**Table 1S.** Characteristics of selected studies showing the effects of olive oil and/or its phenolic compounds on miRNAs (expression)

| **Reference** | **Compound**<br>**(Dose)** | **Model** | **Epigenetic Effects** | **Other effects**<br>**(Health related effects)** |
|---|---|---|---|---|
| Tunca, 2012 [21] | *Olea europaea* leaf extract: OLE (5-2000 µg/ml, 15% oleuropein)<br><br>Tested the effects in combination with TMZ[1] | In vitro:<br>-T98G human GBM[2] cell line | 40 miRNAs were screened<br>OLE:<br>↑miRNA-584, miRNA-210, miRNA-219-1-3b, miRNA-181b, miRNA-145, miRNA-137<br>↓miRNA-24<br>=miRNA-153, let-7d<br>OLE + TMZ:<br>↑miRNA-181b, miRNA-153, miRNA-145, miRNA-137, let-7d | ↓Proliferation<br>Synergistic effect with TMZ<br><br>**(Anti-cancer)** |
| Tezcan, 2014 [22] | *Olea europaea* leaf extract: OLE (5-2000 µg/ml, 15% oleuropein)<br><br>Tested the effects in combination with TMZ | In vitro:<br>-T98G, U-138MG and U-187MG human GBM cell lines<br>-GBM stem-like cells (GSCs) | OLE in GSCs<br>↑miRNA-153, miRNA-137<br>=miRNA-181b, miRNA-145, Let-7d<br>OLE + TMZ in GSCs:<br>↑miRNA-153, miRNA-137, miRNA-181b, miRNA-145,<br>=Let-7d | ↓Proliferation(U-138MG and U-187MG)<br>↑Apoptosis (T98G,U-138MG and U-187MG)<br>↓mRNA of: *TP53, OCT-4, SOX2, BCL2, c-myc*, *c-Met* (GSCs)<br>**(Anti-cancer)** |
| Casas-Agustench, 2015, [23] | Olive oil as a source of n-9 fatty acids | In vivo:<br>-Female Sprague-Dawley rats | ↑miRNA-215, miRNA-10b, miRNA-26, miRNA-377-3p, miRNA-21, miRNA-192 | No effect on 88 genes related to insulin signaling<br>**(Insulin sensitivity)** |
| Di Francesco, 2015 [60] | -EVOO[3]<br>(In vitro: 100 ppm containing 320 mg of total phenols/kg)<br>(In vivo: gavage, 250 µl/300 g) | In vitro:<br>-CaCo-2 human colorectal cancer cells<br>In vivo:<br>-Female Sprague-Dawley rats | In vivo:<br>↓miRNA-23, miRNA-301a<br>=miRNA-27a, miRNA-29a | ↑CB1[4] (protein)<br>↑mRNA of: *CNR1*<br>↓Proliferation (Caco-2 cells)<br>**(Anti-cancer)** |

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| Tomé-Carneiro, 2016 [24] | Hydroxytyrosol (HT)<br>(0.03 % HT in diet, long term)<br>(Gavage, 15mg of HT, acute)<br>(in vitro: 10 μM)<br>(Human: 25 mg/d) | In vitro:<br>-CaCo-2, InEpCells[5], mouse primary intestinal organoids or "miniguts"<br>In vivo:<br>-C57BL/6mice (8 weeks)<br>Human trial:<br>-PBMC | In vitro:<br>CaCo2: ↓miRNA-196b-3p<br>InEpCells: ↑miRNA-483-3p, miRNA-1247-5p<br>Miniguts: ↑miRNA-193a-5p, miRNA-1247-5p<br>In vivo: 752 miRNAs screened<br>↑miRNA-483-3p, miRNA-135a-1-3p, miRNA-1982-5p miRNA-196b-3p, miRNA-1898<br>↓miRNA-346- 5p<br>Human:<br>↑miRNA-193a-5p in PBMCs | ↑plasma, liver and intestine triacylglycerol (mice)<br>mRNA microarrays:<br>↓332 genes including Cd36, Cyp4a10, Gsta3, Hsd3b2, Paqr7, Pdk4 and Slc35e3<br>↑342 genes including Car2, Crym, Cxcl13, Dusp6, Hsph1 and Il33<br>**(Lipid metabolism and Anti-CVD)** |
| D'Amore, 2016 [25] | EVOO (50 mL, 4h)<br>(High phenols: 491 mg/kg)<br>(Low phenols: 270 mg/Kg) | Human trial:<br>-Healthy subjects (n=12)<br>-MetS[6] subjects (n=12) | ↓8 miRNA:<br>miRNA-146b-5p, miRNA-19a-3p, miRNA-181b-5p, miRNA-107, miRNA-769-5p, miRNA-192-5p<br>↑6 miRNA:<br>miRNA-23b-3p, miRNA-519b-3p | ↓glucose, insulin, HOMA-IR<br>↓1062 genes healthy<br>↑1376 genes healthy<br>↓551 genes MetS<br>↑403 genes MetS<br>**(Anti-inflammatory, Anti-CVD and Anti-cancer)** |
| Xu, 2017[26] | Oleuropein<br>(In vitro: 200 μM)<br>(In vivo:drinking water, 1% w/v) | In vitro:<br>-NPC[7]HNE1 and HONE1 cell lines<br>In vivo:<br>-xenograft NPC mouse model | ↑22 different miRNAs<br>↑miRNA-519d | ↑Radio-sensitivity<br>↓mRNA and protein levels ofHIF1α[8], p53 and PDRG1[9]<br><br>**(Anti-cancer)** |
| D'Adamo, 2017 [27] | Hydroxytyrosol<br>100 μM | In vitro:<br>-Human primary and C-28/I2 chondrocytes | ↓Up-regulation of miRNA-9 induced by $H_2O_2$ | ↑Down-regulation of SIRT-1 induced by $H_2O_2$<br>**(Anti-osteoarthritis and anti-oxidant)** |
| Bigagli, 2017 [28] | Hydryxytyrosol, Oleuropein<br>(10 μM) | In vitro:<br>-RAW264.7 macrophage cells stimulated with LPS | ↓ miRNA-146a | ↓Oxidative burst<br>↓NO and PGE2<br>↓CD11b expression<br>↑Nrf2 translocation |

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| | | | | **(Anti-inflammatory)** |
| Luceri, 2017 [29] | EVOO<br>(10 g/100 g of diet)<br>(High phenols: 718.8 mg/kg)<br>(Low phenols: 9.3 mg/Kg) | In vivo:<br>-Middle-aged C57Bl/6J mice 6 months | ↑miRNA-484, miRNA-27, miRNA-137, miRNA-30, miRNA-34, miRNA-124 | ↑Motor and cognitive behavior<br>↑Notch1, BMPs, NGFR GLP1R, CRTC3<br>**(Anti-aging)** |
| Xing, 2017 [30] | Oleuropein<br>(In vitro: 200 µM)<br>(In vivo: drinking water, 1% w/v) | In vitro:<br>-Caov3 and Skov3 ovarian cancer cell lines<br>In vivo:<br>-xenograft ovarian cancer mouse model | ↑10 different miRNAs<br>↑miRNA-299 | ↑Radio-sensitivity<br>↓mRNA of HPSE1<br>↓HIF1α<br><br>**(Anti-cancer)** |
| Abtin, 2018 [31] | Oleuropein<br>(600-1000µg/mL) | In vitro:<br>-Human MCF-7 breast cancer cell line | ↓miRNA-21, miRNA-155 | ↑Apoptosis<br>↓Viability, Migration<br>↑APAF-1, PTEN, TP53INP-1, and FADD genes<br>**(Anti-cancer)** |
| ArunSundar, 2018 [62] | Hydroxytyrosol<br>(In vitro: 100 µM)<br>(In vivo: not reported) | In vivo:<br>-Animal model: Alzheimer's Disease induced in mouse by oA42i[10]<br>-Organotypic hippocampal slice cultures (OHSCs) | ↑ miRNA-124 | ↑Cognitive impulsivity<br>↓Anxiety-like behavior<br>↓HDAC6, HSP90<br><br>**(Anti-Alzheimer's Disease)** |
| Nanda, 2019 [61] | EVOO<br>(Thrice a week, 1 g/kg body weight, gavage) | In vivo:<br>-Sprague Dawley rats exposed to DHM[11] (model of colon carcinogenesis) | ↑miRNA-143 and miRNA-145 expression<br>↓Methylation of promoter region of miR-143 and miR-145 | ↑body weights<br>↓tumor or polyp incidence, multiplicity and size<br>↓mRNA and protein expression of NF-κB, VEGF, MMP-9<br>↑mRNA and protein expression of caspase-3 and caspase-9<br>(Anti-cancer and Anti-inflammatory) |

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| Juli, 2019 [63] | Oleacein (3,4-DHPEA-EDA)<br>(2,5-10 µM) | In vitro:<br>-NCI-H929, RPMI-8226, U266, MM1s and JJN3 MM[12] cell lines | ↑miRNA-29b and miRNA-22 in JJN3 | ↓Viability and clonogenicity of MM cells<br>=viability of normal PBMC<br>↓Cell cycle progression<br>↑Apoptosis<br>↓ Sp1 protein expression<br>↑in vitro anti-MM activity of the proteasome inhibitor carfilzomib<br>**(Anti-cancer)** |
| Benincasa, 2019 [32] | Hydroxytyrosol oleate<br>(5 µM) | In vitro:<br>-HaCat human immortalized keratinocyte cell line | ↑miRNA-34a, miRNA-21, miRNA-29a | ↑Viability<br>↓Intracellular ROS formation<br>↓SOD and GST enzyme activity<br>↓MDA<br>**(Anti-oxidant)** |
| Lopez De Las Hazas, 2019 [33] | Hydroxytyrosol<br>(0.03 % HT in the Diet) | In vivo:<br>-Mice liver samples obtained from a previous study [24] | 247 different miRNAs detected in mouse liver samples<br>↑miRNA-802-5p, miRNA-30a-5p, miRNA-146b-5p<br>↓miRNA-423-3p | Expression of several genes and proteins<br>↑Fgf21 and Rora<br>**(Lipid metabolism and Anti-CVD)** |
| Tezcan, 2019 [34] | Oleuropein<br>(277.5 and 555 µM)<br><br>Tested the effects in combination with TMZ | In vitro:<br>-T98G human GBM cell line | ↑miRNA-181b, miRNA-137 and Let-7d<br>=miRNA-153 | ↓Viability/proliferation<br><br>**(Anti-cancer)** |
| Scoditti, 2019 [35] | Hydroxytyrosol<br>(1-10 µM) | In vitro:<br>-Human SGBS[13] adipocytes stimulated with TNF-α | ↓ upregulation of miRNA-34a, miRNA-155 induced by TNF-α<br>↑let-7c expression level decreased by TNF-α | ↓TNF-α induced upregulation of mRNA of: MCP-1, CXCL-10, M-CSF, IL-1, VEGF, COX-2, MMP-2, IL-6, PAI-1, ICAM-1, SOD-1, GPX-1<br>↑ TNF-α induced downregulation of mRNA of: eNOS, PGC-1α, GLUT-4. |

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| | | | | ↓ NFkB activation<br>**(Anti-inflammatory)** |
| D'Adamo, 2019 [36] | Hydroxytyrosol<br>(100 μM) | In vitro:<br>-Human primary and C-28/I2 chondrocytes | Restores the methylation of promoters of miRNA-9 decreased by $H_2O_2$ | **(Anti-osteoarthritis and anti-oxidant)** |
| Carpi, 2019 [37] | Oleocanthal (*p*-DHPEA-EDA)<br>Oleacein (3,4-DHPEA-EDA)<br>25μM | In vitro:<br>-Human SGBS adipocytes stimulated with TNF-α | Counteract the TNF-α effects in cells and exosomes:<br>↓ miRNA-34a-5p and miRNA-155-5p<br>↑let-7c-5p | =Cell viability<br>↓TNF-α induced upregulation of mRNA of: IL-1β, COX-2, VEGF/KDR, MMP-2, NADPH oxidase, SOD, GPX, MCP-1, CXCL-10, MCS-F<br>↑expression of the anti-inflammatory/metabolic effector PPAR<br>↓ NFkB activation<br>**(Anti-inflammatory)** |
| Terzuoli, 2020 [38] | Hydroxytyrosol-3-O-sulphate (major HT plasma metabolite, 10 μM) | In vitro:<br>-Human umbilical endothelial cells (HUVEC)<br>-Human retinal endothelial cells (HREC)<br>(stimulated withIL-1β) | ↑*let-7* miRNA decreased by IL-1β | ↓ IL-1β induced endothelial-to-mesenchymal transition (EndMT)<br>↑CD31, FGFR1 (protein)<br>↓α-SMA, vimentin (protein)<br>↓TGF-β signaling<br>↓nuclear translocation of SMAD2/3<br>↓ACTA2, ZEB2, SNAI1, VIM, NOTCH3, CNN1, MMP2, MMP9 (mRNA)<br>↑ CD31, FGFR1 (mRNA)<br>**(Anti-inflammatory)** |

[1]Temozolomide, [2]Glioblastoma multiforme, [3]Extra virgin olive oil, [4]Type 1 cannabinoid receptor,[5]Human primary epithelial intestinal cells,[6]Metabolic syndrome[7]Nasopharyngeal carcinoma,[8]Hypoxia-inducible factor-1α,[9]DNA damage-regulated protein, [10]Soluble oligomeric amyloid $\beta_{1-42}$ plus ibotenic acid, [11]1,2-dimethylhydrazine,[12]Multiple myeloma,[13]Simpson-Golabi-Behmel syndrome.

**Table S2.** Characteristics of selected studies showing the effects of olive oil and/or its phenolic compounds on DNA methylation

| Ref. | Compound (dose) | Model | Epigenetic Effects | Other effects<br>Health related effects |
|---|---|---|---|---|
| Hoile, 2014 [39] | -Olive oil<br>(4 g daily, “1 g capsules”)<br>-n-3 LC-PUFA | Human trial:<br>-29 Chronic kidney disease patients, 8 weeks<br>-Peripheral blood mononuclear cells | DNA methylation of CpGs in 5’ regulatory regions of:<br>↑FADS2<br>= FADS1, ELOVL2<br>↑ELOVL5 in some regions and ↓in others | ↓mRNA of: *FADS2, FADS1, ELOVL5* (only female), *ELOVL2*<br><br>**(PUFA metabolism)** |
| Rodríguez-Miguel, 2015 [58] | -Low fat<br>-Corn oil (CO)<br>-EVOO[1]<br>(17% in the diet) | In vivo:<br>-DMBA[2]-Induced Breast Cancer in rats | ↑Global DNA methylation<br>↓promoter methylation of *RASSF1A* and *TIMP3 vs.* CO<br>↓mRNA of *DNMT1, DNMT3a DNMT3b vs.* CO<br>↓DNMT activity vs. CO | Weak tumor enhancing effect<br>↓mRNA of: *RASSF1A, TIMP3,*<br>**(Anti-cancer)** |
| Di Francesco, 2015 [60] | -ROO[3]<br>-EVOO<br>(In vitro: 100 ppm containing 320 mg of total phenols/kg)<br>(In vivo: gavage, 250 µl/300 g)<br>-OPE[4] (50 µM)<br>-Hydroxytyrosol (50 µM) | In vitro:<br>-CaCo-2 human colorectal cancer cells<br>In vivo:<br>-Female Sprague-Dawley rats (Single dose and 10 days of EVOO) | *CNR1* gene promoter DNA methylation:<br>=ROO<br>↓EVOO (in vitro and in vivo)<br>↓OPE<br>↓HT | CB1[5] (mRNA and protein expression):<br>↑EVOO (in vitro and in vivo)<br>↑OPE<br>↑HT<br>↓Proliferation (OPE, HT)<br>**(Anti-cancer)** |
| Liao, 2015 [40] | Fish oil (FO as control)<br>Olive oil<br>(80 g/kg of diet) | In vivo:<br>-Yellow croakers (*Larimichthyscrocea*)<br>70 days | Mitochondrial DNA methylation<br>↑*TR* and *ND4L*<br>↓*RNR1*<br>=*D-loop*<br>mRNA and protein:<br>↓DNMT1, DNMT3B<br>↑DNMT3A, HIF1a | ↑Liver lipid<br>↑Hydroxyl radical scavenging activity<br>**(Anti-oxidant)** |

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| Govindarajah, 2016 [41] | Butter fat<br>Safflower oil<br>Olive oil<br>(40% fat from olive oil) | In vivo:<br>-DMBA-Induced Breast Cancer in rats<br>(prenatal exposure, cancer in prepubertal mammary glands) | ↑ mRNA expression of *DNMT3a*, *Mbd1* | =Tumor volume, latency, multiplicity<br>↓mRNA of: *Lrrn1, Nf1, Dbf4, Cadm4,*<br>↑mRNA of: *Tmem45b, Btn1a1*<br>**(Anti-cancer)** |
| Garcìa-Escobar, 2017 [42] | Coconut oil (CO)<br>Sunflower oil (SO)<br>Olive oil<br>(10% fat from oils) | In vivo:<br>-Sprague-Dawley rats<br>-Adipocytes | TNFα promoter methylation<br>↓ versus SO<br>↑ versus CO | ↓mRNA of TNFα versus CO<br>↓release of TNFα from adipocytes versus CO<br>**(Anti-inflammatory)** |
| Monastero, 2017 [43] | Coconut oil (CO)<br>Sunflower oil (SO)<br>Olive oil<br>(10% fat from oils) | In vivo:<br>-Sprague–Dawley rats | ↑VEGF promoter methylation versus CO | ↓ mRNA and protein of VEGFB versus CO<br><br>**(Anti-obesity)** |
| Tezcan, 2017 [44] | *Olea europaea* leaf extract: OLE (5-2000 µg/ml, 15% oleuropein)<br><br>Tested the effects in combination with TMZ | In vitro:<br>-Human primary GBM[6]tumor cells | ↑ MGMT promoter methylation | ↓Proliferation (with TMZ)<br>↑DNA damage (with TMZ)<br>↓p53 (protein)<br>**(Anti-cancer)** |
| Arpón, 2018 [45] | MedDiet + EVOO (39.6-66.4 g/day)<br>MedDiet + nuts (MN)<br>Low fat (RF) | Human trial:<br>-36 subjects, 5 years<br>-Peripheral white blood cells | 223 CpGs screened<br>↓ DNA methylation of cg17071192–GNAS/GNASAS versus both MN and RF | ↓Diabetes<br>↓Hypercholesterolemia<br>↓Arterial hypertension<br>**(Anti-CVD)** |
| Corominas-Faja, 2018 [46] | Oleacein (3,4-DHPEA-EDA)<br>(0,1-20 µM) | In vitro:<br>-SUM-159 Breast Cancer cells (CSC)<br>-MCF-7<br>In vivo: | ↓DNMT1, 3A/3L and 3B/3Lenzyme activity in nuclear extract<br><br>Act as SAM competitive inhibitor | Antistemness properties:<br>↓ALDH$^+$ cells<br>↓mammospheres formation<br>↓ tumorigenicityin vivo<br>↓mTOR activity<br>↓44 genes |

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| | | -Tumor xenograft and orthotopic transplant studies | | ↑116 genes<br>**(Anti-cancer)** |
| Hunter, 2019 [47] | -EVOO<br>(6 g daily, "capsules")<br>-n-3 PUFA | Human trial:<br>-8 subjects (trained male cyclists), 4 weeks<br>-Whole blood isolated from | =Global DNA methylation<br>=mRNA expression of *DNMT3a, DNMT3b*<br>↓mRNA expression of *DNMT1*<br>=Methylation of PPARGC1A<br>↓Methylation of IL6<br>=Methylation of TNF | =mRNA expression of *IL6, TNF, PPARGC1A*<br><br>**(Anti-inflammatory)** |
| Nanda, 2019 [61] | EVOO<br>(Thrice a week, 1 g/kg body weight, gavage) | In vivo:<br>-Sprague Dawley rats exposed to DHM[7] (model of colon carcinogenesis) | ↑methylation of promoter region of NF-κB, VEGF, MMP-9,<br>↓methylation promoter region of miR-143, miR-145, caspase-3, caspase-9 | ↑body weights<br>↓tumor or polyp incidence, multiplicity and size<br>↓mRNA and protein expression of NF-κB, VEGF, MMP-9<br>↑mRNA and protein expression of caspase-3 and caspase-9<br>**(Anti-cancer and Anti-inflammatory)** |
| Garcia-Contreras, 2019 [48] | Hydroxytyrosol<br>(1.5 mg/kg of feed per day) | In vivo:<br>-Sows (maternal supplementation), 65 days<br>-Blood and plasma (maternal and fetal) | ↑Global DNA methylation of fetus | Undetectable Plasma hydroxytyrosol concentrations<br>↑total antioxidant capacity (TEAC)<br>↓ body and visceral weights<br>↑ diameter of the descending aorta;<br>↓ Parameters for glycemic index (glucose, fructosamine) and lipid profile<br>=SOD1, CAT, HIF1A, VEGFA, NOS2, IGF1 and UCP2 (mRNA) |

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| | | | | **(Anti-intrauterine growth restriction)** |
| Juli, 2019 [63] | Oleacein (3,4-DHPEA-EDA) (2,5-10 μM) | In vitro:<br>-NCI-H929, RPMI-8226, U266, MM1s and JJN3 MM[8] cell lines | =Global DNA methylation<br>=mRNA and protein expression of: DNMT1, DNMT3A, DNMT3B | ↓Viability and clonogenicity of MM cells<br>=viability of normal PBMC<br>↓Cell cycle progression<br>↑Apoptosis<br>↓ Sp1 protein expression<br>↑in vitro anti-MM activity of the proteasome inhibitor carfilzomib<br>**(Anti-cancer)** |
| Bordoni, 2019 [59] | -EVOO<br>(volumes dissolved in DMSO not reported)<br>-*Nigella sativa* oil (NG) | In vitro:<br>-THP-1 (stimulated with PMA and LPS) | ↓mRNA of DNMT3A, DNMT3B<br>=DNMT1<br>↑Global DNA methylation versus NG<br>↓TET2<br>=TET1, TET3 | =Cell viability<br>↓IL-6<br>↓IL-1β<br>↓MCP-1<br>↓MtDNA copy number<br>↓Membrane fluidity<br>= (GSH/GSSG) Ratio<br><br>**(Anti-inflammatory)** |

[1]Extra virgin olive oil, [2]Dimethylbenz(a)anthracene, [3]Rectified olive oil, [4]Olive oil phenolic extract, [5]Type 1 cannabinoid receptor,[6]Glioblastoma multiforme,[7]1,2-dimethylhydrazine, [8]Multiple myeloma

**Table 3.**Characteristics of selected studies showing the effects of olive oil and/or its phenolic compounds on Histone modifications

| Ref. | Compound (dose) | Model | Epigenetic Effects | Other effects<br>Health related effects |
|---|---|---|---|---|
| Oliveras-Ferraros, 2011 [49] | -EVOO[1] phenolic extract from 14 monovarietals (0%, 0.0001, 0.001, 0.01, 0.05 and 0.1 % v/v) | In vitro:<br>-JIMT-1 human breast cancer cell line | ↑Acetylation of Histone H3 at Lysine 18 | ↓Cell viability<br>↓Cell cycle (arrest at the G2/M phase)<br>= AKT<br>↑Stat3<br>↑p38MAPK<br>↑MEK1<br>↑NF-kB phosphorylation status<br>**(Anti-cancer)** |
| Rodríguez-Miguel, 2015 [58] | -Low fat<br>-Corn oil (CO)<br>-EVOO<br>(17% in the diet) | In vivo:<br>-DMBA[2]-Induced Breast Cancer in rats | ↓H4K20me3 in tumor tissue<br>↓H4K16ac in normal and tumor tissue<br>= H3K4me2 and H3K27me3 in normal and tumor tissue | Weak tumor enhancing effect<br>↓mRNA of: *RASSF1A, TIMP3,*<br>**(Anti-cancer)** |
| Luccarini, 2015 [50] | -Oleuropein aglicone (OLE, 100µM)<br>-OLE diet (50 mg/kg of diet) | In vivo:<br>-TgCRND8[3] AD mouse model<br>In vitro:<br>-pE3-Aβ[4] + OLE | ↑H3K9 and H4K5 acetylation<br>↓HDAC2 expression | pE3-Aβaggregation modified<br>↓pE3-Aβ citotoxicity<br>↓Glutaminyl cyclase (QC)<br>↑Autophagy<br>↓ dysfunctions of transgene-induced long-term potentiation(LTP) in the hippocampal area<br>↑OLE metabolites in the brain<br>**(Anti-Alzheimer's Disease)** |
| Bonvino, 2015 [51] | -Hydroxytyrosol<br>(0-100µM) | In vitro: | ↑HDAC6<br>↓KDM1A (LSD1) | = acetylated α tubulin |

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| | A commercial topical antimicrobial spray containing the Olivamine 10 ® formulation, which includes a hydroxytyrosol containing olive extract | -purified enzyme LSD1 + hydroxytyrosol<br>Ex vivo:<br>-Tissue sections obtained from the peri wound of a diabetic ulcer patient | | **(Anti diabetes adverse effects)** |
| ArunSundar, 2018 [62] | Hydroxytyrosol<br>(In vitro: 100 µM)<br>(In vivo: not reported) | In vivo:<br>-Animal model: Alzheimer's Disease induced in mouse by oA42i[5]<br>-Organotypic hippocampal slice cultures (OHSCs) | ↓ HDAC6 | ↓Cognitive impulsivity<br>↓Anxiety-like behavior<br>↓ HSP90<br>**(Anti-Alzheimer's Disease)** |
| Acevedo, 2019 [52] | -Olive oil in the diet | In vivo:<br>-Human Placenta (ALADDIN[6] cohort)<br>Cross-sectional study | ↑H3 acetylation at FOXP3, IL10RA and IL7R promoters | **(Immune system)** |
| Verdura, 2019 [53] | -Oleacein (Decarboxymethyl oleuropein aglycone (DOA) (3,4-DHPEA-EDA) (0.01-100µM) | In vitro:<br>-purified enzyme IDH1 + oleacein<br>-MCF10/HCT116 cells expressing R132H IDH1 mutant and their parental cell lines | ↓ (H3K9me3) | ↓ R132H IDH1<br>↓ 2HG<br>↑PD-L1<br>↓colony formation<br>**(Anti-cancer)** |
| Bayat, 2019 [54] | -Oleuropein glucoside (150-2400µg/ml) | In vitro:<br>MCF7 human breast cancer cell line | ↓HDAC2 e HDAC3 mRNA expression | ↓cell viability<br>↑ cell apoptosis<br>↓cell migration<br>**(Anti-cancer)** |
| Juli, 2019 [63] | -Oleacein (3,4-DHPEA-EDA) (2,5-10 µM) | In vitro: | ↑ H3 and H4 acetylation<br>↓I/II HDACs (HDAC1/2/3/4/6) | ↓Viability and clonogenicity of MM cells<br>=viability of normal PBMC |

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| | | -NCI-H929, RPMI-8226, U266, MM1s and JJN3 MM[7] cell lines | =HDAC activity | ↓Cell cycle progression<br>↑Apoptosis<br>↓ Sp1 protein expression<br>↑in vitro anti-MM activity of the proteasome inhibitor carfilzomib<br>**(Anti-cancer)** |
| Cuyàs, 2019 [55] | -Oleacein<br>(3,4-DHPEA-EDA)<br>(0,01-100µM) | In vitro:<br>- Purified enzyme (KDM1A) + oleacein<br>-BT-474 and MCF7 breast cancer cell lines | ↓KDM1A (LSD1) | ↓SOX2<br>**(Anti-cancer)** |
| Cuyas, 2019 [56] | -Oleacein<br>(3,4-DHPEA-EDA)<br>(1-100µM) | In vitro:<br>-Purified enzyme + oleacein<br>-MCF-7 and BT-474 breast cancer cell lines | ↓KDM6A<br>↓DOT1L | ↓NNMT<br>↓ACLY<br>**(Anti-cancer)** |
| Mansouri, 2019 [57] | -Oleuropein glucoside<br>150-2400µg/ml | In vitro:<br>-MCF-7 breast cancer cell line | ↓mRNA HDAC4 | ↓cell Viability<br>↑ cell apoptosis<br>↓ cell migration<br>**(Anti-cancer)** |
| Bordoni, 2019 [59] | -EVOO<br>(volumes dissolved in DMSO not reported)<br>-*Nigella sativa* oil (NG)<br><br><u>No phenols</u> | In vitro:<br>-THP-1 (stimulated with PMA and LPS) | ↓HDAC1, HDAC3 | =cell viability<br>↓IL-6<br>↓IL-1β<br>↓MCP-1<br>↓MtDNA copy number<br>↓Membrane fluidity<br>= (GSH/GSSG) Ratio<br>**(Anti-inflammatory)** |

[1]Extra virgin olive oil, [2]Dimethylbenz(a)anthracene, [3]Transgenic hemizygous CRND8 mice; [4] pE3-Aβ pyroglutamate-amyloid-β; [5]oligomeric amyloid $\beta_{1-42}$ plus ibotenic acid; [6]Assessment of Lifestyle and Allergic Disease During INfancy (ALADDIN) cohort; [7]Multiple myeloma