



SITOX

20° Congresso Nazionale

Società Italiana di Tossicologia

**Sostanze
di origine naturale:
farmaci, veleni o entrambi**

BOLOGNA 25-26-27 Ottobre 2021

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Effetto dell'Oleuropeina sulla modulazione del microambiente pro-infiammatorio in tumori del colon-retto di un modello sperimentale *in vivo*

Sofia Chioccioli; Ruzzolini, J.; Monaco, N.; Peppicelli, S.; Andreucci, E.; Urciuoli, S.; Romani, A.; Luceri, C.; Tortora, K.; Calorini, L.; Caderni, G.; Nediani, C.; Bianchini, F.

Bologna, 26 Ottobre 2021

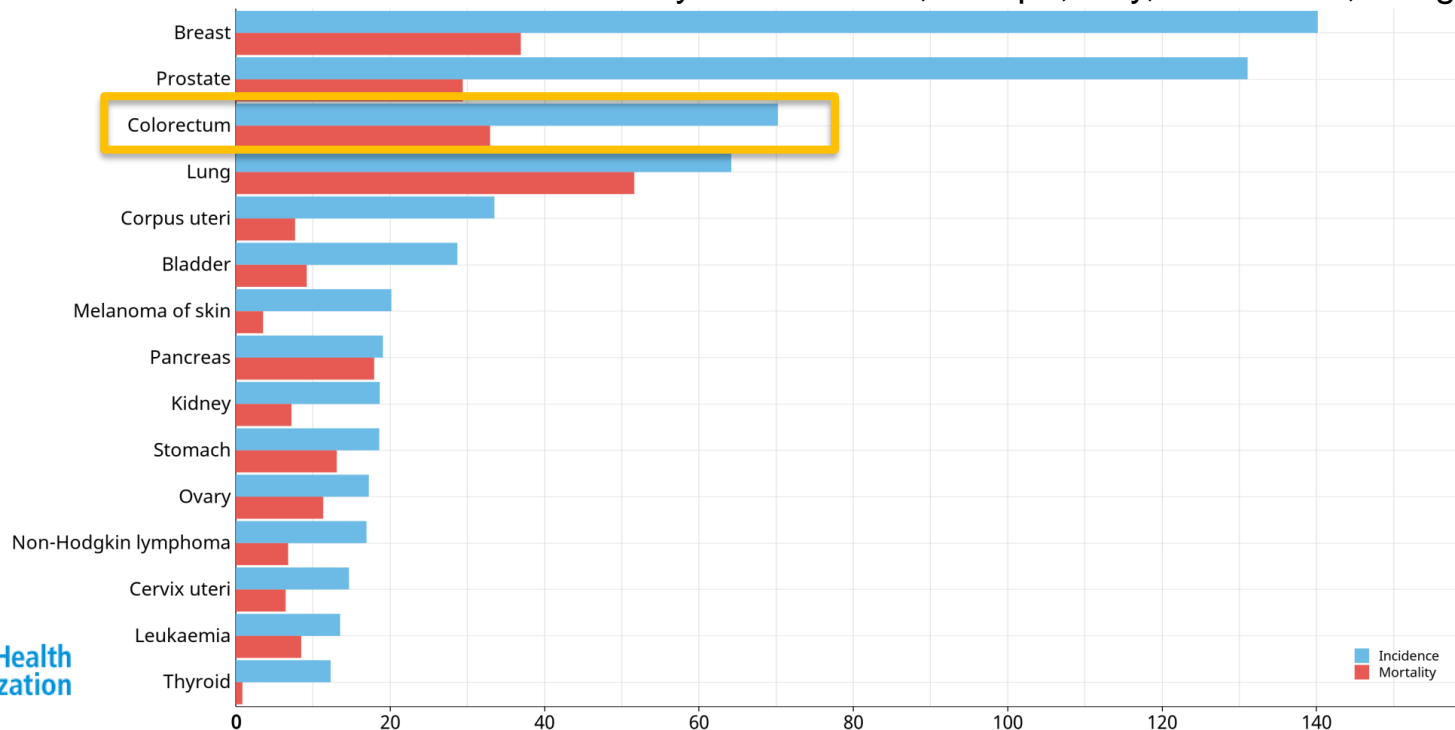


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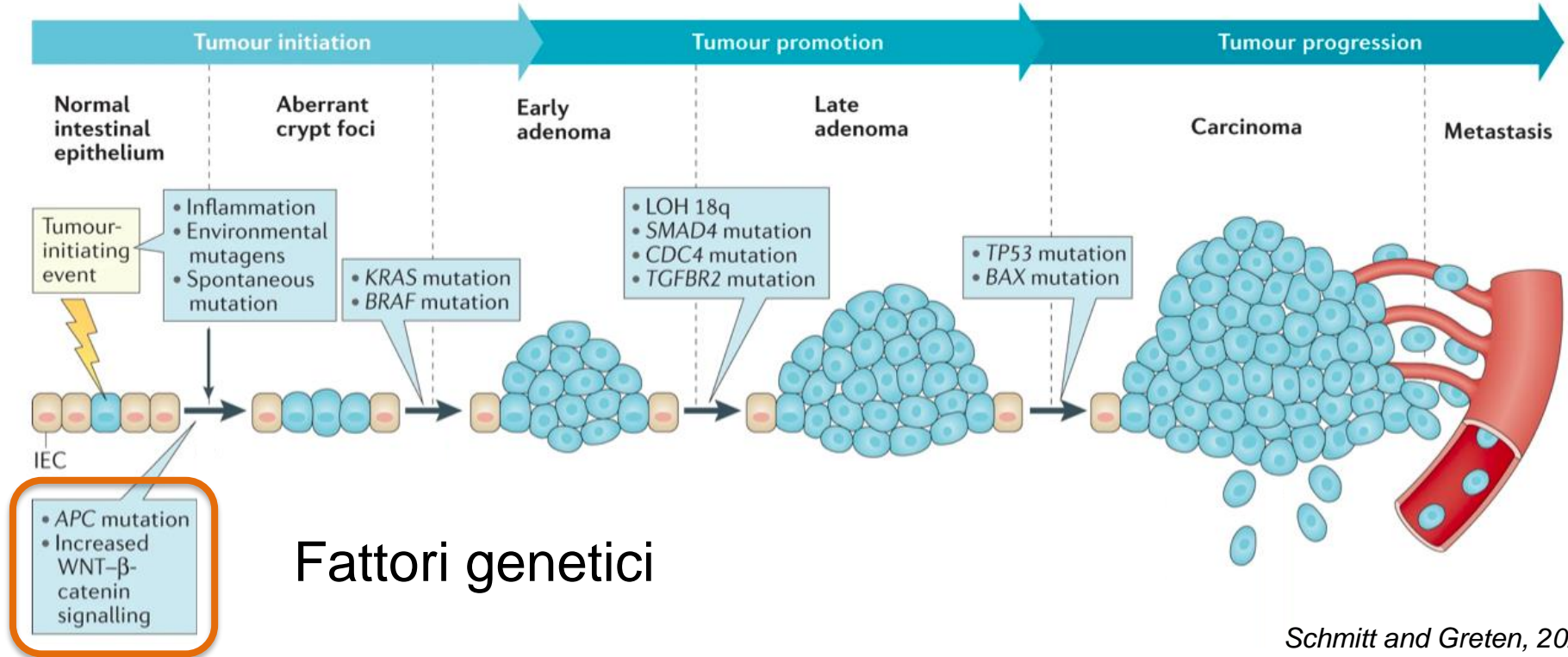
NEUROFARBA
DIPARTIMENTO DI NEUROSCIENZE,
PSICOLOGIA, AREA DEL FARMACO
E SALUTE DEL BAMBINO

Cancro del colon-retto

Estimated crude incidence and mortality rates in 2020, Europe, Italy, both sexes, all ages



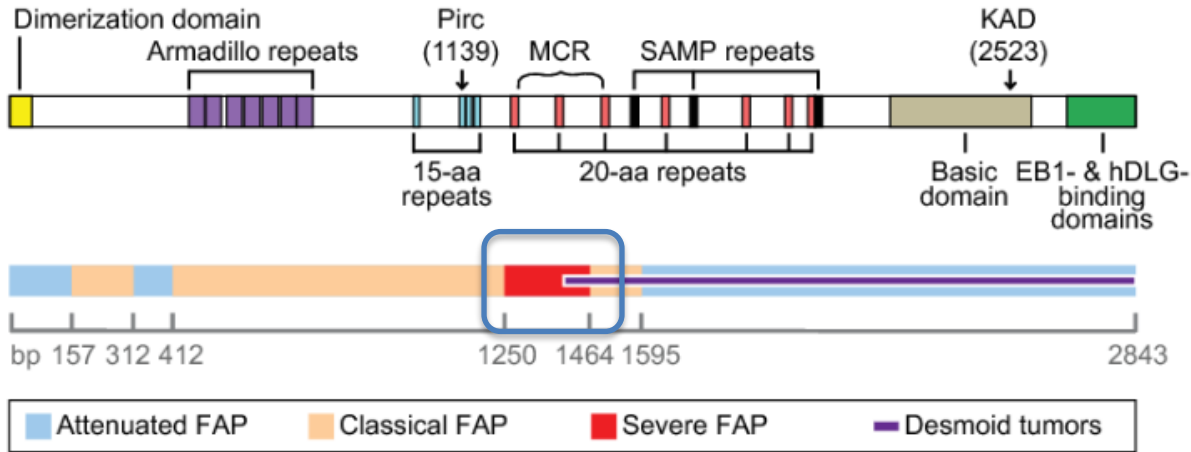
Asse Adenoma-carcinoma



Fattori genetici

Schmitt and Greten, 2021

Il gene APC (Adenomatous Polyposis Coli)

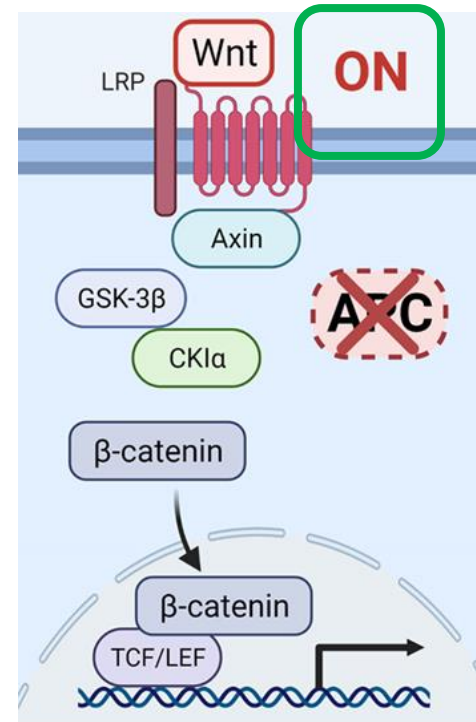
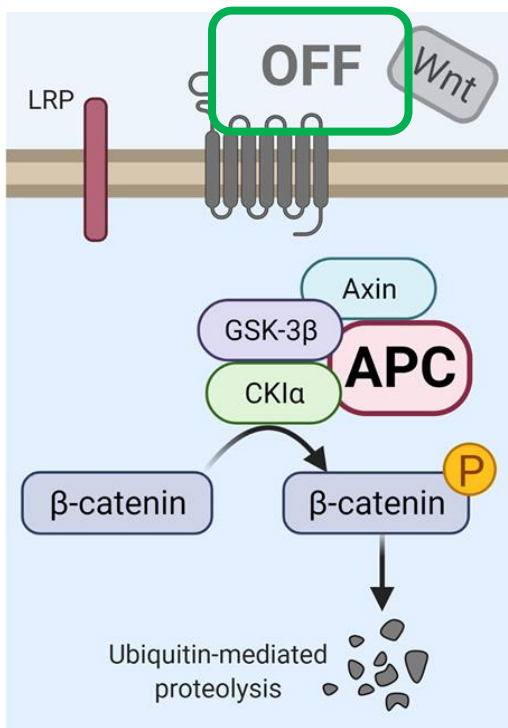


Irving et al., 2014



**FAP: Poliposi
Adenomatosa Familiare**

WNT/ β -catenin pathway



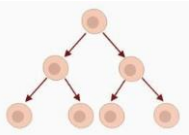
APC funzioni cellulari



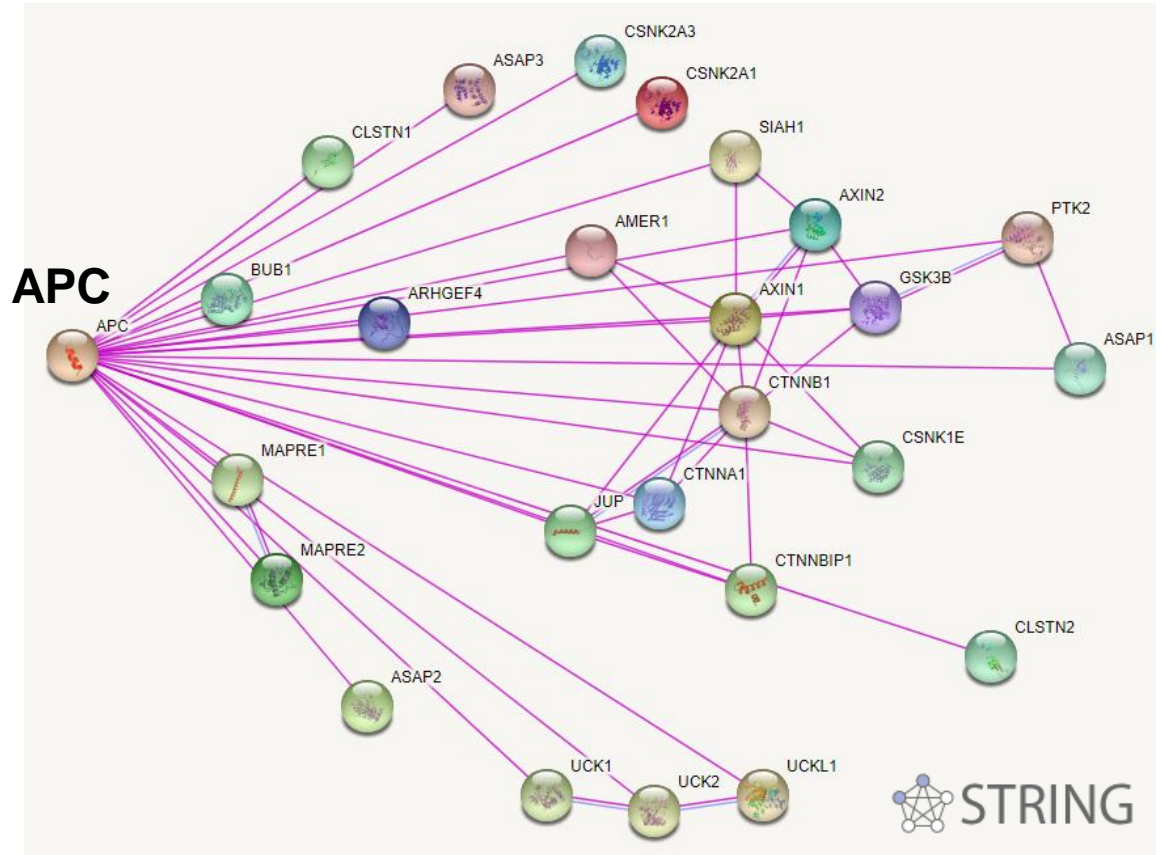
Adesione



Migrazione



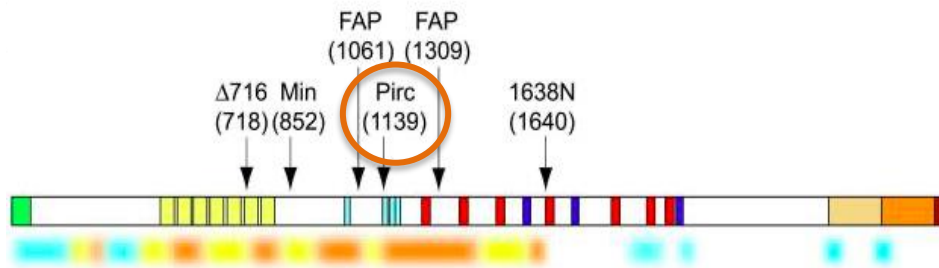
Proliferazione



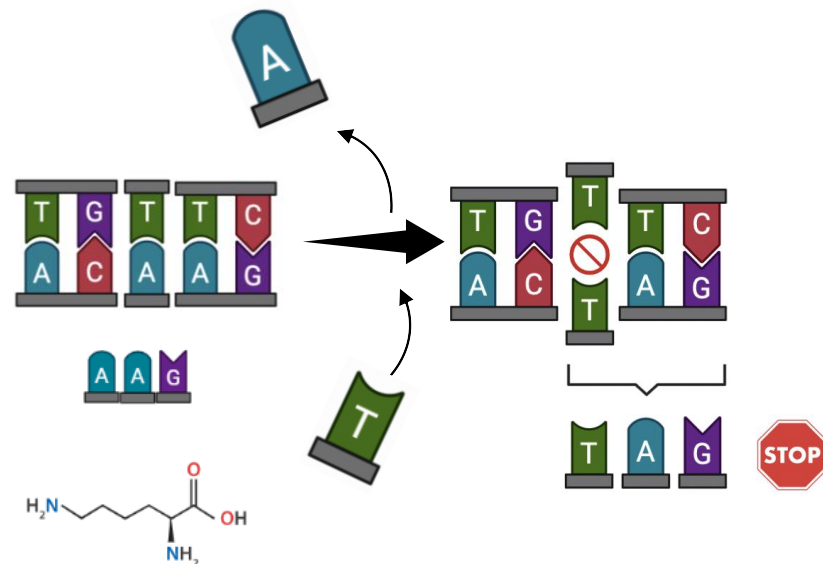


Il ratto PIRC (Polyposis in the rat colon) F344-Apc^{am1137/+}

Apc nel ratto PIRC

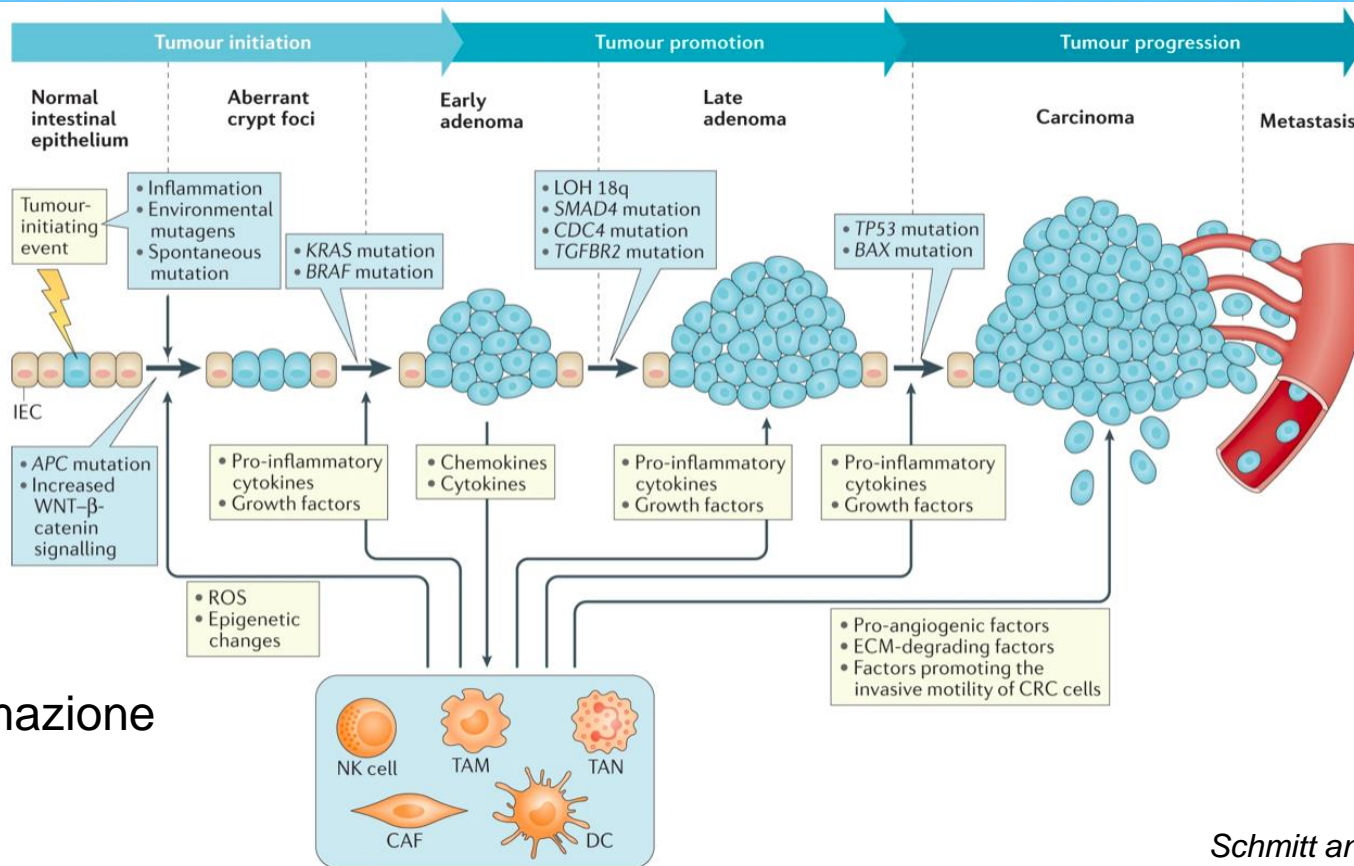


Colon di ratto PIRC



Fattori genetici

Infiammazione

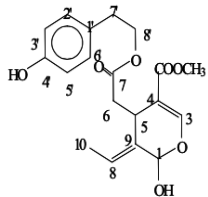


Schmitt and Greten, 2021

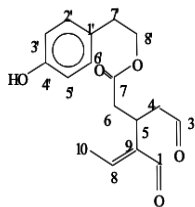
Infiammazione e cancerogenesi colica

- La Colite Ulcerosa e la malattia di Crohn aumentano di circa il 20% il rischio di sviluppare cancro del colon.
- I tumori intestinali presentano un' over-espressione di geni pro-infiammatori.
- I FANS (Farmaci Antinfiammatori Non Steroidei) riducono la cancerogenesi colica sia nell'uomo sia in modelli animali.

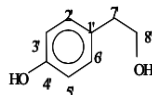
Polifenoli dell' *Olea europaea* L.



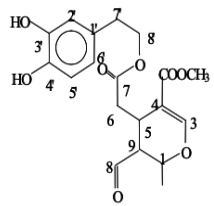
LIGSTROSIDE AGLYCON
(*p*-HPEA-EA)



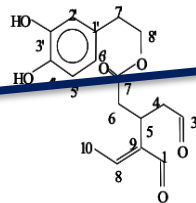
DIALDEHYDIC FORM OF
DECARBOXYMETHYL
EULENOLIC ACID LINKED TO *p*-HPEA
(*p*-HPEA-EDA) = OLEOCHANTAL



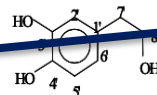
(*p*-HYDROXYPHENYL) ETHANOL
(*p*-HPEA)



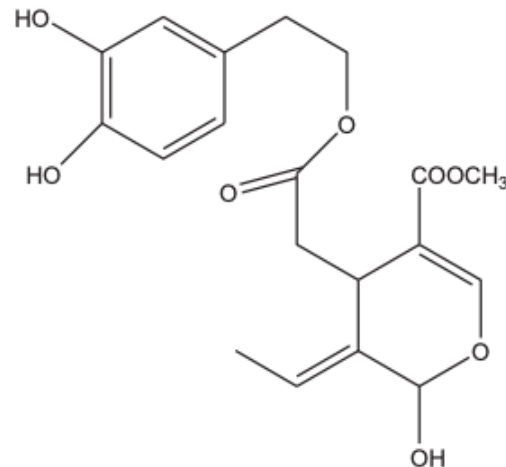
OLEUROPEIN AGLYCON
(3,4-DHPEA-EA)



DIALDEHYDIC FORM OF DECARBOXYMETHYL
ENOLIC ACID LINKED TO 3,4-HPEA
(3,4 DHPEA-EDA)



(3,4-DIHYDROXYPHENYL) ETHANOL
(3,4-DHPEA)



Oleuropeina aglicone

Proprietà Oleuropeina



Article

Oleuropein, the Main Polyphenol of *Olea europaea* Leaf Extract, Has an Anti-Cancer Effect on Human BRAF Melanoma Cells and Potentiates the Cytotoxicity of Current Chemotherapies

Jessica Ruzzolini¹, Silvia Peppicelli¹, Elena Andreucci¹, Francesca Bianchini¹, Arianna Scardigli², Annalisa Romani², Giancarlo la Marca³, Chiara Nediani^{1,*} and Lido Calorini^{1,4,*}



Article

Cancer Glycolytic Dependence as a New Target of Olive Leaf Extract

Jessica Ruzzolini¹, Silvia Peppicelli¹, Francesca Bianchini¹, Elena Andreucci¹, Silvia Urciuoli², Annalisa Romani², Katia Tortora³, Giovanna Caderni³, Chiara Nediani^{1,*} and Lido Calorini^{1,4,*}

Oleuropein Prevents Azoxymethane-Induced Colon Crypt Dysplasia and Leukocytes DNA Damage in A/J Mice

Maria Vittoria Sepporta,^{1,*} Raffaella Fuccelli,^{1,*} Patrizia Rosignoli,¹ Giovanni Ricci,² Maurizio Servili,³ and Roberto Fabiani¹

¹Biochemistry and Molecular Biology Unit, Department of Chemistry, Biology and Biotechnology;
²Laboratory of Histology, Central Animal Unit; ³Food Science and Technology Unit,
Department of Agricultural, Food and Environmental Science; University of Perugia, Perugia, Italy.

Scopo del lavoro

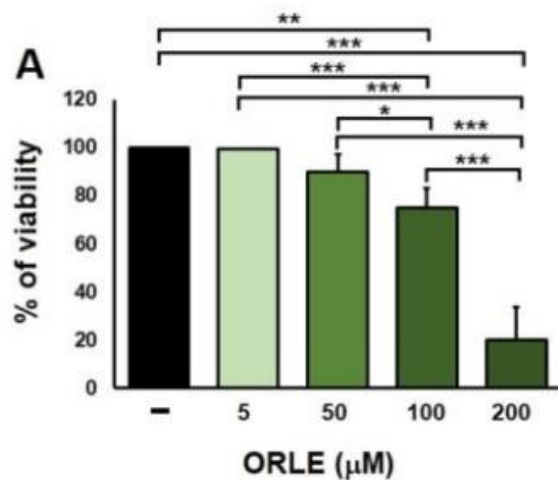
Capire se e come un trattamento con un estratto fogliare arricchito in Oleuropeina (ORLE) sia in grado di influenzare in tumori già formati, processi cellulari essenziali nella progressione tumorale.

- Infiammazione
- Apoptosi
- Proliferazione cellulare

In vivo in ratti PIRC
e *in vitro*

Risultati

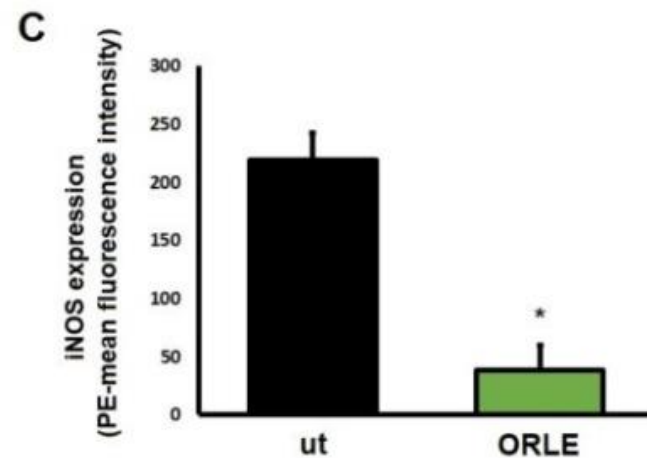
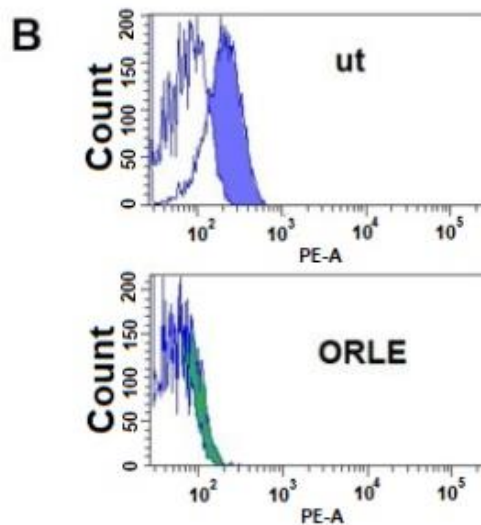
Saggio MTT HCT116



* p < 0.001
** p < 0.0001
*** p < 0.00001

Citofluorimetria a flusso

HCT116 esposte a 50 μM ORLE per 72h

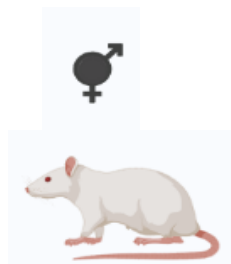


* p < 0.0001

One-way ANOVA with post-hoc Tukey's test

Strategia sperimentale

Analisi *In vivo*



12 mesi

PIRC

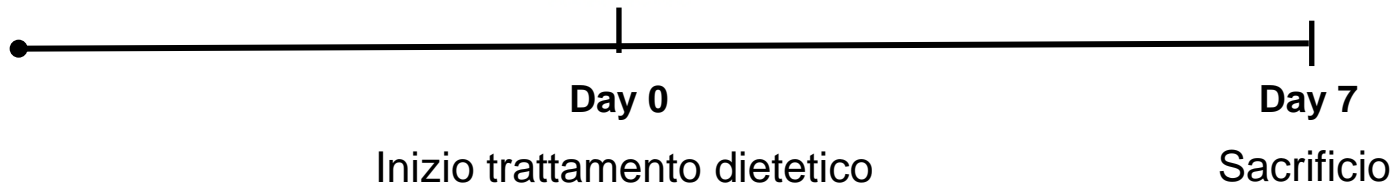


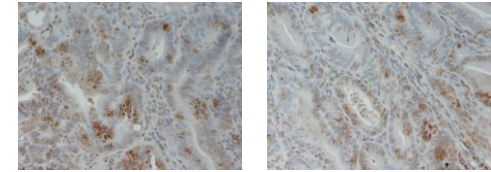
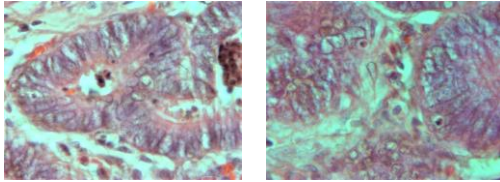
AIN-76

12 g/die/ratto

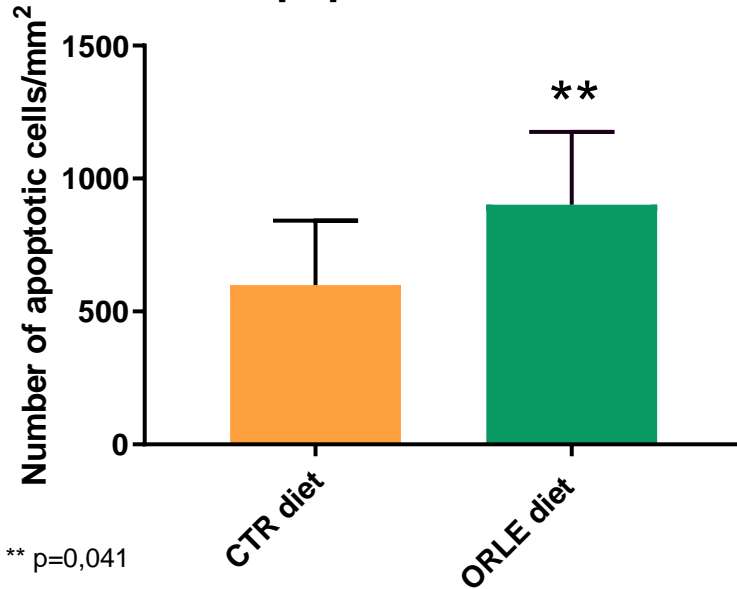


AIN-76 diet + ORLE
2,7 g/kg

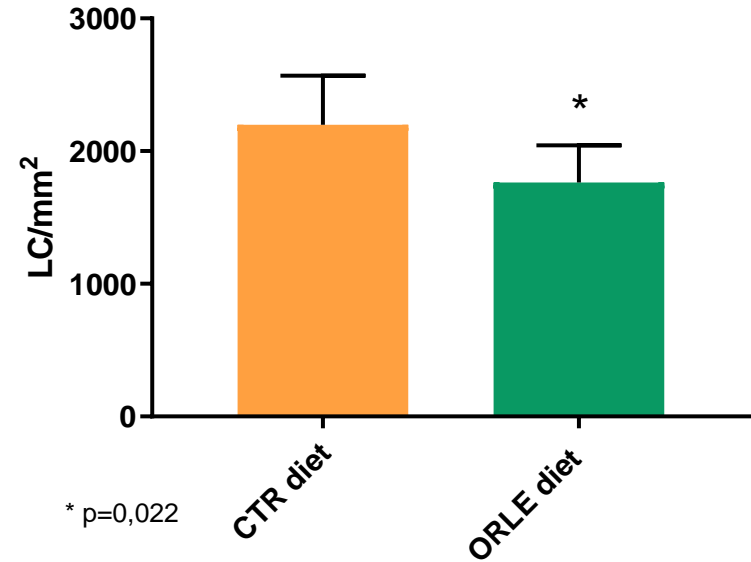


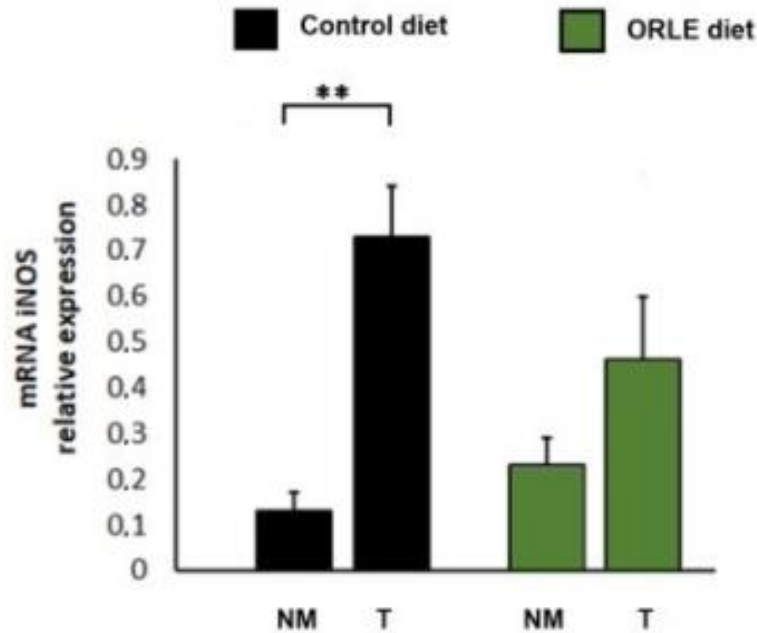


Apoptosi nei tumori



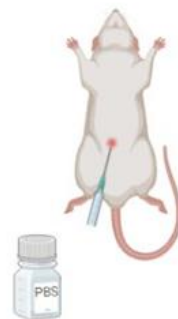
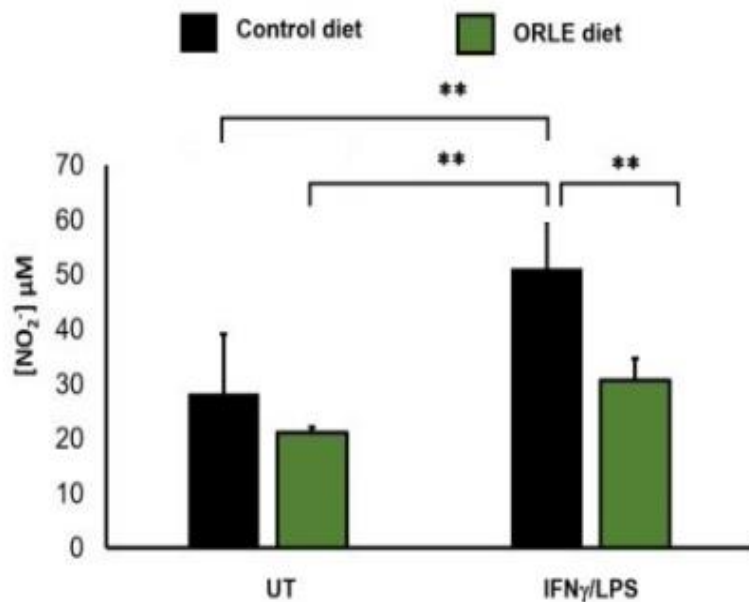
Attività proliferativa nei tumori



Espressione *iNOS* in tumori del colon

**p=0.0016 Two-way ANOVA

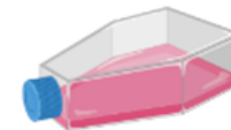
Produzione NO in macrofagi peritoneali



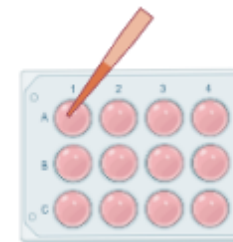
IFN_γ (50 U/mL)
LPS (10 ng/mL)
per 48h

Valutazione produzione NO in macrofagi murini

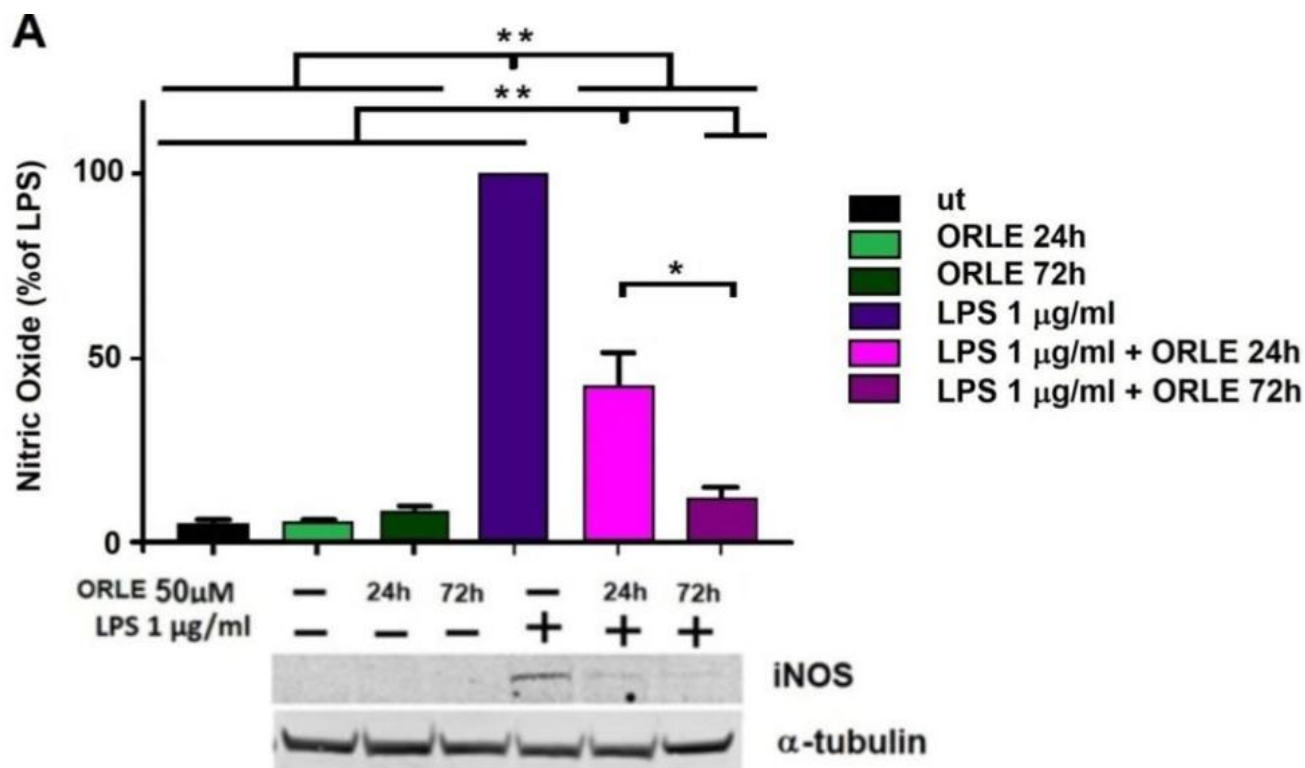
- Co-trattamento per 24h con LPS e 50 μ M ORLE.
- Pre-trattamento per 72h con 50 μ M ORLE a seguire il trattamento per 24h con LPS.



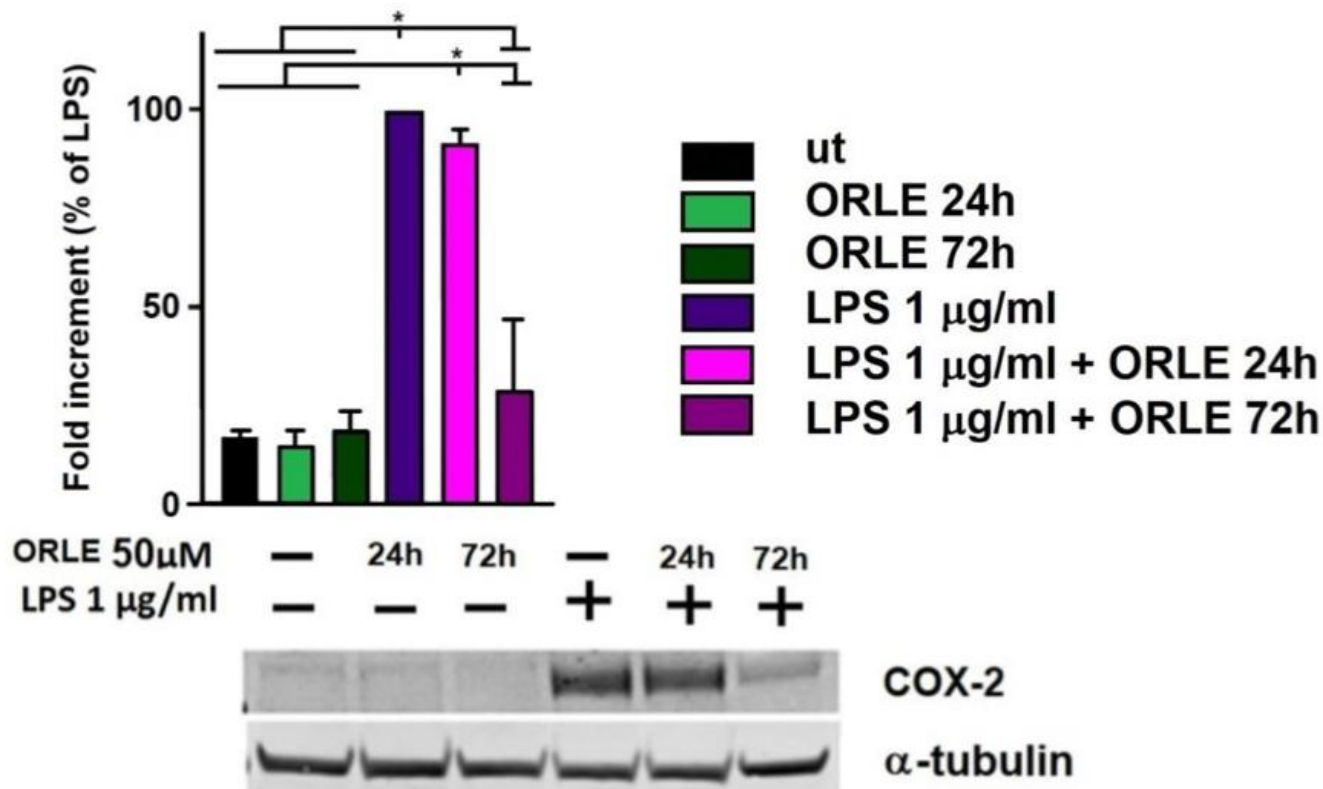
RAW 264.7



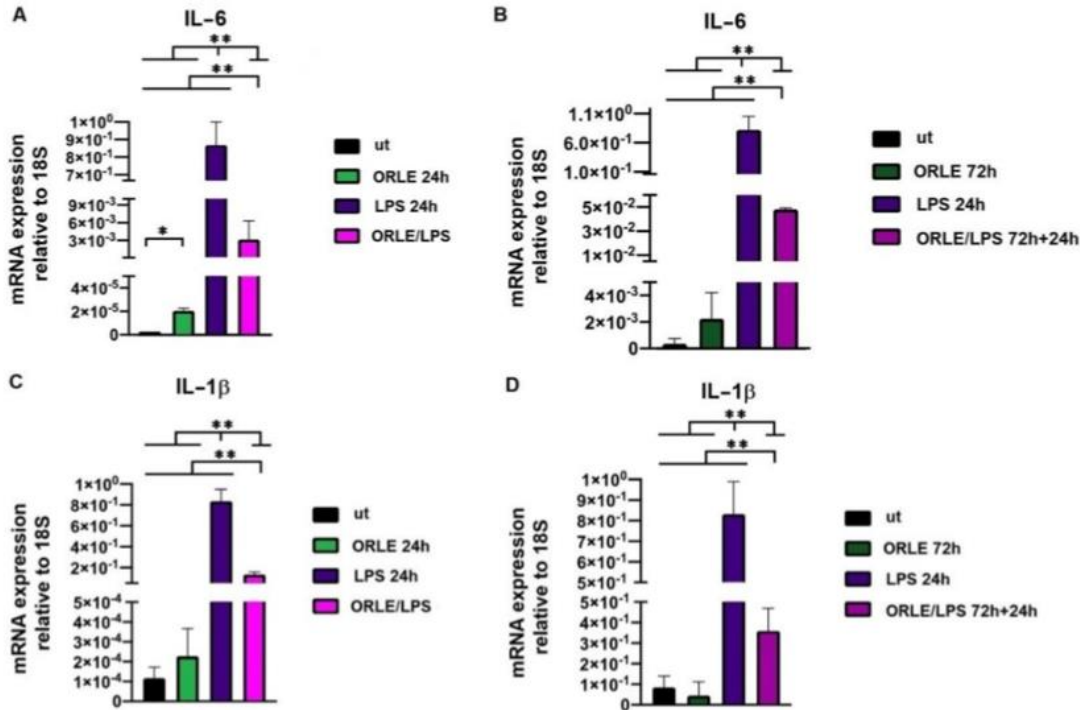
Produzione NO in RAW 264.7



Espressione di COX-2 in RAW 264.7

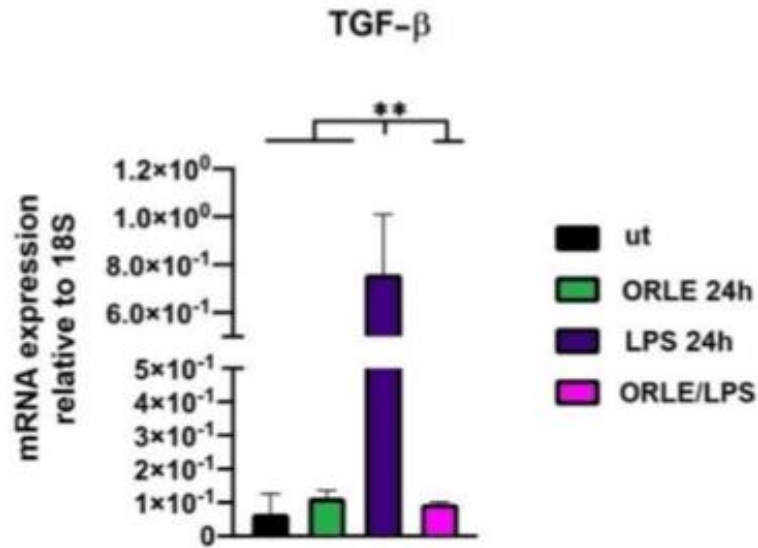


Espressione mRNA in RAW 264.7

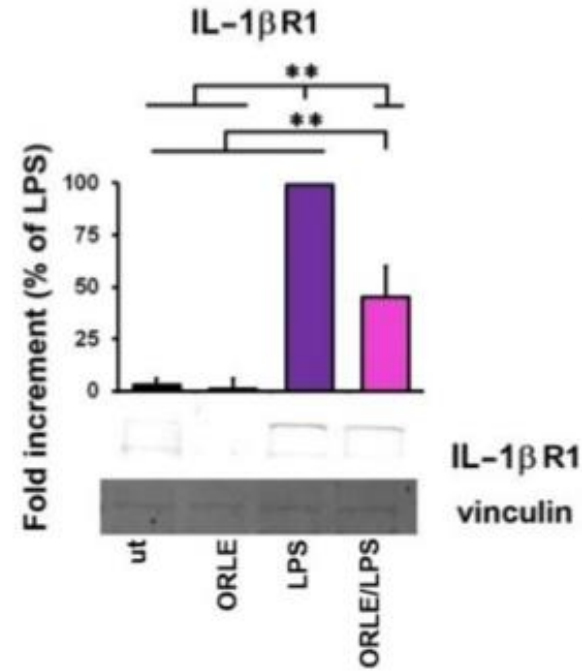
Co-trattamento
ORLE e LPS e
pre-trattamento
con ORLE

Espressione mRNA in RAW 264.7

E



F

Co-trattamento
con ORLE e
LPS

Conclusioni

- ORLE diminuisce la proliferazione, aumenta l'apoptosi e smussa l'over-espressione di *iNOS* in tumori del colon di ratti PIRC.
- ORLE diminuisce la produzione di NO da parte dei macrofagi peritoneali.
- Su linee cellulari di macrofagi ORLE diminuisce la produzione di NO e l'espressione di enzimi e citochine pro-infiammatorie.

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**Grazie per
l'attenzione**



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Production of EVOO and valorization of olea wastes

