Supplementary Information

The Potential of Grapevine Leaves Extract in Treating Hyperpigmentation

Dried extract weight and TPC (from the smallest value to the largest)of the 23 tested grapevine varieties.

Species	TPC [mg gallic acid/g dried extract]	Dried extract [mg]
Petite Sirah	555 ± 47	8 ± 0.61
Cabernet Sauvignon	682 ± 42	7 ± 0.15
Chenin Blanc	686 ± 91	7 ± 0.12
Pumela	749 ± 62	6 ± 0.66
Pinot Noir	756 ± 50	7 ± 0.56
Chardonnay	757 ± 72	7 ± 0.46
Viognier	791 ± 49	7 ± 0.21
Ness Ziona	809 ± 118	6 ± 1.43
Gewurztraminer	838 ± 52	8 ± 0.53
Beer	869 ± 42	7 ± 0.55
Sauvignon Blanc	878 ± 51	8 ± 0.44
Merlot	921 ± 60	9 ± 0.36
Malbec	958 ± 167	10 ± 0.07
Orcha	964 ± 73	7 ± 0.78
Batar Nitzanim	1011 ± 36	7 ± 0.51
Cabernet Franc	1032 ± 44	8 ± 0.64
Zeituni	1057 ± 80	7 ± 1.25
Tel Tzuba	1087 ± 26	7 ± 0.98
Harduf	1121 ± 23	6 ± 0.15
Dishon	1135 ± 46	7 ± 0.85
Shikama	1146 ± 47	6 ± 0.61
Nitzan 3 (Yael)	1161 ± 61	6 ± 1.53
Darwishi	1201 ± 26	8 ± 0.61

■ Israeli, Red　■ European, Red　■ Israeli, White　■ European, White

Table S1: Total polyphenol content and the dry weight of the extract for each of the tested varieties, n>8

A table summarizing the TPC value and the dry weight for all the tested varieties, it can be seen that there is no correlation between the dry weight and the total polyphenol content, it may be that there are additional substances that undergo extraction in the process.

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Total polyphenol content (TPC) levels were compared via the Tukey-Kramer test, where statistical significance was defined as *p<0.05. .The concetration of the extract is 6 mg/mL in 10% DMSO .

Variety	Letter	Mean
Darwishi	A	1201.7
Nitzan 3 (Yael)	AB	1161.8
Shikama	ABC	1146.6
Dishon	ABC	1135.8
Harduf	ABCD	1121.5
Tel Tzuba	BCDE	1087.4
Zeituni	CDEF	1057.7
Cabernet Franc	DEFG	1033.0
Batar Nitzanim	EFGH	1011.4
Orcha	FGHI	965.0
Malbec	GHI	957.0
Merlot	HIJ	921.6
Sauvignon Blanc	IJK	878.5
Beer	IJK	869.0
Gewurztraminer	JKL	838.7
Ness Ziona	KL	809.7
Viognier	KL	791.3
Chardonnay	LM	757.2
Pinot Noir	LM	756.9
Pumela	LM	749.9
Chenin Blanc	M	686.1
Cabernet Sauvignon	M	682.1
Petite Sirah	N	555.0

Table S2: Statistical analysis which proves the differences in the total polyphenol content in the tested varieties.

The *S*un protection factor (SPF) value of 1.5 mg/mL of L. Extracts in 10% DMSO of the tested grapevine varieties. Results represent the mean of n>3. Statistical analysis was conducted using the Tukey-Kramer test.

Variety	Letter	Mean
Dishon	A	37.5

Zeituni	**A**	**37.4**
Darwishi	**A**	**37.0**
Tel Tzuba	**A**	**37.0**
Cabernet Franc	**AB**	**36.7**
Shikama	**AB**	**36.7**
Ness Ziona	**AB**	**36.5**
Batar Nitzanim	**ABC**	**36.0**
Nitzan 3 (Yael)	**ABC**	**35.4**
Harduf	**ABCD**	**34.9**
Malbec	**ABCD**	**34.6**
Viognier	**ABCD**	**34.5**
Merlot	**ABCD**	**33.8**
Beer	**ABCD**	**33.7**
Chardonnay	**ABCDE**	**33.2**
Gewurztraminer	**ABCDE**	**32.8**
Pumela	**BCDE**	**30.3**
Chenin Blanc	**CDE**	**29.8**
Cabernet Sauvignon	**CDE**	**29.6**
Orcha	**DE**	**28.8**
Pinot Noir	**EF**	**26.9**
Sauvignon Blanc	**EF**	**26.8**
Petite Sirah	**F**	**21.2**

Table S3: Statistical analysis which proves the differences in the sun protection factor in the tested varieties.

Statistical analysis of % inhibition of tyrosinase enzyme value was conducted using the Tukey-Kramer test

Variety	**Letter**	**Mean**
Darwishi	**A**	**83.1**
Nitzan 3 (Yael)	**AB**	**75.6**
Ness Ziona	**AB**	**74.7**
Cabernet Franc	**ABC**	**70.8**
Zeituni	**ABC**	**67.9**
Sauvignon Blanc	**BCD**	**59.0**
Harduf	**CD**	**53.2**

Variety	Letter	Mean
Merlot	CD	52.5
Malbec	CD	51.1
Batar Nitzanim	DE	47.8
Dishon	DEF	38.9
Beer	EFG	27.3
Tel Tzuba	FG	26.9
Gewurztraminer	FG	26.3
Cabernet Sauvignon	FG	25.7
Pumela	FGH	23.0
Viognier	FGH	21.4
Chardonnay	FGH	19.9
Pinot Noir	FGH	19.3
Shikama	GH	18.2
Petite Sirah	GH	17.0
Shanin Blanc	HI	2.6
Orcha	H	1.8

Table S4: Statistical analysis which proves the differences in the Statistical analysis of the % inhibition of tyrosinase enzyme in the tested varieties.

The half-maximal inhibitory concentration-IC50 [mg/mL] of 6 mg/mL of L. Extracts in 10% DMSO of the tested grapevine varieties. Results represent the mean of n>3. Statistical analysis was conducted using the Tukey-Kramer test.

Variety	Letter	Mean
Chenin Blanc	A	13.6
Harduf	AB	11.9
Cabernet Sauvignon	ABC	10.5
Tel Tzuba	ABCD	9.8
Pumela	ABCDE	8.8
Pinot Noir	BCDE	8.3
Petite Sirah	BCDE	7.8
Gewurztraminer	BCDEF	7.3
Viognier	CDEF	6.3
Nitzan 3 (Yael)	CDEF	6.2
Malbec	CDEF	5.7

Batar Nitzanim	**CDEF**	**5.7**
Shikama	**CDEF**	**5.6**
Merlot	**DEF**	**4.9**
Sauvignon Blanc	**EF**	**4.2**
Zeituni	**EF**	**4.1**
Darwishi	**EF**	**3.8**
Orcha	**EF**	**3.6**
Cabernet Franc	**FE**	**3.6**
Ness Ziona	**F**	**2.8**
Beer	**F**	**2.6**
Dishon	**F**	**2.6**
Chardonnay	**F**	**2.4**

Table S5: Statistical analysis which proves the differences in the Statistical analysis of the IC50 of tyrosinase enzyme in the tested varieties

High-performance liquid chromatography (HPLC)

An HPLC analysis was performed for each of the extracts mentioned above, the following figure shows a chromatogram from the HPLC device which shows a nice and good separation of all the substances in the extract.
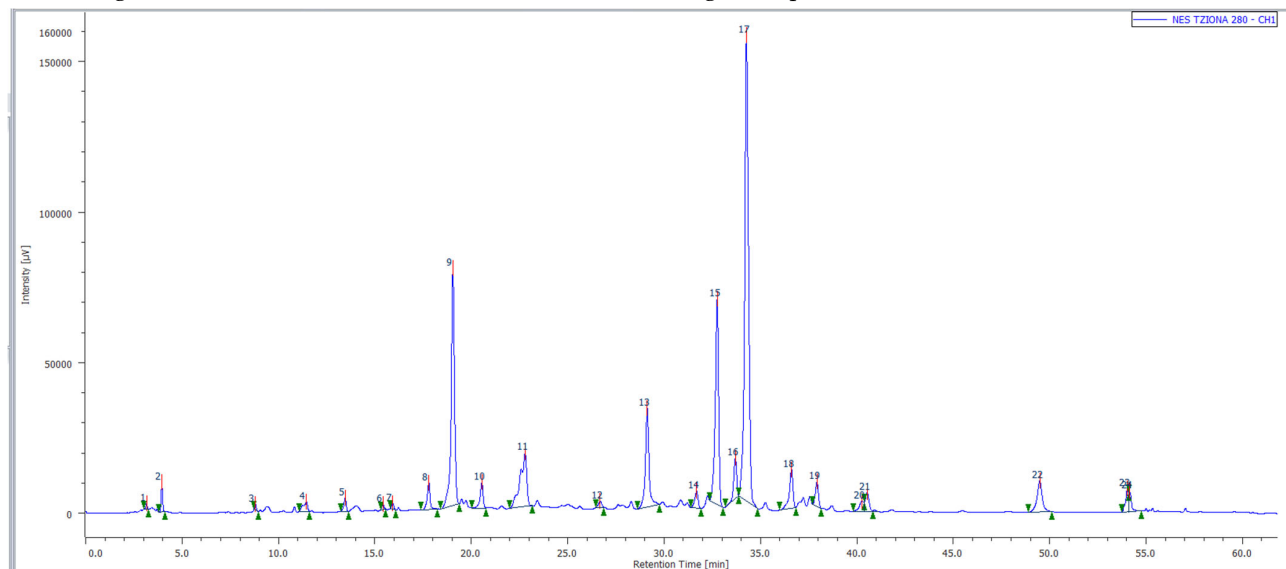
Figure S1: HPLC chromatogram.

Preliminary HPLC analysis of 11 European and 12 Israeli grapevine leaf extracts to quantify the polyphenols. The number of peaks found in the leaf extracts [at concentration 6 mg/mL] of all the tested varieties. The colors represent the different groups: Red Israeli, White Israeli, Red European, and White European.

Israeli Varieties	Number of peaks	European Varieties	Number of peaks
Orcha	16	Cabernet Sauvignon	16
Pumela	18	Malbec	16
Dishon	20	Petite Sirah	16
Zeituni	20	Pinot Noir	16
Harduf	21	Cabernet Franc	18
Nitzan 3 (Yael)	21	Merlot	20
Ness Ziona	24		
Beer	17	Chenin Blanc	13
Shikama	19	Gewurztraminer	13
Darwishi	20	Sauvignon Blanc	13
Tel Tzuba	20	Viognier	13
Batar Nitzanim	21	Chardonnay	15

Table S6: The amount of peaks for each of the tested varieties.