pharmaceuticals

Supplementary material

Technological Optimization and Antioxidant Efficacy via the NRF-2-Mediated Defense Pathway of *Corylus avellana* L. Skin Extracts: A Sustainable Approach for Developing Health-Promoting Natural Products

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Index

Table S1. Matrix used for the 3^3 full factorial experimental design.

Run	Independent Variables			Dependent Variables				
	X_1	X_2	X_3	TPC	ABTS	DPPH	FRAP	BCB
	(% EtOH)	(°C)	(h)	mg GAE/g[1]	mg TE/g[2]	mg TE/g[2]	mg TE/g[2]	% AA at 2 mg/mL[3]
1	100	30	1	177.88	844.23	1951.90	1371.14	1.13
2	100	30	2	149.61	644.22	1802.43	1145.24	4.71
3	100	30	3	122.78	511.40	1332.40	981.86	7.26
4	50	30	1	379.46	1772.54	4298.96	2831.25	52.06
5	50	30	2	382.49	1799.72	4578.43	3048.14	73.09
6	50	30	3	342.18	1489.73	4004.60	2857.70	66.37
7	0	30	1	347.03	1852.37	4279.49	2776.19	87.89
8	0	30	2	316.52	1769.14	3870.59	2503.28	65.24
9	0	30	3	324.37	1651.94	3915.26	2460.24	73.98
10	100	50	1	137.83	673.95	1565.33	1154.86	4.71
11	100	50	2	149.88	682.87	1726.26	1185.76	13.84
12	100	50	3	96.62	424.77	1126.23	679.50	6.35
13	50	50	1	348.95	1722.43	4179.84	3103.92	32.10
14	50	50	2	315.77	1511.81	3745.74	2462.17	38.69
15	50	50	3	342.00	1680.82	4135.17	2724.74	48.41
16	0	50	1	387.35	1862.56	4295.52	2701.89	63.79
17	0	50	2	348.63	1805.66	4397.46	2648.99	70.55
18	0	50	3	343.46	1696.05	4240.54	2755.75	76.28
19	100	70	1	151.39	776.29	2082.47	1269.19	25.09
20	100	70	2	146.13	723.63	2012.03	1177.71	27.88
21	100	70	3	126.15	608.13	1588.24	991.48	15.99
22	50	70	1	339.14	1764.90	4289.80	2816.10	42.45
23	50	70	2	363.94	1878.70	4666.63	2999.32	48.61
24	50	70	3	343.07	1734.32	4358.52	2662.94	55.20
25	0	70	1	371.83	1891.19	4522.31	2711.75	50.46
26	0	70	2	314.27	1574.66	4154.64	2475.63	58.03
27	0	70	3	357.91	1736.62	4440.99	2724.01	69.60
28	50	50	2	348.50	1785.40	4310.25	3012.45	68.40
29	50	50	2	332.15	1722.15	4185.60	2895.60	56.15
30	50	50	2	341.80	1758.60	4240.30	2954.20	62.30

Table S2 ANOVA analysis of the model.

Response 1: TPC [1]						
Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	***p*-value**	
Model	276100.00	10	27609.25	66.87	< 0.0001	significant
A-EtOH/H_2O	190800.00	1	190800.00	462.06	< 0.0001*	
B-TEMPERATURE	45.09	1	45.09	0.1092	0.7447	
C-TIME	3262.17	1	3262.17	7.9	0.0112*	
AB	569.80	1	569.80	1.38	0.2546	
AC	140.63	1	140.63	0.3406	0.5663	
BC	530.80	1	530.80	1.29	0.271	
A^2	79099.79	1	79099.79	191.58	< 0.0001*	
B^2	337.48	1	337.48	0.8174	0.3773	
C^2	122.33	1	122.33	0.2963	0.5925	
ABC	55.76	1	55.76	0.135	0.7173	
Residual	7844.70	19	412.88			
Lack of Fit	7239.09	16	452.44	2.24	0.2766	not significant
Pure Error	605.61	3	201.87			
Cor Total	283900.00	29				
Response 2: ABTS [2]						
Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	***p*-value**	
Model	7573000.00	10	757300.00	84.15	< 0.0001	significant
A-EtOH/H_2O	5501000.00	1	5501000.00	611.26	< 0.0001*	
B-TEMPERATURE	6928.61	1	6928.61	0.7699	0.3912	
C-TIME	147000.00	1	147000.00	16.34	0.0007*	
AB	2675.46	1	2675.46	0.2973	0.5919	
AC	4357.12	1	4357.12	0.4842	0.495	
BC	17845.57	1	17845.57	1.98	0.1752	
A^2	1810000.00	1	1810000.00	201.16	< 0.0001*	
B^2	8498.19	1	8498.19	0.9443	0.3434	
C^2	2664.17	1	2664.17	0.296	0.5927	
ABC	1764.48	1	1764.48	0.1961	0.6629	
Residual	171000.00	19	8999.23			
Lack of Fit	124500.00	16	7779.60	0.5018	0.8443	not significant
Pure Error	46511.78	3	15503.93			
Cor Total	7744000.00	29				
Response 3: DPPH [3]						
Source	**Sum of Squares**	**df**	**Mean Square**	**F-value**	***p*-value**	
Model	42090000.00	10	4209000.00	87.2	< 0.0001	significant
A-EtOH/H_2O	29210000.00	1	29210000.00	605.21	< 0.0001*	
B-TEMPERATURE	240700.00	1	240700.00	4.99	0.0378*	
C-TIME	300000.00	1	300000.00	6.22	0.0221*	
AB	17372.87	1	17372.87	0.36	0.5556	
AC	92277.94	1	92277.94	1.91	0.1828	
BC	49570.17	1	49570.17	1.03	0.3236	

A^2	11630000.00	1	11630000.00	241.06	< 0.0001*	
B^2	202200.00	1	202200.00	4.19	0.0548	
C^2	49897.58	1	49897.58	1.03	0.322	
ABC	3106.30	1	3106.30	0.0644	0.8025	
Residual	917000.00	19	48262.51			
Lack of Fit	721900.00	16	45121.72	0.694	0.732	not significant
Pure Error	195000.00	3	65013.39			
Cor Total	43000000.00	29				

Response 4: FRAP [4]

Source	Sum of Squares	df	Mean Square	F-value	*p*-value	
Model	17940000.00	10	1794000.00	64.77	< 0.0001	significant
A-EtOH/H_2O	10580000.00	1	10580000.00	382.04	< 0.0001*	
B-TEMPERATURE	1199.03	1	1199.03	0.0433	0.8374	
C-TIME	200100.00	1	200100.00	7.23	0.0146*	
AB	4467.56	1	4467.56	0.1613	0.6924	
AC	66382.66	1	66382.66	2.4	0.1381	
BC	5640.70	1	5640.70	0.2037	0.6569	
A^2	6751000.00	1	6751000.00	243.72	< 0.0001*	
B^2	3498.55	1	3498.55	0.1263	0.7262	
C^2	1652.17	1	1652.17	0.0596	0.8097	
ABC	5866.61	1	5866.61	0.2118	0.6506	
Residual	526300.00	19	27697.75			
Lack of Fit	337900.00	16	21121.64	0.3365	0.9369	not significant
Pure Error	188300.00	3	62770.34			
Cor Total	18470000.00	29				

Response 5: BCB [5]

Source	Sum of Squares	df	Mean Square	F-value	*p*-value	
Model	17414.43	10	1741.44	20.01	< 0.0001	significant
A-EtOH/H_2O	14385.47	1	14385.47	165.25	< 0.0001*	
B-TEMPERATURE	82.01	1	82.01	0.942	0.3439	
C-TIME	198.40	1	198.40	2.28	0.1476	
AB	916.65	1	916.65	10.53	0.0043*	
AC	30.24	1	30.24	0.3474	0.5625	
BC	22.03	1	22.03	0.2531	0.6207	
A^2	1236.37	1	1236.37	14.2	0.0013*	
B^2	89.64	1	89.64	1.03	0.323	
C^2	111.79	1	111.79	1.28	0.2712	
ABC	291.37	1	291.37	3.35	0.0831	
Residual	1653.95	19	87.05			
Lack of Fit	1161.44	16	72.59	0.4422	0.8795	not significant
Pure Error	492.52	3	164.17			
Cor Total	19068.38	29				

[1] Total Phenolic Content (TPC); [2] 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS); [3] 2,2-diphenyl-1-picrylhydrazyl (DPPH); [4] Ferric Reducing Antioxidant Power (FRAP); [5] *β*-Carotene Bleaching assay (BCB); df: Degree of freedom; *p*-value < 0.05 was considered significant.

Table S3. Fit statistics of the model.

	TPC [1]	ABTS [2]	DPPH [3]	FRAP [4]	BCB [5]
Std. Dev.	20.32	94.86	219.69	166.43	9.33
Mean	284.97	1411.69	3476.60	2269.43	45.55
C.V. % [6]	7.13	6.72	6.32	7.33	20.48
R^2	0.97	0.98	0.98	0.97	0.91
Adjusted R^2	0.96	0.97	0.97	0.96	0.87
Predicted R^2	0.94	0.95	0.95	0.94	0.81
Adeq Precision	20.80	24.26	23.87	20.91	14.95

[1] Total Phenolic Content (TPC); [2] 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS); [3] 2,2-diphenyl-1-picrylhydrazyl (DPPH); [4] Ferric Reducing Antioxidant Power (FRAP); [5] β-Carotene Bleaching assay (BCB); C.V.%: coefficient of variation.

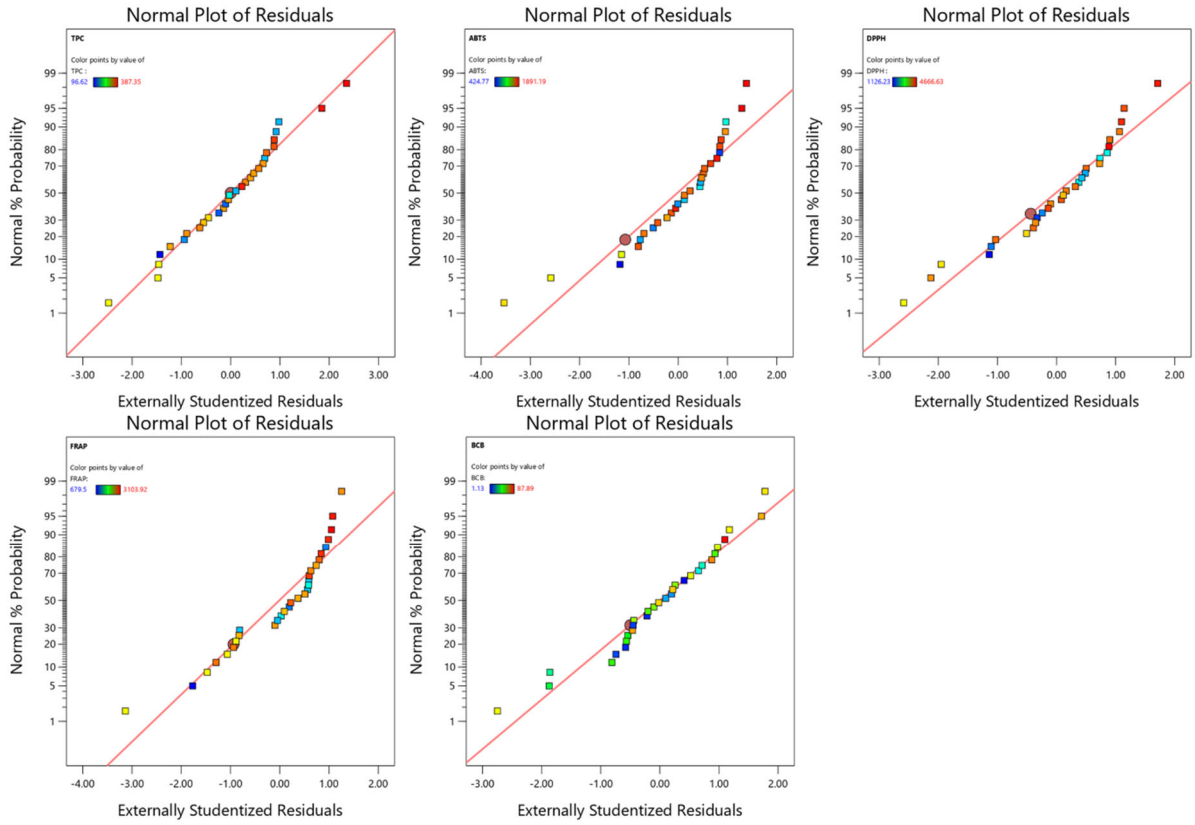

Figure S1. Normal Plot of residuals for Total Phenolic Content (TPC), 2,2′-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid) (ABTS), 2,2-diphenyl-1-picrylhydrazyl (DPPH), Ferric Reducing Antioxidant Power (FRAP), and β-Carotene Bleaching assay (BCB).