610
(-)-threo-isodihomocitric acid	<u>0.846</u>	<u>0.838</u>	0	0.446	0	0	0	0.420
(Hydroxyethyl)methacrylate	0	0	0	0.279	0.145	0	0.057	0.182
(R)-2-hydroxystearic acid	<u>0.877</u>	<u>0.912</u>	0	0.586	0	0	0	0.544
alpha-linolenic acid	<u>0.887</u>	<u>0.851</u>	0	0.664	0.093	0	0.075	<u>0.800</u>
2-caffeoylisocitric acid	0.402	0.419	0	0.292	0	0	0	0.194
2-Isopropylmalic acid	<u>0.712</u>	<u>0.729</u>	0	0.347	0	0	0.075	0.264
2-methylcitric acid	0.672	<u>0.699</u>	0	0.33	0	0	0.066	0.248
2-O-ethyl ascorbic acid	0.2	0.289	0	0.299	0	0	0	0.124
4-Coumaric acid	<u>0.711</u>	0.679	0.189	0.412	0.165	0.106	0.071	0.213
4-Methyleneglutamic acid	0.463	0.466	0	0.271	0	0	0.069	0.123
9,10-Dihydroxystearic acid	<u>0.917</u>	<u>0.936</u>	0	0.671	0	0	0	0.623
alpha-Methylene-gamma-butyrolactone	0.458	0.404	0.108	0	0.17	0.14	0	0.242
butyl acrylate	0.481	0.535	0	0.32	0	0	0	0.279
D-(+)-Malic acid	<u>0.788</u>	<u>0.862</u>	0	0.470	0	0	0	0.406
Dehydroascobic acid	0.373	0.466	0	0.346	0	0	0	0.137
Ethyl vanillin isobutyrate	0.217	0.323	0	0.188	0	0	0.139	0
Geranylacetone	0.298	0.482	0	0.289	0	0	0.305	0.268
n-Butyl lactate	0.639	<u>0.747</u>	0	0.398	0	0	0	0.324
N-linoleoyl-4-aminobutyric acid	<u>0.812</u>	0.646	0	<u>0.754</u>	0	0	0	0.732
Spermine	0.457	0.402	0	0.292	0	0	0	0
Succinylacetone	<u>0.812</u>	0.646	0	<u>0.754</u>	0	0	0	<u>0.732</u>

Supplementary Table 5. Anti-inflammatory, non-steroidal antiinflammatory agent, antiinflammatory steroid, free radical scavenger, interleukin agonist, and interleukin antagonist activities of the secondary metabolites of pineapple.

Name of compound	Antiinflammatory	Non-steroidal antiinflammatory agent	Antiinflammatory steroid	Free radical scavenger	Interleukin 6 antagonist	Interleukin 2 agonist
CMB	0.501	0	0	<u>0.724</u>	0	0.614
1-O-Caffeoyl-3-O-feruloylglycerol	0.641	0.447	0	<u>0.678</u>	0.239	0
Ascorbic acid	<u>0.779</u>	0.443	0	0.564	0.116	0.304
Caffeic acid	0.651	0.318	0	0.647	0.219	0.338
Citric acid	0	0.203	0.013	0.196	0.15	0.412
Ferulic acid	0.604	0.37	0	<u>0.731</u>	0.235	0.26
Linoleic acid	<u>0.730</u>	0.393	0	0.315	0.182	0.484
Oleic acid	0.614	0.352	0	0.36	0.212	0.505
Palmitic Acid	0.515	0.31	0	0.315	0.238	0.583
Palmitoleic acid	0.614	0.352	0	0.36	0.212	0.505
Pantothenic acid	0	0	0	0	0	0.417
Serotonin	0	0	0	0.318	0.16	0.342
Stearic Acid	0.515	0.31	0	0.315	0.238	0.583
(-)-threo-isodihomocitric acid	0.337	0	0	0.209	0.193	0.462
(Hydroxyethyl)methacrylate	0.631	0.496	0	0.283	0.174	
(R)-2-hydroxystearic acid	0.339	0.267	0	0.245	0.229	0.546
alpha-linolenic acid	<u>0.804</u>	0.443	0	0.281	0.16	0.455
2-caffeoylisocitric acid	0.468	0	0	0.513	0	0.288
2-Isopropylmalic acid	0	0.169	0	0.167	0	0.385
2-methylcitric acid	0	0.157	0	0.146	0	0.362
2-O-ethyl ascorbic acid	0.606	0.313	0	0.559	0	0.255
4-Coumaric acid	0.641	0.293	0	0.627	0.218	0.353
4-Methyleneglutamic acid	0	0.16	0	0.278	0.192	0.455
9,10-Dihydroxystearic acid	0.502	0.35	0	0.24	0.233	0.672
alpha-Methylene-gamma-butyrolactone	<u>0.804</u>	0.458	0	0.184	0.222	0.106
butyl acrylate	0.428	0.225	0	0.292	0.172	0
D-(+)-Malic acid	0	0.183	0	0.229	0.198	0.480
Dehydroascobic acid	0.61	0.283	0.014	0.488	0.156	0.313
Ethyl vanillin isobutyrate	0.271	0	0	0.279	0	0
Geranylacetone	<u>0.698</u>	0.245	0	0.507	0	0
n-Butyl lactate	0.602	0.238	0	0.219	0	0.344
N-linoleoyl-4-aminobutyric acid	0.466	0.238	0	0.277	0	0.465
Spermine	0	0	0	0.249	0.346	0.603
Succinylacetone	0.466	0.238	0	0.277	0	0.465

Supplementary Table 6. Results of AdmetSAR analysis to determine the metabolism potential and toxicity of bioactive compounds from pineapple.

Name of compounds	Molecular weight	logP	No. rotatable bonds	No. H-bond acceptors	No. H-bond donors	Human Intestinal Absorption		Blood brain barrier		Human oral bioavailability	
						Value	Probability	Value	Probability	Value	Probability
CMB	1026.94	- 12.15	16	29	18	-	0.9763	-	0.8494	-	0.8714
1-O-Caffeoyl-3-O-feruloylglycerol	268.26	0.31	6	6	3	+	0.9543	+	0.8124	-	0.7
Ascorbic acid	176.12	- 1.41	2	6	4	+	0.815	+	0.9785	+	0.5857
Caffeic acid	180.16	1.2	2	3	3	+	0.9645	-	0.4365	+	0.6429
Citric acid	192.12	- 1.25	5	4	4	+	0.7691	-	0.3067	+	0.6143
Ferulic acid	194.19	1.5	3	3	2	+	0.9774	+	0.8504	+	0.6571
Linoleic acid	280.45	5.88	14	1	1	+	0.9087	+	0.9646	-	0.6
Oleic acid	282.47	6.11	15	1	1	+	0.9087	+	0.9646	-	0.6143
Palmitic Acid	256.43	5.55	14	1	1	+	0.8417	+	0.9725	-	0.6714
Palmitoleic acid	254.41	5.33	13	1	1	+	0.9087	+	0.9646	-	0.6143
Pantothenic acid	219.24	- 1.04	6	4	4	-	0.5211	+	0.9878	+	0.5857
Serotonin	176.22	1.37	2	2	3	+	0.9831	+	0.9883	+	0.5714
Stearic Acid	284.48	6.33	16	1	1	+	0.8417	+	0.9725	-	0.6714
(-)-threo-isodihomocitric acid	220.18	- 0.61	7	4	4	+	0.9062	-	0.6543	+	0.6
(Hydroxyethyl)methacrylate	130.14	0.1	3	3	1	+	0.9858	+	0.9676	-	0.5
(R)-2-hydroxystearic acid	300.48	5.3	16	2	2	+	0.8505	+	0.8005	-	0.6857
alpha-linolenic acid	278.44	5.66	13	1	1	+	0.9087	+	0.962	-	0.5714
2-caffeoylisocitric acid	354.27	0.28	8	7	5	+	0.9771	-	0.3316	-	0.5714
2-Isopropylmalic acid	176.17	- 0.07	4	3	3	+	0.9411	+	0.9307	+	0.6143
2-methylcitric acid	206.15	-1	5	4	4	+	0.9411	+	0.836	-	0.5
2-O-ethyl ascorbic acid	204.18	- 0.93	4	6	3	+	0.8302	+	0.9499	+	0.5143
4-Coumaric acid	164.16	1.49	2	2	2	+	0.9711	-	0.7372	-	0.6
4-Methyleneglutamic acid	159.14	- 0.57	4	3	3	+	0.8386	+	0.9225	+	0.6714

9,10-Dihydroxystearic acid	316.48	4.27	16	3	3	+	0.7357	-	0.3669	-	0.7286
alpha-Methylene-gamma-butyrolactone	98.1	0.49	0	2	0	+	0.9742	+	0.954	+	0.6714
butyl acrylate	128.17	1.52	4	2	0	+	0.9898	+	1	-	0.6429
D-(+)-Malic acid	134.09	1.09	3	3	3	+	0.7732	-	0.444	+	0.6143
Dehydroascobic acid	174.11	-2.6	2	6	2	+	0.8587	+	0.945	+	0.6286
Ethyl vanillin isobutyrate	236.27	2.46	5	4	0	+	1	+	0.9695	+	0.5714
Geranylacetone	194.32	4.05	6	1	0	+	0.9672	+	0.9939	-	0.5714
n-Butyl lactate	146.19	0.71	4	3	1	+	0.949	+	0.9923	-	0.5857
N-linoleoyl-4-aminobutyric acid	365.56	5.78	18	2	2	-	0.406	+	0.9867	-	0.6571
Spermine	202.35	0.36	11	4	4	+	0.8966	+	0.9776	+	0.8857
Succinylacetone	158.15	0.4	5	3	1	+	0.8977	-	0.3747	+	0.6

Supplementary Table 6 (continued). Results of AdmetSAR analysis to determine the metabolism potential and toxicity of bioactive compounds from pineapple.

Name of compounds	Carcinogenicity (binary)		Carcinogenicity (trinary)		Hepatotoxicity		Acute oral toxicity (c)		Water solubility		Acute oral toxicity (c)
	Value	Probability	Value	Probability	Value	Probability	Value	Probability	Value	Unit	Value
CMB	-	0.9571	Non-required	0.6601	+	0.65	III	0.5408	-1.495	logS	2.895
1-O-Caffeoyl-3-O-feruloylglycerol	-	0.8041	Non-required	0.7368	-	0.775	III	0.7192	-1.042	logS	1.729
Ascorbic acid	-	0.8589	Non-required	0.7591	-	0.9	IV	0.5871	0.108	logS	1.318
Caffeic acid	-	0.8018	Non-required	0.5848	-	0.675	IV	0.5588	-1.694	logS	1.568
Citric acid	-	0.9143	Non-required	0.7129	-	0.725	III	0.8407	0.447	logS	2.332
Ferulic acid	-	0.8025	Non-required	0.5903	-	0.7	IV	0.6265	-2.477	logS	1.407
Linoleic acid	-	0.6714	Non-required	0.7021	-	0.925	IV	0.8289	-4.04	logS	1.605
Oleic acid	-	0.6714	Non-required	0.7021	-	0.95	IV	0.8289	-4.04	logS	1.696
Palmitic Acid	-	0.6571	Non-required	0.7057	-	0.8	IV	0.6378	-3.502	logS	1.376

Palmitoleic acid	-	0.6714	Non-required	0.7021	-	0.95	IV	0.8289	-4.04	logS	1.706
Pantothenic acid	-	0.8143	Non-required	0.6952	-	0.95	III	0.5568	-0.799	logS	1.706
Serotonin	-	0.9286	Non-required	0.634	-	0.625	II	0.4319	-1.472	logS	1.666
Stearic Acid	-	0.6571	Non-required	0.7057	-	0.725	IV	0.6378	-3.502	logS	1.311
(-)-threo-isodihomocitric acid	-	0.9429	Non-required	0.7429	-	0.75	III	0.6417	0.006	logS	1.56
(Hydroxyethyl)methacrylate	-	0.5714	Non-required	0.6908	-	0.775	IV	0.6307	-1.044	logS	1.384
(R)-2-hydroxystearic acid	-	0.7857	Non-required	0.7285	-	0.675	IV	0.5875	-2.783	logS	1.446
alpha-linolenic acid	-	0.6714	Non-required	0.6373	-	0.725	IV	0.6387	-3.068	logS	1.303
2-caffeoylisocitric acid	-	0.9149	Non-required	0.653	+	0.65	III	0.7231	-1.852	logS	1.877
2-Isopropylmalic acid	-	0.9286	Non-required	0.7761	-	0.725	III	0.7256	-0.167	logS	3.452
2-methylcitric acid	-	0.9286	Non-required	0.7614	-	0.75	III	0.779	0.155	logS	3.81
2-O-ethyl ascorbic acid	-	0.8589	Non-required	0.7461	-	0.775	IV	0.4746	-0.252	logS	1.014
4-Coumaric acid	-	0.7875	Non-required	0.6034	-	0.6	III	0.4898	-2.224	logS	1.999
4-Methyleneglutamic acid	-	0.8	Non-required	0.6471	-	0.725	III	0.6015	-0.965	logS	0.871
9,10-Dihydroxystearic acid	-	0.8143	Non-required	0.7556	-	0.775	IV	0.6001	-2.712	logS	2.822
alpha-Methylene-gamma-butyrolactone	-	0.8857	Non-required	0.6172	-	0.85	III	0.5217	-0.235	logS	1.872
butyl acrylate	-	0.6	Non-required	0.5283	-	0.875	III	0.7892	-1.824	logS	1.746
D-(+)-Malic acid	-	0.8714	Non-required	0.7593	-	0.75	III	0.8028	0.277	logS	0.844
Dehydroascobic acid	-	0.8879	Non-required	0.7447	-	0.7	IV	0.5265	0.683	logS	1.494
Ethyl vanillin isobutyrate	-	0.7714	Non-required	0.601	-	0.55	III	0.738	-3.258	logS	2.008
Geranylacetone	-	0.5745	Non-required	0.6029	-	0.875	III	0.8221	-3.141	logS	1.915
n-Butyl lactate	-	0.6714	Non-required	0.6687	-	0.925	III	0.8388	-0.696	logS	2.246
N-linoleoyl-4-aminobutyric acid	-	0.7429	Non-required	0.6598	-	0.75	IV	0.5585	-2.912	logS	1.701
Spermine	-	0.8143	Non-required	0.6532	-	0.8	III	0.6931	-0.5	logS	2.339
Succinylacetone	-	0.6905	Non-required	0.6907	-	0.7	III	0.7913	-0.966	logS	2.21

Supplementary Table 7. Results of Protox II analysis to determine the metabolic potential and toxicity of active compounds of secondary metabolites from pineapple

Name	LD50 (mg/kg)	Toxicity Class	Average similarity	Prediction accuracy	Molecular weight	Number of hydrogen bond acceptors	Number of hydrogen bond donors	Number of atoms	Number of bonds
CMB	5000	5	83.23%	70.97%	1026.94	97	18	136	141
1-O-Caffeoyl-3-O-feruloylglycerol	978	4	74.76%	69.26%	268.26	22	3	35	35
Ascorbic acid	3367	5	100%	100%	176.12	14	4	20	20
Caffeic acid	2980	5	88.59%	70.97%	180.16	12	3	21	21
Citric acid	80	3	100%	100%	192.12	15	4	21	20
Ferulic acid	1772	4	86.10%	70.97%	194.18	14	2	24	24
Linoleic acid	10000	6	100%	100%	280.45	34	1	52	51
Oleic acid	48mg/kg	2	100%	100%	282.46	36	1	54	53
Palmitic Acid	900mg/kg	4	100%	100%	256.42	34	1	50	49
Palmitoleic acid	48mg/kg	2	100%	100%	254.41	32	1	48	47
Pantothenic acid	10000mg/kg	6	78.40%	69.26%	219.24	23	4	32	31
Serotonin	2300mg/kg	5	60.70%	68.07%	176.22	14	3	25	26
Stearic Acid	900mg/kg	4	100%	100%	284.48	38	1	56	55
(-)-threo-isodihomocitric acid	9800mg/kg	6	87.03%	70.97%	220.18	19	4	27	26
(Hydroxyethyl)methacrylate	3275mg/kg	5	100%	100%	130.14	13	1	19	18
(R)-2-hydroxystearic acid	3400mg/kg	5	100%	100%	300.48	39	2	57	56
alpha-linolenic acid	10000mg/kg	6	100%	100%	278.43	32	1	50	49
2-caffeoylisocitric acid	5000mg/kg	5	63.00%	68.07%	354.27	24	5	39	39
2-Isopropylmalic acid	1000mg/kg	3	88.00%	70.97%	176.17	17	3	24	23
2-methylcitric acid	80mg/kg	3	100%	100%	206.15	17	4	24	23
2-O-ethyl ascorbic acid	5000mg/kg	5	81.71%	70.97%	204.18	18	3	26	26
4-Coumaric acid	2850mg/kg	5	100%	100%	164.16	11	2	20	20
4-Methyleneglutamic acid	10000mg/kg	5	74.29%	69.26%	159.14	14	3	20	19
9,10-Dihydroxystearic acid	3400mg/kg	5	95.24%	72.90%	316.48	40	3	58	57

alpha-Methylene-gamma-butyrolactone	1990mg/kg	6	69.30%	68.07%	98.1	8	0	13	13
butyl acrylate	900mg/kg	4	100%	100%	128.17	14	0	21	20
D-(+)-Malic acid	2497mg/kg	5	100%	100%	134.09	11	3	15	14
Dehydroascobic acid	10600mg/kg	6	75.30%	69.26%	174.11	12	2	18	18
Ethyl vanillin isobutyrate	2000mg/kg	4	71.07%	69.26%	236.26	20	0	33	33
Geranylacetone	5000mg/kg	5	100%	100%	194.31	23	0	36	35
n-Butyl lactate	2000mg/kg	4	100%	100%	146.18	17	1	24	23
N-linoleoyl-4-aminobutyric acid	50000mg/kg	6	79.14%	69.26%	365.55	43	2	65	64
Spermine	820mg/kg	4	83.97%	70.97%	202.34	30	4	40	39
Succinylacetone	1600mg/kg	4	88.01%	70.97%	158.15	14	1	21	20

Supplementary Table 7 (Continued). Results of Prottox II analysis to determine the metabolic potential and toxicity of active compounds of secondary metabolites from pineapple.

Name	Number of rotatable bonds	Molecular refractivity	Topological Polar Surface Area	octanol/water partition coefficient(logP)	Hepatotoxicity		Carcinogenicity	
					Prediction	Probability	Prediction	Probability
CMB	18	213.43	483.41	-11.36	Inactive	0.8	Inactive	0.79
1-O-Caffeoyl-3-O-feruloylglycerol	7	67.88	96.22	0.31	Inactive	0.89	Inactive	0.83
Ascorbic acid	2	35.12	107.22	-1.41	Inactive	0.86	Inactive	0.92
Caffeic acid	2	47.16	77.76	1.2	Inactive	0.57	Active	0.78
Citric acid	5	37.47	132.13	-1.25	Inactive	0.89	Inactive	0.67
Ferulic acid	3	51.63	66.76	1.5	Inactive	0.51	Inactive	0.61
Linoleic acid	14	89.46	37.3	5.88	Inactive	0.55	Inactive	0.64
Oleic acid	15	89.94	37.3	6.11	Inactive	0.55	Inactive	0.64
Palmitic Acid	14	80.8	37.3	5.55	Inactive	0.52	Inactive	0.63
Palmitoleic acid	13	80.32	37.3	5.33	Inactive	0.55	Inactive	0.64
Pantothenic acid	7	52.21	106.86	-0.65	Inactive	0.93	Inactive	0.65

Serotonin	2	52.8	62.04	2.08	Inactive	0.83	Inactive	0.74
Stearic Acid	16	90.41	37.3	6.33	Inactive	0.52	Inactive	0.63
(-)-threo-isodihomocitric acid	7	47.05	132.13	-0.61	Inactive	0.88	Inactive	0.67
(Hydroxyethyl)methacrylate	4	32.93	46.53	0.1	Inactive	0.79	Inactive	0.59
(R)-2-hydroxystearic acid	16	91.57	57.53	5.3	Inactive	0.68	Inactive	0.58
alpha-linolenic acid	13	88.99	37.3	5.66	Inactive	0.54	Inactive	0.63
2-caffeoylisocitric acid	9	80.83	178.66	0.28	Inactive	0.66	Inactive	0.69
2-Isopropylmalic acid	4	40.51	94.83	-0.07	Inactive	0.86	Inactive	0.66
2-methylcitric acid	5	42.28	132.13	-1	Inactive	0.88	Inactive	0.67
2-O-ethyl ascorbic acid	4	44.25	96.22	-0.93	Inactive	0.84	Inactive	0.89
4-Coumaric acid	2	45.13	57.53	1.49	Inactive	0.51	Active	0.5
4-Methyleneglutamic acid	4	36.73	100.62	0.13	Inactive	0.76	Inactive	0.68
9,10-Dihydroxystearic acid	16	92.74	77.76	4.27	Inactive	0.71	Inactive	0.55
alpha-Methylene-gamma-butyrolactone	0	24.85	26.3	0.49	Inactive	0.62	Inactive	0.65
butyl acrylate	5	36.57	26.3	1.52	Inactive	0.75	Active	0.67
D-(+)-Malic acid	3	26.05	94.83	-1.09	Inactive	0.9	Inactive	0.71
Dehydroascobic acid	2	32.85	100.9	-2.6	Inactive	0.9	Inactive	0.83
Ethyl vanillin isobutyrate	6	64.24	52.6	2.46	Inactive	0.69	Inactive	0.67
Geranylacetone	6	63.86	17.07	4.05	Inactive	0.72	Inactive	0.81
n-Butyl lactate	5	38.21	46.53	0.71	Inactive	0.77	Inactive	0.54
N-linoleoyl-4-aminobutyric acid	19	111.69	66.4	6.17	Inactive	0.86	Inactive	0.51
Spermine	11	61.2	76.1	1.83	Inactive	0.93	Inactive	0.67
Succinylacetone	5	37.93	71.44	0.4	Inactive	0.69	Inactive	0.67

Supplementary Table 7 (Continued). Results of Prottox II analysis to determine the metabolic potential and toxicity of active compounds of secondary metabolites from pineapple.

Name	Immunotoxicity		Mutagenicity		Cytotoxicity	
	Prediction	Probability	Prediction	Probability	Prediction	Probability
CMB	Active	0.96	Inactive	0.81	Inactive	0.68
1-O-Caffeoyl-3-O-feruloylglycerol	Active	0.96	Inactive	0.76	Inactive	0.86
Ascorbic acid	Inactive	0.99	Inactive	0.87	Inactive	0.65
Caffeic acid	Inactive	0.5	Inactive	0.98	Inactive	0.86
Citric acid	Inactive	0.99	Inactive	0.97	Inactive	0.73
Ferulic acid	Active	0.91	Inactive	0.96	Inactive	0.88
Linoleic acid	Inactive	0.96	Inactive	1	Inactive	0.71
Oleic acid	Inactive	0.99	Inactive	1	Inactive	0.71
Palmitic Acid	Inactive	0.99	Inactive	1	Inactive	0.74
Palmitoleic acid	Inactive	0.99	Inactive	1	Inactive	0.71
Pantothenic acid	Inactive	0.99	Inactive	0.96	Inactive	0.66
Serotonin	Inactive	0.93	Inactive	0.91	Inactive	0.71
Stearic Acid	Inactive	0.99	Inactive	1	Inactive	0.74
(-)-threo-isodihomocitric acid	Inactive	0.99	Inactive	0.92	Inactive	0.73
(Hydroxyethyl)methacrylate	Inactive	0.99	Inactive	0.95	Inactive	0.75
(R)-2-hydroxystearic acid	Inactive	0.96	Inactive	0.95	Inactive	0.64
alpha-linolenic acid	Inactive	0.99	Inactive	0.95	Inactive	0.71
2-caffeoylisocitric acid	Active	0.77	Inactive	0.85	Inactive	0.88
2-Isopropylmalic acid	Inactive	0.99	Inactive	0.84	Inactive	0.72
2-methylcitric acid	Inactive	0.99	Inactive	0.83	Inactive	0.73
2-O-ethyl ascorbic acid	Inactive	0.98	Inactive	0.71	Inactive	0.64
4-Coumaric acid	Inactive	0.91	Inactive	0.93	Inactive	0.81
4-Methyleneglutamic acid	Inactive	0.99	Inactive	0.75	Inactive	0.65
9,10-Dihydroxystearic acid	Inactive	0.99	Inactive	0.95	Inactive	0.62

alpha-Methylene-gamma-butyrolactone	Inactive	0.98	Inactive	0.72	Inactive	0.72
butyl acrylate	Inactive	0.96	Inactive	0.92	Inactive	0.79
D-(+)-Malic acid	Inactive	0.99	Inactive	0.97	Inactive	0.74
Dehydroascobic acid	Inactive	0.99	Inactive	0.82	Inactive	0.7
Ethyl vanillin isobutyrate	Active	0.61	Inactive	0.74	Inactive	0.82
Geranylacetone	Inactive	0.99	Inactive	0.97	Inactive	0.82
n-Butyl lactate	Inactive	0.98	Inactive	0.8	Inactive	0.81
N-linoleoyl-4-aminobutyric acid	Inactive	0.95	Inactive	0.92	Inactive	0.72
Spermine	Inactive	0.98	Inactive	0.87	Inactive	0.75
Succinylacetone	Inactive	0.99	Inactive	0.97	Inactive	0.77

Supplementary Table 8. The results of the network analysis using cytoscape.

Gene	Protein	Biological Process	Betweenness centrality	Closeness centrality	Degree	Stress
EP300	Histone acetyltransferase p300	Response to Reactive Oxygen Species, Response to Oxidative Stress, Regulation of Interleukin-88 Production, Positive Regulation of Interleukin-6 Production	0.193032	0.408451	25	125 94
APP	Amyloid-beta protein A4	Immune Response Regulating Signalling Pathway	0.189908	0.424908	27	114 04
PTGS2	Prostaglandin G/H synthase 2	Response to Cytokine Stimulus, Response to Oxidative Stress, Response to Steroid Hormone Stimulus, Regulation of Apoptosis, Cyclooxygenase Pathway	0.169444	0.401384	21	842 4
PPARG	Peroxisome proliferator-activated receptor gamma	Immune response, Response to Oxidative Stress, Innate Immune Response, Regulation of Inflammatory Response	0.12498	0.421818	16	809 8
EGFR	Epidermal growth factor receptor	Positive Regulation of Inflammatory Response, Regulation of NF-kappaB Import into Nucleus	0.122505	0.418773	21	734 0
JUN	Transcription factor AP-1	Response to ROS, Response to Cytokine Stimulus, Regulation of Apoptosis, Response to Oxidative Stress	0.114139	0.451362	24	985 8
SAT1	Diamine acetyltransferase 1	I-kappaB Kinase/NF-kappaB Cascade	0.112307	0.278177	7	822 0
NFE2L2	Nuclear factor erythroid 2-related factor 2	I-kappaB Kinase/NF-kappaB Cascade	0.105701	0.348348	4	807 4
TNF- α	Tumor-necrosis factor	Positive Regulation of Inflammatory Response, Positive Regulation of Interleukin-6 Production, Regulation of Immune System Process, I-kappaB Kinase/NF-kappaB Cascade, Immune	0.088498	0.431227	22	516 4

			Response, Inflammatory Response, Regulation of Interleukin-10 Production, Regulation of Immune Effector Process, Response to Reactive Oxygen Species, Positive Regulation of NF-KappaB Import Into Nucleus, Activation of Immune Response, Regulation of Interleukin-6 Production, Regulation of Inflammatory Response, Immune System Response				
CXCL8	Interleukin-8		Inflammatory Response, Leukocyte Activation, Leukocyte Migration, Immune Response, Immune System Process	0.074387	0.432836	24	6248
FABP5	Fatty acid-binding protein		Positive Regulation of Interleukin-6 Production	0.067487	0.318681	7	2464
FOS	Proto-oncogene c-Fos		Response to ROS, Response to Cytokine Stimulus, Response to Oxidative Stress, Response to Steroid Hormone Stimulus, Inflammatory Response	0.062977	0.426471	16	5622
CDC25A	M-phase inducer phosphatase 1		Regulation of Immune System Process	0.048986	0.336232	4	2758
FABP4	Fatty acid-binding protein		Positive Regulation of NF-KappaB Import into Nucleus, Positive Regulation of Inflammatory Response, Cellular Response to Reactive Oxygen Species	0.048395	0.351515	6	1898
A CAMK2	Calcium/calmodulin-dependent protein kinase type II subunit alpha		Regulation of Interleukin-10 Production, Cellular Response to Reactive Oxygen Species	0.039125	0.317808	5	1948
PTGES	Prostaglandin E synthase		Cellular Response to Reactive Oxygen Species	0.036639	0.305263	5	1614

KDM2A	Lysine-specific demethylase 2A	Cellular Response to Reactive Oxygen Species	0.035805	0.295165	3	2070
CNR1	Cannabinoid receptor 1	Activation of Immune Response, Positive Regulation of Immune System Process, Regulation of Immune System Process, Regulation of Immune Response, Response to Reactive Oxygen Species, Positive Regulation of NF-KappaB Import Into Nucleus, Innate Immune Response	0.035498	0.367089	12	2936
CDC25C	M-phase inducer phosphatase 3	Cellular Response to Reactive Oxygen Species	0.035422	0.262443	4	2038
MAOB	Amine oxidase [flavin-containing] B	Cellular Response to Reactive Oxygen Species	0.035102	0.275534	5	1752
BCHE	Cholinesterase	Cellular Response to Reactive Oxygen Species	0.034953	0.326761	3	1678
CXCL12	Stromal cell-derived factor 1	Immune response, Regulation of Immune System Process, Positive Regulation of Immune System Process, Cellular Response to Reactive Oxygen Species, Immune System Process	0.03488	0.37785	18	2920
AKR1C3	Aldo-keto reductase family member C3	Cellular Response to Reactive Oxygen Species	0.0345	0.257206	5	1322
TRPV1	Transient receptor potential cation channel, subfamily V, member 1	Cellular Response to Reactive Oxygen Species	0.034183	0.282238	4	2320
RELA	Transcription factor p65	Positive Regulation of Inflammatory Response, Positive Regulation of Interleukin-6 Production, Regulation of Immune System	0.032519	0.405594	19	4010

Process, I-kappaB
Kinase/NF-kappaB
Cascade, Immune
Response, Inflammatory
Response, Regulation of
Interleukin-10
Production, Regulation
of Immune Effector
Process, Response to
Reactive Oxygen
Species, Positive
Regulation of NF-
KappaB Import Into
Nucleus, Activation of
Immune Response,
Regulation of
Interleukin-6
Production, Regulation
of Inflammatory
Response, Immune
System Response
