

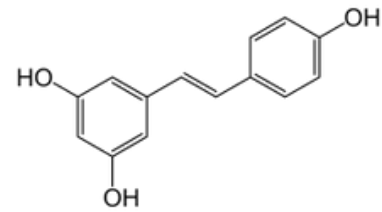
RESVERATROL

COMMON NAME: Grape seed/skin extract

OCCURRENCE: Resveratrol is found in highest concentrations in the skin of red grapes and other fruits (mulberries, blueberries, blackberries).

CHEMICAL CLASS: Natural plant polyphenol (3,5,4'-trihydroxystilbene)

ACTIVE FORM: Trans-resveratrol



PROPERTIES OF RESVERATROL ACCORDING TO CLINICAL TRIALS

Anti-inflammatory, antiarthritic (4) (5), antidiabetic (6), neuroprotective (7), antiviral (8), cardioprotective (9), anti-neoplastic, anti-angiogenic (10), hypotriglyceridemic effects (5)

SYNERGY WITH CHEMOTHERAPY

The combination of resveratrol and copper may be able to reduce chemotherapy-related non-haematological toxicities in patients with advanced gastric cancer. (1)

APPLICATIONS IN ONCOLOGY ACCORDING TO CLINICAL TRIALS

1. Resveratrol may act as a pro-oxidant to eliminate toxic free chromatin particles (cfChPs), released from chemotherapy-induced dying cells. (1)
2. Resveratrol could reduce tumor cell proliferation by 5%. Daily oral doses of resveratrol at 0.5 or 1.0 g produce levels in the human gastrointestinal tract of an order of magnitude sufficient to elicit anticarcinogenic effects. (2)
3. Grape seed procyanidin extract (GSE) might act as an anti-neoplastic and chemopreventive agent against lung cancer. (3)

CLINICAL SAFETY AND TOXICITY

Topical and oral formulations of Resveratrol were well-tolerated with no serious adverse events. Minor side effects such as gastrointestinal symptoms, nausea, diarrhea and weight loss were reported. No dose-related signs of toxicity were observed even at 5g/day of resveratrol. (39), (40), (41), (42)

FORMULATION CHARACTERISTICS OF "PUROBEST RESVERATROL"

Each capsule of Purobest Resveratrol contains 500mg of Resveratrol as 98% Transresveratrol from Grape Skin.

MECHANISM OF ACTION

The signaling pathways by which resveratrol suppresses the malignant biological behaviors of cancer cells, including proliferation, antiapoptosis, invasion, migration, EMT progress, levels of ROS, and stemness are as shown in the figure A.

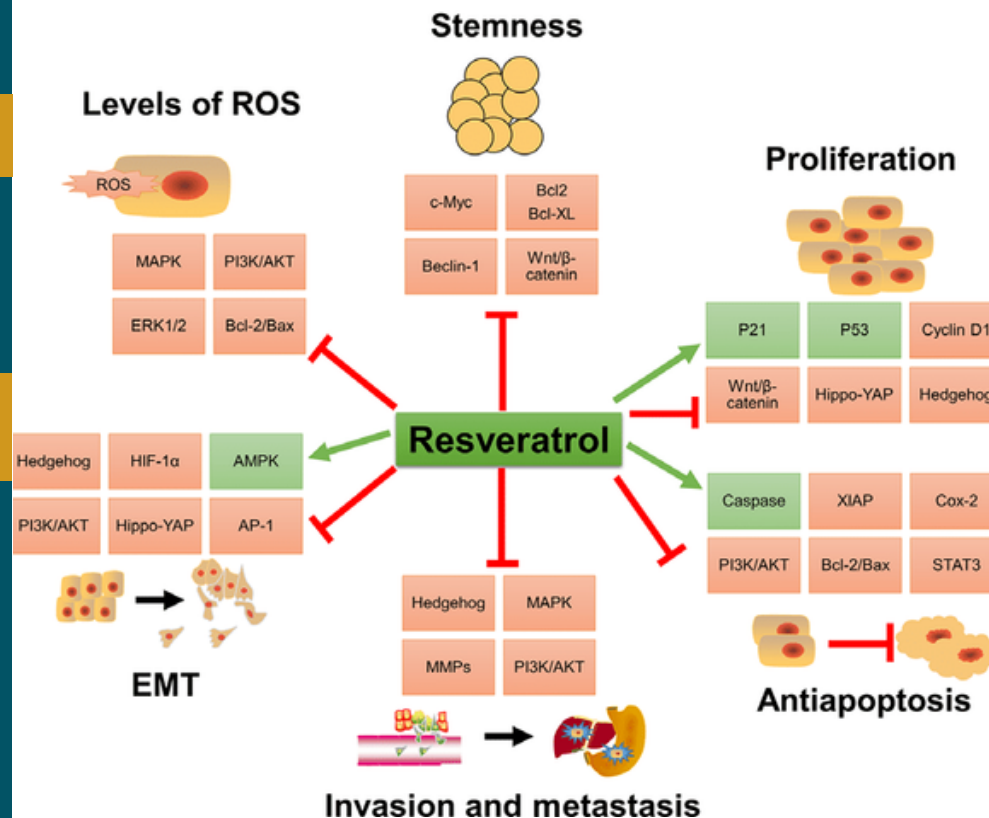


FIGURE A) CELLULAR PATHWAYS AFFECTED BY RESVERATROL

1. Proliferation:

- Upregulation of cyclin-dependent kinase inhibitors, tumor suppressor genes, death-induced cytokines, and their receptors. (11), (12)
- Downregulation of hedgehog (HH), hippo-YAP, Wnt/β-catenin pathway, and cyclin D1. (13), (14), (15)

2. Stemness:

- Downregulation of the expression of survival proteins associated with the development of chemoresistance, including survivin, cFLIP, cIAPs, and antiapoptotic proteins (Bcl-2 and Bcl-XL), c-myc, Wnt/β-catenin pathway, and beclin-1. (13), (16), (17), (18)

3. Levels of ROS:

- Downregulation of survival proteins (i.e survivin, cFLIP, cIAPs), antiapoptotic proteins, inhibition of MAPK, PI3K/Akt and ERK1/2 signaling pathways. (19), (16), (17), (20)

4. EMT progress:

- Upregulation of AMPK. (15)
- Downregulation of hedgehog (HH), hippo-YAP activating protein-1 (AP-1), HIF-1a, PI3K/Akt. (14), (15), (21), (22), (23), (19)

5. Invasion and migration:

- Downregulation of MAPK, PI3K/Akt, hedgehog (HH), and MMP. (19), (14), (24)

6. Antiapoptosis:

- Regulation of mitochondrial and caspase cascade enzymatic system activation. (25), (26)
- Downregulation of survival proteins (survivin, cFLIP, cIAPs), antiapoptotic proteins (Bcl-2 and Bcl-XL), PI3K/Akt, STAT3, and COX-2. (19), (16), (17), (27), (28), (29)

ROLE OF RESVERATROL IN THE TUMOR MICROENVIRONMENT AND THE SENSITIZATION OF CANCER CELLS FOR CHEMOTHERAPY AND RADIOTHERAPY

1. Inhibition of Angiogenesis:

- Resveratrol impairs VEGF expression through downregulation of HIF-1. (30)

2. Inhibition of proliferation, invasion, migration, and chemoresistance:

- Resveratrol suppresses the activation of cancer-associated fibroblasts by inhibiting the NF-κB and EGFR/Akt/ERK1/2 signaling pathways. (31), (32), (33), (34)

3. Anti-inflammatory activity:

- Resveratrol exhibits anti-inflammatory activity by inhibiting COX-2, NF-κB or AP-1, decreasing the secretion of proinflammatory factors (IL-1, IL-6, and TNF-α) (35), inhibition of activated immune cells, such as T cells, B cells, and macrophages as well as increasing anti-inflammatory factors like IL-10 and TGF-β. (21), (29), (35), (36), (37) (38)

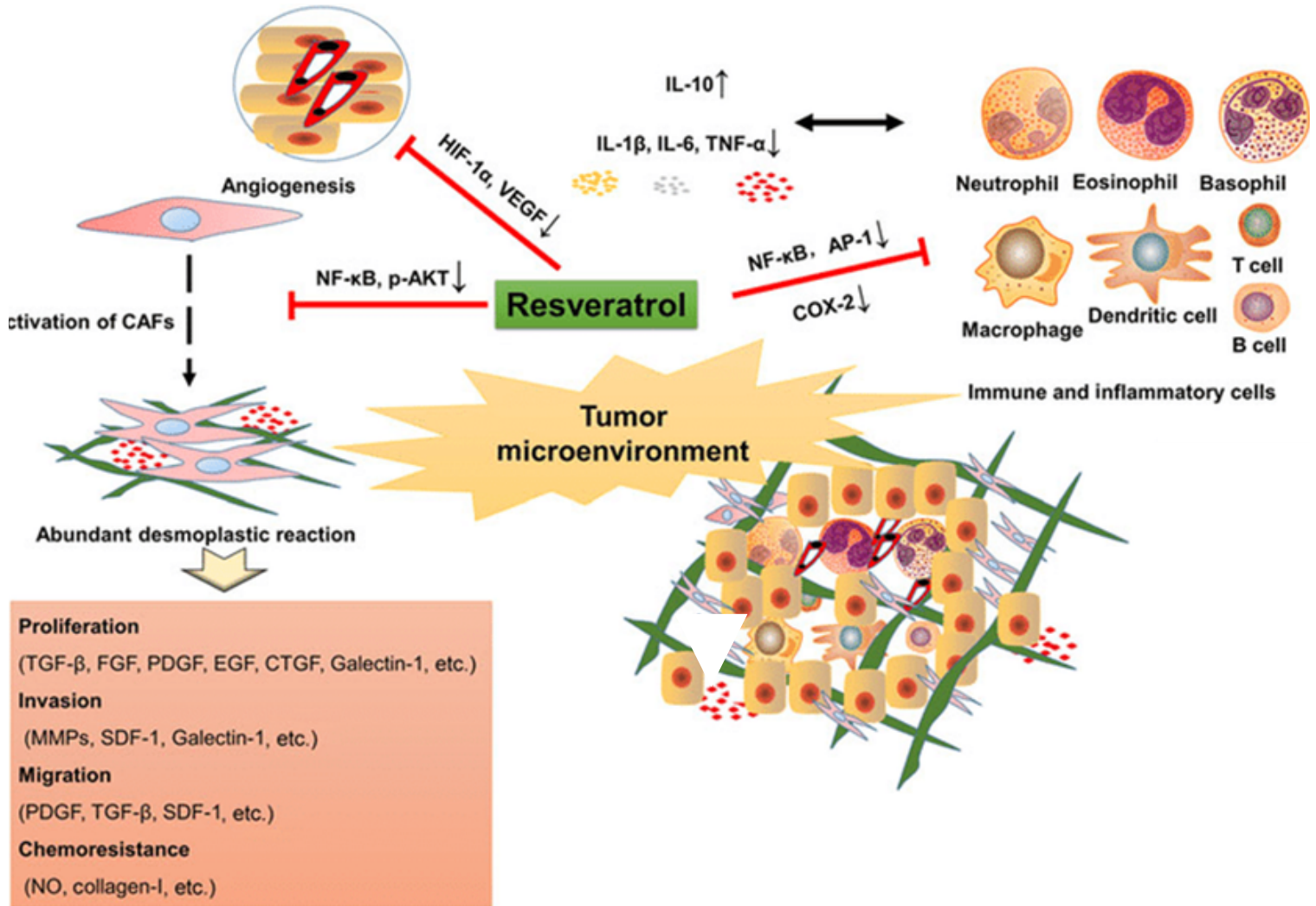


Figure B) The effects of resveratrol on the tumor microenvironment

DOSE RECOMMENDED IN PUBLISHED CLINICAL TRAILS OF CANCER

5.0 g resveratrol daily (42)
OR
0.5 or 1.0 g resveratrol daily (2)

PUROBEST RESVERATROL RECOMMENDED DOSAGE

One capsule of Purobest Resveratrol once or twice a day with water or as recommended by the healthcare practitioner. Quality of active ingredient is ensured via third party testing.

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