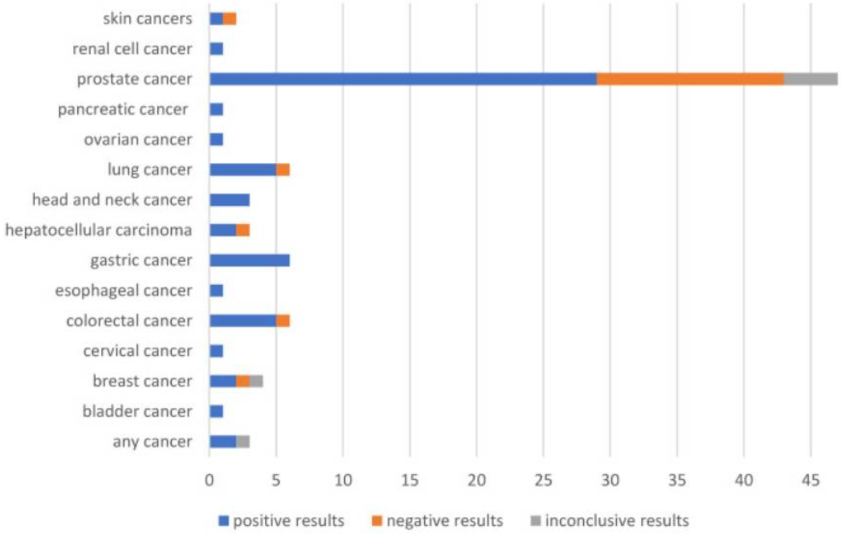
Lycopene

-listed as part of "Extending the Pro-Oxidant Strategy" under cancerTreatmentResearch.com
- low doses, it acts as an antioxidant, but at high doses, it acts as a pro-oxidant (not univerisally accepted)

https://www.cancertreatmentsresearch.com/modulating-the-yin-and-yang-energy-of-cells-to-fight-cancer-pro-oxidant-strategy/?highlight=lycopene
Extending the "Pro-Oxidant Strategy" Strategy
Cellular Building Blocks" inhibition and inhibition of the the Melavonate Pathway
Inhibition of Melavonate Pathway has been discussed on this website extensively here and here. The following are the major inhibitors I would use:
HydroxyCitrate (HCA) found as supplement online and typically used in a dose of about 1.5g/day or more
Atorvastatin typically used in cancer treatments in a dose of 40-80mg/day
Dipyridamole typically used in the range of 200mg 2x/day
Lycopene typically used in a 100mg/day range

https://pmc.ncbi.nlm.nih.gov/articles/PMC9741066/
The Anti-Cancer Activity of Lycopene: A Systematic Review of Human and Animal Studies 2022
We concluded that the results of most of the reviewed in vivo studies confirmed the anti-cancer activities of lycopene.
The reported mechanisms of lycopene action in vivo included regulation of oxidative and inflammatory processes, induction of apoptosis, and inhibition of cell division, angiogenesis, and metastasis formation. The predominance of particular mechanisms seemed to depend on tumour organ localisation and the local storage capacity of lycopene.
It is naturally found mainly as the trans isomer in varying concentrations in tomatoes, but also in other red fruits and vegetables such as red carrots, watermelons, grapefruits, and papayas [2]. The lycopene content of tomatoes ranges from 0.88 to 7.74 mg/100 g and depends on the species and ripening stage [3]
The accumulation of lycopene also depends on other factors, such as age, body weight, gastrointestinal status, lifestyle habits, or food intake [5]. Large molecules such as pectins hinder lycopene absorption, while fat facilitates it. Therefore, oil-resolved lycopene dietary supplements may be more efficient than food sources [6].
An interesting feature of lycopene is its dual effect on oxidative processes. In addition to the aforementioned antioxidant capacity, in the process of oncogenesis, lycopene may show an opposite pro-oxidative effect that supports the elimination of pathological cells.



https://pmc.ncbi.nlm.nih.gov/articles/PMC7244072/
Lycopene prevents carcinogen-induced cutaneous tumor by enhancing activation of the Nrf2 pathway through p62-triggered autophagic Keap1 degradation 2020
Lycopene stimulated the activation of antioxidant enzymes and the translocation of the transcription factor Nrf2 (nuclear factor erythroid 2-related factor 2) that predominantly maintained intracellular redox equilibrium. The cancer chemopreventive effects were mediated by Nrf2. Further, lycopene enhanced the expression of autophagy protein p62. Therefore this led to the degradation of Keap1(Kelch ECH associating protein 1), the main protein locking Nrf2 in cytoplasm. In conclusion, our study provides preclinical evidence of the chemopreventive effects of lycopene on cutaneous tumors and reveals the mechanistic link between lycopene's stimulation of Nrf2 signaling pathway and p62-mediated degradation of Keap1 via the autophagy-lysosomal pathway.

https://pubmed.ncbi.nlm.nih.gov/11137891/
Antioxidant and pro-oxidant effects of lycopene in comparison with beta-carotene on oxidant-induced damage in Hs68 cells 2000
Lycopene has become a focal point in recent research following clinical trials that suggest that beta-carotene may promote lung cancer in smokers. Because lycopene only differs from beta-carotene in lacking the beta-ionone structure, and beta-carotene is known to have pro-oxidant activity in vitro, we sought to determine whether lycopene might also have pro-oxidant activity in vitro in comparison with beta-carotene. Human foreskin fibroblasts (Hs68 cells) were first enriched with 10 and 20 μM lycopene or beta-carotene for 1 hr followed by incubation with various oxidants. Lipid peroxidation was measured as thiobarbituric acid-reactive substances (TBARS) released into the medium and DNA damage was measured as formation of comet and 8-hydroxy-2'-deoxyguanosine. The results showed that lycopene at 20 μM significantly decreased levels of TBARS induced by ferric nitrilotriacetate (Fe/NTA) but enhanced levels of TBARS induced by a lipid-soluble radical generator (2,2'-azobis[2,4-dimethylvaleronitrile]; AMVN). Both the antioxidant and pro-oxidant effects of lycopene tended to be dose-dependent. beta-Carotene at 20 μM did not significantly decrease TBARS induced by Fe/NTA but significantly increased TBARS induced by AMVN. Lipid peroxidation induced by a water-soluble radical generator 2,2'-azobis(2-amidinopropane)dihydrochloride was not significantly affected by either lycopene or beta-carotene. Neither lycopene nor beta-carotene affected DNA damage or changes in cell morphology induced by any of the three oxidants tested. The present study in Hs68 cells demonstrates that lycopene can be either an antioxidant or a pro-oxidant depending on the oxidants used, and that lycopene and beta-carotene behave similarly under the in vitro oxidative conditions. Although it is unclear whether lycopene may have pro-oxidant activity in vivo, our results caution that it

may be premature to undertake clinical trials with lycopene.

https://pmc.ncbi.nlm.nih.gov/articles/PMC8868303/
Lycopene: A Natural Arsenal in the War against Oxidative Stress and Cardiovascular Diseases 2022
Lycopene can increase the cellular antioxidant defense system by regenerating non-enzymatic antioxidants, such as vitamins E and C, from their radicals [26]. Vitamin E is suggested to be protected by lycopene [87,112,113]. Lycopene serves as an antioxidant in systems that create singlet oxygen, but as a pro-oxidant in systems that generate peroxide. Lycopene serves as an antioxidant due to its redox potential [114,115,116]. Indeed, lycopene behaves as a pro-oxidant in high doses while acting as an antioxidant in low ones [117]. Many factors impact pro-oxidant potency, including tissue oxygen tension, lycopene concentration, and interactions with other antioxidants [115]. As a pro-oxidant, lycopene may have both good and negative impacts in biological systems, as well as influence the course of human illnesses. If lycopene works as a pro-oxidant in previously damaged cells, it may help prevent the creation and progression of cancerous lesions as well as tumor cytotoxicity. Carotenoids' pro-oxidant effects can be limited by antioxidant connections, enhancing the antioxidant capabilities of these bioactive molecules [115].

https://pmc.ncbi.nlm.nih.gov/articles/PMC6681007/
Nutritional Importance of Carotenoids and Their Effect on Liver Health: A Review 2017
Some in vivo studies have shown that exposure to high doses of carotenoids has a pro-oxidant effect.
For lycopene, an intake of 5 to 7 mg per day was recommended for healthy people to maintain the circulating levels of this carotenoid, in order to combat oxidative stress and prevent chronic diseases [92]. Heath et al. [93] reported that higher concentrations of lycopene (35–75 mg/day) may be required when there is a disease, such as cancer and cardiovascular diseases.

https://pmc.ncbi.nlm.nih.gov/articles/PMC7402151/
Lycopene Protects against Smoking-Induced Lung Cancer by Inducing Base Excision Repair 2020
Several in vivo and human studies have shown that exposure to high doses of carotenoids has a pro-oxidant effect [43]. Although we did not observe higher oxidative stress in the high-dosage groups, we found that lycopene only exerted antioxidative effects at low-dosage, while such beneficial effects were diminished at high-dosage.

https://pmc.ncbi.nlm.nih.gov/articles/PMC11179732/
Lycopene: A Potent Antioxidant with Multiple Health Benefits 2024
In addition, lycopene acts as an antioxidant in systems that produce singlet oxygen but behaves as a pro-oxidant in systems that create peroxide [89]. In low doses, it acts as an antioxidant, but at high doses, it acts as a pro-oxidant [90]. Factors such as lycopene concentration, tissue oxygen tension, and interaction with other antioxidants have been reported to influence the pro-oxidant potency of lycopene [6]. In situation where there is an imbalance between antioxidant defences and ROS production, such as during inflammation or exposure to environmental toxins [91], lycopene may switch from its antioxidant role to a pro-oxidant role [89]. Under these conditions, lycopene radicals may contribute to oxidative stress by reacting with cellular components and promoting further ROS generation [92]. Studies have suggested that under conditions of low oxygen levels, its antioxidant properties predominate [93, 94].

https://pmc.ncbi.nlm.nih.gov/articles/PMC5489781/
Lycopene reduces ovarian tumor growth and intraperitoneal metastatic load 2017
Lycopene treatment synergistically enhanced anti-tumorigenic effects of paclitaxel and carboplatin. Immunostaining of tumor and metastatic tissues for Ki67 revealed that lycopene reduced the number of proliferating cancer cells. Lycopene decreased the expression of the ovarian cancer biomarker, CA125. The anti-metastatic and anti-proliferative effects were accompanied by down-regulated expression of *ITGA5, ITGB1, MMP9, FAK, ILK* and EMT markers, decreased protein expression of integrin α5 and reduced activation of MAPK. These findings indicate that lycopene interferes with mechanisms involved in the development and progression of ovarian cancer and that its preventive and therapeutic use, combined with chemotherapeutics, reduces the tumor and metastatic burden of ovarian cancer *in vivo*.

https://pubmed.ncbi.nlm.nih.gov/32560478/
Pro-Oxidant Actions of Carotenoids in Triggering Apoptosis of Cancer Cells: A Review of Emerging Evidence 2020
Carotenoids are well known for their potent antioxidant function in the cellular system. However, in cancer cells with an innately high level of intracellular reactive oxygen species (ROS), carotenoids may act as potent pro-oxidant molecules and trigger ROS-mediated apoptosis. In recent years, the pro-oxidant function of several common dietary carotenoids, including astaxanthin, β-carotene, fucoxanthin, and lycopene, has been investigated for their effective killing effects on various cancer cell lines. Besides, when carotenoids are delivered with ROS-inducing cytotoxic drugs (e.g., anthracyclines), they can minimize the adverse effects of these drugs on normal cells by acting as antioxidants without interfering with their cytotoxic effects on cancer cells as pro-oxidants. These dynamic actions of carotenoids can optimize oxidative stress in normal cells while enhancing oxidative stress in cancer cells. This review discusses possible mechanisms of carotenoid-triggered ROS production in cancer cells, the activation of pro-apoptotic signaling by ROS, and apoptotic cell death. Moreover, synergistic actions of carotenoids with ROS-inducing anti-cancer drugs are discussed, and research gaps are suggested.

https://pmc.ncbi.nlm.nih.gov/articles/PMC5905192/
Anti-inflammatory Activity of β-Carotene, Lycopene and Tri-n-butylborane, a Scavenger of Reactive Oxygen Species 2018
Both β-carotene and lycopene had weak antioxidant activity, but β-carotene showed pro-oxidant activity at higher concentrations.
The anti-inflammatory and pro-inflammatory activities of carotinoids remain to be clarified.
As β-carotene was sensitive to PhCOO· radicals, it was thought to be more sensitive to ROS than lycopene. β-Carotene also showed dual antioxidant and pro-oxidant properties, whereas lycopene showed antioxidant activity alone, as judged from the IP value.

https://pmc.ncbi.nlm.nih.gov/articles/PMC3942711/
Potential Role of Carotenoids as Antioxidants in Human Health and Disease 2014
The molecular mechanisms underlying these reactions are still not fully understood, especially in the context of the anti- and pro-oxidant activity of carotenoids, which, although not synthesized by humans and animals, are also present in their blood and tissues, contributing to a number of biochemical processes.
Another important collection of data comes from the studies on prostate cancer. Thus, a large number of epidemiological studies generally support the idea that several Crts, as well as Crt-rich food, could be involved in the reduction of the risk of prostate cancer [115,116]. Among various Crts, lycopene is regarded as the most potent agent against the risk of this type of tumor, in particular in its more lethal form [117]. The preclinical studies suggest several possible ways of lycopene action, indicating, at the same time, its significance in the enhancement of the oxidation stress defense system [118].
This unexpected Crt behavior might be partially explained in terms of: (i) the generation of Crts oxygenation products of pro-oxidant activity [3]; as well as (ii)

pronounced changes in their optical and chemical properties, *i.e.*, antioxidant activity. As has been demonstrated recently in the course of EPR (electron paramagnetic resonance) spin trapping experiments, the formation of H-type aggregates of Crts in aqueous media results in a considerable lowering of their antioxidant potential (e.g., lutein) or even leads to pro-oxidant behavior (*i.e.*, zeaxanthin) [136].

https://pmc.ncbi.nlm.nih.gov/articles/PMC6361147/

The role of carotenoids in the prevention of human pathologies 2004

The initial antioxidant activity of β-Carotene is followed by a prooxidant action at high oxygen tension. Thus, in thymocytes, β-Carotene is an antioxidant at low oxygen pressure but a pro-oxidant at high oxygen concentrations [82]. In addition, lycopene may have also prooxidant activities depending on the type of oxidants used. Thus, it can be either antioxidant or prooxidant at normal oxygen tension in human foreskin fibroblasts cells (Hs68) [83]. The prooxidant effects of β-Carotene may be related to adverse effects observed under the supplementation of high doses of β-Carotene [84,85]. However, it has been suggested that some of the degradation products of β-Carotene rather than β-Carotene itself may be prooxidant or procarcinogenic [86,87].

https://www.semanticscholar.org/paper/Lycopene-for-the-prevention-and-treatment-of-Ili%C4%87/f7d959461c8fc8cd465ede82bc5b963f70073bcc

Lycopene for the prevention and treatment of prostate disease 2014

Lycopene, a member of the carotenoid family, found commonly in red pigmented fruit and vegetables has been established as having strong antioxidant and pro-oxidant properties.

https://link.springer.com/referenceworkentry/10.1007/978-3-030-45299-5_4-1

Antioxidant and Pro-oxidant Activities of Carotenoids 2020

However, lycopene (50 μM) exhibited pro-oxidant effects in in vitro cellular assays with several cancer cell lines [human prostate cancer (PC-3), human alveolar epithelial adenocarcinoma (A549), human cervical cancer (HeLa), human breast adenocarcinoma (MCF-7), human epidermoid carcinoma (A431), and human hepatocellular carcinoma (HepG2)

https://www.semanticscholar.org/paper/Lycopene%2C-resveratrol%2C-vitamin-C-and-FeSO4-increase-Due%C3%B1as-Garc%C3%ADa-Heres-Pulido/bda54f083ab984160e34f0c823cdc9237462da4e

Lycopene, resveratrol, vitamin C and FeSO4 increase damage produced by pro-oxidant carcinogen 4-nitroquinoline-1-oxide in Drosophila melanogaster: Xenobiotic metabolism implications. 2017

https://link.springer.com/referenceworkentry/10.1007/978-981-16-5422-0_209

Phytochemicals as Pro-oxidants in Cancer 2022

Antioxidant activity is demonstrated by phytochemicals with established antioxidant capabilities at low concentrations; but, when provided at high doses, the same antioxidant may operate as a pro-oxidant. As a result, maintaining redox homeostasis is crucial, and it is influenced by dietary sources of antioxidant and pro-oxidant phytochemicals. For instance, certain dietary phytochemicals such as Ascorbic Acid exhibit antioxidant activity (at low concentration) and pro-oxidant activity (at higher concentration).