New tricks of old drugs: Repurposing non-chemo drugs and dietary phytochemicals as adjuvants in anti-tumor therapies

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Mei Zhang[a,b], Xianfeng Chen[b*], Norbert Radacsi[a]

[a]School of Engineering, Institute for Materials and Processes, University of Edinburgh, Robert Stevenson Road, Edinburgh, EH9 3FB, United Kingdom

[b]School of Engineering, Institute for Bioengineering, University of Edinburgh, The King's Buildings, Edinburgh, EH9 3JL, United Kingdom

Mei Zhang, Email address: M.Zhang-55@sms.ed.ac.uk

Norbert Radacsi, Email address: N.Radacsi@ed.ac.uk

*Corresponding author:

Dr. Xianfeng Chen. Tel.: +44 131 650 2784. E-mail address: Michael.Chen@ed.ac.uk

Abstract

Combination therapy has long been applied to enhance therapeutic effect and deal with the occurrence of multi-drug resistance in cancer treatment. However, the overlapping toxicity of multiple anticancer drugs to healthy tissues and increasing financial burden on patients emerged as major concerns. As promising alternatives to chemo agents, repurposed non-chemo drugs and dietary phytochemicals have been investigated as adjuvants to conventional anti-tumor therapeutics, offering a safe and economic strategy for combination therapy. In this review, we aim to highlight the advances in research about combination therapy using conventional therapeutics and repurposed drugs or phytochemicals for an enhanced anti-tumor efficacy, along with the mechanisms involved in the synergism. Beyond these, we outlined the potential challenges and solutions for clinical translation of the proposed combination therapy, providing a safe and affordable strategy to improve the reach of cancer therapy to low income regions with such new tricks of old drugs.

Keywords:

Combination therapy; Chemo therapy; Repurposed drug, Phytochemicals

1. Introduction

Cancer, the term of a collection of diseases with rapid creation of abnormal cells, which could then invade the whole body, has remained the second leading cause of global death, being responsible for approximately 9.6 million death in 2018, according to the World Health Organization (WHO) [1]. Chemotherapy, along with radiotherapy and immunotherapy, has been regarded as conventional therapies for various cancers. By affecting the process of DNA replication or the activities of key proteins in cancer cells, the cytotoxicity of chemo agents has been exploited to inhibit the progress of cancers. However, the clinical outcomes of mono-chemotherapy remain undesirable despite the recent advances in discovery and synthesis of novel anti-tumor drugs, with issues such as low therapeutic efficacy, severe side effects on healthy body tissues, drug-induced multi-drug resistance (MDR) in cancer cells, metastasis, and reoccurrence as a result of drug-induced oncogenic mutations in patients [2].

To address the effectiveness of chemotherapy, combination therapy, often administration of 2 or more types of anti-cancer chemotherapy drugs with different targets in cancer cells, has been explored. So far, improved therapeutic efficacy has been widely proved in both preclinical and clinical studies [3-6]. Beyond this, by regulating different signaling pathways, combination therapy could serve as a good strategy to tackle MDR, resulting in sensitization of cancer's response to applied therapeutics, and subsequent decrease in the dose of each drug. However, the clinical outcomes of conventional combination therapies are not always satisfying due to many reasons including the overlapping toxicity induced by different therapeutics towards normal body tissue and increased cost of using different expensive anti-cancer drugs. Therefore, it is necessary to seek for an alternative of the conventional combination therapy to further advance the clinical application of combination therapy.

Emerging evidence suggests that many non-chemo drugs and dietary phytochemicals can be repurposed to supplement chemotherapy drugs for enhanced outcomes of combination therapy, and attractively possess mild cytotoxicity to normal tissue cells as well as a minimal additional cost. These superior characteristics make non-chemo drugs and dietary phytochemicals very promising candidates for clinically valuable combination therapy. As illustrated in Fig. 1, repurposed drugs and dietary phytochemicals could interfere with the development of tumors at different stages. For example, metformin, the first-line therapy for type 2 diabetes, could regulate the activities of multiple signaling pathways and lead to delay in the promotion, progression, and metastasis of tumors [7]. Based on the well-established fact that inflammation and oxidative stress in the tumor microenvironment (TME) play a critical role in the progression and metastasis of various cancers, non-steroidal anti-inflammatory drugs (NSAIDs) including celecoxib and aspirin, as well as dietary phytochemicals

such as curcumin, resveratrol, and quercetin were found to contribute to the amelioration of tumor development [8, 9]. Also, because solid tumors are relying on the vascular network for sufficient supply of nutrient and oxygen, angiogenesis plays an essential role in tumor progression and metastasis, suggesting that inhibitors of renin angiotensin system (RAS) such as captopril and losartan may serve as a potential adjuvant agent for conventional anti-tumor therapeutics [10-12]. Compared with conventional combination therapy of using 2 or more different anti-cancer drugs, incorporating repurposed non-chemo drugs and dietary phytochemicals as adjuvants would be a safer and more affordable treatment, increasing the chance for patients from low- or middle-income regions to get proper medical care. This review will systematically describe the combination of commonly used chemo-therapeutics and repurposed non-chemo drugs or dietary phytochemicals as a novel combination therapy. First, the transduction signaling pathways and key proteins that might be involved in the synergism will be introduced, followed by the presentation of recent advances about how each type of repurposed drugs and phytochemicals participated in the synergy with conventional anti-tumor therapeutics and the detailed molecular mechanisms. We will then discuss and outline the advantages and challenges of using repurposed drugs and phytochemicals with conventional anti-tumor therapeutics. At last, the review will end with the perspectives of using these novel combination therapies for the clinical treatment, which may shed a light on the rational design of new combinatory strategies for an effective, safe and economical therapy of cancers.

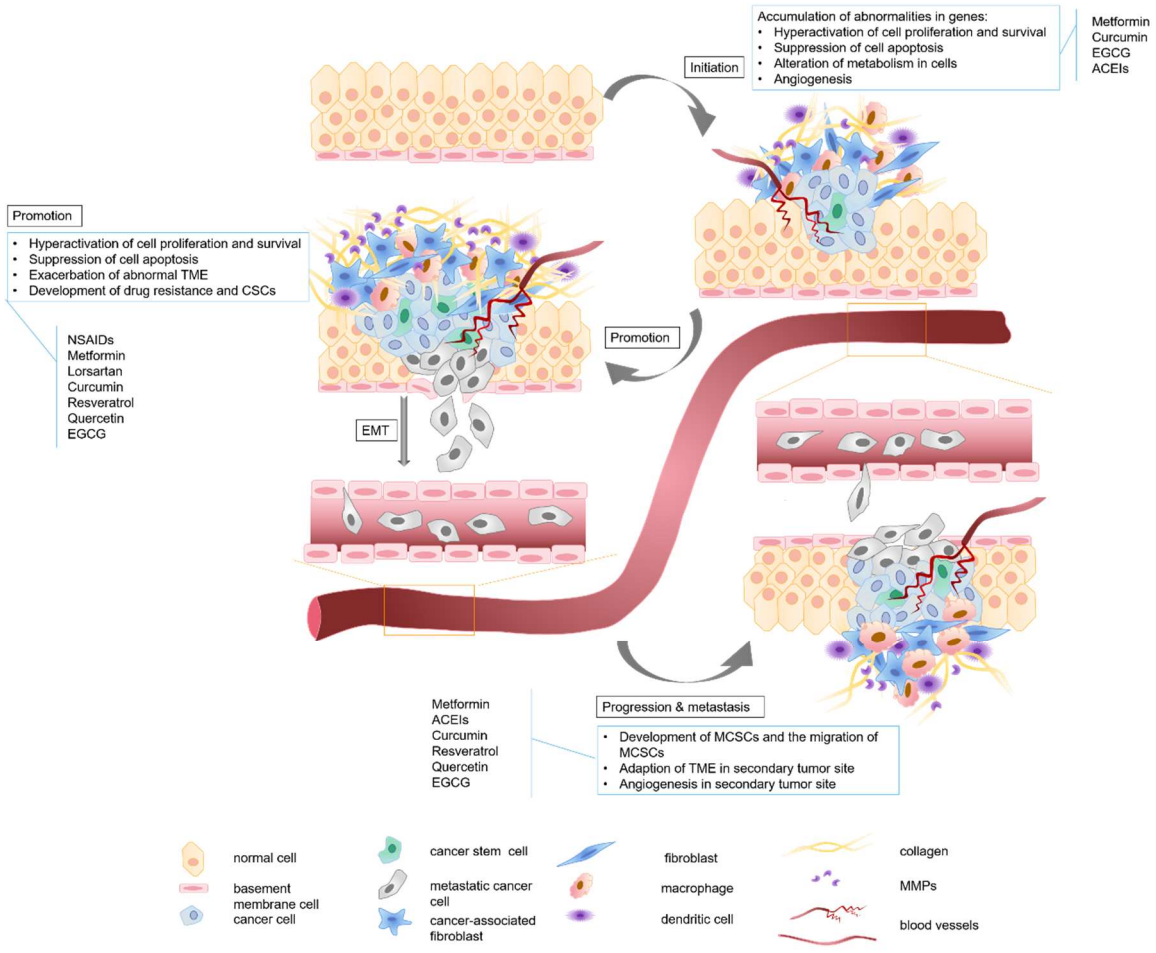


Fig 1. Schematic illustration about the features of tumor at different stages of development. Initiation: accumulated DNA mutation leads to alteration in the metabolism of cells, which then results in increasingly abnormal cell proliferation; promotion, the abnormalities in TME is deteriorated as a result of the interaction with cancer cells, which in return exacerbates cancer cells, contributing to the development of CSCs; progression and metastasis, EMT induces the migration of CSCs, which then invades secondary tissue after the formation of metastasis niche. Color should be used for this figure.

2. Important signaling pathways and key proteins affecting anti-cancer therapy

Molecular studies suggested that the synergism of repurposed non-chemo drugs or phytochemicals with conventional anti-tumor therapeutics could be attributed to the regulation on multiple signaling pathways and key proteins, which led to the augment in apoptosis, the attenuation of drug resistance, the alleviation of cancer stem-like cells (CSCs), or the restoration of immune surveillance in TME. In this section, several important signaling pathways and proteins will be briefly presented, of which a schematic summary is shown in Fig. 2.

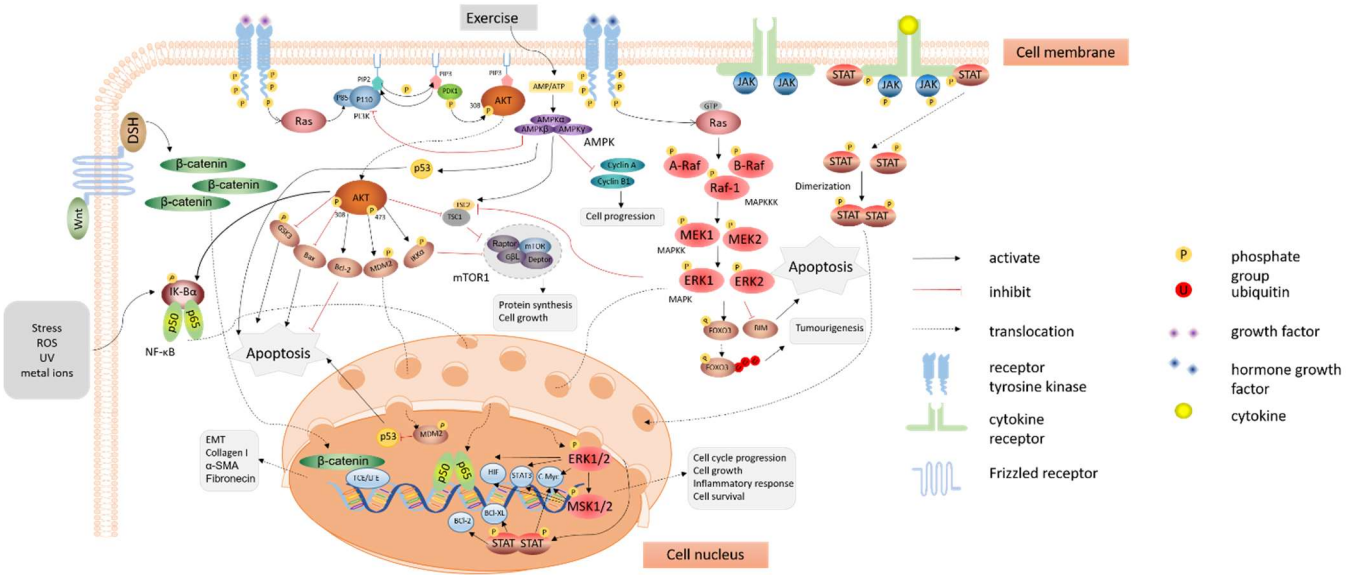


Fig 2. Signaling pathways and key proteins that would be affected by repurposed drugs and dietary phytochemicals for the anti-tumor efficacy. The regulation on activities of PI3K/AKT/mTOR, JAK-STAT, MAPK/ERK, and WNT/β-catenin signaling pathways, as well as AMPK and NF-κB have been proved as major mechanisms. Color should be used for this figure.

2.1 Phosphatidylinositol-3-kinase (PI3K)/protein kinase B (AKT) / mammalian target of rapamycin (mTOR) signaling pathway

The PI3K/AKT/mTOR pathway plays an important role in cell cycle regulation. In response to growth factor stimulation, the phosphorylation of PI3K can activate AKT, leading to further regulation of its downstream molecules, including mTOR. This pathway is frequently hyperactive and proved to be directly related to the growth and survival of cancer cells by upregulating anti-apoptotic gene *BCL-2* while downregulating pro-apoptotic gene *BAX*. By phosphorylating inhibitors of κB, this pathway could activate NF-κB and further contribute to the development of MDR and even metastasis of cancer cells, exacerbating tumor malignancy [13].

Direct inhibition of the phosphorylation of AKT has been observed in several repurposed drugs (NSAIDs including aspirin and celecoxib, as well as certain anti-hypertension agents) and phytochemicals (e.g., curcumin, resveratrol, and quercetin) as one of the anti-tumor mechanisms. Besides, by affecting the regulator protein, phosphatase and tensin homolog detected on chromosome 10 (PTEN) could achieve the indirect inhibition on PI3K/AKT/mTOR axis through the blockage on the process of phosphorylation [14].

2.2 Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway

The JAK-STAT signaling pathway plays an important role in transferring signals from cell-membrane receptors to the cell nucleus, and has been regarded as the pivotal juncture for of multiple signaling pathways. The activation of JAK is driven by the binding of cytokines to cytokine receptors, after which two STATs would be phosphorylated and subsequently form a dimer. The STAT dimer would

then translocate to nucleus, inducing the transcription of target genes to regulate cell immunity, proliferation, differentiation, and apoptosis [15-17]. Hyperactivation of JAK-STAT signaling pathways leads to an overexpression of anti-apoptotic proteins, including BCL-2 and BCL-XL, promoting the initiation and development of cancers [16]. Besides, the JAK-STAT pathway has been reported to play a critical part in the secretion of immunosuppressive cytokines, further aggravating the abnormality in TME [15].

By blocking the nuclear translocation of STAT dimers, phytochemicals including curcumin, resveratrol and quercetin could inhibit the progression of cancers and correct the immunosuppression in TME, serving as a mechanism for the synergism with chemotherapy, immunotherapy, or gene therapy [17-19].

2.3 Mitogen activated protein kinase (MAPK) signaling pathway /extracellular-signal-regulated kinase (ERK) pathway

The MAPK/ERK pathway communicates a signal from the cell surface receptor to the DNA of the cell. As one of the major signaling cassettes of MAPK pathways, the ERK pathway could be activated upon the stimulation of various extracellular signals such as hormone, growth factors, and environmental stress. After phosphorylated by MAPK/ERK kinase (MEK1/2, also termed MAPKK), activated ERK1/2 (MAPK) would then translocate into the nucleus to induce the transcription of various target genes regarding the proliferation and survival of cancer cells, contributing to the malignancy of tumors [20]. Apart from regulating the expression of genes, previous research also suggested that ERK1/2 could affect the activity of transcription factors by inducing ubiquitin-related degradation, contributing to the process of tumorigenesis [21].

By ablating the activation of angiotensin receptors induced by angiotensin II (Ang II), angiotensin converting enzyme inhibitors (ACEIs) exerts inhibitory effect on tumor development *via* the blockage on MAPK/ERK signaling pathway [22, 23]. Interference with the translocation of EKR1/2 into nucleus has also been proved to lead to inhibition towards cancer cells, which explains the chemosensitizaion effect of curcumin [24].

2.4 WNT/β-catenin signaling pathway

The WNT/β-catenin signaling pathway communicates a signal from proteins to a cell *via* cell surface receptors. As a critical transduction signaling pathway, WNT/β-catenin participates in multiple developmental events during both embryogenesis and tissue generation in adult, regulating cell differentiation, proliferation, and migration [25]. WNTs are secreted glycoproteins and can stimulate a multitude of intracellular signal transduction by binding with Frizzled (Fz) receptor family. WNTs can prevent β-catenin from destruction in the cytoplasm so that the cytoplasmic β-catenin can translocate to nucleus and subsequently promote the transcription of several mitogenic genes including *C-MYC* and *Cyclin D1*, contributing to the initiation and progression of cancers [26, 27]. Hyperactive WNT/β-catenin has also been proved to contribute to MDR in various cancers [28]. Besides, WNT has been identified as a key inducer for epithelial-mesenchymal transition (EMT), a process related to tumor metastasis [29].

The blockage of WNT/β-catenin signaling pathway could be achieved by either antagonizing WNT in binding with Fz receptor or promoting the degradation of cytoplasmic β-catenin, which serves as the prominent mechanisms involved in the anti-tumor efficacy of several repurposed non-chemo drugs or phytochemicals [30, 31]. For example, metformin could inhibit β-catenin by affecting the activities of key proteins [32]. By regulating WNT/β-catenin pathway, repurposed non-chemo drugs and phytochemicals could target tumor metastasis and achieve the synergy with conventional anti-tumor therapeutics.

2.5 Nuclear Factor kappa-light-chain-enhancer of activated B cells (NF-κB)

NF-κB is a small family of proteins regulating the transcription of multiple genes in all mammal cells, thereby controlling cell proliferation and survival. The activation of NF- κB can be achieved by the degradation of the inhibitors of κB (IκB) in response to extracellular stimuli, including reactive oxygen species (ROS), ultraviolet light (UV) or metal ions. AKT could also lead to the activation and release of NF-κB. Activated NF-κB would enter the cell nucleus, increasing the expression of anti-apoptotic proteins such as BCL-2, mitogenic proteins such as C-MYC and Cyclin D1, as well as pro-inflammatory cytokine IL-1b [33]. The alteration in the key proteins and cytokines as a result of the activated NF- κB promotes the proliferation and survival of cancer cells, and contributes to the evasion of immune surveillance [34, 35]. Therefore, the blockage of NF-κB has been proved as a major mechanism of the anti-tumor effect of metformin and several phytochemicals [36-38]. Also, given that NF-κB could aggravate TME by inducing the expression of COX-2, some NSAIDs could counteract the pro-tumor activities induced by NF-κB [39].

2.6 5' adenosine monophosphate-activated protein kinase (AMPK)

AMPK is a central regulator of cellular metabolism and can be activated in response to low ATP level. Activated AMPK increases ATP level by promoting the signal transduction of ATP-generating process while inhibiting the ATP-consuming process. Besides, it inhibits the development of cancers by affecting the activities of several proteins and transduction signaling pathways. For example, by phosphorylating tuberous sclerosis complex protein-2 (TSC2), activated AMPK inhibits mTORC1, consequently leading to inhibition of cancer cell proliferation [40]. It can also promote the expression of pro-apoptotic protein p53, and lead to the intrinsic apoptosis of cancer cells [41]. The inhibition towards Forkhead transcription factors (FOXOs) also contributes to the anti-tumor function of activated AMPK, resulting in the compromised formation of CSCs, sensitizing the response of cancer cells to chemo agents [42]. The anti-diabetic efficacy of metformin has been related with its activation upon AMPK, thereby enabling it a promising candidate in attenuation of tumor development and a potential adjuvant with conventional anti-tumor therapeutics [43, 44].

3. Repurposed non-chemo drugs and dietary phytochemicals as adjuvants for conventional anti-tumor therapeutics

3.1 Non-steroidal anti-inflammation drugs (NSAIDs)

Emerging evidence proves that chronic inflammation plays a critical role in the development of various cancers. As a classical feature of innate immunity, inflammation promotes the progression of cancers in multiple ways. Not only do the cytokines secreted from inflammatory cells promote the proliferation of cancer cells, the elevated level of reactive oxygen and nitrogen species (RONS) also potentiate DNA damage, increasing the malignancy of tumors [45, 46]. Moreover, inflammatory cells infiltrating tumors further contribute to progression of cancers by secreting various tumor-promoting cytokines, such as IL-6, stimulating JAK/STAT3 signaling pathway and causing the promotion of tumor development [47-49].

Because of this connection between inflammation and tumor development, it is corollary to combine anti-inflammation agents with chemo agents in cancer treatment in clinical studies (Table. 1). Indeed, epidemiological studies suggest that NSAIDs may serve as good chemopreventive agents, and contribute to a synergistic effect with chemo agents to treat breast cancer, gastric cancer, and colorectal cancer [8, 50-52]. Previous studies suggested that direct inhibition of the activity of cyclooxygenase 2 (COX-2) is one of the major mechanisms of the anti-tumor role of NSAIDs [53-60]. For example, celecoxib, a COX-2 selective NSAID drug, could reduce the mRNA expression of MDR1 and the protein expression of P-gp, subsequently leading to the reversal of drug resistance in breast cancer cells and facilitating anti-tumor efficacy both *in vitro* and *in vivo* [61]. The inhibition towards COX-2 also impeded the proliferation of cancer cells by interfering with the activity of transduction signaling pathways. Celecoxib could upregulate the expression of PTEN, and then hinder

Table 1. Active or completed clinical trials using NSAIDs in combination therapy with chemotherapy.

Name	Composition of Combination Therapy	Condition	Phase	Status	Lead Organization	NCT Number
Celecoxib	Combination with irinotecan, cisplatin, and radiotherapy	Stage II/III/IV esophageal cancer	Phase II	Completed	UNC Linerberger Comprehensive Cancer Center	NCT00520091
	Combination with docetaxel	Advanced non-small cell lung cancer	Phase II	Completed	Barbara Ann Karmanos Cancer Institute	NCT00030420
	Combination with docetaxel and irinotecan	Advanced non-small cell lung cancer	Phase I/II	Completed	Northwestern University	NCT00073866
	Combination with cisplatin, irinotecan, radiotherapy and surgery	Esophageal cancer	Phase II	Completed	Dana-Farber Cancer Institute	NCT00137852
	Combination with paclitaxel and carboplatin	Stage IIIA non-small cell lung cancer	Phase II	Completed	Jonsson Comprehensive Cancer Center	NCT00062179
	Combination with FOLFIRI regimen, capecitabine, fluorouracil, irinotecan hydrochloride, and leucovorin calcium	Metastatic colorectal cancer	Phase III	Completed	European Organization for Research and Treatment of Cancer	NCT00064181
	Combination with Fluorouracil and leucovorin	Resected Stage III colorectal cancer	Phase III	Completed	European Organization for Research and Treatment of Cancer	NCT00085163
	Combination with vinblastine, cyclophosphamide, doxorubicin, etoposide, ifosfamide, vincristine, radiotherapy, MESNA, filgrastim, or surgery	Newly-diagnosed metastatic Ewing's sarcoma	Phase II	Completed	Children's Oncology Group	NCT00061893
	Combination with capecitabine, cyclophosphamide, and methotrexate	Metastatic colorectal cancer	Phase II	Completed	HaEmek Medical Center, Israel	NCT02280694
	Combination with capecitabine and irinotecan	Metastatic colorectal cancer	Phase II	Completed	University of Michigan Rogel Cancer Center	NCT00230399
	Combination with etoposide, cyclophophamide, thalidomide, and fenofibrate	Relapsed or progressive cancer	Phase II	Completed	Dana-Farber Cancer Institute	NCT00357500
	Combination with carboplatin, paclitaxel or radiotherapy	Head and neck cancer	Phase I/II	Completed	University of Alabama at Birmingham	NCT00581971
	Combination with thalidomide, etoposide and cyclophosphamide	Relapsed or progressive cancer	Phase II	Completed	Dana-Farber Cancer Institute	NCT00165451
	Combination with docetaxel	Non-small cell lung cancer	Phase II	Completed	Barbara Ann Karmanos Cancer Institute	NCT00047281
	Combination with paclitaxel and carboplatin	Esophageal cancer	Phase II	Completed	Weill Medical College of Cornell University	NCT00066716
	Combination 5-fluoroucil or radiotherapy	Rectal cancer	Phase I/II	Completed	University Health Network	NCT00188565
	Combination with gemcitabine	Metastatic pancreatic cancer	Phase II	Completed	M.D. Anderson Cancer Center	NCT00068432
	Combination with erlotinib	Recurrent head and neck cancer	Phase I/II	Completed	Icahn School of Medicine at Mount Sinai	NCT00970502
	Combination with gefitinib	Refractory non-small cell lung cancer	Phase II	Completed	Barbara Ann Karmanos Cancer Institute	NCT00068653
	Combination with oxaliplatin, leucovorin calcium, and fluorouracil	Stage III colon cancer after surgery	Phase III	Active	Alliance for Clinical Trials in Oncology	NCT01150045
	Combination with capecitabine and irinotecan	Recurrent or metastatic colorectal cancer	Phase II	Completed	Barbara Ann Karmanos Cancer Institute	NCT00258232

	Combination with 5-fluorouracil and radiotherapy	Stage II/III rectal cancer	Phase II	Completed	Vanderbilt-Ingram Cancer Center	NCT0036960
	Combination with cyclophosphamide	Recurrent or persistent ovarian epithelial, fallopian tube, or primary peritoneal cancer	Phase II	Active	City of Hope Medical Center	NCT00538031
	Combination with irinotecan, cisplatin, and radiotherapy	Unresectable or metastatic colorectal cancer	Phase I	Completed	Roswell Park Cancer Institute	NCT00084721
	Combination with cyclophosphamide	Advanced cancer	Phase I	Completed	City of Hope Medical Center	NCT00551889
	Combination with epirubicin	Hepatocellular carcinoma	Phase I/II	Completed	Northwestern University	NCT00057980
	Combination with dendritic cell vaccine and interferon	Peritoneal surface malignancies	Phase I/II	Completed	David Bartlett	NCT02151448
Aspirin	Combination with tamoxifen, doxorubicin, cyclophosphamide and paclitaxel	Advanced/metastatic urothelial cancer	Phase I	Active	University of Virginia	NCT04038489
	Combination with alvocidib and clopidogrel bisulfate	Recurrent or metastatic head and neck cancer	Phase I	Completed	National Cancer Institute (NCI)	NCT00020189
Indomethacin	Combination with platinum based chemotherapy	Clorectal neoplasms, esophageal neoplasms, and ovarian neoplasms	Phase I	Completed	UMC Utrecht	NCT01719926

the phosphorylation of AKT, resulting in a synergistic anti-tumor efficacy with pan-histone deacetylase inhibitor by inhibiting PI3K/AKT axis in the treatment towards human salivary adenoid cystic cancer cells [14]. The downregulation of PI3K/AKT also led to the alleviation of EMT, as shown in one report in which the addition of celecoxib sensitized the response to cisplatin in an osteosarcoma cell line [62].

Accumulating evidences indicated that COX-2-independent mechanisms also contributed to the boosted anti-tumor efficacy when combining NSAIDs and conventional chemo agents [39, 63, 64]. Curry et al. demonstrated that co-administration of a non-selective NSAID drug, indomethacin, and a cancer vaccine, MUC1 peptide resulted in more apoptosis of cancer cells in tumor site, and consequently, a facilitated therapeutic efficacy in a transgenic mice model [65]. It was noteworthy that, in this study, celecoxib failed to achieve a similar effect when in combination with the vaccine, elucidating that inhibition towards COX-2 was not the major mechanism for the augmented anti-tumor efficacy. Aspirin, another non-selective NSAID, reversed the drug resistance towards cisplatin in CSCs of non-small cell lung carcinoma by inhibiting the AKT-mTOR axis, leading to a repressed migration and an enhanced therapeutic efficacy [66].

The combination of NSAIDs and chemo agents could also interfere with the energy metabolism within cells. Celecoxib has been reported to facilitate the anti-tumor efficacy of DOX by enhancing its inhibitory effect on ATP production and GSH, inhibiting the transport of glucose into cancer cells, leading to a greatly improved efficacy as a result [67].

The influence of NSAIDs on immunotherapy is multifaceted. For immune checkpoint therapy, though excessive COX-2 has been proved to contribute to immune evasion and positively correlate with PD-L1 expression in various cancers, it remains controversial whether or not the inhibition towards COX-2 could achieve synergy with anti-PD-L1 therapy because of the heterogeneity in different types of cancers [68-73]. There are studies of using NSAIDs (e.g., celecoxib) as an adjuvant for immune checkpoint inhibitors (ICIs) (e.g., anti-PD-1 mAb) *via* COX- and prostaglandin E_2 (PGE_2)-independent mechanisms, achieving boosted anti-tumor immunity and alleviated inflammation in TME in melanoma cancer and breast cancer models [74, 75]. However, despite of the promising results of preclinical studies, concurrent administration of NSAIDs with anti-PD-1 showed no improvement in clinical outcomes for advanced melanoma in the respect of response rate and overall survival [69, 72, 76]. Emerging shreds of evidence elucidated that synergism might exist between NSAIDs and chimeric antigen receptor (CAR) T cell therapy because the inhibition towards COX-2 and PGE_2 would restore the immune function of tumor-specific T cells *via* different ways such as inducing the maturation and resuming the functions of dendritic cells (DCs), modulating the balance between Type 1 and Type 2 T helper cells (Th1 and Th2), as well as inducing anti-tumoral M1 polarization of macrophage [77-80]. The results of previous studies suggested that the combination of celecoxib and CAR-T therapy resulted in facilitated anti-tumor efficacy on gliomas and human non-Hodgkin's lymphoma models [81, 82]. The mechanisms might be attributed to increased cytotoxic T lymphocytes as the result of the inhibition of COX-2 and PGE_2. Nevertheless, changes in the secretion of inflammatory cytokines were also observed in the above-mentioned combination therapy, which implies that further investigation is needed for a comprehensive understanding of the mechanisms involved in the synergy between NSAIDs and CAR-T therapy.

3.2 Anti-diabetic agent

The link between diabetes and cancers has long been discussed. Clinical and epidemic research suggested that patients with diabetes may suffer from increased risk of various cancers, and that diabetic cancer patients suffered higher mortality risk than non-diabetic patients [83-89]. Various factors have been elucidated to contribute to the correlation between diabetes and cancers. For instance, hyperglycemia (high levels of sugar in the blood) and dyslipidemia (abnormal amount of lipids in the blood) caused by diabetes lead to vascular damage and result in oxidative stress and inflammation, which may contribute to the occurrence of cancers. Besides, the influence of diabetes

on several transduction signaling pathways, including AMPK signaling axis, has also been proved to promote the development of cancer [90-96].

Metformin, a first-line therapeutic agent for type II diabetes, has been frequently reported as a potential anti-cancer agent in recent years [97-102]. Besides, the adjuvanticity of metformin for conventional anti-tumor therapies has attracted emerging interest in clinical research (Table. 2). Metformin alleviates hyperglycemia by inhibiting the hepatic glucose output, reducing glucose uptake in intestinal cells, and increasing the insulin sensitivity [103]. Metformin can activate AMPK and consequently repress both mTORC1 and mTORC2 signaling pathways, and therefore holds a great potential in anti-tumor therapy [104-106]. Studies demonstrated that addition of metformin led to a decrease of the half maximal inhibitory concentration (IC_{50}) of various commonly used chemo agents in pancreatic cancer cell line [107]. The mechanism might be attributed to metformin's activation upon AMPK and the resultant suppression on mTORC1. By activating AMPK and subsequently affecting its downstream genes, metformin could also lead to the reversal of drug resistance in various cancers. Co-delivery of doxorubicin (DOX) and metformin in liposome has shown an enhanced anti-multidrug resistance effect in MCF-7/ADR cells. The drug resistance reversal was attributed to the direct ablation of P-gp as a result of the reduced HIF-1α through the activation of AMPK and inhibition of mTORC1 [108, 109]. Similar phenomenon was also observed with 5-fluorouracil (5-FU). The drug resistance against 5-FU in colorectal cancer cells was reversed by co-administration with metformin *via* activation of AMPK pathway and blockage of NF-κB [110]. The activation of AMPK signaling by metformin has also been proved to induce cell cycle arrest at G0/G1 phase, showing synergistic anti-tumor efficacy when combined with glutaminase 1 selective inhibitor in head and neck squamous cell carcinoma [111].

Apart from interfering with cancer cells directly, metformin could also affect the dynamics between tumor and TME to enhance the anti-tumor efficacy of chemo agents. By activating AMPK, metformin inhibited the secretion of transforming growth factor β (TGF-β) from cancer cells to TME in pancreatic cancer [112]. The reduction of TGF-β led to the decrease in the extracellular matrix proteins, including collagen I and α-smooth muscle actin (α-SMA), depleting the stromal barrier and facilitating the penetration of gemcitabine-loaded nanoparticles.

Noteworthy, emerging studies suggested that AMPK-independent mechanisms also contributed to the anti-cancer effect of metformin. By inducing mitochondrial dysfunction, metformin led to alteration in tricarboxylic acid (TCA) cycle, disruption in the biosynthesis process of critical macromolecules, and inhibition of tumor oxygen consumption [108, 109, 113-116]. Metformin induced mitochondrial depolarization, ATP ablation and P-gp downregulation in MCF-7/ADR cells, reversing the drug resistance to DOX [109]. The sensitization of drug-resistant cells to DOX could also be attributed to the suppression of oxygen overconsumption induced by metformin, consequently inhibiting the expression of HIF-1α and P-gp in cells treated with liposomes containing both DOX and metformin [108].

Metformin has shown promising perspective as a potential adjuvant for immunotherapy for malignant melanoma and non-small-cell lung cancer. Improved clinical outcomes including overall response rate, disease control rate, and overall survival were observed in patients receiving a combination therapy of metformin and ICIs compared with the patients receiving only ICIs [117, 118]. The mechanism was attributed to the prevention of $CD8^+$ T-cell exhaustion and apoptosis by metformin. This effect was also observed when metformin was used as a neoadjuvant to a BLC-2 inhibitor (venetoclax) in a 2-step therapy with sequential administration of metformin, venetoclax and anti-PD-1 in an MYC-driven breast cancer mouse model [119]. In this study, the continuous inhibition of tumor growth was observed in mice pretreated with metformin even after the withdrawal of venetoclax and anti-PD-1, suggesting the long-lasting effect of metformin in preventing T cell exhaustion. Metformin could also downregulate the expression level of PD-L1 in tumor cells. Metformin-activated AMPK can directly phosphorylate PD-L1, leading to the abnormality of PD-L1

Table 2. Active or completed clinical trials using metformin in combination therapy with chemotherapy.

Composition of Combination Therapy	Condition	Phase	Status	Lead Organization	NCT Number
Combination with chemotherapeutics including docetaxel, carboplatin, trastuzumab, pertuzumab and Pegfilgrastim	HER2 positive breast cancer that can be removed by surgery	Phase II	Active	University of Kansas Cancer Center	NCT03238495
Combination with cisplatin and external beam radiation therapy	Stage III-IV head and neck squamous cell cancer	Phase I/II	Active	Baylor College of Medicine / Dan L Duncan Comprehensive Cancer Center	NCT02949700
Combination with nelfinavir and bortezomib	relapsed and/ or refractory multiple myeloma	Phase I	Active	Mayo Clinic	NCT03829020
Combination with chemotherapeutics including carboplatin, paclitaxel, and docetaxel	Stage III-IV ovarian, fallopian tube or primary peritoneal cancer	Phase II	Active	University of Chicago Comprehensive Cancer Center	NCT02122185
Combination with genomic deletion 11q	relapsed chronic lymphocytic leukemia or untreated chronic lymphocytic leukemia	Phase II	Active	University of Michigan Comprehensive Cancer Center	NCT01750567
Combination with anthracycline, Taxane, platinum, capecitabine or vinorelbine	Metastatic breast cancer	Phase II	Completed	Ozmosis Research Inc	NCT01310231
Combination with carboplatin or paclitaxel	Advanced ovarian cancer	Phase I	Completed	University Medical Ceter Groningen	NCT02312661
Combination with 5-fluorouracil	Refractory colorectal cancer	Phase II	Completed	Instituto do Cancer do Estado de Sao Paulo	NCT01941953
Combination with gemcitabine, and erlotinib	Advanced pancreatic cancer	Phase II	Completed	Academisch Medisch Centrum - Universiteit van Amsterdam (AMC-UvA)	NCT01210911
Combination with rapamycin as maintenance therapy	Pancreatic cancer	Phase I	Completed	Sidney Kimmel Comprehensive Cancer at Johs Hopkins	NCT02048384
Combination with carboplatin and radiotherapy	Stage III non-small cell lung cancer	Phase II	Active	NRG Oncology	NCT02186847
Combination with gemcitabine, and erlotinib	Stage I/II pancreatic cancer	Phase II	Completed	Fudan University	NCT02005419
Combination with liposomal doxorubicin, docetaxel, and trastuzumab	Locally advanced HER2 positive breast cancer	Phase II	Completed	Instituto Scientifico Romagnolo per lo Studio e la cura dei Tumori	NCT02488564
Combination with gemcitabine, paclitaxel albumin-stabilized nanoparticles, and standard dietary supplement	Unresectable pancreatic cancer	Phase I	Active	City of Hope Medical Center	NCT02336087
Combination with metronomic cyclophosphamide and olaparib	Recurrent endometrial cancer	Phase I/II	Active	Hospices civils de Lyon	NCT02755844
Combination with myocet and cyclophosphamide	HER2 negative metastatic breast cancer	Phase II	Completed	Instituto Scientifico Romagnolo per lo Studio e la cura dei Tumori	NCT01885013
Combination with docetaxel	Metastatic hormone-refractory prostate cancer	Phase II	Completed	Centre Antoine Lacassagne	NCT01796028
Combination with oxaliplatin, leucovorin calcium, and fluorouracil	Metastatic pancreatic cancer	Phase II	Completed	Case Comprehensive Cancer Center	NCT01666730
Combination with carboplatin	Stage III, IV or recurrent endometrial cancer	Phase II/III	Active	Gynecologic Oncology Group	NCT02065687
Combination with paclitaxel	Advanced pancreatic cancer after gemcitabine failure	Phase II	Completed	Instituto do Cancer do Estado de Sao Paulo	NCT01971034
Combination with cisplatin and radiotherapy	Advanced head and neck squamous cell carcinoma	Phase I	Active	University of Cincinnati	NCT02325401
Combination with vinscristine, dexamethasone, doxorubicin, and PEG-asparaginase	Relapsed childhood acute lymphoblastic leukemia	Phase I	Completed	H. Lee Moffitt Cancer Center and Research Institute	NCT01324180
Combination with rituximab, cyclophosphamide, vincristine, and prednisone	Diffuse large B cell lymphoma	Phase II	Active	Hospital Universitario Dr. Jose E. Gonzalez	NCT03200015

Combination with temozolomide, memantine hydrochloride, and mefloquine	Glioblastoma multiforme after radiotherapy	Phase I	Active	M.D. Anderson Cancer Center	NCT01430351

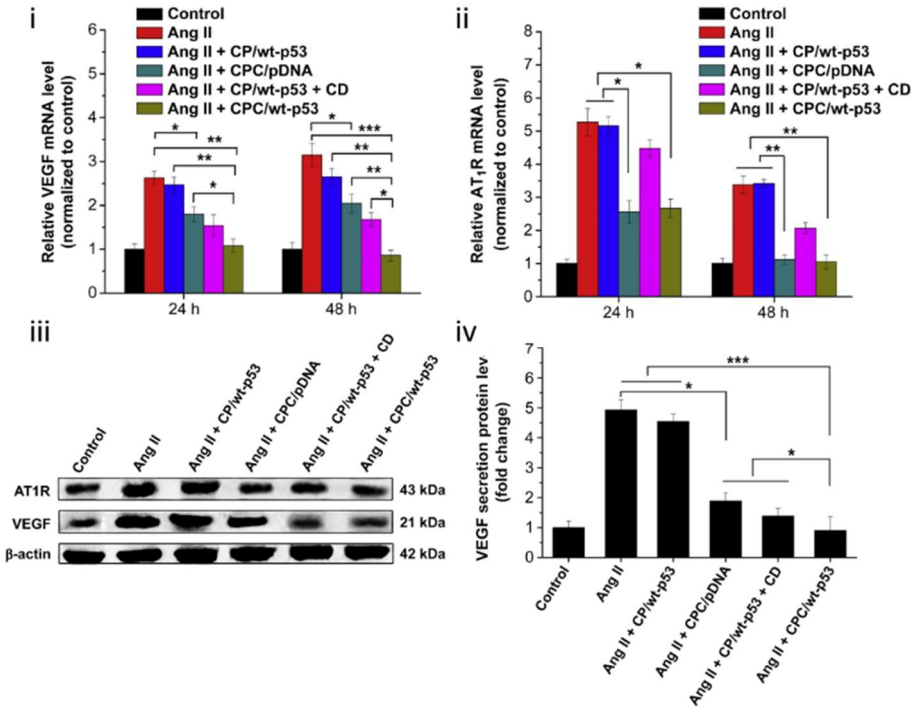
glycosylation, and the degradation of PD-L1 [120]. Besides, the results of multiple *in vitro* studies suggested that the macrophage polarization, the reversal of EMT, and the attenuation of hypoxic TME induced by metformin-activated AMPK might all play a part in potentiating the efficacy of ICIs by the addition of metformin [121-123].

3.3 Anti-hypertension agents

Widely expressed in the epithelial cells of most tissues, RAS could serve as a good target for the combination therapy with other conventional anti-tumor agents. As major components in RAS, angiotensin converting enzyme (ACE) and angiotensin II (Ang II) have both been proved to participate in the carcinogenesis and development of cancers. ACE first converts angiotensin I (Ang I) to Ang II, and Ang II subsequently exhibits regulatory function on target cells by binding to Ang II receptors (AT1R and AT2R). The Ang II-induced AT1R activation would then lead to the activation of various signaling pathways, including MAPK/ERK pathway and PI3K/AKT pathway, contributing to the regulation upon the growth, adhesion, invasion, and migration of certain types of cancer cells [22, 23, 124-127]. Besides, in certain types of cells, ACE could also serve as a membrane receptor for Ang II, the binding of which would induce the proliferation and migration of melanocytes, contributing to the progression of melanoma [128].

Though anti-hypertension agents of different kinds have been studied as potential adjuvants to chemotherapy, only a few showed positive effect on clinical therapeutic outcomes, among which angiotensin converting enzyme inhibitors (ACEIs) and angiotensin receptor blockers (ARBs) remained as the majority [129]. The direct inhibition of ACE and the blockage of AT1R have been proved to reverse the acquired resistance to hormone therapy, where MCF-7 cells were sensitized to tamoxifen by ACEI drug captopril or losartan [130]. Besides, an improvement of the drug perfusion within tumor was observed when captopril or losartan acted as an adjuvant to chemo agents such as DOX or paclitaxel (PTX) [131, 132]. This was due to the dilated blood vessels and enlarged epithelial gaps within tumors, suggesting that the anti-angiogenesis function of ACEIs and ARBs exhibited a positive effect on the outcomes of chemotherapy. Attractively, the affinity between ARBs and ATRs could serve as a targeting strategy in its co-delivery with other anti-angiogenesis agents, such as siRNA or antibodies targeting VEGF or HER, where the secondary and tertiary amine-rich molecular structure also contributed to a facilitated endosomal escape by enhancing the buffering capacity [11, 12, 133-136]. In one study, candesartan was grafted onto chitosan in the fabrication of a nanovector for its co-delivery with wild-typed p53 gene [135]. Compared with the chitosan/p53 and candesartan mixed delivery system, candesartan-chitosan/p53 exhibited higher *in vitro* transfection efficiency, resulting in enhanced inhibition on the expression level of VEGF in cells stimulated with Ang II (as shown in Fig. 3A). Consistently, stronger inhibition on tumor angiogenesis was observed in the tumor site in mice treated with candesartan-chitosan/p53, with lowest microvessel density (MVD) observed in tumor section as shown in Fig. 3B.

A



B

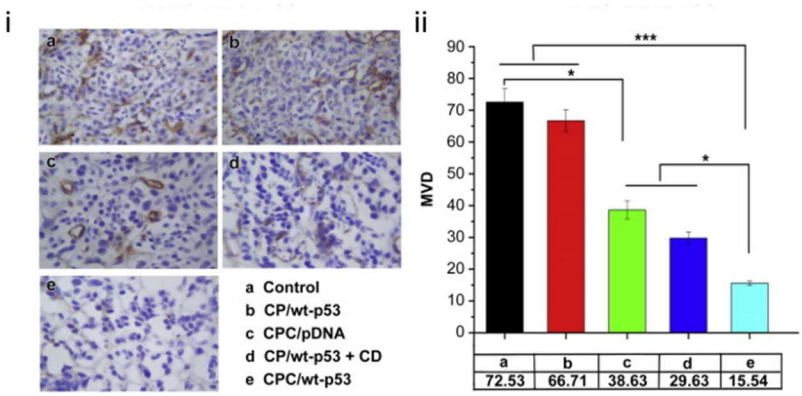


Fig 3. Enhanced anti-angiogenesis efficacy by the co-delivery of candesartan and p53 gene. A, the suppression on the expression levels of VEGF and AT1R in PANC-cells (CP/wt-p53, chitosan/p53 complexes; CPC/pDNA, candesartan-chitosan/pDNA complexes; CP/wt-p53 + CD, mixed delivery of chitosan/p53 and candesartan; CPC/wt-p53, co-delivery of candesartan and p53); B, suppression on the blood vessel formation: i, *ex vivo* tumor section assayed by immunohistology using CD31 antibody; ii, quantification of CD31-positive microvessels in PANC-1 tumor xynografts of nude mice treated with different formulations. Reuse with permission [135]. Copyright with Elsevier. Color should be used for this figure.

Losartan can also improve the therapeutic outcomes of chemo agents by correcting TME *via* depletion of collagen I, achieving increased drug penetration within tumor sites [137-139]. The ablation of collagen I was due to the reduced secretion of TGF-β induced by losartan. This suggested that losartan could potentially eliminate the metastasis by affecting the secretion of growth factors when combined with various therapeutic agents, which was proved in ovarian cancer, breast cancer, and liver cancer both *in vitro* and *in vivo* [140-142].

Though systematic inhibition of RAS led to diverse influence on immune response, emerging evidence indicated that local Ang II contributed to an immunosuppressive TME and that the combination of ARBs (e.g. candesartan or valsartan) with PD-L1 could result in a boosted anti-tumor efficacy on a colon cancer model [143-145]. The adjuvanticity of candesartan and valsartan was

attributed to the attenuation in the secretion of immunosuppressive cytokines, including TGF-β, IL-1, and IL-6, restoring the activation and proliferation of cytotoxic $CD8^+$ T cell as a result. Besides, the inhibitory effect of ACEIs and ARBs on cancer-associated fibroblast (CAF) also led to the reduction of immunosuppressive chemokine CXCL 12, resulting in synergy with anti-PD-L1 antibody. The synergistic mechanisms between ACEIs or ARBs and immunotherapy also included their normalization of TME by the ablation of stroma, through which the hypoxia and the inflammation were alleviated, leading to the attenuation of immunosuppression.

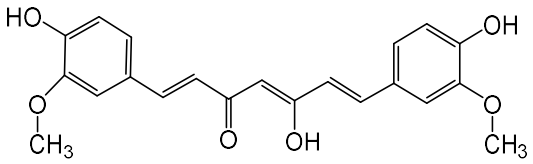
3.4 Dietary phytochemicals

Dietary phytochemicals showed excellent efficacy in attenuating the side effects induced by conventional anti-tumor therapies, making them promising candidate adjuvants [146, 147]. Due to the polyphenol structure, most of the investigated phytochemicals plays manifest anti-oxidant, anti-inflammatory, and immunomodulatory functions, contributing to the alleviation of side effects [148-150]. These functions also raises the possibility to use polyphenol phytochemicals for a synergy with conventional anti-tumor therapies, given that abnormal metabolism, oxidative stress, inflammation, and immunosuppression all contribute to the progress and development of cancers [150, 151]. By affecting the expression level of efflux pumps and membrane receptors, phytochemicals could sensitize cancer cells to multiple conventional anti-tumor agents, reversing drug-induced resistance. Besides, molecular studies suggested that by interfering with intracellular transduction signaling pathways and key proteins, phytochemicals could affect the initiation and development of various cancers. Furthermore, it has been well-elucidated that a majority of phytochemicals could affect the EMT process of cancer cells, inhibiting the development of CSCs, and consequently alleviating tumor metastasis [152-155]. Noteworthy, most phytochemicals exhibited tumor-specific cytotoxicity, with mild or even no harm to normal cells. This selectivity might be attributed to the difference in metabolic patterns between cancer cells and normal cells, further suggesting that the combination of phytochemicals and conventional anti-tumor agents may serve as a novel strategy for the effective and safe treatment of cancers.

3.4.1 Curcumin

Curcumin is a naturally-occurring chemical compound found in the spice turmeric. As a polyphenolic compound (Fig. 4A), curcumin could affect the proliferation and metastasis of cancer cells *via* regulating the expression or activity of critical proteins, including NF-κB, Cyclin D1, and BCL-2, subsequently leading to the regulation upon multiple signaling pathway [156-160]. As listed in Table. 3, a multitude of clinical trials have been registered to investigate the feasibility of using curcumin in combination with chemotherapy to improve therapeutic outcomes.

A.



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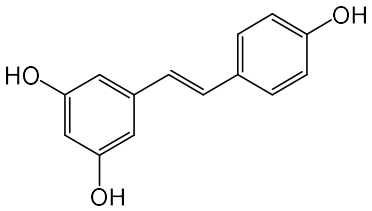

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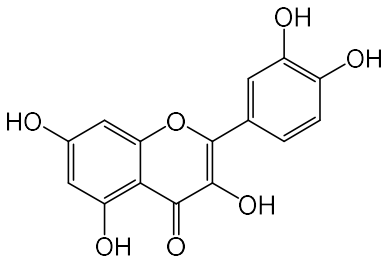

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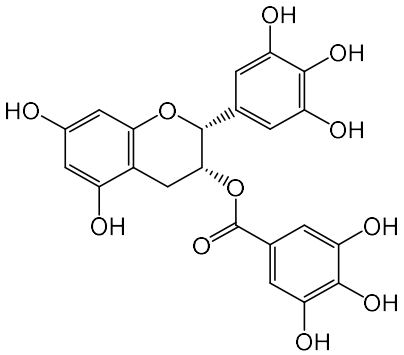

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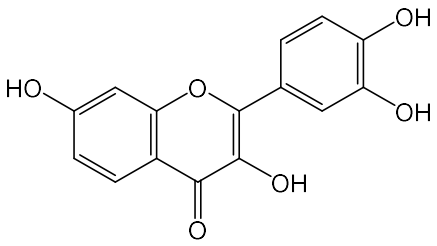


Fig 4. Molecular structure of the main dietary phytochemicals. A, curcumin; B, resveratrol; C, quercetin; D, epigallocatechin gallate (EGCG); E, fisetin.

Table 3. Active or completed clinical trials using curcumin in combination therapy with chemotherapy.

Composition of Combination Therapy	Condition	Phase	Status	Lead Organization	NCT Number
Combination with FOLFOX	Inoperable colorectal cancer	Phase I/II	Completed	University of Leicester	NCT01490996
Combination with paclitaxel	Advanced breast cancer	Phase II	Completed	National Center of Oncology, Armenia	NCT03072992
Combination with 5-fluorouracil	Metastatic colon cancer	Early phase I	Active	Baylor Research Institute	NCT02724202
Combination with Avastin or FOLFIRI	Colorectal cancer with unresectable metastasis	Phase II	Completed	Gachon University Gil Medical Center	NCT02439385
Combination with gemcitabine	Pancreatic cancer	Phase II	Completed	Rambam Health Care Campus	NCT00192842
Combination with capecitabine and radiotherapy	Rectal cancer	Phase II	Active	M.D. Anderson Cancer Center	NCT00745134
Combination with gemcitabine, paclitaxel albumin-stabilized nanoparticles, and standard dietary supplement	Unresectable pancreatic cancer	Phase I	Active	City of Hope Medical Center	NCT02336087

Curcumin could reverse the drug resistance to DOX or PTX by directly inhibiting the expression of P-gp in cancer cells [161-163]. Through counteracting the increased expression of NF-κB induced by platinum, curcumin served as an excellent adjuvant for platinum-based chemotherapy, leading to enhanced anti-proliferative effect in various types of cancers [164-167].

The inhibition of curcumin on STAT signaling pathway contributed to the apoptosis of cancer cells, resulting in the amelioration in the proliferation and migration of cancer cells when combined with conventional anti-tumor agents [168-171]. In an *in vitro* study on skin cancer cell line A431, the highest growth inhibition rate of 72.9 % was achieved by the liposomes containing both curcumin and *STAT* siRNA in comparison with the cells treated with either curcumin (44.9 %) or *STAT* siRNA-loaded liposomes (53.4 %) [172]. This study demonstrated that the greatest inhibition towards the expression level of *STAT* was achieved by co-delivery of curcumin and *STAT* siRNA, further justifying that the direct inhibition on *STAT* induced by curcumin led to the augment in anti-tumor efficacy. A similar outcome was observed in a study of PAMAM-based nanoparticles containing both curcumin and *BCL-2* siRNA. Compared with cells treated with curcumin or *BCL-2* siRNA alone, the greatest inhibition of the cell viability and the most apoptotic event was observed in HeLa cells treated with the dual-loaded nanoparticles [173].

The inhibition on BCL-2 also led to the synergism between curcumin and cisplatin or 5-FU *via* activating the mitochondria-dependent apoptosis, where the regulation upon Caspase 9 and 3, ERK1/2 as well as WNT/β-catenin also played a part [24, 174, 175]. The inhibitory effect of curcumin on the above-mentioned signaling pathways further led to the amelioration of EMT process in cancers, contributing to its anti-metastatic function [176, 177]. Attractively, a recent study found that curcumin could selectively boost the anti-tumor efficacy of an mTORC1/2 inhibitor in cancer cells instead of normal tissue cells by autophagy-induced apoptosis *via* the cytosolic calcium-induced lysosomal membrane permeabilization, accentuating the safety of using curcumin as an adjuvant of conventional anti-tumor therapeutics [178].

It has been proved clinically that administration of curcumin could reduce the number of regulatory T cells (Tregs) while increasing the number of Th1 in the peripheral system of cancer patients, indicating that curcumin might manifest the capacity to correct the immunosuppressive TME by altering the ratios of different immune cells [179, 180]. Results from cell or animal studies also demonstrated that curcumin could abolish the suppression on T cells by stimulating the maturation of DCs and subsequently strengthening the antigen presentation [181]. Besides, curcumin could correct the immunosuppression in TEM *via* affecting the secretion levels of different cytokines, such as increasing the level of IL-2 by blocking its binding with the receptor on Tregs and reducing the level of IL-10 by inhibiting TGF-β [182, 183]. Therefore, it is rational to explore the possibility of using curcumin as an adjuvant in immunotherapy. The synergy between curcumin and immune checkpoint therapy with anti-PD-L1 was validated in a bladder cancer model on mice. Modest tumor growth and the longest survival was achieved in mice treated with both anti-PD-L1 and a curcumin analog, bisdemethoxycurcumin (BDMC) [184]. However, in this study, very few of the BDMC-boosted $CD8^+$ T cells could secret cytotoxic cytokines such as IFN γ and Granzyme B due to the expression of PD-1, necessitating the co-administration of both BDMC and anti-PD-L1 for optimized therapeutic outcomes. For precise targeting delivery, a dual pH-responsive nanodrug was designed where anti-PD-1 served not only as ICIs but also as a targeting strategy for delivering curcumin in to TAMs [185]. The as-prepared nanodrug could first attach on circulating $PD\text{-}1^+$ T cells, by which it could travel to the target tumor site, releasing curcumin to inhibit NF- κB and subsequently reducing the secretion of immunosuppressive cytokines (Fig. 5A-5C). Compared with free curcumin, augmented promotion in the infiltration of $CD8^+$ T cells in tumor site was observed with nanodrug-treated group (Fig. 5D and 5E), leading to an improved anti-tumor efficacy against melanoma both *in vitro* and *in vivo* as a result of simultaneously boosted T cell response and inhibited T cell exhaustion. The maturation of DCs stimulated by curcumin was also investigated in the combination with tumor vaccine, where curcumin contributed to not only the facilitated immunogenicity of tumor cells but

also the enhanced antigen-presenting capacity of DCs, leading to a potent synergy in killing cancer cells [186, 187].

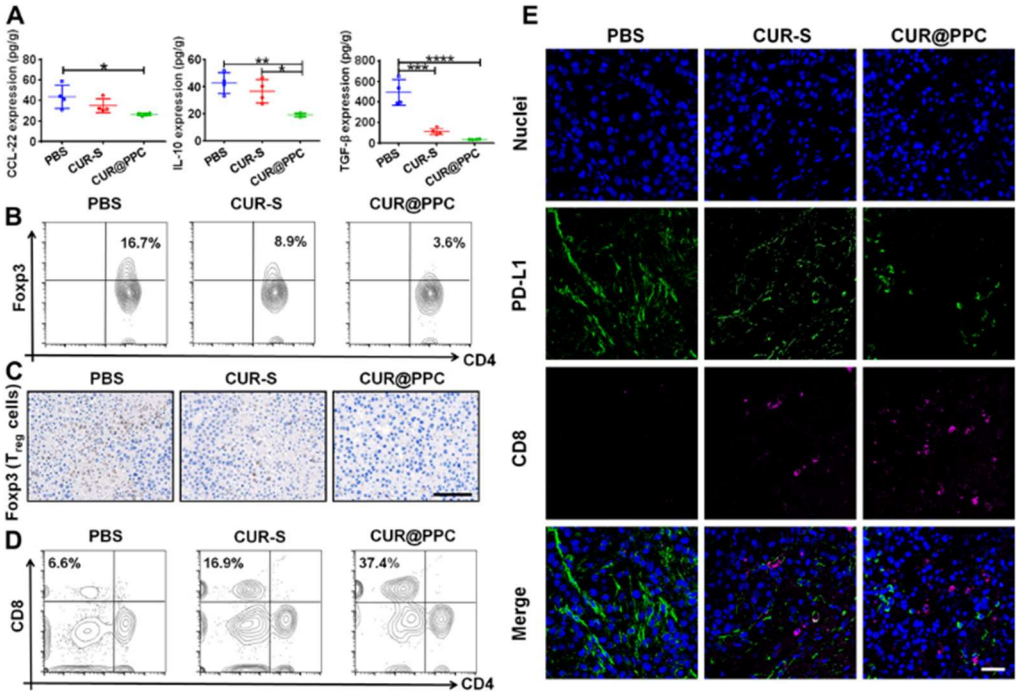


Fig 5. Enhanced correction of immunosuppression by curcumin loaded on nanodrug. A, expression level of immunosuppressive cytokines in B16F10 tumors of mice treated with different formulation (CUR-S, curcumin in DMSO; CUR@PPC, curcumin loaded in nanodrug for further co-delivery with anti- PD-L1 antibody); B and C, $CD4^+Foxp3^+$ T cells (T_{reg} cells) in tumor bearing mice treated with different formulations; D, $CD8^+$ T cells in tumor mice treated with different formulations; E, immunofluorescence of tumor sections showed increased infiltration of $CD8^+$ T cells and reduced expression of PD-L1 in mice treated with curcumin-loaded nanodrug.in tumor bearing mice (Scale bar, 50 μm). Reuse with permission [185]. Copyright with AAAS. Color should be used for this figure.

3.4.2 Resveratrol

Resveratrol, a non-flavonoid polyphenol phytochemical (Fig. 4B) contributing to the health benefits of red wine, has been widely investigated as a protective agent to ameliorate the systematic toxicity induced by chemotherapy or radiotherapy [188-191]. The chemoprotective effect of resveratrol could be attributed to its anti-oxidative and anti-inflammatory properties as a result of the influence on key proteins or transduction signaling pathways which are critical to cell proliferation [192-194].

Resveratrol could reverse drug resistance in cancer cells by directly affecting the efflux pumps. Co-administration of DOX with resveratrol led to the reversal of drug resistance in various cancer cell lines, as a result of the downregulation of MRP1 and the subsequent reduced expression of P-gp [195, 196]. A similar mechanism also contributed to the reversal of drug resistance against docetaxel in advanced pancreatic cancer cell line [197]. In this study, the combination of resveratrol nanoparticles and docetaxel nanoparticles resulted in an IC_{50} (10 nM) decreased by 27-fold compared with docetaxel nanoparticles (280 nM). It should be noted that cells receiving the co-administration also showed a reduced levels of NF-κB, BCL-2, and BCL-XL, indicating that resveratrol facilitated the therapeutic outcome of docetaxel by inducing apoptosis in cancer cells.

Resveratrol could achieve synergism with conventional anti-tumor agents by affecting the activities of key proteins or transduction pathways. For example, resveratrol downregulated β-catenin in MCF-7/ADR, resulting in compromise of EMT, inhibition of CSC formation, as well as restored response to DOX [198]. In addition, by activating PTEN, resveratrol inhibited the activity of the AKT signaling pathway, re-sensitizing gastric cancer cells to DOX while reducing the metastasis capacity of cancer cells [199]. The inhibition of phosphorylated AKT also led to the sensitization of bladder cancer cells

to rapamycin by blocking the negative regulatory feedback from mTORC1 [200]. As a result, increased apoptotic rate, as well as decreased migration and invasion capacity, were observed on the cells treated with co-administration of resveratrol and rapamycin.

Apart from chemosensitizing, resveratrol exhibited synergism with chemotherapy by inducing mitochondrial apoptosis. The augment in mitochondrial depolarization, and cytochrome c release was observed in the lung cancer cells co-administrated with resveratrol and cisplatin in comparison with cisplatin-treated cells [201, 202]. The combination of resveratrol and cisplatin led to an increased ratio of BAX/BCL-2, further confirming apoptosis was involved in the above-mentioned synergism. Previous study also observed that the combination of resveratrol and cisplatin promoted pro-death autophagy in A549 cells, leading to resveratrol-induced mitochondrial apoptosis [203]. The activation of p53 by resveratrol was proved to participate in the induction of apoptosis in the pancreatic cancer cells treated with both docetaxel and resveratrol [204]. Apart from activated p53, the increase in pro-apoptotic proteins (BAX and BID, and BAK) and the decrease in anti-apoptotic proteins (BCL-2 and BCL-XL) also contributed to the increased apoptosis of cells.

Direct regulation of resveratrol on multiple signaling pathways also potentiated its combination with gene therapy. The inhibition towards the viability of leukaemia cells K562 of BCR-ABL siRNA was enhanced by a resveratrol-loaded polymeric nanofiber [205]. Noteworthy, the maximum anti-tumor efficacy was achieved by the combination where the siRNA loaded liposome was introduced 3 days after the administration of resveratrol nanofiber, suggesting that a precise control of the time/spatial release of both agents in target site should be taken into account when seeking for optimal combination with other conventional anti-tumor therapy.

Some studies proved that resveratrol could lead to a synergy with chemo agents in ER-positive breast cancer cell lines (MCF-7 or T47D), but not in ER negative breast cancer cells (MDA-MB-231), indicating a possibility of using resveratrol and hormone therapy as a combination therapy [206, 207].

Because of the complicated effect of resveratrol on tumor immune microenvironment, the feasibility of combining resveratrol and immunotherapy still remained unclear. Low-dose resveratrol (20 μM) could enhance the effector function of $CD4^+$ T cell by stimulating the metabolic alteration in a p53-dependent way, resulting in augment in the secretion of IFNγ and other cytotoxic cytokines, which may subsequently correct the immunosuppressive TME [208]. However, at a higher dose (50 μM) and in combination with piceatannol, resveratrol was reported to upregulate the expression of PD-L1 in breast cancer cells and colon cancer cells [209]. Though the increased level of PD-L1 sensitized cancer cells to anti-PD-L1 therapy, it was unclear whether the upregulation of PD-L1 would counteract with the therapeutic efficacy of ICIs. Therefore, further investigations about the mechanisms involved in the interaction of resveratrol with tumor immune microenvironment remain essential to achieve precise control of the dose of resveratrol in the tumor site for optimized therapeutic outcomes.

3.4.3 Quercetin

As a typical flavonoid with polyphenol structure (Fig. 4C), quercetin exhibited chemopreventive effect through its anti-oxidant property [210]. Apart from modulating oxidative stress, quercetin could also affect the survival and proliferation of cells by regulating the activities of key proteins and multiple signaling pathways, legitimating the feasibility of using quercetin as an adjuvant with conventional anti-tumor therapy [211].

Direct downregulation of the efflux pumps expressed on the surface of drug-resistant cells has been reported as one of the major mechanisms of the chemosensitizing function of quercetin at low dose (< 20 μM) [212-214]. Noteworthy, at non-toxic concentration (0.7 μM), quercetin facilitated the accumulation of DOX in MCF-7 and MDA-MB-231 cancer cells by abolishing P-gp, but exerted no effect on the DOX accumulation in mammary cells MCF-10A and myocardial cells AC16, suggesting that quercetin could alter the safety profile when combined with chemo therapy [215]. A similar

selective cytotoxicity-boosting effect of quercetin on DOX was also observed in hepatoma cells SMMC7721 compared with normal liver cells L02 [216]. The addition of 20 μM quercetin facilitated DOX accumulation in SMMC7721 cells and subsequently augmented cell apoptosis, but exerted no cytotoxicity in L02 cells.

At non-toxic concentration, quercetin exhibited synergy with multiple chemo agents by inducing apoptosis. By downregulating *C-MET* gene in DOX-resistant prostate cancer cell line PC3/R, quercetin directly inhibited the activity of PI3K/AKT signaling pathway, resulting in the correction of mitochondria dysfunction induced by DOX and the subsequent activation of caspase-dependent apoptosis, thus the sensitivity of PC-3/R towards DOX was restored [217]. A similar synergy was reported in PC-3 cells receiving a combination of PTX and quercetin [218]. Compared with the cells treated with PTX alone, the cells co-administrated with PTX and quercetin exhibited enhanced caspase-dependent apoptosis and facilitated cell cycle arrest at G2/M phase as the result of p53 activation, showing stronger inhibition against the proliferation of cancer cells both *in vitro* and *in vivo*.

The influence of quercetin on endoplasmic reticulum also participated in its chemosensitization function. Pre-treatment with quercetin led to significant enhancement in the cytotoxicity of cisplatin in ovarian cancer cells, where the quercetin-induced endoplasmic reticulum stress led to inhibition towards STATs and subsequently resulted in activation of mitochondrial apoptosis [219].

At higher doses (usually higher than 40 μM), quercetin exerted pro-oxidant function, intensifying ROS level, activating pro-apoptosis signals and inhibiting survival signals within cells, which contributed to the chemosensitization function of quercetin [210, 220]. For example, the response of human oral squamous cells to cisplatin was re-sensitized by co-administration with quercetin [221]. This sensitization was attributed to the blockage of cisplatin-induced hyperactive NF-κB and the consequent induction of caspase-dependent mitochondrial apoptosis, subsequently resulting in an enhanced inhibition towards colony formation capacity, as well as a better *in vivo* anti-tumor efficacy in a mouse model.

The regulation of quercetin on TME also took a part in its synergism with conventional chemo agents. It was proved by an *in vivo* Matrigel plug assay that the blockage on VEGF induced by quercetin resulted in anti-angiogenesis, promoting inhibition of tumor growth by cutting off nutrient supply [214]. The synergy brought by the anti-angiogenesis function of quercetin may hinder the metastasis as well, whereby the growth of secondary tumor was limited by the lack of blood vessels [222]. By correcting the abnormality in TME, quercetin in a co-delivery hydrogel with a rapamycin analogue attenuated the inflammation in the TME of an MCF-7 xenograft model [223]. After treatment with the co-delivery hydrogel, reduction of inflammatory factors such as IL-8, IL-6, IL-19, as well as MMP2 and MMP9, was observed, resulting in an enhanced therapeutic outcome.

The inhibition of AKT and ERK signaling pathways may also contribute to the adjuvanticity of quercetin by reducing MMPs in TME. In glioblastoma cell lines A172 and T98MG, the combination of quercetin and temozolomide led to stronger proliferative inhibition as well as a significantly compromised inflammatory TME compared to monotherapy [224, 225].

Emerging evidence proved that quercetin attenuated the maturation of DCs, impeding the antigen presentation in TME [226]. Besides, quercetin contributed to the immunosuppression in TME by inducing the M2-type polarization of TAMs, limiting the potential of quercetin as an adjuvant in immunotherapy [227]. However, a study reported that an enzymatically synthesized quercetin analogue, quercetin 3-O-xyloside, exerted a stronger stimulation on the secretion of cytotoxic TNF-α from macrophages in comparison with quercetin [228]. Therefore, further exploration of the suitable modification on quercetin may raise the possibility of its potential application in the combination with immunotherapy.

3.4.4 Epigallocatechin-3-gallate (EGCG)

Results of several cohort research suggested a potential link between the green tea consumption and the low occurrence rate of certain types of cancer, raising the possibility of using green tea extracts as adjuvants for conventional anti-tumor therapies [229, 230]. EGCG, the most abundant and bio-active catechin in green tea extract, has been associated with potential in chemopreventive and anti-inflammation activities due to the anti-oxidant properties. As shown in Fig. 4D, EGCG is a flavan-3-ol molecule with a gallocatechol group and a gallate ester, whose anti-oxidant capacity could be attributed to the direct capture of free radicals by the gallocatechin ring [231, 232].

As a result of the regulation on multiple transduction signaling pathways, EGCG could directly reverse the drug resistance in cancer cells by abolishing the expression of efflux pumps, resulting in improved therapeutic outcomes [233-235]. The reduced expression of P-gp, along with the downregulation of phosphorylated AKT and BCL-2, was observed in glioma stem-like cells generated from U87 spheres after the administration of EGCG, succeeding in the reversal of the resistance towards carmustine and temozolomide [236]. Likewise, the amelioration of P-gp, as well as the inhibition towards the secretion of VEGF by EGCG contributed to the reversal of drug resistance against 5-FU in gastric cancer cell line SGC-7904/FU, exhibiting enhanced inhibitory effect both *in vitro* and *in vivo* [237]. A similar mechanism also contributed to the restoration of the response to 5-FU in human colon carcinoma cell lines HCT-116 and DLD1 through the downregulation of P-gp as a result of the blockage on NF-κB [238]. The IC_{50} of 5-FU was decreased 8.0-fold (HCT-116) and 13.6-fold (DLD1), respectively, after the addition of 50 μM EGCG. Derivatives of EGCG could also re-sensitize the response of cancer cells to chemo agents by downregulating P-gp directly. The co-administration of ethylated derivate of EGCG Y_6 (10 μM or 15 μM) and DOX led to a 7.7-fold (at 10 μM) or 10.2-fold (at 15 μM) decrease of IC_{50} value in DOX-resistant hepatocellular carcinoma cell line BEL-7404/DOX, as well as an increase in the late-stage apoptosis (2.3-fold and 3.3-fold respectively) [239]. Noteworthy, the anti-tumor efficacy of Y_6 and DOX was better than that of EGCG and DOX, which might be attributed to the enhanced stability of Y_6 due to the ethylated modification. A better bioactivity of EGCG could also be achieved by suitable delivery system. Compared with simple mixture of EGCG and PTX, PLGA-based nanoparticles co-loaded with both drugs exerted a significantly enhanced inhibitory effect toward MCF-7, MDA-MB-231 and patient-derived breast cancer cell samples [240]. The simultaneous release of EGCG, along with PTX, blocked the hyperactive NF-κB induced by PTX, resulting in the most prominent downregulation on the P-gp.

Apart from affecting the expression of P-gp, the attenuation towards the development of CSCs by EGCG also played a dominant role in its chemosensitization function [241-244]. The addition of EGCG (100 μM) could selectively sensitize drug-resistant HCT-116 to 5-FU by inhibiting the self-renewal of cancer cells as well as upregulating the stem-like cell suppressor miRNAs, resulting in the compromised *in vitro* colony formation and *in vivo* tumor formation capacity [245]. The alleviation of CSC formation induced by EGCG could lead to inhibition of pro-survival autophagy induced by DOX in osteosarcoma, contributing to the synergy in the anti-proliferative efficacy on cancer cells [246]. It was also proved in a mouse nasopharyngeal tumor xenograft model that the inhibition on CSC formation by EGCG result in a decrease in the metastasis *via* the blockage on NF-κB and STAT signaling [243-245]. Apart from reduction of EMT markers, the addition of EGCG also depleted secretion of formation factors for lymphangiogenesis, correcting the abnormalities in TME.

Moreover, EGCG could achieve synergism with conventional anti-tumor agents *via* epigenetic modulation through inhibition on DNA methyltransferase. As a competitive inhibitor for DNA methyltransferase, EGCG could reverse the acquired resistance in cancer cells by reactivating the abnormally methylation-silenced genes, restoring the response of drug-resistant cancer cells to various chemo agents including cisplatin and temozolomide [247-249]. Noteworthy, the re-activation of methylation-silenced genes by EGCG preferentially happened in cancer cells rather than in normal cells, as it was validated in glioblastoma cells and normal glio cells, suggesting EGCG holds promising potential as a safe regulator of DNA methylation for further study and application. The

direct inhibition on DNA methyltransferase also led to the epigenetic re-activation of ERα in ERα-negative breast cancer cell line MDA-MB-231, making it possible for EGCG to serve as an adjuvant in anti-hormone therapy [250]. Oral administration of EGCG and tamoxifen greatly hindered the growth of ERα-negative MDA-MB-231 xenograft tumor. EGCG could also reverse the acquired resistance to tamoxifen in ERα-positive breast cancer cell lines MCF-7/TAM and T-47D/TAM by blocking AKT phosphorylation, with greater inhibition of cell proliferation and higher apoptosis rate observed in cells treated with the nanoparticles containing both tamoxifen and EGCG [251].

Despite the regulation of EGCG on multiple signaling pathways regarding the proliferation, metabolism and metastasis of cancer cells, research about the feasibility of using EGCG in combination with immunotherapy was limited. Still, it was reported that the suppression of tumor growth in a murine breast cancer model brought by EGCG was associated with decreased TAMs and pro-tumoral M2 infiltration [252]. Both *in vivo* and *ex vivo* study suggested that EGCG treatment led to reduction of M2 infiltration by reducing the secretion of CSF-1 and CCL-2 in TME, consequently correcting the immunosuppression in TME. Besides, downregulation of IL-6 and TGF-β, as well as upregulation of TNF-α were observed in the mice treated with EGCG as a result of suppressed M2 polarization, further normalizing the immunosuppressive TME. EGCG has also been proved to reduce the IFN-γ-induced PD-L1 expression in human non-small cell lung carcinoma cell lines A549 (by 86 %) and H1299 (data not shown) *via* the inhibition on both JAK/STAT and AKT signaling, suggesting it may serve as a potent adjuvant for immune checkpoint therapy [253].

3.4.5 Fisetin

Fisetin, one of the most ubiquitous bioactive flavonoids (Fig. 4E) found in vegetables and fruit, has been widely proved to manifest anti-oxidant and anti-inflammation functions due to its polyphenol structure, contributing to the perspective in chemoprevention [254-256]. Recent studies suggested that fisetin exhibited anti-proliferative efficacy in multiple cancer cell lines by regulating the activities of various transduction signaling pathways, shedding a light on the possibility of using the combination of fisetin and conventional anti-cancer therapeutics for enhanced treatment outcomes [257, 258].

The induction of apoptosis played a prominent part in the adjuvanticity of fisetin. By elevating the expression of death receptor 5 and inducing the dysfunction of the mitochondrion, the addition of fisetin remarkably increased the apoptosis rate induced by sorafenib in cervical cancer cell line HeLa (4 % in cells treated with sorafenib alone, and 58 % in cells treated with the combination of sorafenib and fisetin) through both extrinsic and intrinsic apoptosis pathways [259]. Apart from inducing apoptosis directly, the simultaneous regulation on survival signaling pathways in cancer cells contributed to the synergistic effect of fisetin with different types of conventional anti-tumor agents. A strong synergy was observed between fisetin and sorafenib in melanoma cancer cell lines, with elevated apoptosis rate (29.6 % in cells treated with sorafenib alone, and 57.3 % in cells treated with sorafenib and fisetin) in cells treated with both drugs as a result of the increased pro-apoptotic protein BAX and decreased anti-apoptotic protein BCL-2 [260]. The downregulation of MAPK and PI3K pathways also participated in the synergy in the above-mentioned study, which was confirmed both *in vitro* and *in vivo*. The inhibition on MAPK and PI3K signaling axis led by the combination of fisetin and sorafenib further attenuated the invasive and metastatic capacity of melanoma, showing the most potent inhibition towards primary tumor and secondary tumor (lung metastasis) in mice treated with both drugs, along with reduction in the expression of EMT makers, MMP2, and MMP9 [261].

In addition to the regulation of apoptosis and transduction signaling pathways, other mechanisms also played a part in the adjuvanticity of fisetin. In a study about the combination of fisetin and PTX, a cell line-specific synergy was observed in non-small cell lung cancer cell line A549, as a result of the influence on mitotic progress and cytoskeleton [262, 263]. After co-administration of fisetin and PTX, A549 cells were arrested at G2/M phase, followed by polyploidy and aneuploidy instead of apoptosis, leading to the formation of giant mononucleated or multinucleated cells and subsequently causing cell death by mitotic catastrophe. The combination of fisetin and PTX further switched the protective

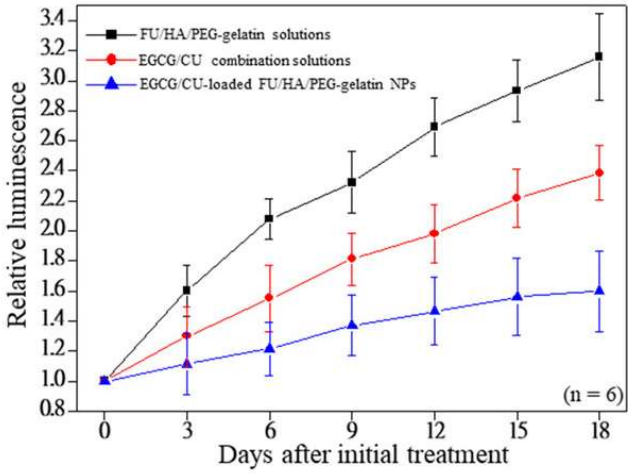
autophagy induced by either PTX or fisetin alone into autophagic cell death, accelerating the killing effect towards cancer cells. Interestingly, the combination of fisetin and PTX attenuated the EMT progress in A549 cells by directly degrading vimentin without affecting its transcription level. It should be noted that at tested doses, no enhanced cytotoxicity was observed in epithelial cells treated with the co-administration of fisetin and PTX, indicating that this combination held a promising perspective for the effective and safe treatment of non-small cell lung cancer.

Few studies have been performed to explore the feasibility of using fisetin in combination with immunotherapy. Though it has been proved that fisetin could block the interaction between PD-1 and PD-L1, the data supporting the synergistic efficacy between fisetin and anti-PD-1 or anti-PD-L1 remained insufficient [264]. So far, the influence of fisetin on the tumor immune microenvironment stayed controversial, with promotion of secretion of cytotoxic cytokine such as IFN-γ and suppression of T lymphocytes observed on different animal models [265, 266]. Besides, fisetin showed a potential as the treatment for an autoimmune disease, systemic lupus erythematosus, further complicating the role of fisetin in immune modulation [267]. Therefore, exploration of the detailed mechanisms involved in the interaction between fisetin and tumor immune microenvironment is essential for the idea of using fisetin as an adjuvant with immunotherapy.

3.4.6 Combination therapy with multiple phytochemicals

It has been well-established that phytochemicals interfere with multiple signaling pathways to achieve the inhibition towards tumor, where the major target for each phytochemical may differ, suggesting potential synergism in the combination of two or more phytochemicals. Besides, due to the tumor-specific cytotoxicity of most phytochemicals, the combination therapy with multiple phytochemicals may hold a promising perspective as an effective and safe anti-tumor strategy. The IC_{50} values of eugenol and amarogentin in HeLa cell line were reduced to half with EGCG at non-toxic concentration (7.5 μM and 10 μM) [268]. In this study, a compromised clonogenic capacity of cancer cells was also observed, without significantly affecting the IC_{50} values in normal cells. A similar effect was achieved in breast cancer cell lines with the combination of grape seed proanthocyanidins and resveratrol at low doses (10 μM and 20 μM) [269]. Similarly, the enhanced inhibition towards cell proliferation and colony formation was only observed in cancer cells (MCF-7 and MDA-MB-231) but not normal cells (MCF-10). However, the apoptosis rate in MCF-7 cells was decreased in spite of the augment in the growth inhibition. Taking the difference in the expression of ERα between MCF-7 (ERα-positive) and MDA-MB-231 (ERα-negative) into account, it may suggest that the booster effect of resveratrol to the therapeutic efficacy of the tested phytochemicals follows an ERα-dependent pattern. In a study about the combination of resveratrol and pterostilbene, the expression of ERα was observed in ERα-negative cells MDA-MB-157 and HCC1806 after incubation with both resveratrol (15 μM) and pterostilbene (5 μM) for 72 h, as a result of the direct inhibition on DNA methyltransferase [270]. Besides, the feasibility of using phytochemical combination to target CSCs was explored as a strategy to impede the metastasis of tumors, since a majority of the reported phytochemicals could interfere with the EMT process. Recently, a PEGylated gelatin-based nanoplatform containing both EGCG and curcumin was evaluated as a CSCs targeting therapeutic agent [271]. In addition to the enhanced anti-metastatic and anti-recurrence efficacy in the orthodox prostate tumor model shown in Fig. 6A, the above-mentioned nanoplatform also exhibited an improved safety profile compared with the mixed administration of EGCG and curcumin, which might be attributed to the preferential accumulation of the nanoparticles in tumor site (Fig. 6B). The drawbacks such as poor stability, uncertain biodistribution and potential drug interactions might all affect the synergism among different phytochemicals, which emphasizes the importance of a suitable co-delivery system and further mechanism study on *in vivo* model for further development of the combination therapy with phytochemicals.

A.



B.

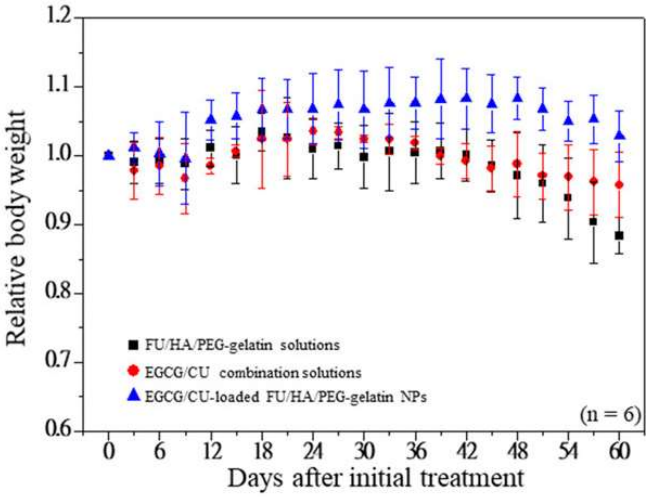


Fig 6. Co-delivery of EGCG and curcumin led to promotion in anti-tumor efficacy and safety profile, A, tumor volume in mice treated with different formulations (FU-HA/PEG-gelatin, blank nanoparticles; EGCG-CU combination solutions, mixed-delivery of EGCG and curcumin; EGCG-CU-loaded FU-HA/PEG-gelatin NPs, co-delivery nanoparticles for EGCG and curcumin); B, body weight of tumor bearing mice treated with different formulations. Reuse with permission [271]. Copyright with ACS. Color should be used for this figure.

4. Advantages, challenges and perspective of combination therapy of conventional anti-cancer drugs and repurposed non-chemo drugs and dietary phytochemicals

4.1 Advantages of the proposed combination therapy

4.1.1 Improved anti-cancer efficacy in various types of cancers

Given the promising results in pre-clinical studies, clinical trials have been performed to legitimate the feasibility of translating the combination therapy of conventional anti-cancer drugs and repurposed non-chemo drugs and dietary phytochemicals into clinical application. As shown in Table 1-3, a multitude of clinical trials have been registered to seek for optimal therapeutic strategies to treat various types of cancer. Results of completed clinical studies demonstrated that reasonable therapeutic outcomes and acceptable toxicities could be achieved by using non-chemo drugs as adjuvants for conventional anti-cancer therapy. For example, the combination of celecoxib and chemotherapy offered significantly prolonged overall survival (14 months in the experimental group compared with

10 months in the control group), progression-free survival (7.5 months in experimental group compared with 5 months in control group), as well as improved quality of life in advanced gastric cancer patients with positive expression of COX-2 without increasing side effects in a preliminary, three center, clinical trial study [272]. Besides, the clinical superiority of metformin as the adjuvant for chemotherapy for the treatment of advanced or metastatic non-squamous non-small cell cancer has been proved by an open-label single-center Phase II study (NCT01578551) [273]. The concurrent administration of metformin with carboplatin, paclitaxel and bevacizumab led to significantly increased overall survival (15.9 months in the experimental group compared with 13.9 months in the control group) and the occurrence of 1-year progression-free survival (47 % in the experimental group compared with 15 % in the control group) without increasing adverse reactions. Improvements in the quality of life and the reduced re-occurrence rate were also observed in the clinical studies of the combination therapy using conventional anti-tumor therapies with repurposed non-chemo drugs or phytochemicals [274, 275]. Conclusions from multiple cohort studies and retrospective studies also suggested an optimistic perspective of using this proposed combination therapy for the effective treatment of different types of cancers [97, 276-279].

4.1.2 Reduced side effect

Compared to conventional anti-cancer agents, repurposed non-chemo drugs and dietary phytochemicals are better tolerated in human body, suggesting a modified safety profile of the proposed combination therapy. A phase III clinical study showed that metformin led to an improvement in the quality of life in patients by alleviating the chronic peripheral sensory neuropathy [280]. In a controlled study, curcumin tempered the prolonged and systemic oxidative and inflammatory effects of cancer treatment [281]. A phase I study and clinical observation demonstrated that indomethacin could ameliorate the fatty acid (75 mg/day) or pain (15.6 ± 3.4 μg/kg) induced by chemotherapy through the amelioration of inflammation [282, 283]. Chemosensitization effect was also observed along with the compromise of side effects in these studies, indicating that the combination therapy of conventional anti-cancer drugs and repurposed non-chemo drugs or dietary phytochemicals holds the potential for an effective therapeutic outcome with reduced side effects.

4.1.3 Reduced cost

A sharp increase in the launch price of novel anti-cancer drugs has been witnessed during the past three decades. As a result, cancer patients nowadays are facing severe financial burden of nearly $12,000 a year for only one drug, according to a recent analysis [284]. To provide a more affordable treatment for patients from middle- or low- income families, repurposing non-chemo drugs could serve as an alternative strategy for the discovery of novel anti-cancer agents [285, 286]. Compared with *de novo* drug development, repurposed drugs exhibited a significant cut-down in the development lifecycle, due to the well-established safety and toxicology profile of the drug candidates [287]. The shorter development period directly contributes to lower economic investment for pharmaceutical companies, leading to reduced costs for patients. Besides, most of the repurposed non-chemo drugs and dietary phytochemicals are either available as generics or at low cost. For example, the annual cost of metformin for patients with type 2 diabetes is usually $300-$1,200 a year, which is much lower than the cost of conventional chemo therapeutics [288]. Therefore, compared to combination therapies of conventional anti-tumor therapeutics, the combination therapies using repurposed non-chemo agents or dietary phytochemicals as adjuvants would serve as a more economic treatment strategy, increasing the chance for patients with poor financial situation to get proper medical care.

4.2 Challenges in the clinical translation of the proposed combination therapy

Though previous studies suggested that the combination of conventional anti-tumor therapeutics and repurposed non-chemo drugs or phytochemicals as a novel combination therapy holds promising perspective for effective, safe, and economical treatment of cancers, several challenges still remain as indispensable hindrance in clinical translation. Here in this section, we will briefly discuss the

potential challenges based on the properties of the above-mentioned repurposed non-chemo drugs or phytochemicals.

4.2.1 Poor bioavailability and the uncertain therapeutic window

Given the complexity of mechanism in the synergy between conventional anti-tumor therapies and repurposed non-chemo drugs or dietary phytochemicals, a controllable accumulation of the active drug in tumor site is necessary for optimal therapeutic outcomes. However, the poor bioavailability may hinder the sufficient accumulation of the above-mentioned drugs. For most NSAIDs and dietary phytochemicals, the extreme hydrophobicity may lead to poor bioavailability, limiting the therapeutic efficacy due to insufficient drug accumulation in tumor sites. Besides, the fast elimination half-life of some hydrophilic drugs may also lead to a poor bioavailability (e.g. captopril, 2 h; resveratrol, 1 - 3h; and EGCG, 3.4 h) [289]. Though metformin manifests relatively high aqueous solubility and slow elimination half-life, the slow absorption may temper its effective accumulation in tumor site for an ideal synergy with conventional anti-tumor agents.

It should be noted that some phytochemicals, such as quercetin, resveratrol, and EGCG, exert a dose-dependent hormesis in the anti-oxidant function [220, 290, 291]. The mechanisms of the synergism with conventional anti-tumor therapeutics, as well as the effect on normal tissue cells, may change as the concentration of phytochemicals increases from anti-oxidant level to pro-oxidant level, leading to uncertainty of therapeutic window. Besides, studies about some phytochemicals (fisetin) concluded a discrepancy of IC_{50} value on the same cancer cell line (A549), further leading to the confusion in the design of a suitable combination strategy [263, 292].

4.2.2 Discrepancy between in vitro study and in vivo study results

The mechanisms involved in the synergism between conventional anti-tumor therapeutics and repurposed drugs or phytochemicals have been validated on *in vitro* level in most previous research. However, it should be noted that the *in vivo* metabolism routine may greatly limit the anti-tumor efficacy of these drugs. For example, both losartan and resveratrol exhibit strong affinity to albumin once in serum, resulting in the uncontrollable drug accumulation in tumor site. Also, several phytochemicals (e.g. resveratrol and EGCG) may affect the activity of cytochromes P450 (CYP450), a major enzyme responsible for the metabolism of multiple drugs. The influence on CYP450 would inevitably alter the pharmacodynamic and pharmacokinetic interaction between the drugs in combination, which could not be precisely reflected by *in vitro* models. The influence on drug metabolizing enzymes also raised safety concerns, which *in vitro* study may failed to elucidate precisely, especially for drugs going through hepatic (e.g. resveratrol, EGCG, losartan, and captopril) or renal clearance (e.g. metformin) [241]. Full-round biodistribution study is necessary for the comprehensive understanding of the safety profile of the proposed combination therapy with conventional anti-tumor therapeutics and repurposed non-chemo agents or dietary phytochemicals.

4.2.3 Potential individual heterogeneity caused by the metabolic status in different patients

Diabetes and hypertension promote the development and progress of cancers by affecting the metabolism of patients [293, 294]. As a result, the metabolic status may affect the anti-tumor efficacy of anti-diabetic or anti-hypertension agents. Previous studies elucidated that the cancer types, comorbidities, as well as patient heterogeneity all affect the anti-tumor outcomes of metformin, losartan, and captopril [129, 295, 296]. Therefore, it remains a necessity as well as a challenge to collect clinical data from patients with different metabolic status for the comprehensive understanding about the feasibility of the clinical application of the proposed combination therapy.

4.3 Potential solution to the existed challenges

Based on the advances in recent research, here in this section, we will briefly discuss the potential solutions to the current challenges in the clinical translation of the combination therapy.

4.3.1 *Design of suitable delivery systems using biocompatible materials*

To achieve the simultaneous delivery of therapeutics into tumor site, as well as to evade the elimination in blood circulation for a facilitated bioavailability, different co-delivery strategies based on various nanoDDS have been fabricated and evaluated [297-299]. As illustrated in Fig. 7, one superiority of co-delivery system is that a precise control over the time/spatial-release of the therapeutics in the combination therapy could be achieved by the design of the polymer structure and the nanoparticle assembly mechanism, leading to maximum synergism.

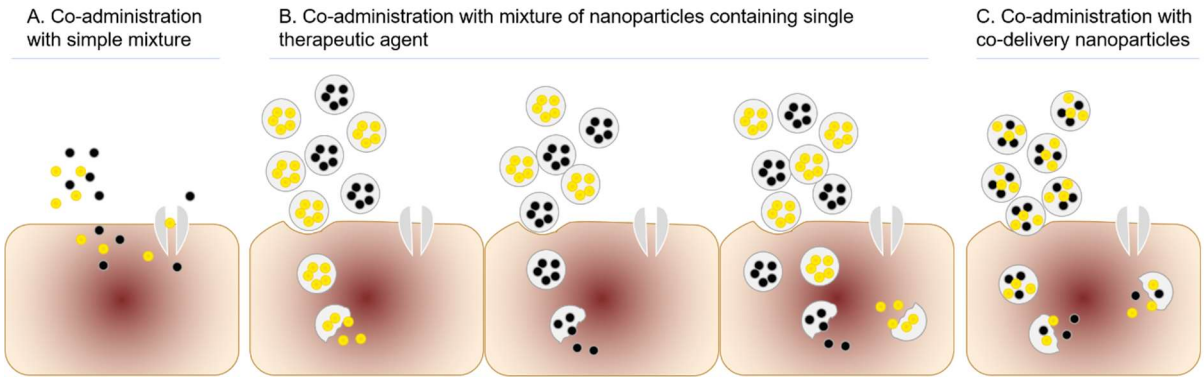


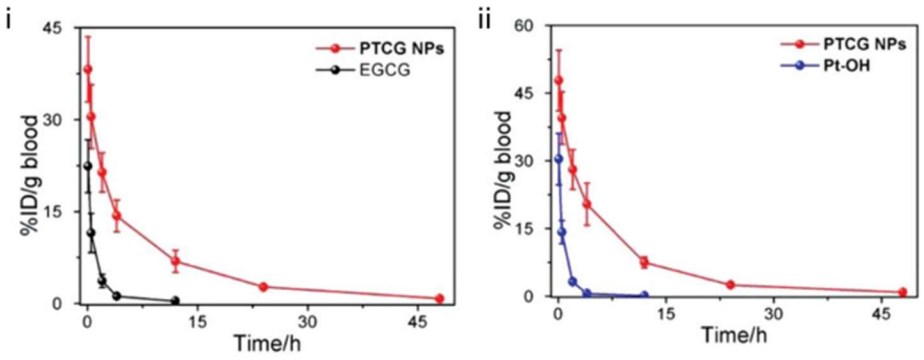
Fig 7. Influence of different co-administration strategies on the synergism of different therapeutic agents. A, for co-administration with the physical mixture of therapeutics, the efflux caused by the transporter would reduce the drug accumulation within cancer cell, resulting in lower therapeutic outcome; B, co-administration with mixture of nanoparticles containing mono-therapeutics may fail to concentrate both therapeutic agents in the same cell, thus resulting in a limited synergistic anti-tumor efficacy; C, co-administration with co-delivery system containing both therapeutics would lead to the accumulation of both drugs in cancer cell according to a well-designed ratio, where a maximum synergy was expected due to the sufficient accumulation of both therapeutic agents in the same target cell. Color should be used for this figure.

As a versatile carrier for various drugs regardless the aqueous solubility, liposomes has been investigated as a co-delivery platform for repurposed drugs or phytochemicals with conventional anti-tumor therapeutics [102, 137, 139, 141, 172, 205, 300]. Because of the enhanced permeability and retention (EPR) effect, the drug accumulation at tumor site would be facilitated using liposomes as carrier, which would be further promoted by using suitable targeting ligand.

The application of biocompatible materials in the fabrication of bio-polymeric nanoparticles/micelles has also been evaluated for efficient co-delivery of therapeutics [223, 224, 301-303]. For precise control of drug release and accumulation in tumor site, strategies including polymeric prodrug, polymeric hydrogel, and self-assembled micelles have all been utilized in the fabrication of co-delivery systems, with promising perspective validated both in cancer cells and in mouse models of various types of tumors [214, 223, 224, 302]. Inorganic materials have also been investigated as the promising carrier for the combination of conventional anti-tumor therapeutics and repurposed drugs or phytochemicals. For example, mesoporous silica nanoparticles (MSNs) showed a promising perspective due to its applicability in encapsulating drugs with different structure and physical properties [251]. Also, the emerging application of using coordination bond in the preparation of nanoparticles provides new strategies in the design of delivery systems for the novel combination therapy, especially for phytochemicals with polyphenol structure. For example, the spatially distant pyrogallol group and galloyl group within the molecular structure of EGCG provides independent coordinating sites for metal ions, suggesting the possibility for the preparation of the co-delivery system through the formation of coordination bonds [241, 304]. A chemodynamic therapy was achieved by using ferric ions as the coordinating agent for the co-delivery of EGCG and a phenolic platinum prodrug with a polyphenol modified block copolymer, leading to superb inhibition towards tumor development both *in vitro* and *in vivo* [305]. It should be noted that the as-prepared co-delivery system (PTCG NPS Group) also led to an alternation in the pharmacodynamics in addition to an augment in the therapeutic efficacy, where prolonged circulation half-life of both EGCG and the platinum prodrug was observed in mice treated with PTCG NPs compared with mice treated with free

EGCG or platinum prodrug Pt-OH (Fig. 8Ai and ii). As illustrated in Fig. 8Bi-v, co-delivery of EGCG and Pt-OH led to an improved safety profile, with no apparent changes in the level of alkaline phosphatase (ALP), aspartate aminotransferase (AST), alanine aminotransferase (ALT), creatinine (CREA), and blood urea nitrogen (BUN) detected in blood from tumor-bearing mice treated with PTCG NPs compared with mice in control group.

A



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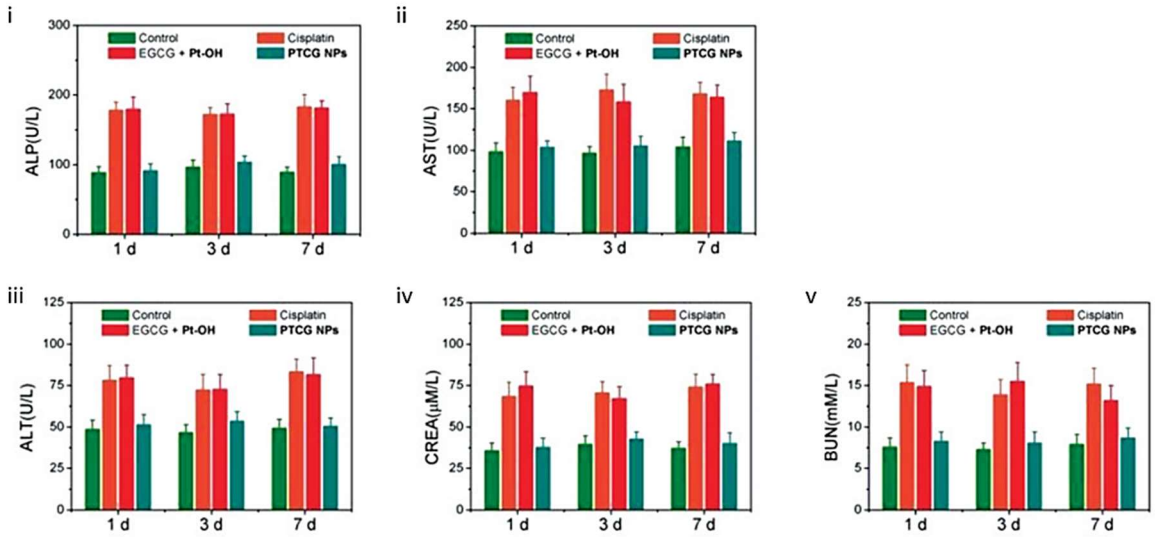

Fig 8. The pharmacodynamics and safety profile of EGCG and platinum-based chemo agent (Pt-OH) were improved by administration with co-delivery nanoparticles. A, the circulation half-life of EGCG i) and Pt-OH ii) was prolonged after being loaded onto the as-prepared nanoparticles PTCG; B, Blood biochemistry tests of ALP i), AST ii), ALT iii), CREA iv), and BUN v) from the mice treated with different formulations, the haemotoxicity of EGCG and Pt-OH could be compromised by loading onto co-delivery nanoparticles. Reuse with permission [305]. Copyright with Wiley-VCH. Color should be used for this figure.

Beyond using different types of nanoparticles including polymers, inorganics, or liposomes as carriers for drug delivery which usually have the problem of low drug loading capacity and may lead to safety concern, another elegant solution is to make nanoparticles directly from drug molecules [306-313].

When developing delivery systems based on nanoparticles, it should be noted that the unsteady reproductivity of nanoparticles might be a hindrance in the scale-up industrial production. Besides, the potential toxicity of the polymeric carriers in the fabrication of nanoparticles/micelles may also bring concerns regarding safety issues. Therefore, the development of biocompatible materials, as well as their application in suitable design of co-delivery system will contribute to the further progress of the combination therapy using conventional anti-tumor agents and repurposed drug or phytochemicals.

4.3.2 Design of suitable in vitro model and emphasis on the in vivo confirmation of the mechanisms

To address the discrepancy between the results of *in vitro* and *in vivo* study, it is vital to design suitable models for *in vitro* studies to better simulate the complex *in vivo* physical conditions. One solution is to reduce the exposure time of cells to therapeutics in *in vitro* study, which was used to mimic the short retention time of most therapeutics in tumor site [314]. Change in the exposure time in the *in vitro* study greatly affected the cytotoxicity of the tested therapeutics, implying that the mechanisms confirmed by *in vitro* study might not be applicable for explanation of *in vivo* pharmacokinetics. To better reflect the *in vivo* physical condition, some alterations in the components of cell culturing medium might also help, such as addition of albumin and enzymes. Also, confirmation of proposed synergetic mechanisms in *in vivo* model has also been performed by previous studies regarding the anti-tumor efficacy of several phytochemicals, which may serve as a feasible strategy to narrow the discrepancy between the results of *in vitro* study and *in vivo* study, contributing to a more precise prediction of clinical pharmacokinetic and pharmacodynamics studies [315].

4.3.3 *Full-rounded study on the influence of metabolic heterogeneity on therapeutic efficacy*

Controversial results have been illustrated by various cohort studies about the adjuvantic efficacy of metformin, ACEIs and ABRs, which might be attributed to the metabolic state of the patients involved in the studies [97, 276, 277, 316-318]. Therefore, it would provide more information to predict the therapeutic efficacy in patients if the pharmacokinetic and pharmacodynamics study is performed on animal models of different metabolic states. Besides, using animals of different metabolic states to perform *in vivo* study could also contribute to a better understanding about the safety profiles of the proposed novel combination therapy, given that several phytochemicals may affect the function of liver and kidney. For clinical study, comparison of therapeutic response among patients with or without metabolic diseases would also generate valuable data for the further development of the combination therapy using conventional anti-tumor therapeutics and repurposed drugs or phytochemicals.

5. Conclusion

As a leading cause of global death, cancer has been proved to be related with various kinds of diseases during its development and progression, which inspired the idea of using drugs with indication other than cancer treatment for prevention or even cure of cancers. With promising results from studies performed on both cellular level and animal level, as well as the chemoprevention effect confirmed in clinic, using repurposed drugs and phytochemicals as adjuvants with conventional anti-tumor therapeutics holds encouraging perspectives for efficient and safe treatment of cancer. Moreover, it would be a cost-friendly way to discover new therapies for cancers, which would increase the reach of proper cancer therapy to patients from low-income regions. It should be noted that there is no significant difference between approval rates of repurposing drugs and innovative drugs, further validating the feasibility of applying repurposing non-chemo drugs for anti-cancer therapies [285]. Recently, the emergence of computational screening greatly accelerated the progress of the rational design of optimal combination of different repurposing therapeutics, which would further reduce the cost and time spent on the discovery of new treatments [319]. By presenting the recent advance of the combination therapies using conventional anti-tumor agents and repurposed drugs or phytochemicals in this review, we aim to raise the awareness of the scientific community to further investigate the mechanisms involved in the synergism, and conduct well-controlled clinical studies, for the development of an affordable therapeutic way to benefit cancer patients worldwide.

Declaration of Competing Interest

The authors declare that there are no conflicts of interest regarding the publication of this article.

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