Resveratrol Action on Lipid Metabolism in Cancer

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Abstract: Cancer diseases have the leading position in human mortality nowadays. The age of oncologic patients is still decreasing, and the entire scientific society is eager for new ways to fight against cancer. One of the most discussed issues is prevention by means of natural substances. Resveratrol is a naturally occurring plant polyphenol with proven antioxidant, anti-inflammatory, and anticancer effects. Tumor cells display specific changes in the metabolism of various lipids. Resveratrol alters lipid metabolism in cancer, thereby affecting storage of energy, cell signaling, proliferation, progression, and invasiveness of cancer cells. At the whole organism level, it contributes to the optimal metabolism extent with respect to the demands of the organism. Thus, resveratrol could be used as a preventive and anticancer agent. In this review, we focus on some of the plethora of lipid pathways and signal molecules which are affected by resveratrol during carcinogenesis.

Keywords: resveratrol; cancer; lipid metabolism

1. Background

In the last decades, cancer diseases have reached the leading position in human mortality. The process of tumorigenesis includes changes at the cellular, tissue, and systemic levels. One of the main features of neoplastic transformation is altered metabolism. Rapidly proliferating cancer cells need more energy and consequently they metabolize more glucose to lactate than normal cells, in the presence of sufficient oxygen (Warburg effect) [1]. Malignant transformation is associated with an increased rate of intracellular glucose transport via glucose transporters (GLUTs) [2–4]. GLUT transporters use existing gradients in membrane sugar concentrations to translocate into the cell [5]. GLUT1 is slightly expressed in some human tissues, although high levels of it were found in many types of cancer [6–10]. The expression of GLUT1 is regulated by p53 via several mechanisms, such as reducing the expression of GLUT1 or inhibition of GLUT1 translocation to the plasma membrane, and, because of p53 deregulation during cancer, the levels of this transporter remain high [5]. GLUT4 is an insulin-sensitive transporter, expressed in some tissues such as muscle, heart, and adipose tissue. Elevated expression of GLUT4 is associated with many human tumors, e.g., head, neck, or breast tumors [11–14]. Finally, GLUT4, similarly to GLUT1, displays an interesting connection with cancer, as both transporters are transcriptionally repressed by p53 [15].

Fatty acid (FA) synthesis strongly depends on glucose through the generation of acetyl-CoA, a central metabolic precursor [16,17]. In tumor cells, most fatty FAs are synthesized de novo by fatty acid synthase (FASN) to arrange the intensive bioenergetics and structural changes. Indeed, FASN has been defined as a marker of cell proliferation and a drug target in oncology [18–21].

The occurrence of intense catabolism of sugar, lipid, and protein stores; body weight loss; and weakness leads to cancer cachexia syndrome [22–25]. Considering the intense lipid catabolism, high fasting triacylglycerols (TAGs) and low serum high density lipoprotein (HDL)-cholesterol were, for example, significantly associated with an increased breast cancer risk [26,27]. On the other hand,
an increase of total cholesterol in the plasma could accelerate the development of tumors and is associated with the aggressiveness of the disease [28], together with increased low density lipoprotein (LDL) levels from patients with breast, colon, gastric, and ovarian cancer [27]; though, low total cholesterol levels have been considered as a risk marker for future cancer [29,30].

The altered tumor metabolism leads to the accumulation of specific metabolites in the tumor microenvironment and creates ideal conditions for tumor growth and metastasis. Low pH forms the tumor milieu and has positive effects on the migration of tumor cells [31–33]. Lactate also induces other factors important for tumor progression, such as CD44, hyaluronic acid, and transforming growth factor (TGF)-beta [34–36]. Furthermore, cytokines and growth factors released by fibroblasts and macrophages, some of the tumor infiltrating immune cells, could promote chronic inflammation and tumor progression [37–40]. On the other hand, cancer cells produce factors to attenuate immune cells, causing uncontrolled tumor growth [41,42]. A variety of metabolites is often deregulated within the tumors and supports the immune escape [43]. For example, the enhanced metabolism of L-arginine in myeloid cells declines the response of lymphocytes to tumor antigens, resulting in the failure of immune reactions and intensive tumor growth [44–47].

All of the bioenergetics and metabolic features not only permit cancer cells to survive under adverse conditions, but also allow their proliferation, progression, and invasiveness [3].

2. Resveratrol

Resveratrol (RES) is a well-known plant polyphenol nowadays. It has a stilbene structure and belongs to the group of phytoalexins that are produced under stress conditions in plants. According to its chemical structure, RES exists in two forms—cis and trans. Moreover, its isomers, adducts, derivates, and conjugates are intensively studied for their antioxidant and anti-carcinogenic effects.

After an oral administration, RES accumulates in some organs, such as the kidney [48], intestine, or liver [48,49], which may probably relate to the places of its extensive absorption and metabolism. Our recent results indicate that RES also accumulates in breast tumors together with its main metabolites: 3-sulphate, and 4- and 3-glucuronide [50,51]. According to Bresciani et al., RES and its metabolites could accumulate in myocardial tissue [52]. However, no RES accumulation in tumor tissue of neuroblastoma in athymic mice was observed [53].

Due to its low water solubility, RES binds to proteins and protein transporters in the blood stream. It interacts with albumin, one of the plasma carriers, to catch the cell surface, or with lipoproteins in the order HDL < LDL < very low density lipoprotein (VLDL) [54,55]. RES absorption occurs by passive diffusion [56] or by a transport via ion channels [57] to pass the cell membrane, allowing its intracellular biological actions in the cell [58,59].

RES is a polyphenolic compound, playing its important role in many disorders. The extensive research of RES started through the “French paradox”, one of the most fascinating phenomena currently studied by scientists [60–62]. The French population has a relatively low incidence of coronary diseases despite its high intake of dietary cholesterol and saturated fat [63]. Moreover, oxidative damage and reactive oxygen species (ROS) action are involved in the pathogenesis of cardiovascular diseases [64]. The cardioprotective effects of polyphenols have been predicated to an increase in the plasma level of HDL cholesterol, protecting LDL from oxidation, a decrease in prostanoid synthesis from arachidonic acid, and the inhibition of platelet aggregation [65,66]. ROS formation causes oxidative damage to biomolecules, such as lipids, proteins, and DNA, resulting in many chronic diseases such as atherosclerosis, diabetes, cardiovascular diseases, and other degenerative diseases in humans [67]. Hydroxyl radicals damage cell membrane lipids via lipoperoxidation. Further, RES inhibits lipid peroxidation of LDL, prevents the cytotoxicity of oxidized LDL, and reduces platelet aggregation [68,69]. The antioxidant activity of RES may inhibit oxidation of LDL and, therefore, decrease endothelial damage associated with cardiovascular disease [70]. RES has been shown to act as an antioxidant by decreasing ROS generation in human [71–73] and animal models [74–77].
3. Resveratrol as a Modulator of Lipid Metabolism in Cancer

3.1. Resveratrol and Fatty Acid Synthesis

The role of FA metabolism, including both anabolic and catabolic reactions in cancer has gained increasing attention in recent years [78]. Lipid synthesis includes processes that convert carbons derived from nutrients into FAs. FAs are converted into diacylglycerides and TAGs via glycerol-3-phosphate to form the glycerol backbones of the lipids [79,80]. In healthy adults, de novo FA biosynthesis occurs in liver, adipose tissue, lactating breast tissue [81], or the brain [82]. However, in cancer cells, FAs are esterified to phospholipid (PL) for membrane lipid synthesis, promoting cell replication, rather than using TAG storage [83,84]. Indeed, it has been shown, that blocking of FASN in cancer cells results in cell growth arrest and induction of apoptosis [18–21]. RES significantly reduced lipid synthesis through the downregulation of FASN in many cancer cell lines [85–87]. Concomitantly, cell viability and mammosphere formation in breast cancer stem cells was significantly reduced (see Table 1) [87]. Growth arrest of pancreatic adenocarcinoma cells after RES application was associated with a significant decrease in glycogen breakdown and glucose carbon redistribution toward FAs by reducing FASN [83].

The expression of many genes involved in FA and cholesterol biosynthesis is activated via the phosphoinositide-3-kinase/protein kinase B/mammalian target of rapamycin (PI3K/AKT/mTOR) pathway [88–90]. It has been shown that RES could inactivate the PI3K/AKT/mTOR pathway and thus decrease the growth of various cancer cells in a dose-dependent manner [91–93]. For example, in glioblastoma-initiating cancer cells isolated from patients, RES in the doses of 5, 10 and 20 µM inhibited the invasion of these cells via downregulation of the PI3K/AKT/NF-κB signaling pathway in vitro and in vivo [85]. In HCT116 colon cancer cells, RES in the dose of 10–80 µM inactivated PI3K/AKT signaling via the upregulation of bone morphogenic protein, BMP7, and decreased the growth of these cells in a time- and dose-dependent manner [93]. In gastric MGC-803 cells, RES caused a dose-dependent decrease in the protein levels of p-PI3K and p-PTEN (inactivate) and caused a cell cycle arrest in the G0/G1 phase [92]. In HeG2, Bel-7402, and SMMC-7721 hepatocellular carcinoma cells, RES inhibited the viability and proliferation of cancer cells and increased the apoptosis in a dose-dependent manner (20–200 µmol/L) via SIRT1 activation and concomitant inhibition of SIRT1-mediated post-translational modification of PI3K/AKT signaling [91]. Various agents inhibiting the PI3K/AKT/mTOR (PAM) pathway, such as rapamycin, are currently in various stages of clinical development in oncology, ranging from some in early phase evaluations to others that have already received regulatory approval for treatment in advanced cancers [94]. Rapamycin together with RES led to cell death in TSC−/− MEFs bladder cancer cells, but not wild-type MEFs [95]. Combining rapamycin (20 nM) with RES (60 µM) had a synergistic effect in human multiple myeloma cells [96]. Moreover, PAM pathways play an important role in the synthesis and secretion of TAGs. However, RES as a potent inhibitor of the PAM pathway did not influence TAG concentration in the liver of female Sprague Dawley rats with breast cancer [97].

3.2. Resveratrol and Cholesterol Pathway

Another class of lipids, important for membrane function, is sterols, predominantly cholesterol and cholesteryl-esters. Cholesterol provides the structural backbone for the synthesis of steroid hormones, such as estrogen and progesterone [80].

A family of sterol regulatory element-binding proteins (SREBPs) is involved in FA and cholesterol biosynthesis [80]. Abnormally elevated cholesterol levels may be attributed to SREBP’s mediated by 3-hydroxy-3-methyl glutaryl coenzyme A reductase (HMGCR) [98]. RES inhibited the mevalonate pathway, reduced HMGCR expression and activity, and decreased cholesterol synthesis in rat theca-interstitial cells [99]. Moreover, it has been found to inhibit lipid synthesis via SREBP1 inhibition in MiaPaCa-2 and Panc-1 pancreatic cancer cells in the dose of 50 µmol/L as well as in a transgenic mouse model of pancreatic cancer in the dose of 50 mg/kg body weight [100] or to reduce breast tumor
volume concomitantly with the reduction of lipid content in serum in female nude mice in the dose of 22.4 mg/kg body weight [101].

SREBP1s are also a target of the AMP-regulated protein kinase (AMPK) [102]. Professor Ido’s group revealed several mechanisms of RES action. First, it was the RES-induced activation of AMPK via SIRT1 activation [103]. They further supposed that the variability of this cascade may be responsible for the inconsistency of RES effects. They revealed that the effect of RES as a SIRT1 activator may not be solely via the activation of SIRT1, but also via an integrated effect of SIRT1-liver kinase B1 (LKB1)–AMPK. Thus, RES activates SIRT1 via direct binding to SIRT1 and through increasing nicotinamide adenine dinucleotide (NAD)$^{+}$ levels by upregulating the salvage pathway through nicotinamide phosphoribosyl transferase (NAMPT) activation, an effect mediated by AMPK [104]. RES not only promotes deacetylation of a limited number of SIRT1 substrate proteins (for example, peroxisome proliferator-activated receptor gamma coactivator 1-alpha—PGC-1α) but activates other sirtuins in addition to SIRT1. For cancer treatment, RES may accelerate cell death if the cellular energy production is already impaired [104]. In ovarian A2780 and SKOV3 cancer cells and in female BALB/c nude mice with ovarian cancer, RES inhibited the growth of cells and tumors in vivo and induced apoptosis via increased expression and activation of AMPK and caspase 3, as well as decreased expression and activation of AMPK downstream kinase mTOR [105]. It has been shown that high doses of RES (4 g/kg body weight/day) activate AMPK in a SIRT1-independent manner, demonstrating that the dosage is a critical factor of RES functioning. Thus, RES-induced SIRT1 activation may play a role in the activation of AMPK both in vitro and in vivo [106].

Sirtuins are highly conserved NAD-dependent enzymes. The mammalian sirtuin family is involved in diverse cellular processes including DNA repair, lipid and glucose metabolism, and tumorigenesis [107]. The family consists of many sirtuin proteins, such as SIRT1, SIRT6, or SIRT7 localized predominantly in the nucleus; SIRT2 in the cytoplasm; or SIRT3, SIRT4, and SIRT5 localized in the mitochondria [108–110]. For example, SIRT1 deacetylates and destabilizes SREBP1, a hepatic transcription factor for lipogenesis and cholesterol synthesis [110–113]. SREBP2 controls cholesterol homeostasis via targeting the genes involved in cholesterol biosynthesis [114–116]. RES has been shown to modulate the expression and activity of sirtuins [117–121]. In gastric cancer cell lines, RES inhibited the viability and proliferation of BGC-823 and SGC-7901 cells in a SIRT1-dependent manner [122]. In MCF7 and MDA-MB-231 breast cancer cell lines, RES decreased breast cancer cell mass and viability in a dose-dependent manner, concomitantly with an increase in SIRT1 and SIRT3 protein content [123]. In colorectal cancer cells, RES stimulated the expression of SIRT1 in a dose-dependent manner, resulting in the downregulation of the nuclear localization of NF-κB and its related gene products, involved in tumor invasion and metastasis [124]. In hepatocellular cancer cell lines (HepG2, Bel-7402, SMMC-7721), RES activated SIRT1 protein and inhibited SIRT1-mediated post-translational modification of PI3K/AKT signaling [91]. SIRT2 activity mediated the inhibitory action of RES on the cell cycle of glioblastoma stem cells derived from human patients. Moreover, RES blocked the proliferation of glioblastoma stem cells without influencing the behavior of neural stem cells in a SIRT2-independent mechanism [125]. For more details, see Table 1.

Lipid homeostasis may only be maintained if the excess of lipids that the cell has uptaken or synthesized can be metabolized or transported outside of the cell membrane [98]. Cholesterol-sensing liver-X-receptor (LXR) proteins are involved in maintaining cholesterol homeostasis. LXRs act to enhance the reverse transport of cholesterol from peripheral tissues via stimulating the expression of the ATP-binding cassette transporter A1 (ABCA1). These transport proteins direct cholesterol to apolipoprotein AI to form high-density lipoproteins. Apolipoproteins interact with lipids to form soluble lipid–protein complexes called lipoproteins. It is in this form that the major lipids—cholesterol, TAGs, and PLs—circulate in the plasma [126,127]. In addition to the known role of ApoA-1 as the key carrier of high density lipoprotein (HDL) and cholesterol receptor, it also enhances HDL influx and cholesterol efflux. Furthermore, it promotes excessive cholesterol excretion from peripheral liver tissue [98]. RES has been found to exert a biphasic effect on apolipoprotein M (apoM) in hepatoma
cells and C57BL/6 mice. RES in the doses of 1 µM and 10 µM increased intra- and extracellular levels of apoM together with intracellular sphingosine 1-phosphatase (S1P) levels. However, at the higher dose of 100 µM it decreased extracellular apoM content [128]. But, nowadays there are not many publications dealing with RES action and apolipoproteins in cancer. RES action on apolipoproteins is rather studied with regard to obesity and atherosclerosis [129–132]. On the other hand, apolipoproteins are used as nanovehicles in targeted intracellular delivery of RES to glioblastoma [133] or breast cancer cells [134].

Low HDL and total cholesterol have been described as a marker of poor prognosis for current or future cancer [135–138]. Plasma levels of total cholesterol, LDL, VLDL, and TAG were significantly reduced in patients with benign breast disease in comparison with a healthy control group [139]. In breast cancer patients, the levels of total cholesterol and HDL were significantly lower, while VLDL and TAG levels increased markedly. Hence, higher levels of total cholesterol and HDL are associated with a reduction of breast cancer risk, whereas higher levels of VLDL and TAG are strongly associated with increased breast cancer risk [139]. RES (50 ppm) suppressed the serum TAG levels and VLDL and LDL cholesterol levels in hepatoma-bearing male Donryu rats, together with the suppression of hepatoma incidence and tumor growth. The data suggest that RES is a hypolipidemic agent with anticarcinogenic and antimetastatic properties [140].

Table 1. Main molecular mechanisms involved in resveratrol action regarding lipid metabolism in cancer.

| Molecule | Cancer Type | Model | Dosage | Action | Ref. |
|----------|-------------|-------|--------|--------|------|
| FASN     | Breast cancer | SKBR-3 | 5-150 µM (IC50 ~ 80 µM) | • decrease in FASN and Her2 expression in a dose-dependent manner | [86] |
|          | Pancreatic cancer | MIA PaCa-2 | 50 and 100 µM | • cell growth arrest via significant decrease in glycogen breakdown and glucose carbon redistribution toward FAs by reducing FASN | [83] |
| SIRTUIN  | Colorectal cancer | HCT116 | 1, 5, 10, 20, and 50 µM | • stimulation of the expression of SIRT1 in a dose-dependent manner | [124] |
|          |              | SW480 |         | • downregulation of nuclear localization of NF-κB, NF-κB phosphorylation and its acetylation, causing attenuation of NF-κB-regulated gene products involved in tumor invasion and metastasis | |
|          | Breast cancer | MCF7 | 10, 25, and 50 µM | • decrease in breast cancer cell mass and viability in a dose-dependent manner | [123] |
|          |              | MDA-MB-231 |         | • increase in SIRT1 and SIRT3 protein content | |
|          | Hepatocellular carcinoma | HepG2 | 20-200 µmol/L | • inhibition of cell viability and proliferation and increase in apoptosis in a dose-dependent manner | [91] |
|          |              | Bel-7402 |         | • activation of SIRT1 and inhibition of SIRT1-mediated post-translational modification of PI3K/AKT signaling | |
|          |              | SMMC-7721 |         | |
|          | Glioblastoma | GSCs derived from human biopsies | 0-300 µM | • alteration of cell morphology after RES in the doses above 150 µM induction of GSCs necrosis • no effect on NSCs • blockade of SIRT2 activity or downregulation of SIRT2 expression with siRNAs counteracted the inhibitory effect of RES on cell proliferation | [125] |
|          | Chondrosarcoma cancer | JJO12 | 5, 10, 25, 50, 100, and 200 µM | • increase in the protein expression of SIRT1 in a dose-dependent manner • significant reduction of the acetylation of NF-κB-p65 in a time-dependent manner (dose 50 µM) | [141] |
|          |              | BALB/c-A nu (nu/nu) mice | 50 or 100 mg/kg body weight | • reduction in size and weight of JJO12 tumors • reduction in tumor growth without affecting the body weight of the mice • increase in SIRT1 and cleaved caspase-3 expressions | [141] |
### 3.3. Resveratrol, Ceramide, and Arachidonic Acid Pathway

Other lipids generated from FAs are sphingolipids, phosphoinositides, and eicosanoids [80]. Sphingolipids, including the two central bioactive lipids—ceramide and S1P, have opposing roles in cancer cell death and survival. While ceramide mediates cell death, S1P induces tumor cell proliferation, treatment resistance, and cancer metastasis [144–146]. Firstly, RES may act as an inhibitor of the S1P synthesis catalyzing enzyme—sphingosine kinase 1 and, thus, affect sphingosine kinase 1 expression and cell growth of breast MCF7 cancer cells [147]. On the other hand, RES has been shown to increase the intracellular concentration of ceramide, sphinganine, and sphingosine and the expression of enzymes related to the de novo ceramide synthesis pathway in hepatocellular HepG2 cells.
In addition, it reduced intracellular TAGs accumulation in lipid overload conditions [148]. In human gastric cancer cells, RES lead to cell cycle arrest and cell death through the sphingolipid metabolism pathway [149]. Moreover, 10 µM of RES for 24 h could modulate the lipidomic profile of Caco2 colon cancer cells (e.g., increase in diacylglycerol, TAG, phosphatidylcholine, phosphatidylinositol, and sphingomyelin species), leading to cell growth arrest [150].

Key enzymes in lipid metabolism are cyclooxygenases (COX-1 and COX-2), lipoxygenases (LOXs), and cytochrome P450 monoxygenases. COXs catalyze prostaglandin synthesis from arachidonic acid (ARA); in contrast, LOX enzymes insert oxygen at the carbon of ARA [151–153]. ARA is a polyunsaturated omega-6 fatty acid present in PL (phosphatidylcholine, phosphatidylinositides) of cell membranes and is generated for signaling purposes. The release of ARA from the cell membrane is initiated by phospholipase A2 (PLA2) and, thereafter, converted to eicosanoids [154]. Eicosanoids, including prostaglandins and leukotrienes, are products of local cell type-specific metabolism of ARA and form an important class of bioactive lipid mediators, playing critical roles in diverse physiological and pathological processes, such as inflammation and cancer [155–158]. In cancer patients, the level of PLA2 elevates significantly [159–161]. RES (5 mg/kg) inhibited the p38 MAPK—cytosolic phospholipase A2–arachidonic acid–TxA2–[Ca²⁺]i cascade, resulting in the inhibition of phospholipase C and/or protein kinase C (PKC) activation and significant prolongation of platelet plug formation in mice [162]. In a plethora of other proteins and enzymes, RES inhibited cell viability via PLA2 decrease and sensitized breast cancer cells to doxorubicin therapy [163] or lead to p53-mediated cell death of prostate LNCAP cancer cells [164].

COX enzymes have been implicated in the development of malignant tumors. While COX-1 is expressed in vascular endothelial cells and contributes to angiogenesis, COX-2 is functional in tumorigenesis and tumor growth. The overexpression of COX-2 leads to cell escape from apoptosis and the cancer cells invade the matrix [165–168]. RES was able to block the expression and/or activity of COX-2 in many cancer studies in vitro and in vivo conditions [51,169–171]. Zykova et al. found out that RES and its analogs directly bind with COX-2 and through this they inhibit COX-2-mediated prostaglandin production. Thereby, the colony-forming ability of human colon adenocarcinoma HT-29 cells was repressed [171]. In F344 rats, RES in concentrations of 1 and 2 mg/kg body weight, respectively, reduced NMBA-induced esophageal tumorigenesis by targeting COXs and thus influencing the levels of prostaglandin. In tumor tissue, the higher expression of COX-1, the upregulated COX-2 expression, and the increased levels of prostaglandin 2 were all significantly decreased by RES administration [172].

LOXs in mammals, especially 12/15 LOX, modify cell membranes by peroxidation and on the other hand, 5-LOX produces signaling lipid mediators which exert effects via G protein-coupled plasma membrane-bound receptors. In some types of cancer cells, the LOXs are expressed constitutively and their activity is associated with cell proliferation, tumor angiogenesis, and metastatic potential [173,174]. RES (100 µg/rat) administered for 24 weeks significantly inhibited 5-LOX activity, reduced lipid peroxidation, and prevented DNA damage in DMBA-induced breast cancer in female Sprague Dawley rats [175]. RES was able to prevent apoptosis by inhibiting LOX and COX activity in the leukemia K562 cell line [176].

The superfamily of cytochrome P450 proteins is a large group of enzymes catalyzing many important biochemical processes, including steroid hormone, prostaglandin, and leukotriene biosynthesis. RES strongly inhibits the expression and activity of cytochrome P450 1A1 and 1B1 in many types of cancer cells [148,177–180]. Moreover, RES significantly attenuated the intracellular reactive oxygen species (ROS) formation and oxidative DNA damage as well as the cytotoxicity induced by the catechol estrogens [177].

As described above, eicosanoids are formed in reactions catalyzed by COXs, LOXs, and CYPs. This group of molecules encompasses a wide array of hormones which build the different classes, such as prostaglandins, thromboxanes, leukotrienes, lipoxins, epoxyeicosatrienoic acids, etc. Above all, the importance of prostanoid and leukotriene biosynthetic pathway in carcinogenesis and chronic inflammation is supported by a plenty of in vivo and clinical studies [156,157,181,182]. Prostaglandins
and leukotrienes promote tumor growth by regulating tumor epithelial cells themselves and controlling the complex interactions between transformed epithelial cells and surrounding stromal cells to establish a tumor microenvironment that facilitates tumor-associated angiogenesis and evades attack by the immune system [182]. They may also lead to irreversible tissue damage [157]. In 1998, the chemopreventive potential of RES was examined by investigating its effect on eicosanoid production in mouse skin tumors [183]. RES significantly blocked PGE2 prostaglandin production, catalyzed by COX-1, proportionally to the RES concentration added to the reaction mixture. Moreover, the COX-2-induced production of prostaglandins PGE2, PGD2, and PGF2α was markedly decreased after RES treatment [183]. Sexton et al. revealed that concomitantly with the reduction of COX metabolites, PGE2 and PGF2α, the cellular levels of the phosphorylated/active form of antiapoptotic kinase AKT were decreased [184]. Further, the decreased expression and phosphorylation of AKT led to enhanced RES-induced cell death after mTOR inhibitor rapamycin in glioma cancer cells [185]. In pancreatic cancer, a relevant target is leukotriene A4 hydrolase. RES directly bound to this hydrolase and suppressed proliferation and anchorage-independent growth of pancreatic cancer by inhibiting leukotriene B4 production and expression of its receptor in a xenograft mouse model of human pancreatic cancer [186].

3.4. Resveratrol, Lipid Peroxidation, and Reactive Oxygen Species

Lipid peroxidation is a natural metabolic process under normal conditions and is one of the most investigated consequences of ROS actions on membrane structure and function. Lipid hydroperoxides and oxygenated products of lipid peroxidation as well as lipid peroxidation initiators (e.g., ROS) participate in signal transduction, cell proliferation control, and apoptosis [187–189]. RES prevents lipid peroxidation in many types of cancers [190–194]. On the other hand, damage to mitochondria induced by lipid peroxidation can lead to further ROS generation and in the presence of radicals, double bonds of FAs phospholipids can oxidize [195]. Treatment with RES leads to DNA damage and cancer cells death in vitro and in vivo in an ROS-dependent way [50,196–198]. Henceforward, healthy cells need more antioxidant activity; prooxidant mechanisms in cancer cells should inevitably lead to the cell death [199].

As mentioned previously, lipid mediators and other lipid molecules play a central role not only in cancer, but they are implicated in inflammation and tissue homeostasis. In addition to the cancer cells and their surrounding stroma the tumor microenvironment also contains innate immune cells such as macrophages, neutrophils, natural killer cells or dendritic cells, and adaptive immune cells (T and B lymphocytes). They communicate together by means of direct contact of cytokine and chemokine production and act in autocrine and paracrine manners to control tumor growth. The current available literature shows RES contradictory immunomodulatory effects in vitro and in vivo [200–202]. Though, Soto et al. confirmed its potential therapeutic activity with respect to tumor immunotherapy [203]. RES exerts its effects at multiple levels. These include lipoxygenases and cyclooxygenases synthesizing proinflammatory mediators from ARA, protein kinases such as PKC and PKD, lipid kinases, as well as I kappa B kinase α (IKKα), an activator of the NF-κB pathway, which establishes a strong link between inflammation and tumorigenesis [204].

The key mechanisms in the tumorigenesis, such as the modulation of the metabolism, tumor growth, progression and metastasis to distant sites, the development of acquired treatment resistance, etc., take place in the tumor microenvironment [205–207]. This milieu consists of cancer cells and infiltrating immune cells, cancer-associated fibroblasts, angiogenic endothelial cells, or endothelial precursors, etc. [205–208]. The high rate of lactate causes pH lowering in the extracellular space [206]. Further, a hypoxic microenvironment inhibits β-oxidation of FAs in different tissues, resulting in the enhanced storage of TAG. Hypoxia-inducible factor 1 (HIF-1) promotes lipid accumulation, the uptake of free FAs and TAG production in liver and adipose tissue [81]. The up-regulation of HIF-1 results in tumor progression, followed by release of a variety of growth factors, cytokines and pro-angiogenic factors, such as vascular endothelial growth factor (VEGF) and GLUT-1 transporter [154].
RES shows an enhanced growth inhibitory and apoptotic potential at a pH lower than 7.5 in pancreatic cancer cell lines [209]. In hypoxic conditions at low pH, hypoxia-inducible factor HIF is activated. Its overexpression has been associated with the aggressiveness in many human tumors. RES in the dose of 100 mmol/L significantly inhibited HIF-1α protein accumulation concomitant with the reduction of VEGF-promoter activity and expression in human tongue squamous carcinoma cells [210]. However, VEGF expression after RES administration was not found to be eliminated in all in vivo experiments [211].

4. Clinical Trials

Clinical trials are predominantly focused on safety, adverse effects, and the overall tolerability of RES in human. There are several clinical trials describing the effects of RES in cancer patients, however, none of them describes some lipid mechanism involved in cancer. Nonetheless, the main problem of RES in human studies is its low bioavailability and possible side effects in the form of mild gastrointestinal discomfort, including diarrhea, nausea, flatulence, and abdominal discomfort [212]. Some review reports give an overview of clinical trials [213–216].

5. Conclusions

Preclinical and clinical evidence clearly shows that lipid metabolism plays a crucial role in tumor development and invasion. Numerous proteins which take part in lipid metabolism are also involved in cancer cell survival and proliferation. Many drugs and natural compounds are studied due to their ability to modulate lipid metabolism and thus influence the process of carcinogenesis. RES is a well-known natural substance showing some modulatory effects on lipid metabolism. RES alters lipid metabolism in cancer via various mechanisms and contributes to the optimal metabolism extent with respect to the demands of the organism. RES inhibits lipid synthesis via SREBP's inhibition, activates sirtuins concomitantly with the activation of AMPK, and downregulates the PI3K/AKT/mTOR pathway resulting in cancer cell apoptosis. RES decreases tumor volume and metastasis via decreasing serum TAG, VLDL, and LDL levels in cancer patients. Thus, it could be used in the modulation of cancer initiation and progression. However, further research is needed to use resveratrol widely in cancer management.

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Abbreviations

| Abbreviation | Description |
|--------------|-------------|
| ABCA | ATP binding cassette transporter A |
| AKT | protein kinase B |
| AMPK | regulated protein kinase |
| Apo | apolipoprotein |
| ARA | arachidonic acid |
| BMP7 | bone morphogenic protein |
| COX | cyclooxygenase |
| FA | fatty acid |
| FASN | fatty acid synthase |
| GLUTs | glucose transporters |
| HDL | high density lipoprotein |
| HIF | hypoxia-inducible factor |
| HMGCR | 3-hydroxy-3-methyl glutaryl coenzyme A reductase |
| IKKα | I kappa B kinase α |
| LDL | low density lipoprotein |
| LKB1 | liver kinase B1 |
LOX  lipoxygenase  
LRX  liver-X-receptor  
mTOR  mammalian target of rapamycin  
NAMPT  nicotinamide phosphoribosyl transferase  
NF-κB  nuclear factor kappa-light-chain-enhancer of activated B cells  
NAD  nicotinamide adenine dinucleotide  
PAM  PI3K/AKT/mTOR pathway  
PG  prostaglandin  
PGC  peroxisome proliferator-activated receptor gamma coactivator 1-alpha  
P3K  phosphoinositide-3-kinase  
PKC  protein kinase C  
PL  phospholipid  
PLA2  phospholipase A2  
PTEN  phosphatase and tensin homolog  
RES  resveratrol  
ROS  reactive oxygen species  
S1P  sphingosine 1-phosphatase  
SIRT  silent mating type information regulation  
SREBP  sterol regulatory element-binding protein  
TAG  triacylglycerol  
TGF-beta  transforming growth factor beta  
VEGF  vascular endothelial growth factor  
VLDL  very low density lipoprotein

References

1. Bensinger, S.J.; Christofk, H.R. New aspects of the Warburg effect in cancer cell biology. *Semin. Cell Dev. Biol.* 2012, 23, 352–361. [CrossRef] [PubMed]  
2. Adekola, K.; Rosen, S.T.; Shanmugam, M. Glucose transporters in cancer metabolism. *Curr. Opin. Oncol.* 2012, 24, 650–654. [CrossRef] [PubMed]  
3. Dakubo, G. The Warburg phenomenon and other metabolic alterations of cancer cells. In *Mitochondrial Genetics and Cancer*; Springer: Heidelberg/Berlin, Germany, 2010; pp. 39–66.  
4. Labak, C.M.; Wang, F.Y.; Arora, R.; Guda, M.R.; Asuthkar, S.; Tsung, A.J.; Velpula, K.K. Glucose transport: Meeting the metabolic demands of cancer, and applications in glioblastoma treatment. *Am. J. Cancer Res.* 2016, 6, 1599–1608.  
5. Calvo, M.B.; Figueroa, A.; Pulido, E.G.; Campelo, R.G.; Aparicio, L.A. Potential role of sugar transporters in cancer and their relationship with anticancer therapy. *Int. J. Endocrinol.* 2010, 2010, 205357. [CrossRef] [PubMed]  
6. Ganapathy, V.; Thangaraju, M.; Prasad, P.D. Nutrient transporters in cancer: Relevance to Warburg hypothesis and beyond. *Pharmacol. Ther.* 2009, 121, 29–40. [CrossRef] [PubMed]  
7. Ma, Y.; Wang, W.; Idowu, M.O.; Oh, U.; Wang, X.-Y.; Temkin, S.M.; Fang, X. Ovarian cancer relies on glucose transporter 1 to fuel glycolysis and growth: Anti-tumor activity of BAY-876. *Cancers* 2018, 11, 33. [CrossRef]  
8. Oh, S.; Kim, H.; Nam, K.; Shin, I. Glut1 promotes cell proliferation, migration and invasion by regulating epidermal growth factor receptor and integrin signaling in triple-negative breast cancer cells. *BMB Rep.* 2017, 50, 132–137. [CrossRef]  
9. Xiao, H.; Wang, J.; Yan, W.; Cui, Y.; Chen, Z.; Gao, X.; Wen, X.; Chen, J. GLUT1 regulates cell glycolysis and proliferation in prostate cancer. *Prostate* 2018, 78, 86–94. [CrossRef]  
10. Yu, M.; Yongzhi, H.; Chen, S.; Luo, X.; Lin, Y.; Zhou, Y.; Jin, H.; Hou, B.; Deng, Y.; Tu, L.; et al. The prognostic value of GLUT1 in cancers: A systematic review and meta-analysis. *Oncotarget* 2017, 8, 43356–43367. [CrossRef]  
11. Acharya, S.; Xu, J.; Wang, X.; Jain, S.; Wang, H.; Zhang, Q.; Chang, C.-C.; Bower, J.; Arun, B.; Seewaldt, V.; et al. Downregulation of GLUT4 contributes to effective intervention of estrogen receptor-negative/HER2-overexpressing early stage breast disease progression by lapatinib. *Am. J. Cancer Res.* 2016, 6, 981–995.
12. Chang, Y.-C.; Chi, L.-H.; Chang, W.-M.; Su, C.-Y.; Lin, Y.-F.; Chen, C.-L.; Chen, M.-H.; Chang, P.M.-H.; Wu, A.T.H.; Hisiao, M. Glucose transporter 4 promotes head and neck squamous cell carcinoma metastasis through the TRIM24-DDX58 axis. *J. Hematol. Oncol.* 2017, 10, 11. [CrossRef] [PubMed]

13. Garrido, P.; Osorio, F.G.; Moran, J.; Cabello, E.; Alonso, A.; Freije, J.M.; Gonzalez, C. Loss of GLUT4 induces metabolic reprogramming and impairs viability of breast cancer cells. *J. Cell. Physiol.* 2015, 230, 191–198. [CrossRef] [PubMed]

14. Wei, C.; Bajpai, R.; Sharma, H.; Heitmeier, M.; Jain, A.D.; Matulis, S.M.; Nooka, A.K.; Mishra, R.K.; Hruz, P.W.; Schiltz, G.E.; et al. Development of GLUT4-selective antagonists for multiple myeloma therapy. *Eur. J. Med. Chem.* 2017, 139, 573–586. [CrossRef] [PubMed]

15. Schwartzenberg-Bar-Yoseph, F.; Armoni, M.; Karnieli, E. The tumor suppressor p53 down-regulates glucose transporters GLUT1 and GLUT4 gene expression. *Cancer Res.* 2004, 64, 2627–2633. [CrossRef] [PubMed]

16. Edmunds, L.R.; Sharma, L.; Kang, A.; Lu, J.; Vockley, J.; Basu, S.; Uppala, R.; Goetzman, E.S.; Beck, M.E.; et al. c-Myc programs fatty acid metabolism and dictates acetyl-CoA abundance and fate. *J. Biol. Chem.* 2014, 289, 25382–25392. [CrossRef] [PubMed]

17. Petruzzelli, M.; Wagner, E.F. Mechanisms of metabolic dysfunction in cancer-associated cachexia. *Genes Dev.* 2016, 30, 489–501. [CrossRef] [PubMed]

18. Porporato, P.E. Understanding cachexia as a cancer metabolism syndrome. *Oncogenesis* 2016, 5, e200. [CrossRef] [PubMed]

19. Agnoli, C.; Berrino, F.; Abagnato, C.A.; Muti, P.; Panico, S.; Crosignani, P.; Krogh, V. Metabolic syndrome and postmenopausal breast cancer in the ORDET cohort: A nested case-control study. *Nutr. Metab. Cardiovasc. Dis.* 2010, 20, 551–562. [CrossRef] [PubMed]

20. Menendez, J.A.; Lupu, R. Fatty acid synthase (FASN) as a therapeutic target in breast cancer. *Expert Opin. Ther. Targets* 2017, 21, 1001–1016. [CrossRef] [PubMed]

21. Richardson, A.D.; Yang, C.; Osterman, A.; Smith, J.W. Central carbon metabolism in the progression of mammary carcinoma. *Breast Cancer Res. Treat* 2008, 110, 297–307. [CrossRef] [PubMed]

22. Aoyagi, T.; Terracina, K.P.; Raza, A.; Matsubara, H.; Takabe, K. Cancer cachexia, mechanism and treatment. *World J. Gastrointest. Oncol.* 2015, 7, 17–29. [CrossRef] [PubMed]

23. de Lima, C.; Alves, L.E.; Iagher, F.; Machado, A.F.; Bonatto, S.J.; Kuczera, D.; de Souza, C.F.; Pequito, D.C.; Muritiba, A.L.; Nunes, E.A.; et al. Anaerobic exercise reduces tumor growth, cancer cachexia and increases macrophage and lymphocyte response in Walker 256 tumor-bearing rats. *Eur. J. Appl. Physiol.* 2008, 104, 957–964. [CrossRef]

24. Petruzzelli, M.; Wagner, E.F. Mechanisms of metabolic dysfunction in cancer-associated cachexia. *Genes Dev.* 2016, 30, 489–501. [CrossRef] [PubMed]

25. Petruzzelli, M.; Wagner, E.F. Mechanisms of metabolic dysfunction in cancer-associated cachexia. *Genes Dev.* 2016, 30, 489–501. [CrossRef] [PubMed]

26. Agnoli, C.; Berrino, F.; Abagnato, C.A.; Muti, P.; Panico, S.; Crosignani, P.; Krogh, V. Metabolic syndrome and postmenopausal breast cancer in the ORDET cohort: A nested case-control study. *Nutr. Metab. Cardiovasc. Dis.* 2010, 20, 41–48. [CrossRef] [PubMed]

27. Ghahremanfard, F.; Mirmohammadkhani, M.; Shahnazari, B.; Gholami, G.; Meh dizadeh, J. The valuable role of measuring serum lipid profile in cancer progression. *Oman Med. J.* 2015, 30, 353–357. [CrossRef] [PubMed]
33. Huber, V.; Camisaschi, C.; Berzi, A.; Ferro, S.; Lugini, L.; Triulzi, T.; Tuccitto, A.; Tagliabue, E.; Castelli, C.; Rivoltini, L. Cancer acidiity: An ultimate frontier of tumor immune escape and a novel target of immunomodulation. *Semin. Cancer Biol.* 2017, 43, 74–89. [CrossRef] [PubMed]

34. Chen, C.; Zhao, S.; Karnad, A.; Freeman, J.W. The biology and role of CD44 in cancer progression: Therapeutic implications. *J. Hematol. Oncol.* 2018, 11, 64. [CrossRef]

35. Rudrabhatla, S.R.; Mahaffey, C.L.; Mummert, M.E. Tumor microenvironment modulates hyaluronan expression: The lactate effect. *Investig. Dermatol.* 2006, 126, 1378–1387. [CrossRef]

36. Toole, B.P. Hyaluronan-CD44 interactions in cancer: Paradoxes and possibilities. *Clin. Cancer Res.* 2009, 15, 7462–7468. [CrossRef] [PubMed]

37. Albini, A.; Bruno, A.; Noonan, D.M.; Mortara, L. Contribution to tumor angiogenesis from innate immune cells within the tumor microenvironment: Implications for immunotherapy. *Front. Immunol.* 2018, 9, 527. [CrossRef]

38. Landskron, G.; De la Fuente, M.; Thuwajit, P.; Thuwajit, C.; Hermoso, M.A. Chronic inflammation and cytokines in the tumor microenvironment. *J. Immun. Res.* 2014, 2014, 149185. [CrossRef]

39. Seyfried, T.N.; Shelton, L.M. Cancer as a metabolic disease. *Nutr. Metab. (Lond.)* 2010, 7, 7. [CrossRef]

40. Shalapour, S.; Karin, M. Immunity, inflammation, and cancer: An eternal fight between good and evil. *J. Clin. Invest.* 2015, 125, 3347–3355. [CrossRef] [PubMed]

41. Li, Y.; Zhu, B. Editorial: Metabolism of cancer cells and immune cells in the tumor microenvironment. *Front. Immunol.* 2018, 9, 3080. [CrossRef]

42. Mantovani, A.; Allavena, P.; Sica, A.; Balkwill, F. Cancer-related inflammation. *Nature* 2008, 454, 436–444. [CrossRef]

43. Russo, V. Metabolism, LXR/LXR ligands, and tumor immune escape. *J. Leukoc. Biol.* 2011, 90, 673–679. [CrossRef] [PubMed]

44. Awad, R.M.; De Vlaeminck, Y.; Maebe, J.; Goyvaerts, C.; Breckpot, K. Turn back the TiMe: Targeting Tumor Infiltrating Myeloid cells to revert cancer progression. *Front. Immun.* 2018, 9, 1977. [CrossRef]

45. Bronte, V.; Serafini, P.; Mazzoni, A.; Segal, D.M.; Zanovello, P. l-Arginine metabolism in myeloid cells controls T-lymphocyte functions. *Trends Immunol.* 2003, 24, 302–306. [CrossRef]

46. Monu, N.R.; Frey, A.B. Myeloid-derived suppressor cells and anti-tumor T cells: A complex relationship. *Immunol. Investig.* 2012, 41, 595–613. [CrossRef]

47. Raber, P.; Ochoa, A.C.; Rodriguez, P.C. Metabolism of l-arginine by myeloid-derived suppressor cells in cancer: Mechanisms of T cell suppression and therapeutic perspectives. *Immunol. Invest.* 2012, 41, 614–634. [CrossRef]

48. Vitrac, X.; Desmouliere, A.; Brouillaud, B.; Krisa, S.; Deffieux, G.; Barthé, N.; Rosenbaum, J.; Merillon, J.M. Distribution of [14C]-trans-resveratrol, a cancer chemopreventive polyphenol, in mouse tissues after oral administration. *Life Sci.* 2003, 72, 2219–2233. [CrossRef]

49. Chaplin, A.; Carpenne, C.; Mercader, J. Resveratrol, Metabolic Syndrome, and Gut Microbiota. *Nutrients* 2018, 10, 1651. [CrossRef]

50. Kiskova, T.; Demeckova, V.; Jendzelovska, Z.; Kiktava, M.; Venglovskova, K.; Bohmdorfer, M.; Jager, W.; Thalhammer, T. Nocturnal resveratrol administration inhibits chemically induced breast cancer formation in rats. *J. Physiol. Pharmacol*. 2017, 68, 867–875.

51. Kiskova, T.; Jendzelovsky, R.; Rentsen, E.; Maier-Salamon, A.; Kokosova, N.; Papcova, Z.; Mikes, J.; Orendas, P.; Bojkova, B.; Kubatka, P.; et al. Resveratrol enhances the chemopreventive effect of celecoxib in chemically induced breast cancer in rats. *Eur. J. Cancer Prev.* 2014, 23, 506–513. [CrossRef]

52. Bresciani, L.; Calani, L.; Bocchi, L.; Delucchi, F.; Savi, M.; Ray, S.; Brighenti, F.; Stilli, D.; del Rio, D. Bioaccumulation of resveratrol metabolites in myocardial tissue is dose-time dependent and related to cardiac hemodynamics in diabetic rats. *Nutr. Metab. Cardiovasc. Dis.* 2014, 24, 408–415. [CrossRef] [PubMed]

53. Van Ginkel, P.R.; Sareen, D.; Subramanian, L.; Walker, Q.; Darjatmoko, S.R.; Lindstrom, M.J.; Kulkarni, A.; Albert, D.M.; Polans, A.S. Resveratrol inhibits tumor growth of human neuroblastoma and mediates apoptosis by directly targeting mitochondria. *Clin. Cancer Res.* 2007, 13, 5162–5169. [CrossRef]

54. CN, N.s.-K.; St-Louis, C.; Beauregard, M.; Subirade, M.; Carpentier, R.; Hotchandani, S.; Tajmir-Riahi, H.A. Resveratrol binding to human serum albumin. *J. Biomol. Struct. Dyn.* 2006, 24, 277–283.
55. Jannin, B.; Menzel, M.; Berlot, J.P.; Delmas, D.; Lancon, A.; Latruffe, N. Transport of resveratrol, a cancer chemopreventive agent, to cellular targets: Plasmatic protein binding and cell uptake. *Biochem. Pharmacol.* 2004, *68*, 1113–1118. [CrossRef] [PubMed]

56. Frombaum, M.; Le Clanche, S.; Therond, P.; Nubret, E.; Bonnefont-Rousselot, D.; Borderie, D. Penetration of resveratrol into bovine aortic endothelial cells (BAEC): A possible passive diffusion. *C. R. Biol.* 2012, *335*, 247–252. [CrossRef]

57. Gohovic-Bukarica, L.; Novakovic, A.; Kanjuh, V.; Bumbasirevic, M.; Lesic, A.; Heinle, H. A role of ion channels in the endothelium-independent relaxation of rat mesenteric artery induced by resveratrol. *J. Pharmacol. Sci.* 2008, *108*, 124–130. [CrossRef] [PubMed]

58. Chen, M.L.; Yi, L.; Jin, X.; Xie, Q.; Zhang, T.; Zhou, X.; Chang, H.; Fu, Y.J.; Zhu, J.D.; Zhang, Q.Y.; et al. Absorption of resveratrol by vascular endothelial cells through passive diffusion and an SGLT1-mediated pathway. *J. Nutr. Biochem.* 2013, *24*, 1823–1829. [CrossRef] [PubMed]

59. Lancon, A.; Delmas, D.; Osman, H.; Thenot, J.P.; Jannin, B.; Latruffe, N. Human hepatic cell uptake of resveratrol: Involvement of both passive diffusion and carrier-mediated process. *Biochem. Biophys. Res. Commun.* 2004, *316*, 1132–1137. [CrossRef] [PubMed]

60. Davies, J.M.S.; Cillard, J.; Friguet, B.; Cadenas, E.; Cadet, J.; Cayce, R.; Fishmann, A.; Liao, D.; Bulteau, A.-L.; Derbré, F.; et al. The Oxygen Paradox, the French Paradox, and age-related diseases. *GeroScience* 2017, *39*, 499–550. [CrossRef]

61. Ferri, J. The French paradox: Lessons for other countries. *Heart* 2004, *90*, 107–111. [CrossRef]

62. Opie, L.H.; Lamont, K.; LeCour, S. Wine and heart health: Learning from the French paradox: The French paradox. *SA Heart* 2011, *11*, 168–177.

63. Timmers, S.; Auwerx, J.; Schwarcz, P. The journey of resveratrol from yeast to human. *Aging* 2012, *4*, 146–158. [CrossRef] [PubMed]

64. Schirr, E.L. Antioxidants in hypertension and cardiovascular disease. *Mol. Interv.* 2010, *10*, 354–362. [CrossRef] [PubMed]

65. Marx, W.; Kelly, J.; Marshall, S.; Nakos, S.; Campbell, K.; Itsiopoulos, C. The effect of polyphenol-rich interventions on cardiovascular risk factors in haemodialysis: A systematic review and meta-analysis. *Nutrients* 2017, *9*, 1345. [CrossRef] [PubMed]

66. Rasines-Perea, Z.; Teissedre, P.-L. Grape polyphenols’ effects in human cardiovascular diseases and diabetes. *Molecules* 2017, *22*, 68. [CrossRef] [PubMed]

67. Uttara, B.; Singh, A.V.; Zamboni, P.; Mahajan, R.T. Oxidative stress and neurodegenerative diseases: A review of upstream and downstream antioxidant therapeutic options. *Curr. Neuropharmacol.* 2009, *7*, 65–74. [CrossRef] [PubMed]

68. Catalogol, B.; Batirel, S.; Taga, Y.; Ozer, N.K. Resveratrol: French paradox revisited. *Front. Pharmacol.* 2012, *3*, 141. [CrossRef]

69. Guo, R.; Su, Y.; Liu, B.; Li, S.; Zhou, S.; Xu, Y. Resveratrol suppresses oxidised low-density lipoprotein-induced macrophage apoptosis through inhibition of intracellular reactive oxygen species generation, LOX-1, and the p38 MAPK pathway. *Cell. Physiol. Biochem.* 2014, *34*, 603–616. [CrossRef]

70. Vidavalur, R.; Otani, H.; Singal, P.K.; Maulik, N. Significance of wine and resveratrol in cardiovascular disease: French paradox revisited. *Exp. Clin. Cardiol.* 2006, *11*, 217–225.

71. Gohovic, B.; Sia, C.L.; Abuaysheh, S.; Korzeniewski, K.; Patnaik, P.; Marumganti, A.; Chaudhuri, A.; Dandona, P. An antiinflammatory and reactive oxygen species suppressive effects of an extract of Polygonum cuspidatum containing resveratrol. *J. Clin. Endocrinol. Metab.* 2010, *95*, E1–E8. [CrossRef]

72. Mamalis, A.; Koo, E.; Jagdeo, J. Resveratrol prevents reactive oxygen species-induced effects of light-emitting diode-generated blue light in human skin fibroblasts. *Dermatol. Surg.* 2016, *42*, 727–732. [CrossRef]

73. Song, J.; Huang, Y.; Zheng, W.; Yan, J.; Cheng, M.; Zhao, R.; Chen, L.; Hu, C.; Jia, W. Resveratrol reduces intracellular reactive oxygen species levels by inducing autophagy through the AMPK-mTOR pathway. *Front. Med.* 2018, *12*, 697–706. [CrossRef]

74. Cheng, P.W.; Ho, W.Y.; Su, Y.T.; Lu, P.J.; Chen, B.Z.; Cheng, W.H.; Lu, W.H.; Sun, G.C.; Yeh, T.C.; Hsiao, M.; et al. Resveratrol decreases fructose-induced oxidative stress, mediated by NADPH oxidase via an AMPK-dependent mechanism. *Br. J. Pharmacol.* 2014, *171*, 2739–2750. [CrossRef]
Cheng, P.W.; Lee, H.C.; Lu, P.J.; Chen, H.H.; Lai, C.C.; Sun, G.C.; Yeh, T.C.; Hsiao, M.; Lin, Y.T.; Liu, C.P.; et al. Resveratrol inhibition of Rac1-derived reactive oxygen species by AMPK decreases blood pressure in a fructose-induced rat model of hypertension. *Sci. Rep.* **2016**, *6*, 25342. [CrossRef]

Lin, Y.T.; Wu, Y.C.; Sun, G.C.; Ho, C.Y.; Wong, T.Y.; Lin, C.H.; Chen, H.H.; Yeh, T.C.; Li, C.J.; Tseng, C.J.; et al. Effect of resveratrol on reactive oxygen species-induced cognitive impairment in rats with angiotensin II-induced early Alzheimer’s disease. *J. Clin. Med.* **2018**, *7*, 329. [CrossRef]

Sebori, R.; Kuno, A.; Hosoda, R.; Hayashi, T.; Horio, Y. Resveratrol decreases oxidative stress by restoring mitophagy and improves the pathophysiology of dystrophin-deficient mdx mice. *Oxid. Med. Cell. Longev.* **2018**, *2018*, 9179270. [CrossRef] [PubMed]

Kuo, C.Y.; Ann, D.K. When fats commit crimes: Fatty acid metabolism, cancer stemness and therapeutic resistance. *Cancer Comm.* **2018**, *38*, 47. [CrossRef]

Ahmadian, M.; Duncan, R.E.; Jaworski, K.; Sarkadi-Nagy, E.; Sul, H.S. Triacylglycerol metabolism in adipose tissue. *Future Lipidol.* **2007**, *2*, 229–237. [CrossRef] [PubMed]

Baenke, F.; Peck, B.; Miess, H.; Schulze, A. Hooked on fat: The role of lipid synthesis in cancer metabolism and tumour development. *Dis. Model. Mech.* **2013**, *6*, 1353–1363. [CrossRef]

Santos, C.R.; Schulze, A. Lipid metabolism in cancer. *FEBS J.* **2012**, *279*, 2610–2623. [CrossRef] [PubMed]

Knobloch, M.; Pilz, G.-A.; Ghesquière, B.; Kovacs, W.J.; Wegleiter, T.; Moore, D.L.; Hruzova, M.; Zamboni, N.; Carmeliet, P.; Jessberger, S. A fatty acid oxidation-dependent metabolic shift regulates adult neural stem cell activity. *Cell. Rep.* **2017**, *20*, 2144–2155. [CrossRef]

Harris, D.M.; Li, L.; Chen, M.; Lagunero, F.T.; Go, V.L.; Boros, L.G. Diverse mechanisms of growth inhibition by luteolin, resveratrol, and quercetin in MIA PaCa-2 cells: A comparative glucose tracer study with the fatty acid synthase inhibitor C75. *Metabolomics* **2012**, *8*, 201–210. [CrossRef]

Petan, T.; Jarc, E.; Jusovíc, M. Lipid droplets in cancer: Guardians of fat in a stressful world. *Oncol. Rep.* **2016**, *35*, 1353–1363. [CrossRef] [PubMed]

Han, J.; Wang, Y. mTORC1 signaling in hepatic lipid metabolism. *Protein Cell.* **2018**, *9*, 145–151. [CrossRef]

Saxton, R.A.; Sabatini, D.M. mTOR signaling in growth, metabolism, and disease. *Cell* **2017**, *168*, 960–976. [CrossRef] [PubMed]

Yu, J.S.L.; Cui, W. Proliferation, survival and metabolism: The role of PI3K/AKT/mTOR signalling in pluripotency and cell fate determination. *Development* **2016**, *143*, 3050–3060. [CrossRef]

Chai, R.; Fu, H.; Zheng, Z.; Liu, T.; Ji, S.; Li, G. Resveratrol inhibits proliferation and migration through SIRT1 mediated post-translational modification of PI3K/AKT signaling in hepatocellular carcinoma cells. *Mol. Med. Rep.* **2017**, *16*, 8037–8044. [CrossRef] [PubMed]

Jing, X.; Cheng, W.; Wang, S.; Li, P.; He, L. Resveratrol induces cell cycle arrest in human gastric cancer MGC803 cells via the PTEN-regulated PI3K/Akt signaling pathway. *Oncol. Rep.* **2016**, *35*, 472–478. [CrossRef] [PubMed]

Zeng, Y.H.; Zhou, L.Y.; Chen, Q.Z.; Li, Y.; Shao, Y.; Ren, W.Y.; Liao, Y.P.; Wang, H.; Zhu, J.H.; Huang, M.; et al. Resveratrol inactivates PI3K/Akt signaling through upregulating BMP7 in human colon cancer cells. *Oncol. Rep.* **2017**, *38*, 456–464. [CrossRef]

Busaidy, N.L.; Farooki, A.; Dowlati, A.; Perentesis, J.P.; Dancey, J.E.; Doyle, L.A.; Brell, J.M.; Siu, L.L. Management of metabolic effects associated with anticancer agents targeting the PI3K-Akt-mTOR pathway. *J. Clin. Oncol.* **2012**, *30*, 2919–2928. [CrossRef] [PubMed]

Alayev, A.; Salamon, R.S.; Schwartz, N.S.; Berman, A.Y.; Wiener, S.L.; Holz, M.K. Combination of rapamycin and resveratrol for treatment of bladder cancer. *J. Cell. Physiol.* **2017**, *232*, 436–446. [CrossRef] [PubMed]
96. Jin, H.-G.; Wu, G.-Z.; Wu, G.-H.; Bao, Y.-G. Combining the mammalian target of rapamycin inhibitor, rapamycin, with resveratrol has a synergistic effect in multiple myeloma. *Oncol. Lett.* **2018**, *15*, 6257–6264. [CrossRef] [PubMed]

97. Kiskova, T.; Kassayova, M.; Orendas, P.; Bojkova, B. The effect of resveratrol on lipid metabolism in breast cancer in rats. In Proceedings of the YSA-Young Scientist Association of the Medical University of Vienna, Vienna, Austria, 23 April 2013; p. 147.

98. Long, J.; Zhang, C.-J.; Zhu, N.; Du, K.; Yin, Y.-F.; Tan, X.; Liao, D.-F.; Qin, L. Lipid metabolism and carcinogenesis, cancer development. *Am. J. Cancer Res.* **2018**, *8*, 778–791. [PubMed]

99. Zhou, C.; Qian, W.; Ma, J.; Cheng, L.; Jiang, Z.; Yan, B.; Li, J.; Duan, W.; Sun, L.; Cao, J.; et al. Resveratrol enhances the chemotherapeutic response and reverses the stemness induced by gemcitabine in pancreatic cancer cells via targeting SREBP1. *Cell. Prolif.* **2019**, *52*, e12514. [CrossRef]

100. Pandey, P.R.; Xing, F.; Sharma, S.; Watabe, M.; Pai, S.K.; Iiizumi-Gairani, M.; Fukuda, K.; Hirota, S.; Mo, Y.Y.; Watabe, K. Elevated lipogenesis in epithelial stem-like cell confers survival advantage in ductal carcinoma in situ of breast cancer. *Oncogene* **2013**, *32*, 5111–5122. [CrossRef]

101. Ye, X.; Li, M.; Hou, T.; Gao, T.; Zhu, W.-G.; Yang, Y. Sirtuins in glucose and lipid metabolism. *Hum. Genom.* **2016**, *5*, 33–36. [PubMed]

102. Hall, J.A.; Dominy, J.E.; Lee, Y.; Puigserver, P. The sirtuin family’s role in aging and age-associated pathologies. *Cancer Res.* **2005**, *65*, 5358–5366. [PubMed]

103. Hardie, D.G. AMP-activated/AMPK protein kinases: Conserved guardians of cellular energy. *Nat. Rev. Mol. Cell. Biol.* **2007**, *8*, 774–785. [CrossRef]

104. Lan, F.; Weikel, K.A.; Cacicedo, J.M.; Ido, Y. Resveratrol-induced AMP-activated protein kinase activation is cell-type dependent: Lessons from basic research for clinical application. *Nutrients* **2017**, *9*, 751. [CrossRef] [PubMed]

105. Liu, Y.; Tong, L.; Luo, Y.; Li, X.; Chen, G.; Wang, Y. Resveratrol inhibits the proliferation and induces the apoptosis in ovarian cancer cells via inhibiting glycolysis and targeting AMPK/mTOR signaling pathway. *J. Cell. Biochem.* **2018**, *119*, 6162–6172. [CrossRef] [PubMed]

106. Price, N.L.; Gomes, A.P.; Ling, A.J.Y.; Duarte, F.V.; Martin-Montalvo, A.; North, B.J.; Agarwal, B.; Ye, L.; Kemper, J.K. SIRT1 deacetylates and inhibits SREBP-1C activity in regulation of hepatic lipid metabolism. *J. Lipid Res.* **2016**, *57*, 973–979. [CrossRef]

107. Mei, Z.; Zhang, X.; Yi, J.; Huang, J.; He, J.; Tao, Y. Sirtuins in metabolism, DNA repair and cancer. *Nat. Rev. Mol. Cell. Biol.* **2011**, *12*, 1252–1258. [CrossRef]

108. Hall, J.A.; Dominy, J.E.; Lee, Y.; Puigserver, P. Sirtuin family protein kinases: Conserved guardians of cellular energy. *Nat. Rev. Mol. Cell. Biol.* **2005**, *5*, 5358–5366. [PubMed]

109. Pandey, P.R.; Xing, F.; Sharma, S.; Watabe, M.; Pai, S.K.; Iiizumi-Gairani, M.; Fukuda, K.; Hirota, S.; Mo, Y.Y.; Watabe, K. Elevated lipogenesis in epithelial stem-like cell confers survival advantage in ductal carcinoma in situ of breast cancer. *Oncogene* **2013**, *32*, 5111–5122. [CrossRef]

110. Ye, X.; Li, M.; Hou, T.; Gao, T.; Zhu, W.-G.; Yang, Y. Sirtuins in glucose and lipid metabolism. *Hum. Genom.* **2016**, *5*, 33–36. [PubMed]

111. Defour, A.; Dessalle, K.; Castro Perez, A.; Poyot, T.; Castells, J.; Gallot, Y.S.; Durand, C.; Euthine, V.; Gu, Y.; Béchet, D.; et al. Sirtuin 1 Regulates SREBP-1c Expression in a LXR-Dependent Manner in Skeletal Muscle. *PLoS ONE* **2012**, *7*, e34900. [CrossRef]

112. Lin, L.; Zheng, X.; Qiu, C.; Dongol, S.; Lv, Q.; Jiang, J.; Kong, B.; Wang, C. SIRT1 promotes endometrial tumor growth by targeting SREBP1 and lipogenesis. *Oncol. Rep.* **2014**, *32*, 2831–2835. [CrossRef]

113. Kiskova, T.; Kassayova, M.; Orendas, P.; Bojkova, B. The effect of resveratrol on lipid metabolism in breast cancer in rats. In Proceedings of the YSA-Young Scientist Association of the Medical University of Vienna, Vienna, Austria, 23 April 2013; p. 147.

114. Defour, A.; Dessalle, K.; Castro Perez, A.; Poyot, T.; Castells, J.; Gallot, Y.S.; Durand, C.; Euthine, V.; Gu, Y.; Béchet, D.; et al. Sirtuin 1 Regulates SREBP-1c Expression in a LXR-Dependent Manner in Skeletal Muscle. *PLoS ONE* **2012**, *7*, e34900. [CrossRef]

115. Vassilopoulos, A.; Fritz, K.S.; Petersen, D.R.; Gius, D. The human sirtuin family: Evolutionary diversences and functions. *Hum. Genom.* **2011**, *5*, 485–496. [CrossRef]

116. Eid, W.; Dauner, K.; Courtney, K.C.; Gagnon, A.; Parks, R.J.; Sorisky, A.; Zha, X. mTORC1 activates SREBP-2 by suppressing cholesterol trafficking to lysosomes in mammalian cells. *Proc. Natl. Acad. Sci. USA* **2017**, *114*, 7999–8004. [CrossRef]

117. Hardie, D.G. AMP-activated/AMPK protein kinases: Conserved guardians of cellular energy. *Nat. Rev. Mol. Cell. Biol.* **2007**, *8*, 774–785. [CrossRef]

118. Pan, H.; Jin, H.; Ren, J.; Zhang, Y.; Wang, M.; Liu, F.; Zhan, X.; Gao, W.; Wang, J.; et al. Resveratrol inhibits the proliferation and induces the apoptosis in ovarian cancer cells via inhibiting glycolysis and targeting AMPK/mTOR signaling pathway. *J. Cell. Biochem.* **2018**, *119*, 6162–6172. [CrossRef] [PubMed]

119. Defour, A.; Dessalle, K.; Castro Perez, A.; Poyot, T.; Castells, J.; Gallot, Y.S.; Durand, C.; Euthine, V.; Gu, Y.; Béchet, D.; et al. Sirtuin 1 Regulates SREBP-1c Expression in a LXR-Dependent Manner in Skeletal Muscle. *PLoS ONE* **2012**, *7*, e34900. [CrossRef]

120. Lin, L.; Zheng, X.; Qiu, C.; Dongol, S.; Lv, Q.; Jiang, J.; Kong, B.; Wang, C. SIRT1 promotes endometrial tumor growth by targeting SREBP1 and lipogenesis. *Oncol. Rep.* **2014**, *32*, 2831–2835. [CrossRef]

121. Kiskova, T.; Kassayova, M.; Orendas, P.; Bojkova, B. The effect of resveratrol on lipid metabolism in breast cancer in rats. In Proceedings of the YSA-Young Scientist Association of the Medical University of Vienna, Vienna, Austria, 23 April 2013; p. 147.

122. Defour, A.; Dessalle, K.; Castro Perez, A.; Poyot, T.; Castells, J.; Gallot, Y.S.; Durand, C.; Euthine, V.; Gu, Y.; Béchet, D.; et al. Sirtuin 1 Regulates SREBP-1c Expression in a LXR-Dependent Manner in Skeletal Muscle. *PLoS ONE* **2012**, *7*, e34900. [CrossRef]

123. Lin, L.; Zheng, X.; Qiu, C.; Dongol, S.; Lv, Q.; Jiang, J.; Kong, B.; Wang, C. SIRT1 promotes endometrial tumor growth by targeting SREBP1 and lipogenesis. *Oncol. Rep.* **2014**, *32*, 2831–2835. [CrossRef]
117. Borra, M.T.; Smith, B.C.; Denu, J.M. Mechanism of human SIRT1 activation by resveratrol. J. Biol. Chem. 2005, 280, 17187–17195. [CrossRef]
118. Chung, J.H. Metabolic benefits of inhibiting cAMP-PDEs with resveratrol. Adipocyte 2012, 1, 256–258. [CrossRef]
119. Gambini, J.; Inglés, M.; Olaso, G.; Lopez-Gruese, R.; Bonet-Costa, V.; Gimeno-Mallench, L.; Mas-Bargues, C.; Abdelaziz, K.M.; Gomez-Cabrera, M.C.; Vina, J.; et al. Properties of Resveratrol: In Vitro and In Vivo Studies about Metabolism, Bioavailability, and Biological Effects in Animal Models and Humans. Oxid. Med. Cell. Longev. 2015, 2015, 837042. [CrossRef] [PubMed]
120. Kaeberlein, M.; McDonagh, T.; Heltweg, B.; Hixon, J.; Westman, E.A.; Napper, A.; Curtis, R.; Di Stefano, P.S.; Fields, S.; et al. Substrate-specific activation of sirtuins by resveratrol. J. Biol. Chem. 2005, 280, 17038–17045. [CrossRef] [PubMed]
121. Maugeri, A.; Barchitta, M.; Mazzone, M.G.; Giuliano, F.; Basile, G.; Agodi, A. Resveratrol Modulates SIRT1 and DNMT Functions and Restores LINE-1 Methylation Levels in ARPE-19 Cells under Oxidative Stress and Inflammation. Int. J. Mol. Sci. 2018, 19, 2118. [CrossRef]
122. Yang, Q.; Wang, B.; Zang, W.; Wang, X.; Liu, Z.; Li, W.; Jia, J. Resveratrol Inhibits the Growth of Gastric Cancer by Inducing G1 Phase Arrest and Senescence in a Sirt1-Dependent Manner. PLoS ONE 2013, 8, e70627. [CrossRef]
123. Deus, C.M.; Serafim, T.L.; Magalhaes-Novais, S.; Vilaca, A.; Moreira, A.C.; Sardao, V.A.; Cardoso, S.M.; Oliveira, P.J. Sirtuin 1-dependent resveratrol cytotoxicity and pro-differentiation activity on breast cancer cells. Arch. Toxicol. 2017, 91, 1261–1278. [CrossRef] [PubMed]
124. Buhrmann, C.; Shayan, P.; Popper, B.; Goel, A.; Shakibaee, M. Sirt1 is required for resveratrol-mediated chemopreventive effects in colorectal cancer cells. Nutrients 2016, 8, 145. [CrossRef] [PubMed]
125. Sayd, S.; Thirant, C.; El-Habr, E.A.; Lipecka, J.; Cabral, M.; Gomez-Cabrera, M.C.; Vina, J.; et al. Properties of Resveratrol: In Vitro and In Vivo Studies about Metabolism, Bioavailability, and Biological Effects in Animal Models and Humans. Oxid. Med. Cell. Longev. 2015, 2015, 837042. [CrossRef] [PubMed]
126. Baek, A.E.; Nelson, E.R. The contribution of cholesterol and its metabolites to the pathophysiology of breast cancer. Horm. Cancer 2016, 7, 219–228. [CrossRef] [PubMed]
127. Nogueiras, R.; Habegger, K.M.; Chaudhary, N.; Sinha, S.; Schramm, M.P.; Vinson, J.A.; Narayanaswami, V. Targeted intracellular delivery of resveratrol to glioblastoma cells using apolipoprotein E-containing reconstituted HDL as a nanovehicle. PLoS ONE 2015, 10, e0135130. [CrossRef] [PubMed]
128. Chang, G.-R.; Chen, P.-L.; Hou, P.-H.; Lin, C.-Y.; Jia, J. Resveratrol protects against diet-induced atherosclerosis by reducing low-density lipoprotein cholesterol and inhibiting inflammation in apolipoprotein E-deficient mice. Int. J. Mol. Sci. 2015, 16, 2805–2806. [CrossRef] [PubMed]
137. Kitahara, C.M.; Berrington de González, A.; Freedman, N.D.; Huxley, R.; Mok, Y.; Jee, S.H.; Samet, J.M. Total cholesterol and cancer risk in a large prospective study in Korea. J. Clin. Oncol. 2011, 29, 1592–1598. [CrossRef] [PubMed]
138. Silvente-Poirot, S.; Poirot, M. Cholesterol and cancer, in the balance. Science 2014, 343, 1445–1446. [CrossRef] [PubMed]
139. Franky Dhaval, S.; Shilin Nandubhai, S.; Pankaj Manubhai, S.; Patel, H.R.; Prabhudas Shankerbhai, P. Significance of alterations in plasma lipid profile levels in breast cancer. Integr. Cancer Ther. 2008, 7, 33–41. [CrossRef]
140. Miura, D.; Miura, Y.; Yagasaki, K. Hypolipidemic action of dietary resveratrol, a phytoalexin in grapes and red wine, in hepatoma-bearing rats. Life Sci. 2003, 73, 1393–1400. [CrossRef]
141. Chao, S.-C.; Chen, Y.-J.; Huang, K.-H.; Kuo, K.-L.; Yang, T.-H.; Huang, K.-Y.; Wang, C.-C.; Tang, C.-H.; Yang, R.-S.; Liu, S.-H. Induction of sirtuin-1 signaling by resveratrol induces human chondrosarcoma cell apoptosis and exhibits antitumor activity. Sci. Rep. 2017, 7, 3180. [CrossRef]
142. Tang, L.Y.; Chen, Y.; Rui, B.B.; Hu, C.M. Resveratrol ameliorates lipid accumulation in HepG2 cells, associated with down-regulation of lipin1 expression. Can. J. Phys. Pharmacol. 2016, 94, 185–189. [CrossRef]
143. Clark, P.A.; Bhattacharya, S.; Elmayan, A.; Darjatmoko, S.R.; Thuro, B.A.; Yan, M.B.; van Ginkel, P.R.; Polans, A.S.; Kuo, J.S. Resveratrol targeting of AKT and p53 in glioblastoma and glioblastoma stem-like cells to suppress growth and infiltration. J. Neurosurg. 2017, 126, 1448–1460. [CrossRef] [PubMed]
144. Ogretmen, B. Sphingolipid metabolism in cancer signalling and therapy. Nat. Rev. Cancer 2017, 18, 33. [CrossRef] [PubMed]
145. Ponnusamy, S.; Meyers-Needham, M.; Senkal, C.E.; Saddoughi, S.A.; Sentelle, D.; Selvam, S.P.; Salas, A.; Ogretmen, B. Sphingolipids and cancer: Ceramide and sphingosine-1-phosphate in the regulation of cell death and drug resistance. Future Oncol. 2010, 6, 1603–1624. [CrossRef] [PubMed]
146. Saddoughi, S.A.; Song, P.; Ogretmen, B. Roles of bioactive sphingolipids in cancer biology and therapeutics. Sub-Cell. Biochem. 2008, 49, 413–440.
147. Lim, K.G.; Gray, A.I.; Pyne, S.; Pyne, N.J. Resveratrol dimers are novel sphingosine kinase 1 inhibitors and affect sphingosine kinase 1 expression and cancer cell growth and survival. Br. J. Pharmacol. 2012, 166, 1605–1616. [CrossRef]
148. Ciolino, H.P.; Daschner, P.J.; Yeh, G.C. Resveratrol inhibits transcription of CYP1A1 in vitro by preventing activation of the aryl hydrocarbon receptor. Cancer Res. 1998, 58, 5707–5712. [PubMed]
149. Shin, K.-O.; Park, N.-Y.; Seo, C.-H.; Hong, S.-P.; Oh, K.-W.; Hong, J.-T.; Han, S.-K.; Lee, Y.-M. Inhibition of sphingolipid metabolism enhances resveratrol chemotherapy in human gastric cancer cells. Biomol. Ther. 2012, 20, 470–476.
150. Saurier, E.; Antonio, S.; Regazzetti, A.; Auzell, N.; Laprédoute, O.; Shay, J.W.; Cournoul, X.; Barouki, R.; Benelli, C.; Huc, L.; et al. Resveratrol reverses the Warburg effect by targeting the pyruvate dehydrogenase complex in colon cancer cells. Sci. Rep. 2017, 7, 6945. [CrossRef] [PubMed]
151. Ding, X.Z.; Hennig, R.; Adrian, T.E. Lipoxigenase and cyclooxygenase metabolism: New insights in treatment and chemoprevention of pancreatic cancer. Mol. Cancer 2003, 2, 10. [CrossRef]
152. Tian, J.J.; Lei, C.X.; Ji, H.; Jin, A. Role of cyclooxygenase-mediated metabolites in lipid metabolism and expression of some immune-related genes in juvenile grass carp (Ctenopharyngodon idellus) fed arachidonic acid. Fish Physiol. Biochem. 2017, 43, 703–717. [CrossRef]
153. Yui, K.; Imataka, G.; Nakamura, H.; Ohara, N.; Naito, Y. Eicosanoids Derived From Arachidonic Acid and Their Family Prostaglandins and Cyclooxygenase in Psychiatric Disorders. Curr. Neuropharmacol. 2015, 13, 776–785. [CrossRef]
154. Krishnamoorthy, S.; Honn, K.V. Eicosanoids and other lipid mediators and the tumor hypoxic microenvironment. Cancer Metastasis Rev. 2011, 30, 613–618. [CrossRef] [PubMed]
155. Basu, S.; Rossary, A.; Vasson, M.-P. Role of inflammation and eicosanoids in breast cancer. Lipid Tech. 2016, 28, 60–64. [CrossRef]
156. Gomes, R.N.; Felipe da Costa, S.; Colquhoun, A. Eicosanoids and cancer. Clinics 2018, 73, 530s. [CrossRef] [PubMed]
157. Greene, E.R.; Huang, S.; Serhan, C.N.; Panigrahy, D. Regulation of inflammation in cancer by eicosanoids. Prostaglandins Other Lipid Mediat. 2011, 96, 27–36. [CrossRef]
158. Knab, L.M.; Grippio, P.J.; Bentrem, D.J. Involvement of eicosanoids in the pathogenesis of pancreatic cancer: The roles of cyclooxygenase-2 and 5-lipoxygenase. *World J. Gastroenterol.* 2014, 20, 10729–10739. [CrossRef]

159. Brglez, V.; Lambeau, G.; Petan, T. Secreted phospholipases A2 in cancer: Diverse mechanisms of action. *Biochimie* 2014, 107 Pt A, 114–123. [CrossRef]

160. Qu, J.; Zhao, X.; Wang, J.; Liu, C.; Sun, Y.; Cai, H.; Liu, J. Plasma phospholipase A2 activity may serve as a novel diagnostic biomarker for the diagnosis of breast cancer. *Oncol. Lett.* 2018, 15, 5236–5242. [CrossRef]

161. Scott, K.F.; Sajinovic, M.; Hein, J.; Nixdorf, S.; Galettis, P.; Liauw, W.; de Souza, P.; Dong, Q.; Graham, G.G.; Russell, P.J. Emerging roles for phospholipase A2 enzymes in cancer. *Biochimie* 2010, 92, 601–610. [CrossRef]

162. Shen, M.Y.; Hsiao, G.; Liu, C.L.; Fong, T.H.; Lin, K.H.; Chou, D.S.; Sheu, J.R. Inhibitory mechanisms of resveratrol in platelet activation: Pivotal roles of p38 MAPK and NO/cyclic GMP. *Br. J. Haematol.* 2007, 139, 475–485. [CrossRef]

163. Díaz-Chávez, J.; Fonseca-Sánchez, M.A.; Arechaga-Ocampo, E.; Flores-Pérez, A.; Palacios-Rodríguez, Y.; Domínguez-Gómez, G.; Marchat, L.A.; Fuentes-Mera, L.; Mendoza-Hernández, G.; Gariglio, P.; et al. Proteomic profiling reveals that resveratrol inhibits HSP27 expression and sensitizes breast cancer cells to doxorubicin therapy. *PLoS ONE* 2013, 8, e64378. [CrossRef]

164. Narayanan, B.A.; Narayanan, N.K.; Re, G.G.; Nixon, D.W. Differential expression of genes induced by resveratrol in LNCaP cells: P53-mediated molecular targets. *Int. J. Cancer* 2003, 104, 204–212. [CrossRef]

165. Gungor, H.; Ilhan, N.; Eroksuz, H. The effectiveness of cyclooxygenase-2 inhibitors and evaluation of angiogenesis in the model of experimental colorectal cancer. *Biomed. Pharmacother.* 2018, 102, 221–229. [CrossRef]

166. Hashemi Goradel, N.; Najafi, M.; Salehi, E.; Farhood, B.; Mortezaee, K. Cyclooxygenase-2 in cancer: A review. *Carcinogenesis* 2019, 47, 969–975. [PubMed]

167. Hashemi Goradel, N.; Najafi, M.; Salehi, E.; Farhood, B.; Mortezaee, K. Cyclooxygenase-2 in cancer: A review. *Carcinogenesis* 2019, 47, 969–975. [PubMed]

168. Narayanan, B.A.; Narayanan, N.K.; Re, G.G.; Nixon, D.W. Differential expression of genes induced by resveratrol in LNCaP cells: P53-mediated molecular targets. *Int. J. Cancer* 2003, 104, 204–212. [CrossRef]

169. Li, Z.G.; Hong, T.; Shimada, Y.; Komoto, I.; Kawabe, A.; Ding, Y.; Kaganoi, J.; Hashimoto, Y.; Imamura, M. Resveratrol-induced cyclooxygenase-2 targets COX-2 to inhibit carcinogenesis. *Mol. Cancer Therap.* 2005, 4, 1531–1536. [CrossRef] [PubMed]

170. Tang, H.-Y.; Shih, A.; Cao, H.J.; Davis, F.B.; Davis, P.J.; Lin, H.-Y. Resveratrol-induced cyclooxygenase-2 facilitates p53-dependent apoptosis in human breast cancer cells. *Mol. Cancer Therap.* 2006, 5, 2034–2042. [CrossRef] [PubMed]

171. Zykova, T.A.; Zhu, F.; Zhai, X.; Ma, W.Y.; Ermakova, S.P.; Lee, K.W.; Bode, A.M.; Dong, Z. Resveratrol directly targets COX-2 to inhibit carcinogenesis. *Mol. Carcinog.* 2008, 47, 797–805. [CrossRef] [PubMed]

172. Li, Z.G.; Hong, T.; Shimada, Y.; Komoto, I.; Kawabe, A.; Ding, Y.; Kaganoi, J.; Hashimoto, Y.; Imamura, M. Suppression of N-nitrosomethylbenzylamine (NMBA)-induced esophageal tumorigenesis in F344 rats by resveratrol. *Carcinogenesis* 2002, 23, 1531–1536. [CrossRef] [PubMed]

173. Catalano, A.; Procopio, A. New aspects on the role of lipoxigenases in cancer progression. *Histol. Histopathol.* 2005, 20, 969–975. [PubMed]

174. Schneider, C.; Pozzi, A. Cyclooxygenases and lipoxigenases in cancer. *Cancer Metastasis Rev.* 2011, 30, 277–294. [CrossRef] [PubMed]

175. Chatterjee, M.; Das, S.; Janarthan, M.; Ramachandran, H.K.; Chatterjee, M. Role of 5-lipoxygenase in resveratrol mediated suppression of 7,12-dimethylbenz(alpha)anthracene-induced mammary carcinogenesis in rats. *Eur. J. Pharmacol.* 2011, 668, 99–106. [CrossRef] [PubMed]

176. Maccarrone, M.; Lorenzon, T.; Guerrieri, P.; Agrò, A.F. Resveratrol prevents apoptosis in K562 cells by inhibiting lipoxigenase and cyclooxygenase activity. *Eur. J. Biochem.* 1999, 265, 27–34. [CrossRef]

177. Chen, Z.H.; Hurh, Y.J.; Na, H.K.; Kim, J.H.; Chun, Y.J.; Kim, D.H.; Kang, K.S.; Cho, M.H.; Surh, Y.J. Resveratrol inhibits TCDD-induced expression of CYP1A1 and CYP1B1 and catechol estrogen-mediated oxidative DNA damage in cultured human mammary epithelial cells. *Carcinogenesis* 2004, 25, 2005–2013. [CrossRef] [PubMed]

178. Detampel, P.; Beck, M.; Krahenbuhl, S.; Huwyler, J. Drug interaction potential of resveratrol. *Drug Metab. Rev.* 2012, 44, 253–265. [CrossRef]

179. Guthrie, A.R.; Chow, H.H.S.; Martinez, J.A. Effects of resveratrol on drug- and carcinogen-metabolizing enzymes, implications for cancer prevention. *Pharmacol. Res. Perspect.* 2017, 5, e00294. [CrossRef]
180. Orsini, F.; Verotta, L.; Klimo, K.; Gerhauser, C. Synthesis of resveratrol derivatives and in vitro screening for potential cancer chemopreventive activities. Arch. Pharm 2016, 349, 414–427. [CrossRef]

181. Pandey, K.B.; Rizvi, S.I. Resveratrol may protect plasma proteins from oxidation under conditions of oxidative stress in vitro. J. Cell. Biochem. 2009, 108, 515–525. [CrossRef] [PubMed]

182. Wang, D.; Dubois, R.N. Eicosanoids and cancer. Nat. Rev. Cancer 2010, 10, 181–193. [CrossRef]

183. Sexton, E.; Van Themsche, C.; LeBlanc, K.; Parent, S.; Lemoine, P.; Asselin, E. Resveratrol interferes with AKT activity and triggers apoptosis in human uterine cancer cells. Mol. Cancer 2006, 5, 45. [CrossRef] [PubMed]

184. Jang, M.; Pezzuto, J.M. Effects of resveratrol on 12-O-tetradecanoylphorbol-13-acetate-induced oxidative events and gene expression in mouse skin. Cancer Lett. 1998, 134, 81–99. [CrossRef]

185. Sexton, E.; Van Themsche, C.; LeBlanc, K.; Parent, S.; Lemoine, P.; Asselin, E. Resveratrol interferes with AKT activity and triggers apoptosis in mouse uterine cancer cells. Mol. Cancer 2006, 5, 45. [CrossRef] [PubMed]

186. Orsini, F.; Verotta, L.; Klimo, K.; Gerhauser, C. Synthesis of resveratrol derivatives and in vitro screening for potential cancer chemopreventive activities. Arch. Pharm 2016, 349, 414–427. [CrossRef]

187. Niki, E.; Yoshida, Y.; Saito, Y.; Noguchi, N. Lipid peroxidation: Mechanisms, inhibition, and biological effects. Biochim. Biophys. Res. Commun. 2005, 338, 668–676. [CrossRef] [PubMed]

188. Bishayee, A.; Barnes, K.F.; Bhatia, D.; Darvesh, A.S.; Carroll, R.T. Resveratrol suppresses oxidative stress and inflammatory response in diethylnitrosamine-initiated rat hepatocarcinogenesis. Cancer Prev. Res. 2010, 3, 753–763. [CrossRef]

189. Bishayee, A.; Barnes, K.F.; Bhatia, D.; Darvesh, A.S.; Carroll, R.T. Resveratrol suppresses oxidative stress and inflammatory response in diethylnitrosamine-initiated rat hepatocarcinogenesis. Cancer Prev. Res. 2010, 3, 753–763. [CrossRef]

190. Bishayee, A.; Barnes, K.F.; Bhatia, D.; Darvesh, A.S.; Carroll, R.T. Resveratrol suppresses oxidative stress and inflammatory response in diethylnitrosamine-initiated rat hepatocarcinogenesis. Cancer Prev. Res. 2010, 3, 753–763. [CrossRef]

191. Kalra, N.; Roy, P.; Prasad, S.; Shukla, Y. Resveratrol induces apoptosis involving mitochondrial pathways in mouse skin tumorigenesis. Life Sci. 2008, 82, 348–358. [CrossRef] [PubMed]

192. Leonard, S.S.; Xia, C.; Jiang, B.H.; Stinefelt, B.; Klandorf, H.; Harris, G.K.; Shi, X. Resveratrol scavenges radicals and reduces the activity of phospholipase A(2). J. Exp. Ther. Oncol. 2009, 8, 25–33. [PubMed]

193. Pandey, K.B.; Rizvi, S.I. Resveratrol may protect plasma proteins from oxidation under conditions of oxidative stress in vitro. J. Braz. Chem. Soc. 2010, 21, 909–913. [CrossRef]

194. Orsini, F.; Verotta, L.; Klimo, K.; Gerhauser, C. Synthesis of resveratrol derivatives and in vitro screening for potential cancer chemopreventive activities. Arch. Pharm 2016, 349, 414–427. [CrossRef]

195. Adibhatla, R.M.; Hatcher, J.F. Phospholipase A(2), reactive oxygen species, and lipid peroxidation in CNS pathologies. Biochim. Biophys. Acta 2005, 1734, 89–101. [CrossRef] [PubMed]

196. Adibhatla, R.M.; Hatcher, J.F. Phospholipase A(2), reactive oxygen species, and lipid peroxidation in CNS pathologies. Biochim. Biophys. Acta 2005, 1734, 89–101. [CrossRef] [PubMed]

197. Niki, E.; Yoshida, Y.; Saito, Y.; Noguchi, N. Lipid peroxidation: Mechanisms, inhibition, and biological effects. Biochim. Biophys. Res. Commun. 2005, 338, 668–676. [CrossRef] [PubMed]

198. Niki, E.; Yoshida, Y.; Saito, Y.; Noguchi, N. Lipid peroxidation: Mechanisms, inhibition, and biological effects. Biochim. Biophys. Res. Commun. 2005, 338, 668–676. [CrossRef] [PubMed]

199. Bishayee, A.; Barnes, K.F.; Bhatia, D.; Darvesh, A.S.; Carroll, R.T. Resveratrol suppresses oxidative stress and inflammatory response in diethylnitrosamine-initiated rat hepatocarcinogenesis. Cancer Prev. Res. 2010, 3, 753–763. [CrossRef]

200. Bishayee, A.; Barnes, K.F.; Bhatia, D.; Darvesh, A.S.; Carroll, R.T. Resveratrol suppresses oxidative stress and inflammatory response in diethylnitrosamine-initiated rat hepatocarcinogenesis. Cancer Prev. Res. 2010, 3, 753–763. [CrossRef]
202. Trung, L.Q.; An, D.T.T. Is resveratrol a cancer immunomodulatory molecule? *Front. Immunol.* **2018**, *9*, 1255. [CrossRef]

203. Soto, B.L.; Hank, J.A.; Van De Voort, T.J.; Subramanian, L.; Polans, A.S.; Rakhmilevich, A.L.; Yang, R.K.; Seo, S.; Kim, K.; Reisfeld, R.A.; et al. The anti-tumor effect of resveratrol alone or in combination with immunotherapy in a neuroblastoma model. *Cancer Immunol. Immunother.* **2011**, *60*, 731–738. [CrossRef] [PubMed]

204. Tili, E.; Michaille, J.J. Resveratrol, microRNAs, inflammation, and cancer. *J. Nucleic Acids* **2011**, *2011*, 102431. [CrossRef] [PubMed]

205. Fiaschi, T.; Chiarugi, P. Oxidative stress, tumor microenvironment, and metabolic reprogramming: A diabolic liaison. *Int. J. Cell. Biol.* **2012**, *2012*, 762825. [CrossRef] [PubMed]

206. Vaupel, P. Metabolic microenvironment of tumor cells: A key factor in malignant progression. *Exp. Oncol.* **2010**, *32*, 125–127. [PubMed]

207. Wang, M.; Zhao, J.; Zhang, L.; Wei, F.; Lian, Y.; Wu, Y.; Gong, Z.; Zhang, S.; Zhou, J.; Cao, K.; et al. Role of tumor microenvironment in tumorigenesis. *J. Cancer* **2017**, *8*, 761–773. [CrossRef] [PubMed]

208. Gkretsi, V.; Stylianou, A.; Papageorgis, P.; Polyzorou, C.; Stylianopoulos, T. Remodeling components of the tumor microenvironment to enhance cancer therapy. *Front. Oncol.* **2015**, *5*, 214. [CrossRef]

209. Shamim, U.; Hanif, S.; Albanyan, A.; Beck, F.W.; Bao, B.; Wang, Z.; Banerjee, S.; Sarkar, F.H.; Mohammad, R.M.; Hadi, S.M.; et al. Resveratrol-induced apoptosis is enhanced in low pH environments associated with cancer. *J. Cell. Physiol.* **2012**, *227*, 1493–1500. [CrossRef]

210. Zhang, Q.; Tang, X.; Lu, Q.Y.; Zhang, Z.F.; Brown, J.; Le, A.D. Resveratrol inhibits hypoxia-induced accumulation of hypoxia-inducible factor-Ialpha and VEGF expression in human tongue squamous cell carcinoma and hepatoma cells. *Mol. Cancer Ther.* **2005**, *4*, 1465–1474. [CrossRef]

211. Kiskova, T.; Ekmeckioglu, C.; Garajova, M.; Orendas, P.; Bojkova, B.; Bobrov, N.; Jager, W.; Kassayova, M.; Thalhammer, T. A combination of resveratrol and melatonin exerts chemopreventive effects in N-methyl-N-nitrosourea-induced rat mammary carcinogenesis. *Eur. J. Cancer Prev.* **2012**, *21*, 163–170. [CrossRef] [PubMed]

212. Brown, V.A.; Patel, K.R.; Viskaduraki, M.; Crowell, J.A.; Perloff, M.; Booth, T.D.; Vasilinina, G.; Sen, A.; Schinas, A.M.; Piccirilli, G.; et al. Repeat dose study of the cancer chemopreventive agent resveratrol in healthy volunteers: Safety, pharmacokinetics, and effect on the insulin-like growth factor axis. *Cancer Res.* **2010**, *70*, 9003–9011. [CrossRef]

213. Berman, A.Y.; Motechin, R.A.; Wiesenfeld, M.Y.; Holz, M.K. The therapeutic potential of resveratrol: A review of clinical trials. *NPJ Precis. Oncol.* **2017**, *1*, 35. [CrossRef] [PubMed]

214. Haghhighatdoost, F.; Hariri, M. Effect of resveratrol on lipid profile: An updated systematic review and meta-analysis on randomized clinical trials. *Pharmacol. Res.* **2018**, *129*, 141–150. [CrossRef]

215. Jiang, Z.; Chen, K.; Cheng, L.; Yan, B.; Qian, W.; Cao, J.; Li, J.; Wu, E.; Ma, Q.; Yang, W. Resveratrol and cancer treatment: Updates. *Ann. N. Y. Acad. Sci.* **2017**, *1403*, 59–69. [CrossRef] [PubMed]

216. Ramírez-Garza, S.L.; Laveriano-Santos, E.P.; Marhuenda-Muñoz, M.; Storniolo, C.E.; Tresserra-Rimbau, A.; Vallverdú-Queralt, A.; Lamuela-Raventós, R.M. Health effects of resveratrol: Results from human intervention trials. *Nutrients* **2018**, *10*, 1892. [CrossRef] [PubMed]

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