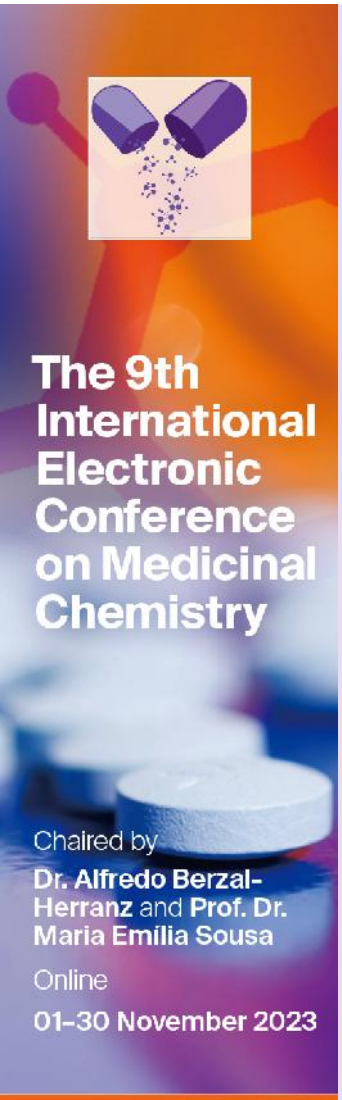


Rosa Amoroso
Department of Pharmacy , University "G. d'Annunzio" of Chieti - Pescara
via dei Vestini 31, 66100 Chieti, Italy

rosa.amoroso@unich.it

ANTIPROLIFERATIVE ACTION IN PANCREATIC CANCER CELLS OF A RESVERATROL DERIVATIVE

Abstract

The naturally occurring resveratrol (3,5,4'-trihydroxy-trans-stilbene, RSV) is a phytoalexin produced by plants in response to various stresses, promoting disease resistance. It received a great attention for its ability to impact on multiple key processes in cancer cell biology, although limitations in terms of poor solubility in water and extensive phase II metabolism reduce the bioavailability to less than 1%.

Chemically, RSV contains a stilbene scaffold that represents a suitable tool for chemical modifications with the aim to obtain derivatives with enhanced bioavailability and pharmacological activity. Bearing in mind that the 4'-OH was considered essential for the antioxidant/antitumor activity, we synthesized analogs of the RSV in which the 4'-OH was preserved, but the 3,5-OH moiety was replaced with 4-substituted phenyls. Two of the synthesized compounds have proven to be active in inhibiting cell viability across three distinct PC cell lines, as compared to the parent compound RSV

Antiproliferative action in pancreatic cancer cells of a resveratrol derivative

KEYWORDS

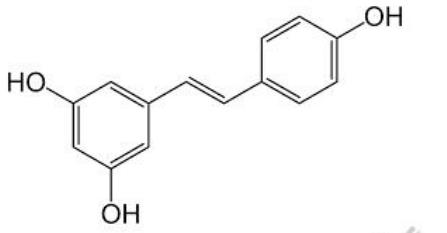
Resveratrol

Resveratrol analogues

Chemical synthesis

Pancreatic cancer

Cell viability

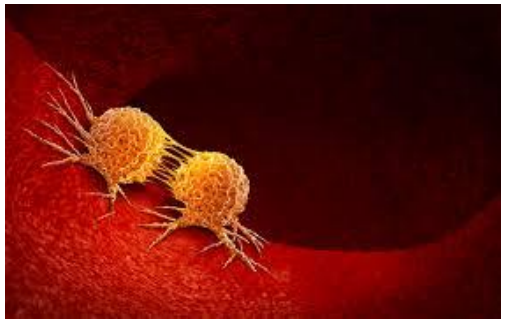


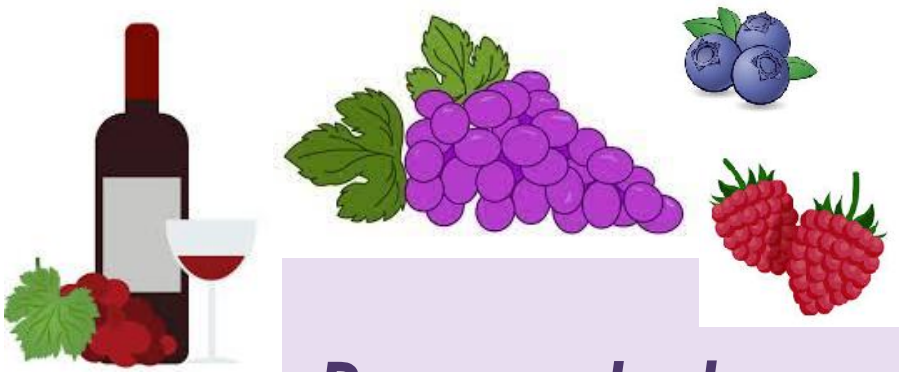
Pancreatic cancer

Pancreatic cancer (PC) is one of the deadliest malignancies, with an increasing incidence and limited response to current therapeutic options. More effective and low-toxic agents are needed to improve PC patients' outcomes

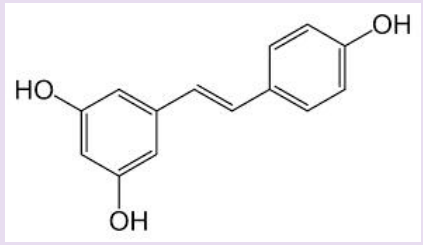
Several strategies are pursued to expand the treatment options in PC:

- new drug discovery
- repurposing of non-anticancer drugs
- use of natural compounds and their derivatives



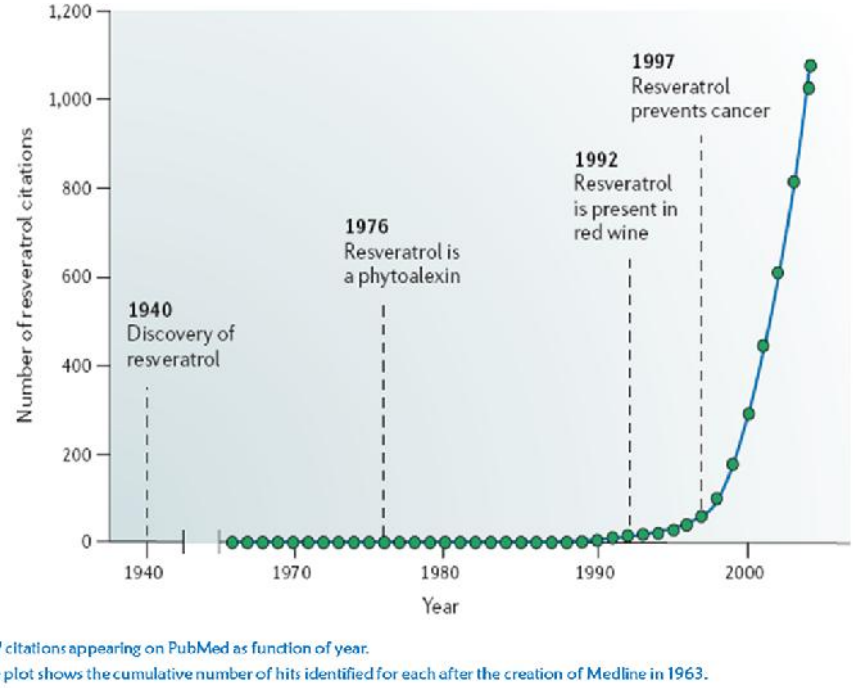


Resveratrol



3,5,4'-trihydroxy-*trans*-stilbene

RSV is a naturally occurring compound, found, in particular, in grapeskin, red wine and seeds

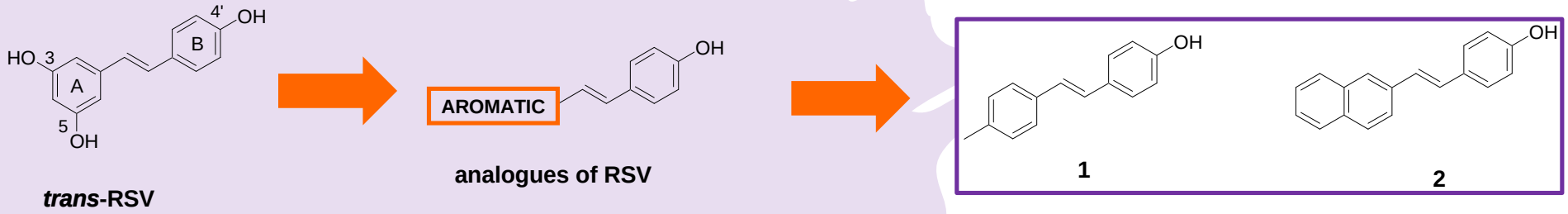


RSV citations appearing on PubMed as function of year.
The plot shows the cumulative number of hits identified for each after the creation of Medline in 1963.

Antioxidant, antitumor, cardioprotective, vasorelaxant, phytoestrogenic and neuroproctive properties …

… but poor bioavailability

Analogues of RSV



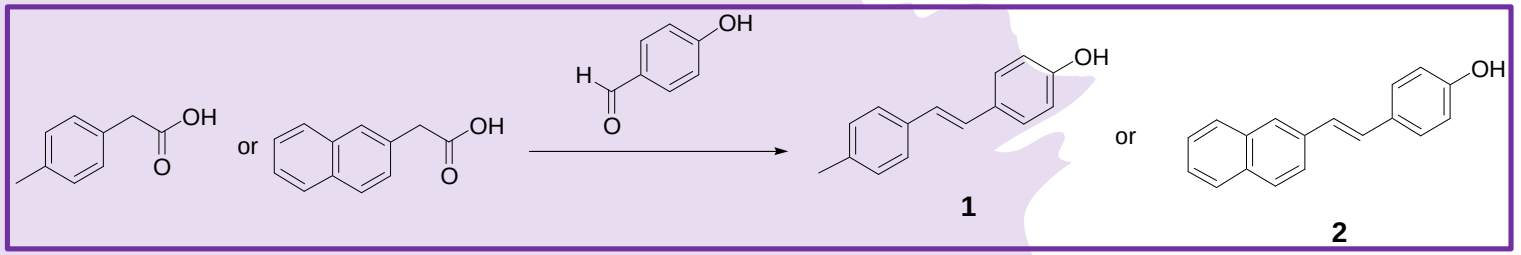
***trans*-RSV**

analogues of RSV

B. De Filippis, L. De Lellis, R. Florio, A. Ammazzalorso, P. Amoia, M. Fantacuzzi, L. Giampietro, C. Maccallini, R. Amoroso, S. Veschi, A. Cama. Synthesis and cytotoxic effects on pancreatic cancer cells of resveratrol analogs. Med. Chem. Res. 2019, 28, 984-991

R. Florio, B. De Filippis, S. Veschi, V. Di Giacomo, P. Lanuti, G. Catitti, D. Brocco, A. Di Rienzo, A. Cataldi, I. Cacciatore, R. Amoroso, A. Cama, L. De Lellis. Resveratrol derivative exhibits marked antiproliferative actions, affecting stemness in pancreatic cancer cells. Int. J. Mol. Sci. 2023, 24, 1977

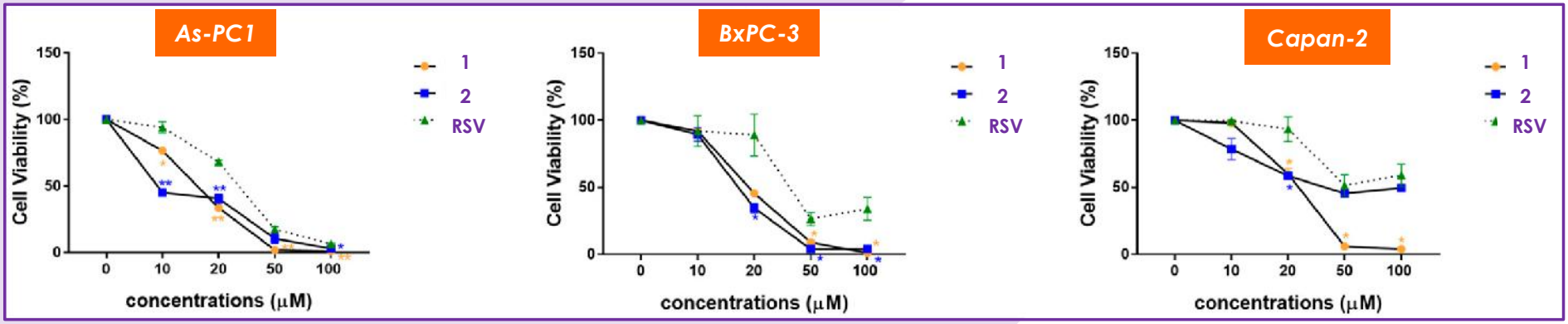
Synthesis



Reagents and conditions: piperidine, 130 °C, 24 h

PC lines viability

MTT assay



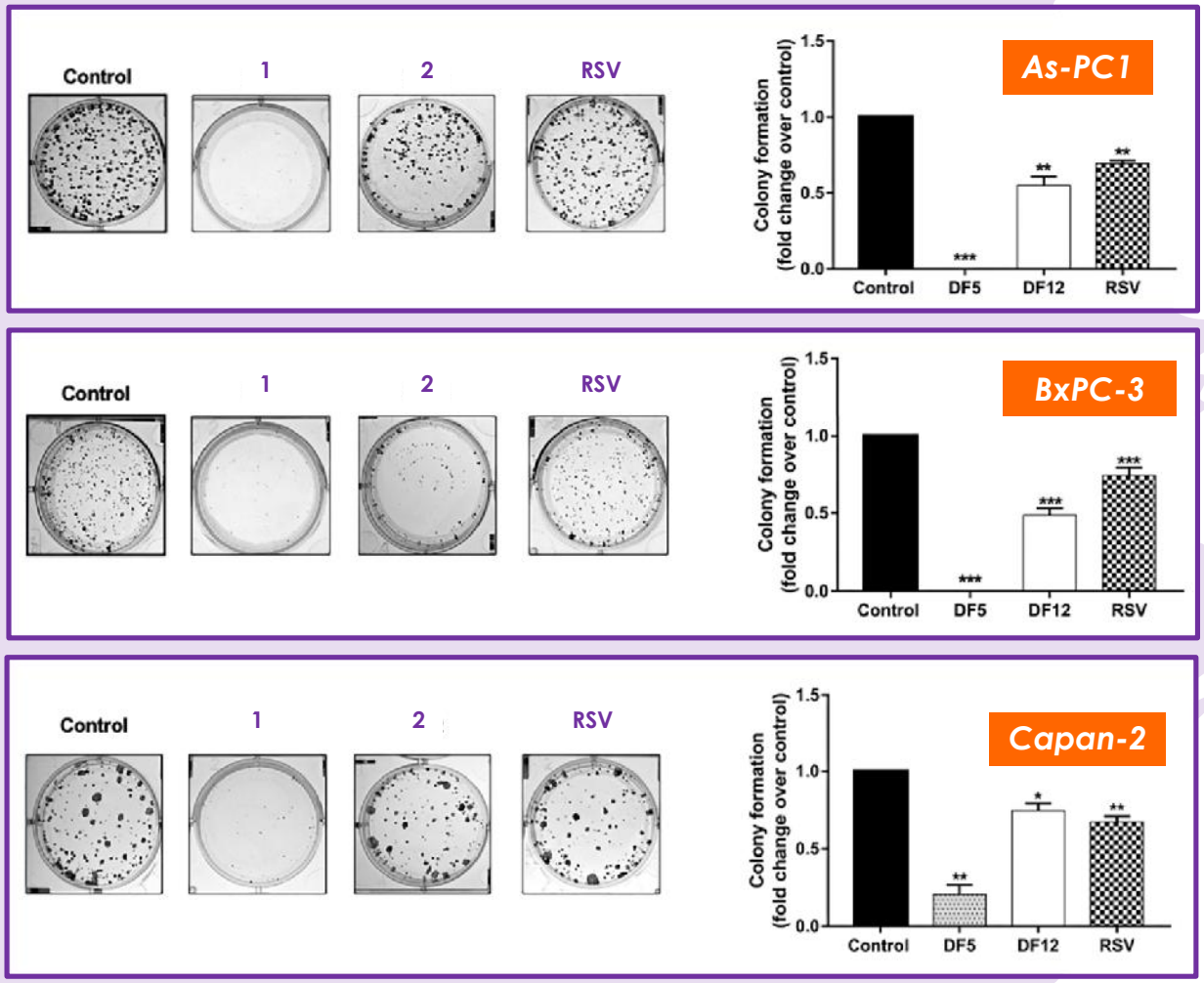
IC_{50} (μg/mL) of resveratrol analogues **1-2**

Compound	AsPC-1	BxPC-3	Capan-2
1	14.72	22.70	27.75
2	11.07	18.28	58.05
Resveratrol	29.01	48.73	>100

Compounds **1-2** inhibited PC cell viability in a dose-dependent manner, although with distinct sensitivities across the three PC cell lines

Best results were obtained with **1**, showing good antiproliferative effects across the three PC cell lines

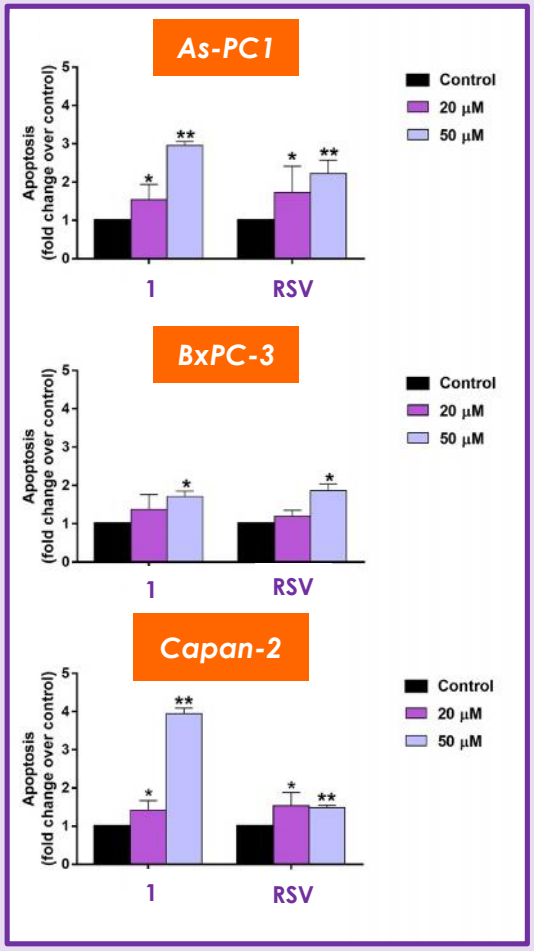
Clonogenic capacity of PC cell lines



The clonogenicity was reduced after treatment with each compound, but best results were obtained with compound **1**. It showed drastic and consistent effects on PC cell clonogenic capacity, totally abolishing colony formation in AsPC-1 and BxPC-3 cells

We selected **1** as a further characterization

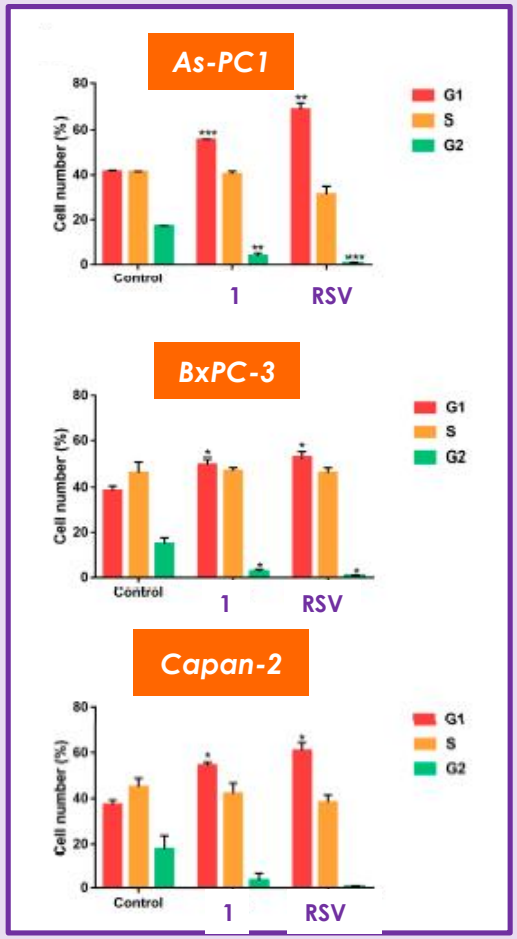
Apoptosis in PC cell lines



At a lower concentration of 20 μM, compound **1** induced a poor apoptosis on three cellular line cellular, as well as the RSV

Instead, at a higher concentration (50 μM), the treatment with **1** resulted in a significant induction of apoptosis, with a sharper increase in AsPC-1 and Capan-2, as compared to BxPC-3 cells. The effects of RSV are less significant

Effects on PC cell cycle

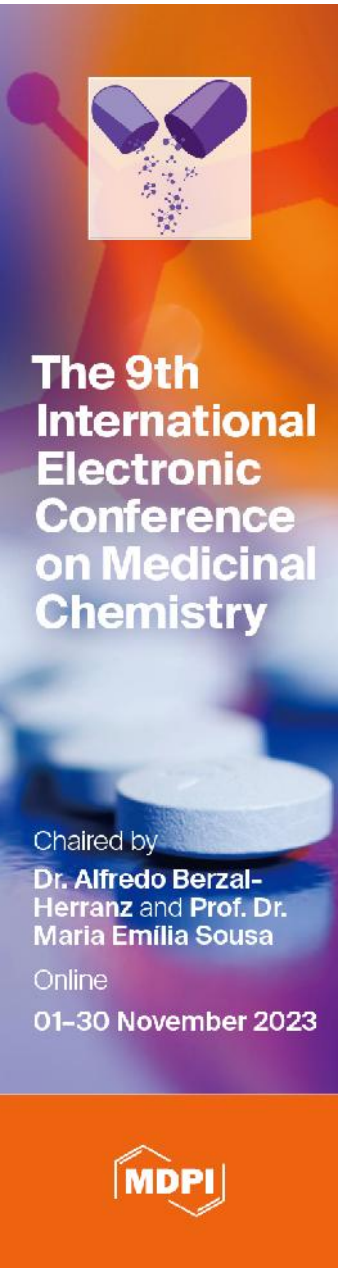


The flow cytometry analyses showed that treatments with compound **1**, at 50 μM, profoundly altered the cell cycle, with similar patterns in the three PC cell lines.

In particular, it promoted a significant accumulation of cells at the G0/G1 phase across the three PC cell lines after a 24 h treatment, along with a drastic depletion of cells in the G2/M phase, as compared with untreated cells

Conclusion

- In this study, we explored the antiproliferative activities of RSV analogues **1** and **2** in a panel of PC cell lines
- Both derivatives exhibit antiproliferative and anticlonogenic action
- The treatment with the most active compound **1** resulted in a significant induction of apoptosis across the three PC cell lines and alteration of cell cycle
- Our results support the potential value of RSV analogues in the search for effective and safe agents for PC treatment



Acknowledgment

Barbara De Filippis

Rosalba Florio

Alessandro Cama

Amelia Cataldi

UNIVERSITÀ DEGLI STUDI G. D'ANNUNZIO CHIETI PESCARA

Department of Pharmacy