Olive tree bioactives: phenolic compounds with hormone-like activities

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ABSTRACT

Olive tree and its edible products (i.e. table olives and extra virgin olive oil EVOO) are common symbols of the Mediterranean landscapes and of the worldwide famous Mediterranean diets. They are a rich source of phenolic compounds - such as secoiridoids (e.g., tyrosol, hydroxytyrosol, oleochantal, verbascoside), flavonoids (e.g., apigenin, luteolin,, quercetin) and lignans - whose proposed physiological activities ranging from anti-inflammatory to anti-oxidant, from anti-proliferative to endocrine-like modulation. Such beneficial role of olive tree bioactives, including those one recovered by by-products such as olive mill wastewaters, have been also investigated in different in vitro experimental models. An overview of olive tree bioactives acting on sex steroid nuclear receptors, such as the androgen (AR) and estrogen receptors (ERs), will be provided showing their predicted ligand-receptor binding obtained by Molecular Docking. Hence, examples of their role as endocrine-like modulators in different hormone-dependent cell lines will be given.

Table 1. Distribution of the main classes of metabolites in the different parts of the plant *Olea europea* L. (*adapted from Mallamaci et al. 2021, DOI: 10.3390/molecules26041072*)

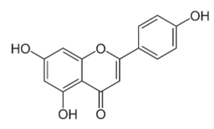
Seed Oil	Virgin Olive Oil	Skin	Pulp	Wood	Leaves
Phenolic acid/aldehydes	Phenolic acid/aldehydes	Phenolic acid/aldehydes	Phenolic acid/aldehydes	Phenolic acid/aldehydes	Phenolic acid/aldehydes
Tocopherols	Tocopherols		Tocopherols		
Sterols	Sterols	Organic acid and coumarins	Organic acid and coumarins	Organic acid and coumarins	Organic acid and coumarins
		Flavonoids	Simple phenols and derivatives	Simple phenols and derivatives	Simple phenols and derivatives
		Lignans	Secoiridoids and derivatives	Secoiridoids and derivatives	Secoiridoids and derivatives
		Fatty acids and derivatives		Flavonoids	Flavonoids
		Pentacyclic triterpenes			Tocopherols

Table 2. Example of a phenolic profile of early harvest mono- and multi-varietal Extra-Virgin Olive Oils (EVOOs). (*adapted from Trombetta et al. 2017, DOI: 10.3390/ijms18040797*)

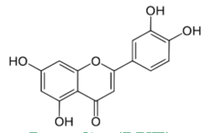
Phenolic Compounds	Early Harvest *Frantoio* (EHF)	Early Harvest *Casaliva* (EHC)	Early Harvest Organic *Casaliva* (EHOC)	Early Harvest MultiVarietal (EHMV)	Early Harvest Organic MultiVarietal (EHOMV)
			mg/kg		
Hydroxytyrosol	0.89 ± 0.00	0.71 ± 0.67	2.32 ± 0.12	6.35 ± 0.22	11.44 ± 0.55
Tyrosol	4.20 ± 0.64	3.13± 0.41	1.71 ± 0.07	2.54 ± 0.39	5.59 ± 0.56
Vanillic acid	1.80 ± 0.15	2.29 ± 0.02	0.90 ± 0.06	2.01 ± 0.37	1.42 ± 0.10
Vanillin	3.28 ± 0.06	3.44 ± 0.27	4.26 ± 0.48	4.99 ± 0.41	4.84 ± 0.18
3,4-DHPEA-AC	1.25 ± 0.16	1.78 ± 0.18	1.67 ± 0.25	3.43 ± 0.20	1.72 ± 0.12
3,4-DHPEA-EDA	76.67 ± 5.83	56.57 ± 4.73	108.21 ± 9.56	102.44 ± 4.63	106.89 ± 12.58
p-HPEA-EDA	6.65 ± 0.97	7.42 ± 0.44	12.29 ± 1.22	10.98 ± 1.01	12.46 ± 0.62
Oleuropein	18.51 ± 1.61	6.61 ± 0.66	12.85 ± 1.91	10.01 ± 1.11	15.41 ± 1.47
Lignans	69.20 ± 1.77	79.90 ± 7.73	83.81 ± 1.91	111.17 ± 5.22	130.99 ± 9.72
3,4-DHPEA-EA	7.98 ± 0.43	3.18 ± 0.12	9.18 ± 0.97	5.50 ± 0.12	8.84 ± 2.96
Luteolin	13.25 ± 1.98	4.67 ± 0.45	22.54 ± 2.91	11.76 ± 0.95	17.72 ± 1.26
Apigenin	5.47 ± 0.56	4.83 ± 0.24	3.39 ± 0.57	8.43 ± 1.24	8.87 ± 1.48
TOTAL	209.15	174.53 *,§	263.13 *	280.16 *,§	326.19 *,§,&

* $p < 0.001$ vs. EHF; § $p < 0.001$ vs. EHOC; § $p < 0.001$ vs. EHMV; & $p < 0.001$ vs. EHC

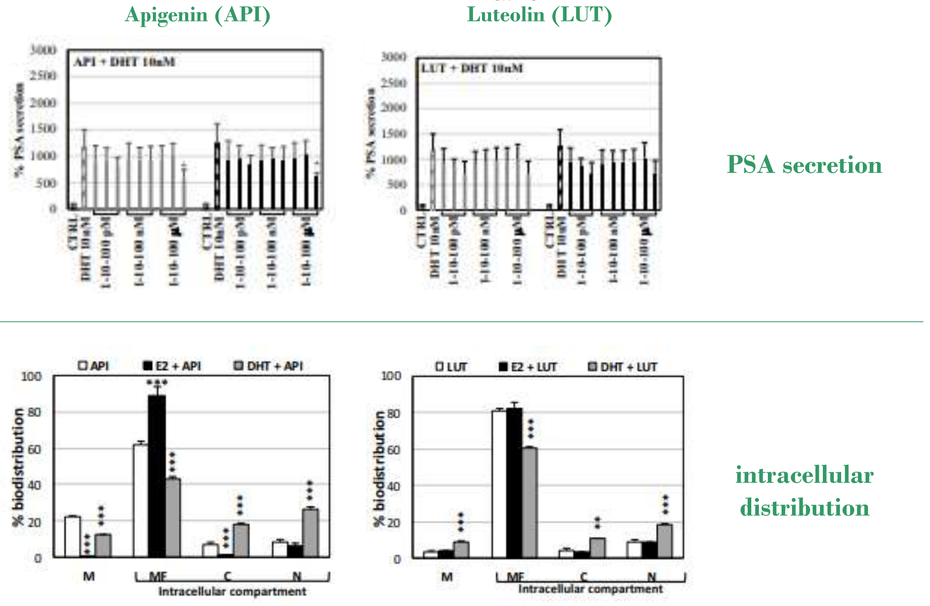
FIGURE 2. Apigenin (API) and Luteolin (LUT) effects on Prostate-Specific Antigen (PSA) secretion in a prostate epithelial cell line, LNCaP, and their intracellular distribution (*adapted from Smeriglio et al. 2014, DOI: 10.2174/1871520614666140624111011*)



Apigenin (API)



Luteolin (LUT)



PSA secretion

intracellular distribution

Figure 2, left panels. ***Free (striped bars on the left) and total (black bars on the right) PSA secretion in LNCaP cells upon dose-dependent treatment with plant bioactives Apigenin/API or Luteolin/LUT ± 10nM DHT.***
P-values (Dunnett test): *p<0.05, **p<0.01, ***p<0.001 *vs* CTRL.

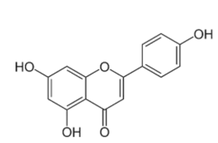
Figure 2, right panels. **Plant bioactive intracellular distribution in LNCaP cells.** (A) Intracellular distribution of apigenin/API alone (white bars), in presence of E2 (black bars), or in presence of DHT (grey bars). (C) Intracellular distribution of luteolin/LUT alone (white bars), in presence of E2 (black bars),or in presence of DHT (grey bars).
P-values (Student t-test): *p<0.05, **p<0.01, ***p<0.001 *vs* CTRL.

Data are expressed as percentage values (± S.D.) in comparison to CTRL values corresponding to 100% and represent mean values of three independent experiments performed in triplicate.

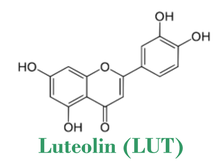
REFERENCES.

- ✓ *D'Arrigo et al. 2021, DOI: 10.3390/molecules26061613;*
- ✓ *Ferramosca et al. 2021, DOI: 10.3390/antiox10020217;*
- ✓ *Mallamaci et al. 2021, DOI: 10.3390/molecules26041072;*
- ✓ *Marcoccia et al. 2014, DOI: 10.1016/j.jep.2014.06.003;*
- ✓ *Marcoccia et al. 2017, DOI: 10.1186/s12263-017-0555-5;*
- ✓ *Smeriglio et al. 2014, DOI: 10.2174/1871520614666140624111011;*
- ✓ *Trombetta et al. 2017, DOI: 10.3390/ijms18040797.*

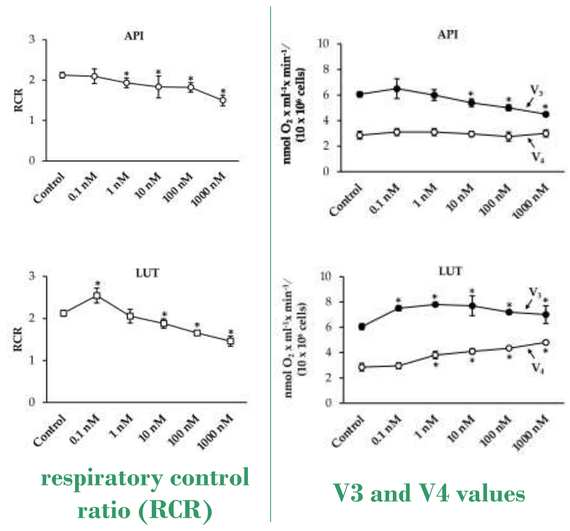
FIGURE 1. Apigenin (API) and Luteolin (LUT) effects on the mitocondrial activity of human spermatozoa (*adapted from Ferramosca et al. 2021, DOI: 10.3390/antiox10020217*)



Apigenin (API)



Luteolin (LUT)

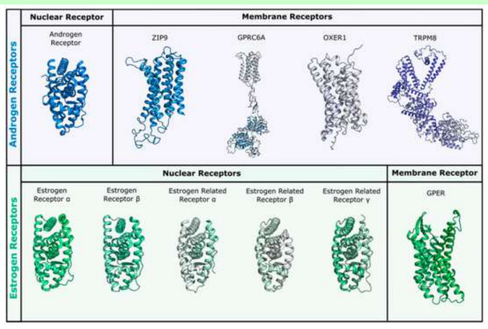


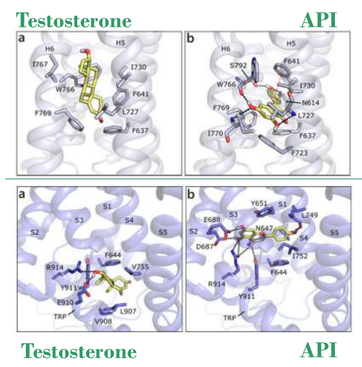
respiratory control ratio (RCR)

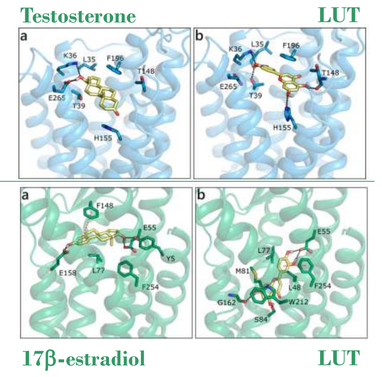
V3 and V4 values

Figure 1. ***The effects of apigenin (API) and luteolin (LUT), on human sperm mitochondria respiratory efficiency.*** The effects of apigenin (API) and luteolin (LUT) on human sperm mitochondria respiratory efficiency. Human sperm cells were incubated with the chemicals at the concentrations of 0.1–1000 nM. **Left panels.** The respiratory control ratio (RCR), which is an index of mitochondrial respiration efficiency, was calculated as V3:V4 ratio. **Right panels.** V3 and V4 values upon dose-dependent treatments with API and LUT, V3 (the rate of oxygen uptake in the presence of pyruvate/malate and ADP) and V4 (the rate of oxygen uptake in the presence of pyruvate and malate alone) were measured as nmol O2 × ml−1× min−1 / (10 × 106 cells).
All data were subjected to Student's t-test (*p<0.05), n=4.

FIGURE 3. Apigenin (API) and Luteolin (LUT) binding to androgen- and estrogen- (nuclear and membrane) receptors by a computational approach, the molecular docking (*adapted from D'Arrigo et al. 2021, DOI: 10.3390/molecules26061613*)







CONCLUSIONS.

- ✓ ***Two minor components of EVOO and other olive tree parts, namely the polyphenols Apigenin (API) and Luteolin (LUT) have a role in modulating cell of the male reproductive tissues.***
- ✓ ***Apigenin (API) and Luteolin (LUT) modulated the mitocondrial activity of human spermatozoa (see Figure 1) as well as the secretion of both free and total Prostate-Specific Antigen (PSA) in a prostate epithelial cell line, LNCaP (see Figure 2).***
- ✓ ***Besides the traditionally known estrogen- (ERα, ERβ) and androgen (AR) receptors, API and LUT appears to recognize, by Molecular Docking (see Figure 3), also non nuclear receptors such as GPRC6A and TRPM8 (API) or ZIP9 and GPER (LUT).***