

Combined Cancer Therapy with Non-Conventional Drugs: All Roads Lead to AMPK

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Abstract: AMP-activated protein kinase (AMPK) is a key energy sensor that regulates cellular energy homeostasis. AMPK activation is associated with decreased phosphorylation of mammalian target of rapamycin (mTOR) and S6 kinase and causes a general reduction in mRNA translation and protein synthesis. Therefore, AMPK is a novel target for anti-cancer therapy. Metformin and aspirin are two traditional drugs that are widely used as anti-diabetes and non-steroidal anti-inflammatory drugs (NSAIDs), respectively. Much evidence has confirmed that these two drugs demonstrated encouraging anti-cancer properties. Most importantly, both inhibited tumor proliferation and were mainly dependent on the AMPK/mTOR signaling pathway. In addition, several other drugs, such as resveratrol, berberine, statins, epigallocatechin gallate (EGCG) and capsaicin, have provided a similar capacity for tumor inhibition, and the anti-cancer effects of most of them were mainly the result of AMPK activation. In the current review, we summarize the literature on combination therapy based on these non-classical drugs and their potential mechanisms for activating AMPK. Combinations of these drugs will provide a novel cancer therapeutic regimen.

Keywords: AMPK, aspirin, berberine, cancer therapy, metformin, resveratrol,.

INTRODUCTION

Non-classical drugs, such as metformin, aspirin and resveratrol, have recently attracted the interests of oncologists and pharmacologists for their anti-cancer effects. Metformin has the beneficial effects of the lowering lipid levels [1] and ameliorating hyperglycemia by improving peripheral sensitivity to insulin. Notably, population-based studies have shown that metformin treatment reduces the incidence of cancer and cancer-related mortality [2]. Aspirin, which has been used as an analgesic/anti-inflammatory prescription, has been used in the prevention of cardiovascular disease for a long time. Following the observation that aspirin induced thrombocytopenia and significantly reduced metastases from fibrosarcomas in animal models, aspirin was investigated as an anti-cancer drug. Growing evidence, mostly in the form of clinical studies, suggested that metformin or aspirin was associated with a reduction in cancer risk and resulted in a sensitive response to chemotherapy or radiotherapy [3].

Several potential mechanisms have been suggested to explain the ability of metformin or aspirin to inhibit cancer proliferation. Among these mechanisms, *in vitro* and *in vivo*

results suggested that the activation of AMP-activated protein kinase (AMPK) could explain the common beneficial effects of metformin and aspirin [4]. AMPK is a heterotrimer, with each subunit having more than one isoform (two alpha, two beta and three gamma isoforms). Recently, increasing evidence has suggested that AMPK is a key regulator of energy homeostasis. AMPK plays a major role in regulating the fatty acid and lipid biosynthesis pathway by phosphorylating and inactivating key enzymes such as acetyl-CoA carboxylase (ACC). In addition to the direct regulation of energy homeostasis, AMPK initiates downstream signaling to inhibit cell proliferation. One of the crucial mechanisms is the inhibition of the activation of the downstream target, mammalian target of rapamycin (mTOR), which is frequently activated in malignant cells and is associated with resistance to anticancer drugs. A link between cancer and metabolism has long been suggested, but solid evidence supporting this hypothesis emerged recently with the molecular characterization of the AMPK/mTOR signaling pathway as a tumor suppressor axis, which is also the essential regulator of cellular autophagy [5].

The preclinical rationale and potential mechanisms of metformin and aspirin as anti-cancer drugs are supported by the finding that both can activate AMPK, which inhibits protein synthesis and gluconeogenesis during cellular stress [6]. It is promising that, currently, several randomized clinical trials that combine metformin or aspirin as an adjuvant to classic chemotherapy are ongoing and aim to evaluate their

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potential benefits in this setting. In addition to metformin and aspirin, other non-classical drugs have been used as anti-cancer therapies, such as berberine, statin, resveratrol from grapes and red wine, epigallocatechin gallate (EGCG) from green tea and capsaicin from peppers. Most importantly, one of the critical and common mechanisms of the anti-cancer effects of all these drugs is the activation of the AMPK/mTOR signaling pathway [7]. In the current review, we describe the literature on combination therapies based on metformin, aspirin, resveratrol, berberine, statins, epigallocatechin gallate (EGCG) and capsaicin for cancer treatment and their potential mechanisms for activating AMPK.

METFORMIN

Metformin is an oral anti-diabetic drug in the biguanide class and is the first-line drug for the treatment of type 2 diabetes. Recently, increasing evidence has shown the potential efficacy of metformin as an anticancer drug. Several epidemiological and case-controlled studies found that diabetics using metformin might have a lower cancer risk when compared to those using other anti-diabetic medications. A large case-control study conducted at M.D. Anderson Cancer Center has suggested that metformin may protect against pancreatic cancer. Another observational study conducted by the University of Dundee has shown a decreased cancer risk of 25-37% in diabetics taking metformin.

Indeed, metformin exhibits a strong and consistent anti-proliferation action on several cancer cell lines. Convincingly, these cellular studies were further confirmed by several preclinical studies that showed a reliable anti-tumor effect in various mouse models. On the one hand, metformin decreases insulin resistance and indirectly reduces the insulin level, which promotes cancer cell growth. On the other hand, most importantly, metformin directly activates the AMP activated protein kinase (AMPK) signaling pathway, which is a major cellular energy sensor, and inhibits mammalian target of rapamycin (mTOR) catalytic activity, which has been proposed as a major driver of cancer proliferation [8, 9].

PRE-CLINICAL ANTI-CANCER EFFECT OF METFORMIN

Metformin was shown to inhibit the proliferation of human prostate cancer cells with a 50% decrease in cell viability *in vitro*. Importantly, in an *in vivo* model using xenografts of LNCaP cells, oral and intraperitoneal treatment with metformin led to a 50% and 35% reduction of tumor growth, respectively [10]. Consistent with the results obtained with prostate cancer cells, metformin also demonstrated a growth inhibitory effect in colon and pancreatic cancer cell lines [11]. More importantly, metformin treatment inhibited lung metastasis and potentiated cisplatin-induced cytotoxicity with approximately a 90% reduction in tumor growth when compared to treatment by either of the drugs alone [12]. In the endometrial cancer cell model, metformin markedly promoted progesterone receptor (PR) expression, which was partially mediated through the activation of AMPK and explained why metformin combination therapy could reverse progesterone-resistant atypical endometrial hyperplasia [13].

Many studies on the ability of metformin to inhibit the proliferation of breast cancer cells have been performed. In

MCF-7 human breast cancer cells, metformin induced growth inhibition by means of AMPK pathway activation and mTOR inhibition [14]. Interestingly, subsequent experiments specifically investigating breast cancer cell lines with different estrogen receptor (ER) statuses confirmed that AMPK stimulation by metformin resulted in complete cell growth inhibition in ER-positive cell lines but only partial inhibition in estrogen receptor-negative cell lines [15]. However, another study found that nude mice bearing tumor xenografts of triple-negative breast cancer cells (MDA-MB-231) revealed significant reductions in tumor growth and proliferation after treatment with metformin when compared to controls. Furthermore, pre-treatment with metformin before injection of MDA-MB-231 cells caused a dramatic decrease in tumor growth and incidence [16]. In another study, Hirsch, H. A. *et al.* showed that metformin inhibited cellular transformation, selectively targeted breast cancer stem cells and acted with chemotherapy to block tumor growth and prolong remission. Table 1 presents a summary of on the available data regarding the use of metformin as an anti-cancer drug.

METFORMIN TARGETS THE AMPK/mTOR SIGNALING PATHWAYS TO INHIBIT CANCER CELL GROWTH

Currently, it is well accepted that metformin is a widely used anti-diabetic agent and that it may exert anti-tumoral and anti-proliferative actions. It would be interesting to combine metformin with other drugs as a way to develop new and promising strategies to fight cancer. Notably, most of the previous cellular studies generally involved preclinical studies that showed a reliable anti-tumoral effect of metformin in various cancer cell lines and mouse models, and this effect occurred mainly through AMPK activation, mTOR inhibition and a global reduction of protein synthesis [11]. Indeed, mTOR is activated by mitogenic responsive signaling pathways and intracellular energy and nutrient stimuli. However, metformin could activate AMPK and negatively regulate mTOR, thus inducing the inhibition of cell growth [17].

Although the anti-cancer effects of metformin mainly function by activating the AMPK/mTOR signaling pathway, which dominantly controls protein synthesis and cell proliferation, metformin could also inhibit cancer cell proliferation independent of AMPK activation. Bhalla, K. *et al.* reported that metformin protected mice from chemically induced liver tumors but did not activate AMPK. This protective effect of metformin was shown to mainly be the result of decreased expression of several lipogenic enzymes and lipogenesis, suggesting that metformin might be useful for patients with other disorders associated with hepatic carcinoma (HCC) in which increased lipid synthesis is observed. More recently, in a C57Bl/6 mouse model of high-fat diet (HFD)-induced liver tumorigenesis, metformin was shown to improve the short-term, HFD-induced accumulation of fat in the liver that was associated with the suppression of adipose tissue inflammation. These results suggested that metformin might prevent liver tumorigenesis via the suppression of liver fat accumulation during the early stages before the onset of Non Alcoholic Fatty Liver Disease (NAFLD). Ben Sahra, I. *et al.* showed that the anti-proliferative action of metformin in prostate cancer cell lines

Table 1. Anti-cancer studies of Metformin.

Research model	Conclusion	<i>in vitro/in vivo</i>	Reference
2,529 patients who received neoadjuvant chemotherapy for early-stage breast cancer between 1990 and 2007	Diabetic patients with breast cancer receiving metformin and neoadjuvant chemotherapy had a higher pCR rate than diabetics not receiving metformin	<i>in vivo</i>	[18]
Ishikawa and HEC-1B EC cell lines	Metformin promoted PR expression, which can be inhibited by overexpressed IGF-II in EC. This effect was partially mediated by the activation of AMPK followed by inhibition of the over-activated mTOR pathway. The effects of metformin on PR A/B and p70S6K were partially reversed by an AMPK inhibitor.	<i>in vitro</i>	[94]
Tumors in mice with diet-induced hyperinsulinemia	Metformin only inhibited the growth of tumors transfected with short hairpin RNA against LKB1. Reduced LKB1 expression resulted in a greater sensitivity to metformin treatment	<i>in vivo</i> and <i>in vitro</i>	[95]
An <i>in vivo</i> mouse model with MC38 colon carcinoma cell xenografts	Metformin blocked the effect of the high-energy diet on tumor growth and caused the activation of AMPK, reduced insulin levels, and attenuated the effect of diet on phosphorylation of AKT and expression of FASN	<i>in vivo</i>	[96]
AMPK $\alpha^{+/+}$ and AMPK $\alpha^{-/-}$ mouse embryonic fibroblasts (MEF) and male C57BL/6 mice	Metformin inhibited the growth of certain neoplasms through AMPK activation, with secondary inhibition of protein synthesis or by an indirect mechanism involving a reduction in gluconeogenesis, leading to a decline in insulin levels and reduced proliferation of insulin-responsive cancers	<i>in vivo</i> and <i>in vitro</i>	[97]
Lewis lung LLC1 carcinoma in C57BL/6J mice	Metformin attenuated the increased insulin receptor activation associated with the high-energy diet and also led to increased phosphorylation of AMPK, two actions that would be expected to decrease neoplastic proliferation	<i>in vivo</i>	[98]
Breast cancer patients	In breast cancer patients without overt diabetes mellitus, metformin given at a dose of 1500 mg/day reduced initially increased fasting insulinemia by 22.4% on average 6 months after the onset of treatment	<i>in vivo</i>	[20]
H4IIE and McA-RH7777 rat hepatoma, HepG2 hepatoblastoma cell lines and C57BL/6J mice	Metformin protected mice against chemically induced liver tumors	<i>in vitro</i> and <i>in vivo</i>	[99]
HCT116 p53(+/+) and HCT116 p53(-/-)	Metformin was selectively toxic to p53-deficient cells and provides a potential mechanism for the reduced incidence of tumors observed in patients being treated with metformin	<i>in vivo</i> and <i>in vitro</i>	[100]

was not mediated by AMPK but by REDD1 (also known as DDIT4 and RTP801), a negative regulator of mTOR, which is a new molecular target of metformin. Thus, metformin inhibits cancer cell proliferation via AMPK-dependent and -independent mechanisms.

ANTI-CANCER EFFECT OF METFORMIN IN THE CLINIC

To evaluate the anti-cancer activity of metformin in the clinic, Jiralerspong, S. *et al.* identified 2,529 patients who received neoadjuvant chemotherapy for early-stage breast cancer between 1990 and 2007 [18]. These authors found that diabetic patients with breast cancer who received metformin and neoadjuvant chemotherapy had a higher pathologic complete response (pCR) rate than those not receiving metformin [18]. The conclusion suggested that metformin might decrease the cancer incidence and mortality rate in diabetic patients. A large case-control study involving

973 patients with pancreatic adenocarcinoma (including 259 diabetics) and 863 controls (including 109 diabetics) found that metformin could reduce the incidence of pancreatic cancer. In another case-control study, 97,430 HCC patients and 19,860 matched controls were recruited. The chemopreventive effects of metformin were examined by multivariate and stratified analyses. The final results showed that metformin use resulted in a 7% reduction in the risk of HCC in diabetic patients, which included nearly all subgroups.

In the therapeutic setting of a clinical trial, to investigate whether metformin could decrease or affect the ability of breast cancer cells to grow and whether metformin would work with other therapies to prevent cancer from recurring, the National Cancer Institute of Canada opened a phase III, randomized study on the effect of metformin versus placebo in early-stage breast cancer (<http://clinicaltrials.gov/ct2/show/study/NCT01101438>). This ongoing study began in July 2010 and is estimated to be completed in December

2016. A total of 3,582 patients will be randomized to receive metformin (850 mg a day) for 5 years and compared to patients who will be given a placebo. Additionally, the patients will be stratified by hormone receptor status, HER2 status and chemotherapy use.

Currently, at least 20 ongoing randomized trials are assessing the anti-cancer effect of metformin combined with or without other chemotherapies on neoadjuvant or metastatic cancer [19]. For example, one neoadjuvant phase II randomized trial is being designed for early breast cancer. Patients with ER+ or PR+ HER2-negative breast cancer are candidates to participate. The main goal of this study is to evaluate the efficacy of metformin plus chemotherapy in terms of a pathologic complete response in comparison to treatment with placebo plus the same chemotherapy regimen. After completion of chemotherapy, all patients will undergo breast surgery to assess their pathologic response. However, the pharmacogenetic aspects and expression profiling of the important metformin targets in tumor tissue, such as AMPK, must be seriously considered in addition to the standard criteria [20].

ASPIRIN

Aspirin was widely recognized as an NSAID (non-steroidal anti-inflammatory drug), and it has been used as an anti-inflammatory analgesic and antipyretic for more than 90 years. Over four decades ago, it was observed that metastases from fibrosarcomas in animal models were significantly reduced by aspirin, and these studies led to the investigation of aspirin as an anticancer drug. Subsequently, the effect of aspirin on cancer has been widely studied, particularly its effect on colorectal cancer (CRC). Recently, multiple meta-analyses have concluded that the regular use of aspirin reduced the long-term risk of colorectal cancer incidence and mortality. Furthermore, anti-cancer prevention is not limited to colorectal cancer because much evidence has shown that aspirin is also associated with a reduced risk of prostate and breast cancer [21, 22]. In addition to its direct inhibition of cyclooxygenase (COX) 2 expression, one of the major mechanisms of aspirin in cancer prevention is to activate the AMPK/mTOR signaling pathway.

PRE-CLINICAL STUDY OF THE ANTI-CANCER EFFECT OF ASPIRIN

A large amount of data confirms that aspirin has a strong growth inhibition effect or synergy with other anti-cancer agents through the induction of apoptosis or cell-cycle arrest (Table 2). Aspirin reduced the incidence and mortality of colorectal cancer by activating the AMPK/mTOR pathway and contributed to protection against the development of CRC [23]. However, other AMPK-independent pathways are also induced by aspirin, such as the IKK β or c-Jun N-terminal kinase pathways [24]. Aspirin induced severe inhibition of the viability and survival of human oral squamous carcinoma YD-8 cells, which were correlated with the activation of I κ B α -dependent proteolysis-dependent caspases and down-regulation of the Mcl-1 protein, ERK-1/2 and AKT.

The survival of patients who underwent resection for esophageal squamous cell carcinoma (ESCC) or gastric adenocarcinoma improved when subjected to adjuvant

therapy with aspirin, and this might occur through decreased expression of cyclin D1. Aspirin robustly enhanced Navitoclax-triggered cytosolic cytochrome c release, activation of the initiator caspase-9 and the effector caspase-3 and the cleavage of PARP [25]. In addition, aspirin improved the anti-tumor efficiency of IFN- α on HCC through the promotion of STAT1 by activating the phosphorylation of JAK1 [26]. Most importantly, the combination of aspirin and doxorubicin (DOX) demonstrated strong growth inhibition, cell-cycle arrest and apoptosis in the treatment of hepatocellular carcinoma. This result is encouraging and suggests that the combination of aspirin and doxorubicin might be used as a novel, synergistic anti-cancer combination regimen in the treatment of hepatocellular carcinoma. Except for doxorubicin, other combined treatments with aspirin also show synergistic anti-tumor effects [27-29]. Aspirin and a triptolide combination treatment had synergistic, anti-tumor effects on cervical cancer Siha and HeLa cells [30], and the combination of aspirin and reversine, a 2, 6-disubstituted purine, synergistically inhibited human cervical cancer cells *in vitro* and *in vivo* [31].

ANTI-CANCER EFFECT OF ASPIRIN IN THE CLINIC

Multiple clinical observational studies on aspirin and cancer risk have confirmed its synergistic, protective effect in colorectal cancer, while modest risk reductions were also observed for breast and prostate cancer [32, 33]. Over 30 clinical studies of aspirin protection in colorectal cancer patients, including at least 37500 cases, indicated that the risk reduction from regular aspirin use was approximately 20%-30% [34, 35], and aspirin reduced the risk of other digestive tract cancers by approximately 30% [36]. Although treatment with aspirin and high-dose aspirin (≥ 500 mg daily) was previously shown to significantly reduce the long-term incidence of colorectal cancer, the adverse effects might limit its potential for long-term prevention. Overall, 26 studies that included 528,705 participants observed a 10% reduction in breast cancer risk when aspirin and other NSAIDs were used together. One hospital-based study in Singapore that included 398 female Chinese primary lung cancer cases and 814 controls that were subjected to regular aspirin use indicated an association between aspirin administration and a reduced risk of lung cancer. These results suggest that aspirin consumption is helpful in reducing lung cancer risk in Asian women and are consistent with the current understanding of the role of COX in lung carcinogenesis.

However, the results are not consistent with the anti-cancer effects of aspirin in all cancer types, although the evidence is too limited to draw any definite conclusions. Today, aspirin is one of the most widely used NSAID medications in the world, with an estimated 40,000 tons being consumed each year [37]. Because the anti-cancer effect of aspirin is well known, currently more than 20 clinical trials using aspirin in combination or alone for cancer prevention or therapy, especially for colorectal and breast cancer, are ongoing. However, a conclusion has still not been reached.

Table 2. Anti-cancer studies of Aspirin.

Research model	Conclusion	<i>in vitro/in vivo</i>	Reference
HepG2 human hepatocellular carcinoma cell line and the HepG2 cell xenograft model in BALB/c nude mice	Aspirin resulted in significant HepG2 cell growth inhibition and a reduction in the growth of HepG2 tumors in nude mice	<i>in vitro/in vivo</i>	[101]
HTATIP2 knockdown and HTATIP2 overexpressing HCC cell lines, HCCLM3 and HepG2 xenograft nude mice	Aspirin suppressed the pro-invasion and pro-metastasis effects of sorafenib in HCC and up-regulated HTATIP2 expression	<i>in vitro/in vivo</i>	[102]
Human hepatocellular carcinoma cell line /HepG2 cell xenograft model in nude mice	The combination of aspirin and doxorubicin could be used as a novel combination regimen that provides a strong anticancer synergy in the treatment of hepatocellular carcinoma	<i>in vitro/in vivo</i>	[103]
Gastric cancer cell line SGC7901	Aspirin inhibited the proliferation of SGC7901 by suppressing survivin at both the transcriptional and translational levels	<i>in vitro</i>	[104]
p48(Cre/+)-LSL-Kras(G12D/+) mice	Low-dose NO-aspirin exhibited inhibitory activity against pancreatic carcinogenesis by modulating multiple molecular targets showing decreased expression of cyclooxygenase COX, inducible nitric oxide synthase, proliferating cell nuclear antigen, Bcl-2, cyclin D1, and β -catenin	<i>in vivo</i>	[105]
AMPK ($\alpha 1/\alpha 2$ -/-) mouse embryonic fibroblasts from colorectal cancer (CRC)/rectal mucosa samples from patients	Aspirin is an inhibitor of mTOR and an activator of AMPK, targeting regulators of intracellular energy homeostasis and metabolism	<i>in vitro/in vivo</i>	[106]

RESVERATROL

Resveratrol is commonly found in grapes, nuts and berries [38]. An epidemiological study prompted the extensive investigation of resveratrol's anti-aging effects and eventually established resveratrol as an anti-mitotic, anti-neoplastic, anti-oxidant, anti-platelet and anti-inflammatory agent [39, 40]. In 1997, Jang reported that resveratrol could prevent skin cancer development in mice treated with a carcinogen [41]. Since then, many studies on the anti-cancer activity of resveratrol in animal models have been performed. Additionally, resveratrol prevented the development of esophageal, intestinal and colon tumors in rats treated with a carcinogen [42]. As shown in Table 3, resveratrol inhibited the growth of esophageal squamous cell carcinoma (ESCC) cells by inducing cell-cycle arrest at the sub-G1 phase, resulting in subsequent apoptosis [43]. Additionally, resveratrol promoted apoptosis and sensitized prostate cancer cells to radiotherapy (RT) through a desirable dual action that activated ATM-AMPK-p53-p21 (cip1)/p27 (kip1) and inhibited the Akt signaling pathways. Of note, the administration of resveratrol could enhance temozolomide (TMZ)-mediated anti-tumor effects in glioblastoma *in vitro* and *in vivo* via the ROS-dependent AMPK-TSC-mTOR signaling pathway [44].

The anti-proliferation activity of resveratrol was mainly mediated through AMPK activation and mTOR inhibition. Further observation found that growth inhibition induced by resveratrol was reversed by compound C, which is an inhibitor of AMPK. Most importantly, AMPK activation induced by resveratrol in cancer cells was due to the expression of Sirtuin type 1 (SIRT1) and elevation of

intracellular NAD(+)/NADH, which suggested that SIRT1 functions as a novel upstream regulator of AMPK signaling. Thus, SIRT1/AMPK signaling activation by resveratrol might have potential therapeutic implications for cancer and age-related diseases.

BERBERINE

Berberine is traditionally used in Chinese medicine for its anti-microbial and anti-diarrheal activities. Recent studies have clearly shown that berberine possesses various pharmacological activities and has a wide spectrum of applications for the treatment of cancer and inflammation, cardiovascular and metabolic disorders [45-47]. In particular, several reports of berberine acting against various cancers have been published. Berberine can inhibit cell proliferation *in vitro* in various cancer cell lines and induce apoptosis or cell cycle arrest [45]. However, no marketable drug uses pure berberine as a curative agent; therefore, the therapeutic value of berberine in the market is only in the form of a compound or in poly-herbal formulations [48-50]. To strengthen the therapeutic effect of berberine, efforts have been made to increase its bioavailability using D- α -tocopherol polyethylene glycol 1000 succinate and P-glycoprotein inhibitors [51].

In most cases, the anti-cancer effects of berberine might be due to the direct induction of apoptosis, which was found to be associated with a reduction in the mitochondrial membrane potential and the AMPK-mediated caspase-dependent mitochondrial pathway [52]. Berberine induced apoptosis in human tongue cancer cells through ROS, caspase-3, and the mitochondria-dependent apoptosis pathways [53]. The same

Table 3. Anti-cancer studies of Resveratrol and Berberine.

Research model	Conclusion	<i>in vitro/in vivo</i>	Reference
Human esophageal squamous cell carcinoma (ESCC)	Resveratrol inhibits ESCC cell growth in a dose-dependent manner by inducing cell cycle arrest at the sub-G1 phase, resulting in subsequent apoptosis. Mechanistically, resveratrol-induced autophagy in the ESCC cells is AMPK/mTOR pathway-independent	<i>in vitro</i>	[43]
GBM cells	Resveratrol can enhance the TMZ-mediated antitumor effects in GBM <i>in vitro</i> and <i>in vivo</i> via the ROS-dependent AMPK-TSC-mTOR signaling pathway	<i>in vitro/in vivo</i>	[44]
Human tongue cancer cells (SCC-4)/murine xenograft animal model	Berberine-mediated apoptosis of SCC-4 cells is regulated by ROS, caspase-3-dependent and mitochondria-dependent pathways. Berberine inhibits tumor growth in a xenograft animal model	<i>in vitro/in vivo</i>	[53]
Esophageal squamous cell carcinomas (ESCC) cells	Berberine radiosensitizes human esophageal cancer cells by down-regulating the homologous recombination repair protein RAD51	<i>in vitro</i>	[62]
Non-small cell human lung cancer cells (A549 and H1299)/A549 and H1299 lung tumor xenografts in athymic nude mice	A549 cells, which express wild-type p53, were more sensitive to berberine-induced cytotoxic effects than H1299 cells which are p53-deficient. p53 contributes to berberine-induced growth inhibition and apoptosis of non-small cell human lung cancer cells <i>in vitro</i> and to tumor xenograft growth <i>in vivo</i>	<i>in vitro/in vivo</i>	[54]
Human hepatic carcinoma cell lines HepG2 and MHCC97-L.	Berberine induces autophagic cell death and mitochondrial apoptosis in liver cancer cells.	<i>in vitro</i>	[57]
A549, HeLa and HepG2 cells	Berberine and doxorubicin exhibited inhibitory effects on A549 and HeLa cells which were likely mediated by inducing apoptosis	<i>in vitro</i>	[61]
Human hepatocellular carcinoma cells (SMMC-7721).	The combined use of berberine and evodiamine could significantly enhance the apoptosis of SMMC-7721 cells.	<i>in vitro</i>	[107]
Breast cancer cells (MCF-7 and MDA-MB-468)	Berberine sensitizes human breast cancer cells to ionizing radiation by inducing cell cycle arrest and the down-regulation of the homologous recombination repair protein RAD51.	<i>in vitro</i>	[108]
Human breast cancer stem cells (CSCs) and CSC xenografts in nude mice	Targeting berberine liposomes were developed to modulate the resistant membrane and mitochondrial proteins of breast CSCs for the treatment and prevention of breast cancer relapse	<i>in vitro/in vivo</i>	[55]
Breast cancer cells	Berberine can reduce the metastatic potential of highly metastatic breast cancer cells and may be a useful adjuvant therapeutic agent in the treatment of breast cancer by targeting the Akt pathway	<i>in vitro</i>	[109]
Prostate cancer cells (DU145/PC-3 and LNCaP)	The berberine-induced inhibition of proliferation is associated with cell cycle arrest and berberine-induced apoptosis mediated primarily through the caspase-dependent pathway	<i>in vitro</i>	[56]
Human melanoma cell line A375	Berberine represses DAXX gene transcription and induces cancer cell apoptosis	<i>in vitro</i>	[58]

mechanism was responsible for the growth inhibition of non-small cell human lung cancer cells (A549 and H1299) [54], human breast cancer stem cells (CSCs) [55] and human prostate cancer cells (DU145/PC-3 and LNCaP) *in vitro* and *in vivo* [56]. In addition, berberine may induce autophagic cell death through the activation of Beclin-1 and inhibition of the mTOR-signaling pathway by suppressing the activity of Akt and up-regulating P38 MAPK signaling [57]. In addition, a recent study in the human melanoma cell line A375 reported that berberine down-regulated expression of the death-domain-associated protein (DAXX) at the transcriptional level by competitive binding to the Sp1 and Ets1 consensus motifs through a p53-dependent pathway,

revealing a novel possible mechanism for the anti-cancer effect of berberine [58]. As shown in Table 3, berberine-induced proliferation inhibition was also closely associated with cell cycle arrest. Berberine could induce cell cycle arrest at G1 phase, G0/G1 phase or G2/M phase, and this effect can be observed in colorectal cancer, breast cancer, bladder cancer and prostate cancer cells [59, 60].

In addition to single-drug use, berberine in combination with other drugs or with radiotherapy has shown beneficial effects. Berberine sensitized cancer cells to chemotherapeutic doxorubicin treatment [61]. Combined use of berberine and evodiamine showed a significant, synergistic inhibitory effect on SMMC-7721 cells. Berberine has shown the ability

to suppress tumor growth and metastasis and overcome multidrug resistance, which indicates its potential in tumor chemotherapy. In addition, berberine can effectively enhance the radio-sensitivity of esophageal cancer cells by down-regulating RAD51 [62].

Berberine was reported to alter cellular processes by regulating their downstream targets. Several essential targets of the anti-cancer phenotype of berberine exist and include but are not limited to AMPK, integrin β 1, β -catenin and Akt. In human colon cancer SW480 cells, berberine can activate the chloride channels that are sensitive to 5-nitro-2-(3-phenylpropylamino)benzoic acid (NPPB) and tamoxifen. Most importantly, berberine strongly increased AMPK activity via reactive oxygen species (ROS) production and inhibited tumor cell adhesion and invasion. Furthermore, knockdown of AMPK α 1 abolished the effect of berberine [63].

STATINS

Statins are used for lowering cholesterol in patients with hypercholesterolemia to reduce the risk of cardiovascular disease. These drugs belong to the HMG-CoA reductase inhibitor family, which block the production of cholesterol. The primary uses of statins are the treatment of dyslipidemia and the prevention of cardiovascular disease. More recently, it has also been documented that statins may trigger cancer cell apoptosis in various types of human cancer cell lines, making them a promising and attractive therapeutic option for the treatment of cancer [64]. Experimental studies involving animal models have clearly demonstrated the potential of statins as a direct, cytotoxic agent or a useful adjuvant, therapeutic agent in the treatment of a variety of cancer cells (Table 4), which can reduce tumor development or metastatic spreading.

A pre-clinical model of liver carcinogenesis showed that lovastatin reduced the number of tumor nodules, which occurred in the absence of modification of the cholesterol levels and was partially antagonized by supplementation with ubiquinone [65]. A population-based case-control study was conducted to explore the association between statin use and risk of developing hepatocellular carcinoma (HCC). The use of statins, including six commercially available statins (simvastatin, lovastatin, fluvastatin, atorvastatin, pravastatin, and rosuvastatin), is correlated with a 28% decreased risk of HCC. Individual statins, including simvastatin, lovastatin and atorvastatin, are associated with a reduced risk of HCC [66]. Furthermore, lovastatin was shown to sensitize A549 lung cancer cells to radiotherapy mediated by a unique, simultaneous inhibition of the pro-survival Akt and activation of the AMPK pathways [67]. Lovastatin also induced apoptosis in the squamous cell carcinoma (SCC) cell lines SCC9 and SCC25 through activation of the LKB1/AMPK pathway [68]. Therefore, cholesterol shortage is not responsible for the anti-cancer effect of lovastatin, and the AMPK pathway might be the crucial target.

Nevertheless, statins could also induce cancer cell apoptosis through other mechanisms. Lovastatin could resensitize gefitinib-resistant human non-small cell lung cancer (NSCLC) cell lines and induce apoptosis, which is accompanied by a reduction in anti-apoptotic Bcl-2 and a

rise in pro-apoptotic Bax, cleaved caspase-3 and PARP [69]. Survivin is a key molecule that renders T790M mutant NSCLC cells resistant to apoptosis induced by EGFR-TKIs and simvastatin [70]. Lovastatin induced apoptosis of ovarian cancer cells by blocking HMG-CoA reductase activity and by sensitizing multi-drug resistant cells to doxorubicin by inhibiting P-glycoprotein, which potentiates DNA damage and tumor cell apoptosis [71]. The combination of lovastatin and celecoxib profoundly suppressed caveolin-1 expression and membrane localization when compared to either agent alone [72]. It is most likely that lovastatin induces the disruption of membrane caveolae and decreases the expression of Cav-1-associated signaling molecules [73]. In addition, to evaluate the statins' potential to treat ovarian cancer, either statins or statins combined with either carboplatin or paclitaxel were assessed on 7 ovarian cancer cell lines. All statins except pravastatin demonstrated single agent activity [74]. Furthermore, lovastatin strongly potentiated the induction of death by 5-FU or cisplatin [75], and it was confirmed that, in breast cancer cells, lovastatin inhibited proliferation through the involvement of the membrane-bound RhoA and RhoB proteins and blockage of the prenylation of small GTPases in the E2F1 and AKT-signaling pathways. In addition, BRCA1 over-expression sensitizes cancer cells to lovastatin via regulation of the cyclin D1-CDK4-p21WAF1/CIP1 pathway [76].

As is amply supported by the above-mentioned studies, combined treatment with statins and anti-cancer agents is a more realistic approach, and it seems reasonable to suggest that statins could be beneficial in an adjuvant setting. As reviewed here, many experimental studies support the idea of using statins in cancer-cure regimens.

EPIGALLOCATECHIN GALLATE (EGCG)

Epigallocatechin gallate (EGCG), also known as epigallocatechin-3-gallate, is the most abundant catechin in green tea and is a potent anti-oxidant that may have therapeutic applications in the treatment of many disorders [77]. As shown in Table 5, EGCG could inhibit cancer development *in vitro* and in animal models during initiation, progression and metastasis in a large variety of cancer types including skin, breast, prostate, colorectal and lung cancer [78]. In an obese mouse model that develops diethylnitrosamine (DEN)-induced liver tumorigenesis, EGCG significantly prevented obesity-related liver tumorigenesis by inhibiting the IGF/IGF-1R axis and attenuating chronic inflammation, suggesting that EGCG might be useful in the chemoprevention of liver tumorigenesis in obese individuals [79]. Most importantly, EGCG induced apoptosis and abolished the cell-proliferative effect that was accompanied by activation of AMPK and decreases in cyclooxygenase-2 (COX-2) and prostaglandin E(2) (PGE(2)) expression. Moreover, decreased COX-2 expression and prostaglandin E(2) secretion by EGCG were completely abolished by inhibiting AMPK using an AMPK inhibitor, Compound C [80, 81].

The synthetic EGCG analogs that activated AMPK were more potent than metformin and EGCG. EGCG activated AMPK in p53-positive and -negative human hepatoma cells. Moreover, AMPK activation decreased the activity and/or expression of lipogenic enzymes, such as fatty acid synthase

Table 4. Anti-cancer studies of Statins.

Research model	Conclusion	<i>in vitro/in vivo</i>	Reference
Squamous cell carcinoma (SCC) cell lines (SCC9, SCC25); the murine embryonic fibroblasts (MEFs), Hela, A549	Lovastatin induced LKB1 and AMPK activation similar to metformin. The combination of lovastatin with gefitinib induced a potent apoptotic response without significant induction of autophagy	<i>in vitro</i>	[68]
Head and neck squamous cell carcinoma (HNSCC) cell lines (KB, HN5, FaDu)	Simvastatin alone had a suppressive effect on HNSCC cell lines and increased the cytostatic efficacy of cisplatin (Cis) or docetaxel (DTX)	<i>in vivo</i> (<i>ex vivo</i>)	[110]
Lung adenocarcinoma cells (A549)	Lovastatin is a promising agent with significant antitumor properties as a single agent and a radiation sensitizer. Simvastatin prevents proliferation and osteolytic bone metastases of lung adenocarcinoma cells <i>in vitro</i> and <i>in vivo</i> .	<i>in vitro</i> <i>in vivo</i>	[67, 111]
Gefitinib-resistant human non-small cell lung cancer (NSCLC) cell lines (A549, NCI-H460, T790M mutation)	Lovastatin combination treatment significantly increased gefitinib-related apoptosis. Similar results were obtained in erlotinib and simvastatin-treated HCC827/ER cells. In NSCLC cells with K-Ras mutations, lovastatin could overcome gefitinib resistance by down regulation of the RAS protein, which leads to inhibition of both RAF/ERK and AKT pathways. Simvastatin may overcome EGFR-TKI resistance in T790M mutant NSCLCs via an AKT/ β -catenin signaling-dependent down-regulation of survivin and apoptosis induction.	<i>in vitro</i>	[69, 70]
Resistant hepatocyte mode	Lovastatin inhibits carcinogenesis in a rat model of liver cancer, despite the absence of an effect on the cholesterol levels. The statin-induced inhibition of cell proliferation may, at least in part, be explained by the inhibition of ubiquinone synthesis.	<i>in vivo</i>	[65]
Hepatocellular carcinoma (HCC)	Individual statins, including simvastatin, lovastatin and atorvastatin, are associated with reduced risk of HCC.	<i>in vivo</i>	[48]
Human colon cancer cell line (HCT-116)	Combination of lovastatin and celecoxib suppressed caveolin-1 expression and membrane localization profoundly when compared to either agent alone. There was a significant suppression of lipid body formation by both lovastatin and celecoxib.	<i>in vitro</i>	[72]
Ovarian cancer cell lines	All statins except pravastatin demonstrated single-agent activity against ovarian cancer cells by a mevalonate-dependent mechanism. Moreover, simvastatin has conflicting effects on the autophagy pathway and this may contribute to its cytotoxic activity. Furthermore, lovastatin synergizes with doxorubicin, an agent that is administered for recurrent disease, by a novel mevalonate-independent mechanism that antagonizes drug resistance.	<i>in vitro</i>	[71, 74]
Mesothelial cell lines ZL55, SDM104/SDM104, breast cancer cell line MCF-7, human lung adenocarcinoma cell line A549	Lovastatin has the potential to protect normal cells from CDDP toxicity without decreasing the sensitivity of cancer cells to CDDP-based therapy, thereby improving the therapeutic index	<i>in vitro</i>	[75]

(FASN) and acetyl-CoA carboxylase (ACC). Interestingly, in p53-positive HepG2 cells, EGCG blocked the progression of the cell cycle at G1 phase by inducing p53 expression and further up-regulating p21 expression. Therefore, EGCG has the potential to be a chemopreventative agent for human hepatoma cells [82].

Moreover, EGCG has the potential to be used as a chemo/radio-sensitizer of cancer cells. The combination of EGCG and 5-FU exhibited encouraging synergism in chemo-resistant hepatoma cells, suggesting the use of EGCG as a novel therapeutic combination for the treatment of advanced-stage liver cancer [83]. In addition, the antioxidant and anti-inflammatory properties of EGCG, which

were associated with the amelioration of adverse side effects derived from cancer therapy, are noteworthy [84, 85]. Nevertheless, it should be noted that most of the studies on the anti-cancer effect of EGCG that have been published to date are preclinical. Further research, especially at the clinical level, is needed to confirm the potential role of EGCG as an adjuvant in cancer therapy.

CAPSAICIN

Capsaicin is the active component of chili peppers and been used in food additives and drugs [86]. In animal studies, controversial reports on the effects of capsaicin on carcinogenesis have been published [87, 88]. Capsaicin itself was mutagenic and promoted tumor formation; however, it

Table 5. Anti-cancer studies of EGCG and Capsaicin.

Research model	Conclusion	<i>in vitro/in vivo</i>	Reference
Human breast cancer MDA-MB-231 cells	Synthetic EGCG analogs were more potent AMPK activators than metformin and EGCG. Activation of AMPK by these EGCG analogs resulted in inhibition of cell proliferation, up-regulation of the cyclin-dependent kinase inhibitor p21, and down-regulation of the mTOR pathway in human breast cancer cells	<i>in vitro</i>	[112]
p53-positive Hep G2 and p53-negative Hep3B cells	EGCG activated AMPK in both p53-positive and -negative human hepatoma cells. EGCG has the potential to be used as a chemoprevention and anti-lipogenesis agent for human hepatoma	<i>in vitro</i>	[82]
C57BL/KsJ-db/db (db/db) obese mice	EGCG prevents obesity-related liver tumorigenesis by inhibiting the IGF/IGF-1R axis, improving hyperinsulinemia, and attenuating chronic inflammation. EGCG, therefore, may be useful in the chemoprevention of liver tumorigenesis in obese individuals.	<i>in vivo</i>	[79]
Hep3B cells	EGCG augmented the anti-tumor effect of 5-FU in Hep3B cells. EGCG sensitizes HCC cells to 5-FU antitumor activity, and the combination of EGCG and 5-FU exhibits synergism in chemo-resistant cancer cells	<i>in vitro</i>	[113]
Mammary glands of mature female rats and human MCF-7 breast cancer cells	Capsaicin, in combination with genistein, exerts anti-inflammatory and anti-carcinogenic effects through the modulation of AMPK and COX-2 and possibly various mitogen-activated protein kinases synergistically or nonsynergistically	<i>in vitro/in vivo</i>	[91]
HT-29 colon cancer cells	Capsaicin-induced apoptosis was revealed by the presence of nucleobodies in capsaicin-treated HT-29 colon cancer cells. Both capsaicin and AICAR, an AMPK activator possess the AMPK-activating capacity as well as apoptosis-inducing properties	<i>in vitro</i>	[114]

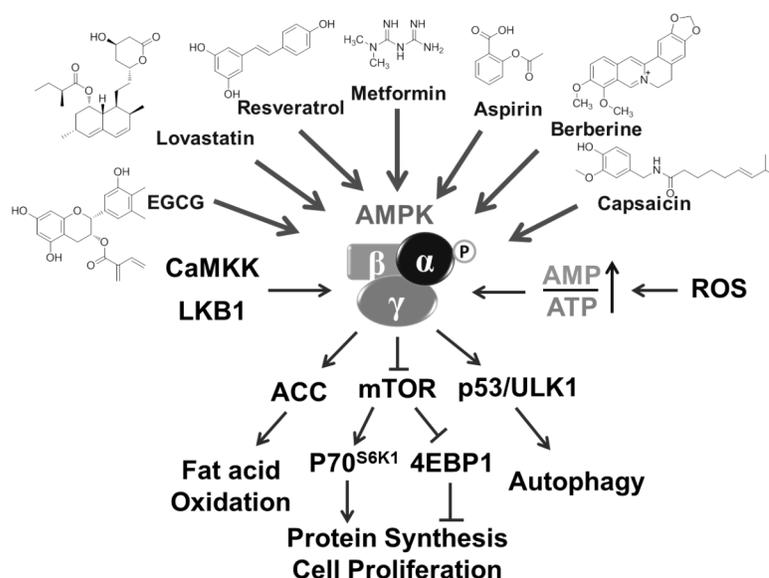


Fig. (1). The anti-cancer effects of metformin, aspirin, resveratrol, berberine, lovastatin, EGCG and capsaicin are mainly the result of increased AMPK activation. These drugs increase the ROS level and AMP/ATP ratio and stimulate the phosphorylation of the AMPK α subunit at Thr172 by LKB1 and CaMKK. Then, AMPK can inhibit the mTOR/P70^{S6K1} pathway, resulting in a reduction of protein synthesis reduction and inhibition of cancer cell proliferation. Alternatively, AMPK activation also induces acetyl-CoA carboxylase (ACC) phosphorylation to stimulate fatty acid oxidation and activates p53 and ULK1 to trigger autophagy.

also showed anti-tumor and anti-mutagenic properties [89, 90]. Recent studies revealed substantial anti-genotoxic and anti-carcinogenic effects of capsaicin (Table 5), suggesting capsaicin as another important dietary phytochemical with a potential chemopreventive activity [88].

It has been shown that capsaicinoid-induced apoptosis was mediated by a caspase-3-dependent pathway [43]. However, the precise mechanism for the anti-proliferative effect of capsaicin has not been clarified. Recent studies demonstrated that capsaicin could activate the AMPK/

mTOR pathway, and this activation was required for the induction of apoptosis by capsaicin [86]. Capsaicin combined with genistein inhibited breast cancer cell proliferation through the modulation of AMPK and COX-2 *in vitro* and *in vivo* [91].

DISCUSSION

It is well known that non-classical anti-cancer drugs, such as metformin, aspirin and resveratrol, demonstrate promising and synergistic efficacy when combined with other chemotherapeutic drugs. Most importantly, nearly all these drugs can activate the AMPK signaling pathway to inhibit cancer cell proliferation. As the critical energy sensor, AMPK monitors intracellular energy alterations and is conserved across all eukaryotes [92]. AMPK is activated by a decrease in intracellular ATP concentration and a concomitant increase in the amount of AMP. Upon ATP depletion or various other stress conditions, AMPK is phosphorylated at 172 Thr by LKB1 and other upstream kinases. Then, AMPK inhibits mTOR signaling and protein synthesis, which has been reported to be critical for tumor growth in experimental animal models as well as in cultured cells [93]. Therefore, AMPK activation is a feasible therapeutic strategy for cancer treatment. Interestingly, as we mentioned in this review, metformin, aspirin, resveratrol, berberine, lovastatin, epigallocatechin gallate (EGCG) and capsaicin activated AMPK and demonstrated anti-cancer effects, regardless of whether they were used alone or in combination with other chemotherapeutic drugs (Fig. 1). Noticeably, metformin, aspirin and berberine could also resensitize cancer cells, even those that were resistant to doxorubicin or radiotherapy. Most promisingly, over 40 randomized clinical trials using metformin and aspirin in combination or alone for cancer prevention or therapy are ongoing, and the results may provide additional choices for anti-cancer regimens in the near future.

CONFLICT OF INTEREST

The author confirms that this article content has no conflict of interest.

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ABBREVIATIONS

AMPK	= adenosine monophosphate-activated protein kinase
mTOR	= mammalian target of rapamycin
NSAIDs	= non-steroidal anti-inflammatory drugs
EGCG	= epigallocatechin gallate
PR	= progesterone receptor
ER	= estrogen receptor

HCC	= hepatic carcinoma or hepatocellular carcinoma
HFD	= high-fat diet
NAFLD	= Non Alcoholic Fatty Liver Disease
pCR	= pathologic complete response
HER2	= human epidermal growth factor receptor-2
CRC	= colorectal cancer
COX	= cyclooxygenase
ESCC	= esophageal squamous cell carcinoma
DOX	= doxorubicin
TMZ	= temozolomide
SIRT1	= Sirtuin type 1
SCC	= squamous cell carcinoma
NPPB	= 5-nitro-2-(3-phenylpropylamino)benzoic acid
NSCLC	= human non-small cell lung cancer
DEN	= develops diethylnitrosamine
PGE(2)	= prostaglandin E(2)
FASN	= fatty acid synthase
ACC	= acetyl-CoA carboxylase.

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