Anticancer Effects and Mechanisms of Berberine from Medicinal Herbs: An Update Review

Ruo-Gu Xiong 1,*, Si-Yu Huang 1, Si-Xia Wu 1, Dan-Dan Zhou 1, Zhi-Jun Yang 1, Adila Saimaiti 1, Cai-Ning Zhao 2, Ao Shang 3, Yun-Jian Zhang 4, Ren-You Gan 5 and Hua-Bin Li 1,6

1 Guangdong Provincial Key Laboratory of Food, Nutrition and Health, Department of Nutrition, School of Public Health, Sun Yat-sen University, Guangzhou 510080, China; xiongrg@mail2.sysu.edu.cn (R.-G.X.); huangsy9@mail2.sysu.edu.cn (S.-Y.H.); wuxs6@mail2.sysu.edu.cn (S.-X.W.); zhoudd6@mail2.sysu.edu.cn (D.-D.Z.); yangzhj57@mail2.sysu.edu.cn (Z.-J.Y.); saimaiti@mail2.sysu.edu.cn (A.S.) 2 Department of Clinical Oncology, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong 99077, China; zhaocn@connect.hku.hk 3 School of Chinese Medicine, Li Ka Shing Faculty of Medicine, The University of Hong Kong, Hong Kong 99077, China; shangao@connect.hku.hk 4 Department of Thyroid and Breast Surgery, The First Affiliated Hospital of Sun Yat-sen University, Guangzhou 510080, China; zhyunj2@mail.sysu.edu.cn 5 Research Center for Plants and Human Health, Institute of Urban Agriculture, Chinese Academy of Agricultural Sciences, National Agricultural Science & Technology Center, Chengdu 610213, China; ganrenyou@caas.cn 6 Correspondence: lihuabin@mail.sysu.edu.cn; Tel.: +86-20-8733-2391

Abstract: Cancer has been a serious public health problem. Berberine is a famous natural compound from medicinal herbs and shows many bioactivities, such as antioxidant, anti-inflammatory, anti-diabetic, anti-obesity, and antimicrobial activities. In addition, berberine shows anticancer effects on a variety of cancers, such as breast, lung, gastric, liver, colorectal, ovarian, cervical, and prostate cancers. The underlying mechanisms of action include inhibiting cancer cell proliferation, suppressing metastasis, inducing apoptosis, activating autophagy, regulating gut microbiota, and improving the effects of anticancer drugs. This paper summarizes effectiveness and mechanisms of berberine on different cancers and highlights the mechanisms of action. In addition, the nanotechnologies to improve bioavailability of berberine are included. Moreover, the side effects of berberine are also discussed. This paper is helpful for the prevention and treatment of cancers using berberine.

Keywords: berberine; anticancer; mechanism; bioavailability; safety

1. Introduction

According to the WHO report in 2020, there were approximately 19.3 million new cancer cases and nearly 10 million deaths, which were mainly attributed to lung, colorectal, liver, stomach, and breast cancers [1]. Under such circumstances, it is urgent to research the prevention and treatment strategies of cancers. The routine treatments for cancers are surgery, radiotherapy, and chemotherapy, but they showed limited actions with some adverse effects. The anticancer effects of natural products have become a research hotspot, due to their low or non-toxicity. Many studies showed that natural compounds from fruits, vegetables, tea, coffee, spices, and medicinal plants could play an important role in the prevention and treatment of cancers with different mechanisms of action [2–9].

Berberine is a famous natural compound and exists in some medicinal herbs [10,11]. The chemical structure of berberine is shown in Figure 1. Berberine shows many bioactivities, such as antioxidant, anti-inflammatory, cholesterol-lowering, anti-diabetic, anti-obesity, and antimicrobial activities [10,12–14]. In addition, its anticancer effects and mechanisms have been widely studied, and the results showed that berberine could be a promising treatment option for cancer.
agent for the prevention and treatment of various cancers, such as breast, lung, gastric, liver, colorectal, ovarian, cervical, and prostate cancers [15–19]. We collected literature from the PubMed and Web of Science databases since 2016 year. This review summarizes effects and mechanisms of berberine on various cancers, and a special attention is paid to its mechanisms. The bioactivities of berberine, including anticancer activity, have been a research hotspot. Therefore, many review papers on berberine have been published in the literature from different points of view [20–23]. This paper is an updated review on anticancer effects and the mechanisms of berberine, and it highlights anticancer activity through targeting antibacterial action, including regulating gut microbiota and inhibiting intratumoral microbes. Now, people consider that the compounds from medicinal herbs exhibit anticancer activity by antioxidant and anti-inflammatory mechanisms. We hope that the compounds from medicinal herbs will attract more attention for their anticancer activity by antibacterial mechanism, and this paper could be very helpful.

![Figure 1. The chemical structure of berberine.](image)

2. Effects of Berberine on Cancers

2.1. Breast Cancer

Breast cancer is a threatening malignant tumor worldwide, with the leading morbidity in females [24,25]. Triple negative breast cancer (TNBC) is one of the most aggressive subtypes in breast cancers [26]. Chronic inflammation is closely related to tumor initiation and progression, and both interleukin-6 (IL-6) and tumor necrosis factor (TNF) are the important indicators of tumor-associated inflammation [27]. One study showed that berberine could suppress TNBC by increasing lactate dehydrogenase (LDH) release from TNBC cell lines, and reducing the secretion of proinflammatory cytokines, TNF-α, IL-1α, IL-1β, and IL-6 [26].

The uncontrolled proliferation of cells is one of the main characteristics of cancer. A study showed that berberine inhibited breast cancer cell proliferation and decreased cell viability [28]. Another study showed that high-expressed metadherin was helpful to cancer cell proliferation, while berberine reduced metadherin and inhibited cancer cell proliferation [25]. In addition, berberine induced TNBC cell cycle arrest under low concentration, but did not injure the normal human breast cells [29]. Moreover, berberine inhibited MDA-MB-468 cells proliferation and induced cell cycle arrest at the G1/S phase by inhibiting the cell cycle kinase complex cyclin D/cyclin-dependent kinase 4 (CDK4), as well as activating the cell growth inhibitor p38 [30]. Berberine also inhibited MDA-MB-231 cells proliferation and induced cell cycle arrest at the G2/M phase by inhibiting the cell cycle kinase complex cyclin A/CDK1 and cell growth-related AKT/ERK pathways [30].

Berberine could suppress breast cancer cell invasion and metastasis through several pathways. For example, berberine could decrease cell migration through downregulating levels of several key chemokine receptors in MCF-7 breast cancer cells, such as chemokine receptor 6 (CCR6) and CCR9 [31]. For MCF-7 and MDA-MB-231 cells, berberine could suppress cell migration by upregulating microRNA (miR)-214-3p and reducing the level of its target secretin (SCT) [32]. Moreover, fibronectin is one of the most abundant extracellular matrix glycoproteins, which is related to cancer cell invasion and metastasis. Berberine could inhibit cell invasion and migration through decreasing fibronectin expression in TNBC cells via inhibiting activator protein 1 (AP-1) activity [33].
Apoptosis could contribute to cancer cell death, which is beneficial to the prevention and treatment of cancers [34]. High-dose berberine (80 µM) directly induced breast cancer cell apoptosis via the AMPK-p53 signaling pathway [35]. Another study showed that berberine inhibited breast cancer cell growth and induced cell death via inducing the nuclear stress response and upregulating p53 [36]. Moreover, berberine induced breast cancer cell apoptosis and G2/M arrest by upregulating miR-214-3p expression [32]. In addition, p21/cip1 and p27/kip1 were important regulators of the cell cycle, while berberine could upregulate levels of p21/cip1 and p27/kip1, as well as increase their nuclear localization and post-translational protein stability via downregulating Akt, and then elevate cell cycle arrest and induce breast cancer cell apoptosis [37].

Berberine could also enhance the anticancer effects of other anticancer drugs. For example, one study revealed that berberine could moderate the X-ray cross complementing group 1 protein (XRCC1)-mediated base excision repair to enhance the sensitivity of cancer cells to chemotherapeutic drugs, such as cisplatin, camptothecin, and methyl methanesulfonate [38]. Another study indicated that the combination of berberine with emodin synergistically inhibited breast cancer cell growth via inhibiting salt-inducible kinases 3 (SIK3) activity and induced G0/G1 phase cell cycle arrest and apoptosis of breast cancer cells by attenuating Akt signaling [39]. In addition, the combination of berberine with chemotherapeutic drugs (cisplatin and 5-fluorouracil) showed synergistic effects on suppressing breast cancer cell proliferation, thus inducing apoptosis and inhibiting cell migration [40,41]. Anyway, berberine could reverse the multidrug resistance of breast cancer by suppressing the efflux function of ATP-binding cassette transporters [42].

A study comprehensively analyzed the intratumoral microbiome, including breast, lung, ovary, pancreas, melanoma, bone, and brain tumors, and found that each tumor type had a distinct microbiome composition, and breast cancer showed a particularly rich and diverse microbiome [43]. Another study found that tumor-resident microbiota played an important role in promoting metastatic colonization in breast cancer [44]. In addition, Helicobacter hepaticus could translocate from the intestine to breast tissues and promote the progression of breast cancer [45]. On the other hand, berberine is widely used as an antimicrobial drug for the treatment of diarrheal infection [46,47] and shows antimicrobial activities against several microorganisms, such as Helicobacter pylori, Candida albicans, and Klebsiella pneumoniae [48–51]. Therefore, we could speculate that berberine might play the anticancer role via inhibiting intratumoral microbes and regulating gut microbiota.

In brief, the related mechanisms of berberine against breast cancer mainly involve inhibiting inflammation, decreasing cell proliferation, suppressing metastasis, and inducing apoptosis. Moreover, the combination of berberine and chemotherapeutic drugs, such as cisplatin, camptothecin, 5-fluorouracil, and methyl methanesulfonate, has a promoting effect in the prevention and management of breast cancer. In addition, berberine possibly exerts anticancer effect via inhibiting intratumoral microbes and regulating gut microbiota, which should be paid special attention in future studies.

2.2. Lung Cancer

Lung cancer is the leading cause of cancer death, and non-small-cell lung cancer (NSCLC) is its most common type [52,53]. Several studies indicated that berberine could inhibit the proliferation of lung cancer cells. For example, berberine suppressed NSCLC cell proliferation and colony formation [54]. Another study showed that berberine inhibited the A549 cells proliferation via matrix metalloproteinase 2 (MMP-2)/Bcl-2/Bcl-2-associated X protein (Bax) and Janus kinase 2 (Jak2)/vascular endothelial growth factor (VEGF)/nuclear factor κB (NF-κB)/AP-1 signaling pathways [55]. Additionally, berberine arrested the cell cycle at G1 phase via the Akt/CREB signaling axis and suppressed lung cancer cell proliferation via inhibiting the proliferative kinase signaling [56]. Another study showed that berberine inhibited NSCLC cell growth via suppressing DNA repair and replication both in vitro and in vivo [57]. Anyway, berberine suppressed tumor growth of human NSCLC xenografts in vivo via SWI-independent-3 transcription regulator family mem-
ber A (Sin3A)/topoisomerase II β (TOP2β) pathway [54]. Moreover, berberine induced NSCLC cell apoptosis by inducing DNA damage via downregulation of TOP2β level [54]. Furthermore, berberine promoted NSCLC cell apoptosis through the miR19a/TF/MAPK signaling pathway [58]. Berberine could also induce NSCLC cell apoptosis via activating the ROS-mediated apoptosis signal-regulating kinase 1/JNK and mitochondrial apoptotic pathways [59].

Berberine could increase the anticancer effect of tyrosine kinase inhibitors against lung cancer. For instance, the combination of berberine with icotinib showed a synergistic inhibiting effect on H460 and H1299 cells by inducing autophagic cell death and suppressing cancer cell migration and invasion [60]. In addition, the combination of berberine and gefitinib synergistically suppressed epithelial-mesenchymal transition (EMT) by regulating the expression of miR-34a-5p and HOX transcript antisense intergenic RNA (HOTAIR) [61]. Berberine could also decrease osimertinib acquired resistance caused by MET gene amplification, therefore enhancing its potency [15].

In short, berberine could prevent and manage lung cancer through several mechanisms, such as inhibiting cell proliferation, inducing apoptosis, and enhancing anticancer activities of tyrosine kinase inhibitors. The related pathways involved MMP-2/Bcl-2/Bax, Jak2/VEGF/NF-κB/AP-1, Akt/CREB, Sin3A/TOP2β, and miR19a/TF/MAPK signaling pathways. More mechanisms of berberine against lung cancer should be explored in the future.

2.3. Gastric Cancer

Gastric cancer is one of the most common cancers in the world [62,63]. Several studies showed that berberine could restrain gastric cancer via different pathways. For instance, berberine inhibited SGC-7901 cells proliferation and induced cell cycle arrest at the G1 phase [64]. Another study showed that berberine inhibited cancer cell proliferation and reduced IL-8 secretion via deactivating the MAPK signaling pathway in vivo and in vitro [65]. In addition, the epidermal growth factor receptor (EGFR) is overexpressed in gastric cancer and positively related to poor clinical outcomes. Berberine inhibited the activation of signal transducer and activator of transcription 3 (STAT3) by suppressing the phosphorylation of EGFR, subsequently downregulating the expression of apoptosis and cell cycle related proteins, such as Bcl-xL and cyclin D1 [66]. The anticancer potential of berberine could also involve activating autophagy. One study showed that berberine induced BGC-823 cells autophagy via the inhibition of the mTOR, Akt, and MAPK pathways [67]. Anyway, a study revealed that berberine influenced cancer-related pathways via modulating the expression of circular RNA ( circRNA) and their corresponding target genes, in such a way to inhibit the gastric cancer progression [68]. Furthermore, berberine could sensitize gastric cancer cells to cisplatin, and the potential mechanism might relate to enhancement of apoptosis, suppression of PI3K/AKT/mTOR signaling, and upregulation of miR-203 expression [69,70]. Berberine also had synergistic effect with erlotinib and cetuximab through enhancing cancer cell apoptosis and cell cycle arrest [66]. Moreover, berberine could increase the anticancer effect of evodiamine (EVO), a natural product, via reducing the upregulation of IL-8 induced by EVO [65].

In general, berberine exhibits good anticancer activity to gastric cancer, and the main mechanisms of action include inhibiting cancer cell proliferation, activating autophagy, and enhancing anticancer activities of other anticancer drugs, such as cisplatin, erlotinib, and EVO. These findings suggest that berberine has potential in the prevention and treatment of gastric cancer.

2.4. Liver Cancer

Liver cancer is one of the most common causes of cancer deaths [71,72]. The anticancer effects and mechanisms of berberine on liver cancer have been widely studied. A study showed that berberine suppressed Hep3B and BEL-7404 cell proliferation by inhibiting glutamine uptake via suppressing SLC1A5 (a glutamine transporter) in vitro, and it could
inhibit the tumor xenografts growth in vivo and reduce the expression of SLC1A5 [73]. Moreover, berberine in high concentrations could inhibit HepG2 cells proliferation and induce cell cycle arrest at G1 phase, and it could arrest HepG2 cell cycle at the S phase in low concentrations [74]. Anyway, berberine upregulated the intracellular ROS level, downregulated mitochondrial membrane potential, and then caused cancer cell apoptosis [74]. Moreover, berberine showed synergistic effect with other antitumor drugs. For example, the combination of berberine and sorafenib synergistically inhibited liver cancer cell proliferation and induced cell apoptosis [75]. Furthermore, berberine could prevent liver cancer by inhibiting the progression of several precursor steps, such as alcoholic fatty liver disease and non-alcoholic steatohepatitis (NASH), through modulating gut microbiota [71,76]. For example, berberine alleviated NASH by increasing the intestinal farnesoid X receptor (FXR) and fibroblast growth factor 15 (FGF15) via modulating gut microbiota, especially increasing the relative abundance of Clostridiales, Lactobacillaceae, and Bacteroidales [77]. Berberine also modulated gut flora, such as increasing the abundance of Akkermansia muciniphila, to exert the hepatoprotective effect in alcoholic liver disease [78].

Overall, berberine has a preventive effect on liver cancer by inhibiting the progression of several liver cancer precursor steps via modulating gut microbiota, and it shows anticancer effects via inhibiting liver cancer cell proliferation, inducing apoptosis, and increasing the anticancer activities of other antitumor drugs.

2.5. Colorectal Cancer

Colorectal cancer (CRC) is one of the most common malignant tumors and became the world’s fourth most lethal cancer [79,80]. One study showed that berberine inhibited colon cancer HCT116 and HT29 cells proliferation via decreasing cyclin D1 and increasing p27 and p21, thereby inducing cell cycle arrest at G1/G0 phase [81]. Another study indicated that berberine inhibited the colon cancer cell proliferation via regulating β-catenin in a dose- and time-dependent manner [82]. Berberine also suppressed β-catenin function by binding to a unique region in nuclear receptor retinoid X receptor α (RXRα), and then inhibited colon cancer cell proliferation [83]. Anyway, β-catenin transcriptionally inhibited fat mass and obesity-associated protein (FTO) via binding to its promoter region, and berberine could downregulate m6A methylation via decreasing β-catenin and increasing FTO [81]. Moreover, berberine inhibited colon cancer cell proliferation via modulating mitochondrial translation and ribosome biogenesis, as well as promoting calcium mobilization and fat-soluble vitamins metabolism [84]. In addition, CRC proliferation was related to elevating telomerase level and activity. Berberine could downregulate the activity of telomerase in HCT 116 cells and inhibit the CRC proliferation eventually [85]. Berberine could also modulate lipogenesis by targeting the SREBP cleavage-activating protein/sterol regulatory element-binding protein-1 (SCAP/SREBP-1) pathway, and then inhibiting colon cancer cell proliferation [86,87]. Additionally, berberine inhibited colon cancer cell metastasis by suppressing lipogenesis via promoting promyelocytic leukaemia zinc finger (PLZF)-mediated SCAP ubiquitination [88].

A total of 40 µM of berberine induced colon cancer HCT116 and HT29 cells apoptosis [81]. Berberine also suppressed the SW480 cells migration and apoptosis by inhibiting glucose-regulated protein 78 (GRP78) expression and upregulating the cytokeratin expression [89]. For HCT116 cell line, berberine suppressed CRC viability, induced cell apoptosis, activated caspase-3 activity, and downregulated miR-21 expression, as well as promoting the expression of integrinβ4 (ITGβ4) and programmed cell death 4 (PDCD4) protein [90]. Anyway, berberine induced cell apoptosis via modulation of long non-coding RNA (lncRNA)/cancer susceptibility candidate 2 (CASC2)/AU-biding factor 2 (AUF1)/B-cell lymphoma 2 (Bcl-2) axis [91].

Bile acids (BAs) upregulation is a risk factor for colorectal cancer, and berberine downregulated BAs via modulating intestine bacteria [92,93]. Moreover, berberine could exert an anticancer effect by increasing the ratio of Firmicutes/Bacteroidetes, thus decreasing the abundance of cancer-related bacteria and improving intestinal barrier function [94].
Furthermore, berberine could inhibit the development of azoxymethane/dextran sodium sulfate-induced precancerous lesions, such as crypt destruction, inflammatory cell infiltration, and tumor formation, which indicated that berberine could prevent the occurrence of colorectal cancer [94]. Furthermore, berberine in combination with some other natural products might synergistically promote the anti-tumorigenic properties in CRC. For instance, the combination of berberine and oligomeric proanthocyanidins synergistically induced CRC cell apoptosis via the downregulation of the expression of MYB in the PI3K-Akt signaling pathway [95].

In a word, berberine has inhibitory effects on colorectal cancer, and the main mechanisms involved inhibiting cancer cell proliferation, inducing apoptosis, and modulating intestinal bacteria. Furthermore, most current studies focus on the role of berberine in inhibiting colorectal cancer cell proliferation and inducing apoptosis, while its roles in other anticancer mechanisms, such as suppressing migration, anti-inflammation, and inducing autophagy, need to be further explored in the future.

2.6. Ovarian Cancer

Ovarian cancer is a common cancer in women, and a global health problem [96]. The Warburg effect (aerobic glycolysis) is catalyzed by rate limiting enzymes, and provides energy and nutrition to cancer cell proliferation, which helps cancer cells escape from the immune system. Berberine suppressed the Warburg effect by increasing ten-eleven translocation (TET3)-related demethylation and upregulating miR-145, which could inhibit tumor cell proliferation and invasion [97]. In addition, one study showed that transcriptional factor GLI1 aggravated cancer cell migration and cancer stem cell (CSC)-like characteristics, while berberine could downregulate CSC-like characteristics and reverse EMT by inhibiting chemotherapy-activated GLI1/BMI1 signaling pathway [98]. Moreover, the EGFR or ERBB2 overexpression could cause resistance to ovarian cancer cell death and increase tumor-initiating capacity [99]. The evidence suggested that berberine consumed EGFR and ERBB2 in ovarian cancer cells and inhibited the activation of EGFR and ERBB2 downstream targets cyclin D1, MMPs, and VEGF via the EGFR-ERBB2/PI3K/Akt signaling pathway [100].

Berberine could enhance the anticancer effects of other anticancer drugs against ovarian cancer. For example, the combination of berberine and cisplatin synergistically induced ovarian cancer cell death by inducing cancer cell apoptosis via the caspase-dependent and RIPK3-MLKL pathways [101]. Another study showed that berberine could reverse the chemotherapeutic drug VP16-induced repopulation of ovarian cancer cells via blocking the independent phospholipase A2 (iPLA2)-arachidonic acid (AA)-cyclooxygenase-2 (COX-2)-prostaglandin E2 (PGE2) pathway and reversing the increased phosphorylation of focal adhesion kinase (FAK) [102]. Berberine could also sensitize ovarian cancer cells to niraparib by inducing oxidative DNA damage and inhibiting homologous recombination repair [103].

In summary, berberine could prevent and treat ovarian cancer by inhibiting cancer cell proliferation, suppressing migration, inducing cancer cell death, and enhancing the anticancer effects of other drugs against ovarian cancer. More anticancer mechanisms of berberine on ovarian cancer should receive attention in the future, such as modulating gut microbiota.

2.7. Cervical Cancer

Cervical cancer is the fourth leading female malignancies all over the world [104]. Berberine could inhibit cancer cell viability and suppress tumor growth in cervical cancer. For example, berberine decreased cervical cancer cell viability, inhibited cell migration and invasion, suppressed EMT, and induced cell apoptosis via suppression of keratin (KRT) 17 expression [105]. Moreover, berberine could reduce SiHa cells invasion and migration by reducing transcriptional activities of MMP-2 and urokinase-type plasminogen activator (u-PA), reversing EMT, upregulating E-cadherin, and inhibiting several mesenchymal
markers, such as N-cadherin and snail-1 [106]. Additionally, berberine increased GADD153 expression by inducing ROS production, and subsequently led to mitochondria dysfunction followed by activating caspase-3 and cytochrome C release, which then resulted in cervical cancer cell apoptosis [106]. Berberine could also reduce tumor-induced angiogenesis through downregulating VEGF [106]. Furthermore, berberine was a potential adjuvant for other anticancer therapy of cervical cancer. For example, the combination of berberine and matrine synergistically inhibited cervical cancer cell proliferation, triggered cell apoptosis, and induced cell cycle arrest at G1 phase [107]. Berberine could also overcome the radioresistance caused by low-glucose and hypoxia in the radiotherapy of cervical cancer via regulating the glucose metabolism through PI3K/HIF-1 pathway [108].

Overall, berberine has significant anticancer effect on cervical cancer. The mechanisms of action include decreasing cervical cancer cell viability, inhibiting cell migration and invasion, and inducing cell apoptosis. In addition, berberine could also overcome the radioresistance to enhance the anticancer effect of radiotherapy.

2.8. Prostate Cancer

Prostate cancer is the fifth leading cause of cancer mortality in men [4,109]. A study showed that berberine inhibited cell proliferation and triggered cell apoptosis of 22RV1 prostate cancer cells, and downregulated the expression of androgen receptor (AR), prostate-specific antigen (PSA), COX-2 and Bcl-2, and subsequently inhibited xenograft tumor growth in vivo [110]. Anyway, berberine induced cell apoptosis and inhibited cell proliferation in prostate cancer cell lines via suppressing androgen receptor signaling pathway [111]. Moreover, berberine suppressed the intracellular androgen synthesis via inhibiting the aldo-keto reductase family 1 member C3 (AKR1C3) enzyme activity, and then inhibited prostate cancer cell growth [112]. Berberine also arrested cell cycle at G1 phase and inhibited cell growth in a dose-dependent manner via inhibiting the activation of EGFR [113]. In addition, berberine inhibited prostate cancer cell invasion and migration by downregulating several EMT-related genes, such as platelet-derived growth factor receptor-beta (PDGFRB), collagen, type I, alpha 2 (COL1A2), and bone morphogenetic protein 7 (BMP7) [114]. Furthermore, hypoxia inducible factor-1α (HIF-1α) and its downstream target genes, such as VEGF, could regulate the cell response to hypoxia, and might confer resistance to radiotherapy of prostate cancer. Berberine could increase radiosensitivity of prostate cancer cells through inhibiting the expression of HIF-1α and VEGF, which indicated that it could be an adjuvant in radiotherapy of prostate cancer [115].

Generally, berberine exhibits anticancer activity on prostate cancer both in vitro and in vivo. The mechanisms include inhibiting cancer cell proliferation, suppressing migration, arresting cell cycle, and inducing cell apoptosis. Additionally, berberine could be an adjuvant to enhance the sensitivity of radiotherapy.

2.9. Other Cancers

Except for cancers mentioned above, berberine also shows anticancer effects on other cancers, such as pancreatic, bladder, endometrial, esophageal, osteosarcoma, neuroblastoma, and hematopoietic cancers (Table 1). For example, STAT3 was a treatment target for bladder cancer therapy, and the anti-bladder cancer effects of berberine might involve disturbing the AK2-STAT3 signaling pathway via upregulation of miR-17-5p [19]. Anyway, berberine had synergistic effects with several chemotherapeutic drugs of bladder cancer, such as epirubicin and gencitabine [116,117]. Moreover, an both in vitro and in vivo study showed that berberine inhibited endometrial cancer cell migration via miR-101/COX-2/PGE2 signaling pathway [118]. In addition, berberine decreased pancreatic cancer cell viability and inhibited cell migration by regulating citrate metabolism and transportation in cell mitochondria [119]. Berberine could also stimulate hematopoietic cancer cell apoptosis to exert its anticancer effect [120]. Additionally, berberine inhibited esophageal cancer cell growth by arresting cell cycle at G2 phase and inducing cell apoptosis, as well as the related mechanisms involved Akt, mTOR/p70S6K and AMPK signaling pathways [121]. Furthermore, the
Table 1. Effects and mechanisms of berberine on several cancers.

| Study Types                  | Models                                                                 | Dosages                          | Effects and Mechanisms                                                                 |
|------------------------------|------------------------------------------------------------------------|----------------------------------|----------------------------------------------------------------------------------------|
| Breast cancer                |                                                                        |                                  |                                                                                         |
| In vitro                     | MCF-7 and MDA-MB-231 cells                                            | 0, 1, 10, 50, 100, and 200 µM    | Inhibit proliferative ability of breast cancer cells by reducing metadherin             |
| In vitro                     | MCF7 and MCF12A cells                                                 | 1, 10, and 100 µM                | Induce the nuclear stress response                                                      |
| In vitro                     | MCF-7 and MDA-MB-231 cells                                            | 25 and 50 µM                     | Upregulate the p53                                                                      |
| In vitro                     | MDA-MB-468, MDA-MB-231, HCC70, HCC38, HCC1937, HCC1143, BT-20, and BT-549 cells | 0.5 and 1 µM                     | Induce cell cycle arrest                                                               |
| In vitro                     | MDA-MB-231 cells                                                      | 2.5, 5, 10, 20, 40, 60, 80, 100 µg/mL | Reduce cell viability                                                                 |
| In vitro                     | MDA-MB-231, MDA-MB-468, MDA-MB-453, and BT-549 cells                 | 25 and 50 µM, 12.5, and 25 µM; MDA-MB-453: 0, 2.5, 5, and 10 µM; MDA-BT-549 cells: 0, 5, 10, and 20 µM | Decrease fibronectin expression through inhibition of AP-1 activity                    |
| In vivo                      | Canine mammary gland carcinoma cell line                             | 10, 25, 50, 100 and 200 µM       | Inhibit cell proliferation                                                              |
| In vitro                     | MCF-7/MDR cells                                                      | 5, 10, 20 µmol/L                 | Decrease cell viability                                                                |
| In vitro                     | MCF-7 cells                                                           | 10, 20, 40, and 80 µg/mL         | Decrease cell migration through downregulation of several chemokine receptors          |
| In vitro                     | MCF-7, T47D, MDA-MB-468, and MDA-MB-231 cells                        | Berberine: 0–40 µM; emodin: 0–40 µM | Inhibit cell growth via inhibiting SIK3 activity                                          |
| Colorectal cancer            |                                                                        |                                  |                                                                                         |
| In vitro                     | HCT116 cells                                                          | 1, 10 and 100 µM                 | Regulate the three-gene network                                                        |
| In vitro                     | CACO2 and LOVO CRC cell lines                                        | 0, 10, 20, 40, 60, 80 µM         | Inhibit mitochondrial protein synthesis, TCA, and respiratory electron transportation |
| In vitro                     | SW480 and HT-29 cells                                                | 0, 20, 50, 100, 200, and 300 µM  | Upregulate cytokeratin expression                                                       |
| In vitro                     | SW480 and HT-29 cells                                                | 0, 25, 50, 100, 200, 400 and 800 µM | Induce cell cycle arrest at G0/G1 phase                                                 |
| In vitro                     | HT29 and HCT116 cells                                                | 0, 10, 20, 40, 60, 80, 100 µM    | Induce cell apoptosis via modulation of lncRNA CASC2/AUF1/Bcl-2 axis                   |
| In vitro                     | HCT 116 cells                                                        | 10.54 µg/mL                      | Decrease the activity and the level of telomerase                                       |
| In vitro                     | DLD-1 and Caco-2 cells                                               | 6.25, 12.5, 25, 50 µM            | Induce cell cycle arrest at G0/G1 phase                                                 |
| In vitro                     | KMI2C cell                                                            | 6.25, 12.5, 25, 50 µM            | Induce cancer cell apoptosis                                                          |
| In vivo                      | BALB/c nude mice                                                     | 10 mg/kg                         | Downregulate miR-429 expression                                                        |
| In vitro                     | Colorectal cancer tissues                                            | 4, 8, 16 µM                      | Regulate the three-gene network                                                        |
| In vitro                     | HCT116 and HT29 cells                                                | 10, 20, and 40 µM                | Decrease mRNA expression and protein levels of SCT                                       |
| In vitro                     | BALB/c nude mice                                                     | 5, 10, or 20 mg/kg               | Induce cell cycle arrest at G0/G1 phase                                               |
| In vivo                      | HT-29, HCT116, and SW620 cell lines                                  | 2, 10, and 50 µM                 | Induce cell proliferation via inhibiting β-catenin                                     |
| In vivo                      | C57BL/6 nude mice                                                    | 5 and 50 mg/kg                   | Decrease β-catenin expression                                                          |
| In vivo                      | C57BL/6 male mice                                                    | 7.5 and 15 mg/kg                 | Decrease the ratio of Firmicutes/Bacteroidetes                                          |
| In vitro                     | HCT-8, HCT-116, and HT-29 cells                                       | 6.25, 12.5, 25, 50 µM            | Decrease the abundance of cancer-related bacteria                                      |
|combination of berberine with galangin synergistically inhibited cell growth, arrested cell cycle at G2/M phase, and induced cell apoptosis in esophageal cancer cells [122]. Berberine also upregulated p38-MAPK via downregulation of PI3/Akt and Ras-Raf-ERK signaling, and subsequently reversed the EMT in neuroblastoma cells [123]. Another study showed that the combination of berberine and cisplatin synergistically induced cell cycle arrest at G0/G1 phase and cell apoptosis in osteosarcoma cells via the MAPK pathway [124].
| Study Type       | Models                                           | Dosages                  | Effects and Mechanisms                                                                 | Ref.     |
|------------------|--------------------------------------------------|--------------------------|----------------------------------------------------------------------------------------|----------|
| **Gastric cancer** |                                                  |                          |                                                                                        |          |
| In vitro        | AGS and HGC27 GC cells                           | 0, 20, 50, 80 µM         | Decrease cell viability; Inhibit cell proliferation; Modulate circRNA expression and their corresponding target genes | [68]     |
| In vitro        | SGC-7901 cells                                   | 2.5, 5, 10, 20, and 30 µM | Induce cell cycle arrest at G1 phase; Induce apoptosis; Induce autophagy                | [64]     |
| In vitro        | BGC-823 cells                                    | 14, 21, 32, 48, 72, and 108 µM | Induce cytostatic autophagy via inhibition of mTOR, Akt, and MAPK (ERK, JNK, and p38) pathways | [67]     |
| In vitro        | SGC-7901, BGC-823, SGC-7901/DDP, and BGC-823/DDP cells | Berberine: 10 µM; cisplatin: 2, 4, 8, 16, 32, 64 µg/mL | Increase cisplatin sensitivity cancer cells by upregulating miR-203 expression; Inhibit the activation of STAT3 via inhibiting the phosphorylation of EGFR | [70]     |
| In vitro        | MKN45, BGC823, and SGC7901 cells                 | Berberine: 15 to 90 µM; cetuximab: 0.03, 0.06, 0.13, 0.25, 0.50, 1.00, 2.00 mg/mL | Downregulate the expression of Bcl-XL and cyclin D1; Synergistic effect with erlotinib and cetuximab | [66]     |
| In vitro        | BALB/C-nu/nu nude mice                           | Berberine: 50 mg/kg; cetuximab: 0.8 mg/mouse/day | Induce cytostatic autophagy via inhibition of mTOR, Akt, and MAPK pathways; Induce apoptosis; Induce autophagy | [67]     |
| In vivo         | MGC 803 cells                                    | 0, 7.5, 15, 30 and 60 µM | Induce IL-8 secretion; Deactivate MAPK signaling pathway; Reduce tumor weight and volume; Reduce tumor weight and volume | [65]     |
| In vitro        | BALB/C nude mice                                 | 15 mg/kg                 | Enhance the growth inhibitory activity of cetuximab; Inhibit EGFR signaling; Inhibit cell proliferation | [66]     |
| **Hepatic cancer** |                                                  |                          |                                                                                        |          |
| In vitro        | Hep3B and BEL-7404 cells                         | 12.5, 25, 50, 75, 100 and 125 µM | Suppress cell proliferation by inhibiting glutamine uptake via suppressing SLC1A5; Suppress xenografts tumor growth; Reduce SLC1A5 expression; Inhibit cell proliferation | [73]     |
| In vivo         | BALB/C nude mice                                 | 20 mg/kg                 | Induce cell cycle arrest at G1 and S phase; Upregulate the intracellular ROS level; Downregulate mitochondrial membrane potential | [73]     |
| In vitro        | HepG2 and HUVEC cells                            | 0.0625 to 8 mg/mL        | Enhance inhibitory activity against the growth of MET-amplified osimertinib-resistant tumors; Suppress cell proliferation via inhibiting proliferative kinase signaling | [56]     |
| **Lung cancer**  |                                                  |                          |                                                                                        |          |
| In vitro        | A549, PC9, H460, H1299, Beas-2b, and 293T cells  | 0, 20, 40, 80, 120, and 160 µM | Induce cell apoptosis through mir19a/TF/MAPK signaling pathway; Promote cell apoptosis by inducing DNA repair and replication | [58]     |
| In vitro        | A549, H1299, and H1975 cells                     | 0, 60, 120 µmol/L        | Inhibit cancer cell growth via suppressing DNA repair and replication; Enlarge tumor necrosis area | [57]     |
| In vivo         | C57BL/6 mice                                     | 200 mg/kg                | Inhibit cell proliferation through MMP-2, Bcl-2/Bax and JAK2/VEGF/NF-κB/AP-1 signaling pathways | [55]     |
| In vitro        | A549 cells                                       | 0, 30, 60, 90, 150 and 200 µM | Suppress the proliferation and colony formation of cancer cells; Induce cell apoptosis by inducing DNA damage via downregulating the level of TOP2β | [54]     |
| In vitro        | NCI-H460, A549 and NCI-H1299 cells               | 10, 20, 40 and 80 µM     | Inhibit tumor growth by deregulating Sn3A/TOP2β pathway; Help osimertinib overcoming the acquired resistance caused by MET gene amplification | [54]     |
| In vivo         | BALB/c nude mice                                 | 25 mg/kg                 | Inhibit tumor growth; Induce cell apoptosis via activation of the ROS/ASK1/JNK pathway | [56]     |
| In vivo         | EGFRm NSCLC cell lines and their derived resistant cell lines | Berberine: 12.5, 25, 50, 100, 200 µM; Osimertinib: 31.25, 62.5, 125, 250, 500 nM | Enhance inhibitory activity against the growth of MET-amplified osimertinib-resistant tumors; Arrest cell cycle at G1 phase via Akt/CREB signaling axis | [15]     |
| In vivo         | nu/nu nude mice                                  | Berberine: 25 mg/kg; osimertinib: 5 mg/kg | Help osimertinib overcoming the acquired resistance caused by MET gene amplification | [15]     |
| In vitro        | H1299 and A549 cells                             | Berberine: 25 and 50 µM; P. amurense extract: 2.5 and 5 µg/mL | Enhance inhibitory activity against the growth of MET-amplified osimertinib-resistant tumors; Suppress cell proliferation via inhibiting proliferative kinase signaling | [56]     |
| In vivo         | Athymic nude mice                                | Berberine: 1000 or 1800 ppm; P. amurense extract: 3000 or 5400 ppm | Inhibit tumor growth | [56]     |
| In vitro        | A549 and PC9 cells                               | 0, 40, and 80 µM         | Induce cell apoptosis via activation of the ROS/ASK1/JNK pathway | [59]     |
| Study Types | Models | Dosages | Effects and Mechanisms | Ref. |
|------------|--------|---------|------------------------|------|
| **Ovarian cancer** | | | | |
| In vitro | MDAH-2774 and SKOV-3 cells | 0, 25, 50, 75 μM | Consume EGFR and ERBB2 in ovarian cancer cells; Inhibit the activation of EGFR and ERBB2 downstream targets cyclin D1, MMPS, and VEGF via EGFR-ERBB2/PI3K/Akt signaling pathway | [100] |
| In vitro | SKOV3 and 3AO cells | SKOV3: 40 μM; 3AO: 80 μM | Suppress Warburg effect by increasing TET3-related demethylation and upregulating miR-145; Reverse chemotherapy drug VP16 induced repopulation of ovarian cancer cells by blocking the iPLA2-AA-COX-2-PGE₂ pathway | [97] [102] |
| In vitro | SKOV3 cells | Bebrerine: 5 μmol/L; VP16: 5 μmol/L | Reverse chemotherapy drug VP16 induced repopulation of ovarian cancer cells by blocking the iPLA2-AA-COX-2-PGE₂ pathway; Reverse the increased phosphorylation of FAK | [102] |
| In vitro | A2780, HEY, SKOV3, FTE-187, HO8910, and OVCAR3 cells | 5, 10, 20 μM | Sensitize cancer cells to PARP inhibitors; Induce oxidative DNA damage; Downregulate HRR | [103] [108] |
| **Cervical cancer** | | | | |
| In vitro | Ca Ski cells | 0, 50, 100, 150 μM | Increase GADD153 expression by inducing ROS production; Induce mitochondria dysfunction; Activate caspase-3 and cytochrome C release; Reduce cell invasion and migration | [127] |
| In vitro | SiHa, HeLa, and CaSki cells | 5, 10, 15, 20 μM | Reduce transcriptional activities of MMP-2 and u-PA; Reverse EMT via upregulating E-cadherin and inhibiting N-cadherin and snail-1; Reduce angiogenesis by downregulating VEGF | [106] |
| In vitro | BALB/c nude mice | 20 mg/kg | Inhibit tumor growth; Reduce tumor-induced angiogenesis; Inhibit cell proliferation | [106] |
| In vitro | HeLa and SiHa cells | 3, 10, 30, 100, 300 μmol/L | Trigger cell apoptosis; Induce cell cycle arrest at G1 phase; Overcome the radio-resistance | [107] |
| In vitro | Hela cells | 0.098, 0.195, 0.391, 0.781, 1.563, 3.125, 6.25, 12.5, 25, and 50 μM | Inhibit cell proliferation; Trigger cell apoptosis; Induce cell cycle arrest at G1 phase | [106] |
| In vitro | A2780, HEY, SKOV3, FTE-187, HO8910, and OVCAR3 cells | 5, 10, 20 μM | Sensitize cancer cells to PARP inhibitors; Induce oxidative DNA damage; Downregulate HRR | [103] [108] |
| **Prostate cancer** | | | | |
| In vitro | AIZ-AR cells | 0.01–50 μM; 0.001–1000 nM | Induce cell apoptosis; Inhibit cell proliferation; Inhibit cell proliferation | [111] |
| In vitro | 22RV1 cell | 1, 2.5, 5, 10, 20, 50 μM | Induce cell apoptosis; Downregulate the expression of AR, PSA, COX-2, and Bcl-2 | [110] |
| In vivo | BALB/c nude mice | 0.01136g/kg | Inhibit xenograft tumor growth; Reduce tumor-induced angiogenesis; Inhibit cell proliferation | [110] |
| In vitro | LNCaP, PC3, PC3M, and 22RV1 cells | 12.5, 25, 50 μmol/L | Inhibit cell growth via inhibiting the activation of EGFR; Decrease cell proliferation; Inhibit cell apoptosis; Downregulate EMT-related genes; Increase radiosensitivity cancer cells through inhibiting the expression of HIF-1α and VEGF | [113] [114] [115] |
| In vitro | LNCaP and PC-3 cells | 20, 100 and 200 μM | Inhibit cell invasion and migration by downregulating EMT-related genes; Increase radiosensitivity cancer cells through inhibiting the expression of HIF-1α and VEGF | [114] [115] |
| In vitro | PC-3 and LNCaP cells | 10, 25, 50, 75 μM | Inhibit cell invasion and migration by downregulating EMT-related genes; Increase radiosensitivity cancer cells through inhibiting the expression of HIF-1α and VEGF | [114] [115] |
| In vitro | LNCaP and DU-145 cells | 20, 50, 100, 150, 200, 250, 300, 400 μM | Inhibit cell apoptosis; Inhibit cell proliferation; Inhibit cell proliferation; Inhibit cell proliferation | [111] |
| **Bladder cancer** | | | | |
| In vitro | T24, 5637, SV-HUC-1 cells | 20, 40, 60 μM | Disturb AK2-STAT3 signaling pathway via up-regulating miR-17-5p | [19] |
| In vivo | BALB/c nude mice | 200 mg/kg | Promote miR-17-5p expression | [19] |
| In vitro | T24 and 5637 cells | 1, 5, 10, 20, 40, 80, 160 μM | Induce cell apoptosis; Decrease cell proliferation; Decrease cell proliferation; Induce cell apoptosis; Decrease cell proliferation; Induce cell apoptosis; Decrease cell proliferation | [19] |
| **Endometrial cancer** | | | | |
| In vitro | AN3 CA and HEC-1-A cells | 0, 10, 20, 40, 80, 160 μM | Inhibit cell progression and migration via miR-101/COX-2/PGE₂ signaling pathway; Inhibit cell invasion and migration | [118] [118] [118] |
| In vivo | nude mice | 50 mg/kg or 100 mg/kg | Enhance gemcitabine-induced cytotoxicity | [116] |
| **Pancreatic cancer** | | | | |
| In vitro | Pan-c-1 and hTERT-HPNE cells | 2.5, 3.75, 5.10 μM | Inhibit cell viability and migration by regulating citrate metabolism and transportation | [119] |
| **Hematopoietic Cancer** | | | | |
| In vitro | HL-60, HL-60/MX1, HL-60/MX2, CCRF/CEM, CEM/C1, J45.01, and U266B1 cells | 40–160 μM | Stimulate cell apoptosis | [120] |

Table 1. Cont.
Collectively, berberine showed anticancer effects on different cancers, such as breast, lung, liver, gastric, colorectal, cervical, ovarian, prostate, pancreatic, bladder, endometrial, and esophageal cancers.

3. Mechanisms of Action

Berberine showed anticancer activity on various cancers, and the mechanisms of action would be summarized below. (1) Berberine could inhibit cancer cell proliferation by upregulating miR-214-3p, reducing the protein levels of its target SCT, regulating β-catenin, downregulating the activity of telomerase, and deactivating the MAPK signaling pathways [32,83,85]. (2) Berberine could arrest cancer cell cycle by increasing the levels of p21, p27, and p38, as well as decreasing the levels of CDK1, CDK4, cyclin A, and cyclin D1 [30,37,81]. (3) Berberine could suppress cancer cell metastasis through reducing transcriptional activities of MMP-2 and u-PA, upregulating E-cadherin, and downregulating several EMT-related genes, such as PDGFRB, COL1A2, and BMP7 [33,106,114]. (4) Berberine could induce cancer cell apoptosis via AMPK-p53, PI3K/AKT/mTOR, miR19a/TF/MAPK signaling pathways, and modulating CASC2/AUF1/B-cell/cyclin D1 [30,37,81]. (5) Berberine could induce cancer cell apoptosis via AMPK/p53, PI3K/AKT/mTOR, miR19a/TF/MAPK signaling pathways, and modulating CASC2/AUF1/B-cell/cyclin D1 [30,37,81]. (6) Berberine could also exert anticancer effects by regulating gut microbiota, such as increasing the ratio of Firmicutes/Bacteroidetes, increasing the relative abundance of Clostridiales, Lactobacillaceae, Bacteroidaceae, and Akkermansia muciniphila [77,78]. (7) Berberine improved effects of antitumor drugs, such as cisplatin, 5-fluorouracil, doxorubicin, niraparib, ictotinib and osimertinib, as well as increased sensitivity of radiotherapy [40,41,60,70]. In brief, the anticancer mechanisms of berberine mainly include inhibiting cancer cell proliferation, suppressing metastasis, inducing apoptosis, activating autophagy, regulating gut microbiota as well as improving the effects of other cancer therapies (Table 1, Figure 2).

---

**Table 1.** Cont.

| Study Types                  | Models               | Dosages                       | Effects and Mechanisms                                      | Ref. |
|------------------------------|----------------------|-------------------------------|-------------------------------------------------------------|------|
| **Esophageal cancer**        | KYSE-70 and SKGT4 cells | 20, 40, 60 and 80 µmol/L     | Arrest cell cycle at G0 phase; Induce cell apoptosis;       | [121]|
| In vitro                     | Eca9706, TE-1, and EC109 cells | Berberine: 90 µM; galangin: 30 µM | Synergistically inhibit cell growth; Synergistically arrest cell cycle at G0/M phase | [122]|
| Neuroblastoma                | N2a cells            | 0–20 µg/mL                    | Inhibit cancer stemness; Reverse the EMT                    | [123]|
| Osteosarcoma                 | MG-63 and HBMSC cells | Berberine: 2.5, 5, or 10 µM; cisplatin: 0, 1.25, 2.5, 5, or 10 µM | Induce apoptosis and cell cycle arrest at G0/G1 phase; Inhibit MMP-2/9, Bcl-2, cyclin D1, and CDK4 expression | [124]|

Abbreviation: AA, arachidonic acid; AKR1C3,aldo-keto reductase family 1 member C3; Akt, protein kinase B; AP-1, activator protein 1; AR, androgen receptor; AUF1, AU-binding factor 1; ASK1, apoptosis signal-regulating kinase 1; Bax, Bcl-2-associated X protein; Bcl-2, B-cell lymphoma 2; BLE: Berberis lyceum extracts; CASC2, cancer susceptibility candidate 2; CDK, cyclin-dependent kinase; circRNA, circular RNA; COX-2, cyclooxygenase-2; CRC, colorectal cancer; EGFR, also known as EBB, epidermal growth factor receptor; EMT, epithelial-mesenchymal transition; FAK, Focal adhesion kinase; GC, gastric cancer; GRP78, glucose-regulated protein 78; HIF-1α, hypoxia inducible factor-1α; HRR, homologous recombination repair; IL-1α, interleukin-1α; IL-1β, interleukin-1β; IL-6, interleukin-6; IL-8, interleukin-8; iPLA2, independent phospholipase A2; ITGβ4, integrinβ4; Jak, Janus kinase; KRT, keratin; JNK, c-Jun N-terminal kinase; LC3, microtubule-associated protein light chain 3; LDH, Lactate dehydrogenase; IncRNA, long non-coding RNA; miR, microRNA; mTOR, mammalian target of rapamycin; MMP-2, matrix metalloproteinase 2; NF-κB, nuclear factor κB; NSCLC, non-small cell lung cancer; N2a, neuro2a; P. amurense, Phellodendron amurense; PDCD4, programmed cell death 4; PGE2, prostaglandin E2; ppm, parts per million; PLZF, promyelocytic leukaemia zinc finger; PI3K, phosphatidylinositol-3-kinase; PSA, serum prostate-specific antigen; RXRα, retinoid X receptor α; SIK3, salt-inducible kinases 3; SCT, secretin; SCAP, sterol-regulatory element-binding proteins cleavage-activating protein; Sin3A, SWI-independent-3 transcription regulator family specific antigen; XRCC1, X-ray cross complementing group 1 protein.
Berberine could reduce cancer cell proliferation by binding RXRα and subsequently suppressing β-catenin function, upregulating miR-214-3p and reducing SCT; berberine could attenuate cell cycle by inhibiting the levels of CDK1, CDK4, cyclin A, and cyclin D1, and increasing the levels of p21, p27, p38; berberine could inhibit the Ras/Raf/ERK pathway to cause cell cycle arrest and inhibit metastasis; berberine could reduce transcriptional activities of MMP-2 and u-PA to inhibit metastasis; berberine could enhance the levels of E-cadherin, subsequently decrease the level of N-cadherin and snail-1, and ultimately inhibit metastasis; berberine could promote DNA damage through downregulating the level of TOP2β and then induce apoptosis; berberine could promote apoptosis through activation of STAT3 via inhibiting the phosphorylation of EGFR, increasing the expression of Bcl-x, and downregulating the expression of Bcl-xL and Bcl-2; berberine could induce apoptosis by suppressing the PI3K/AKT/mTOR signaling pathway and upregulating the expression of miR-203; berberine could inhibit the PI3K/Akt/mTOR pathway, and enhance the expressions of LC3B-II to promote autophagy; berberine could induce autophagy via JNK/Beclin1 pathway; berberine could regulate gut microbiota by increasing beneficial gut bacteria Clostridiales, Bacteroidales, and Lactobacillaceae. Abbreviations: Akt, protein kinase B; Bcl-2, B-cell lymphoma 2; CDK, cyclin-dependent kinase; EGFR, epidermal growth factor receptor; JNK, c-Jun N-terminal kinase; LC3, microtubule-associated protein light chain 3; mTOR, mammalian target of rapamycin; MMP-2, matrix metalloproteinase 2; PI3K, phosphatidylinositol-3-kinase; RXRα, retinoid X receptor α; SCT, secretin; STAT3, transcription 3; TOP2β, Topoisomerase II β; u-PA, urokinase-type plasminogen activator.

4. Bioavailability of Berberine

Berberine could inhibit the initiation and progression of many cancers. However, its poor oral bioavailability and low water solubility could reduce its anticancer activities. Moreover, the administration of berberine by intra-muscular and intra-venous could induce anaphylactic reaction [128,129]. Therefore, various strategies have been developed to improve berberine bioavailability and enhance its anticancer activities. These techniques mainly include diverse novel drug delivery systems. For example, a study showed that berberine-loaded liquid crystalline nanoparticles (LCNs) could overcome the poor water solubility and improve the bioavailability of berberine [130]. Another study showed that berberine-loaded bioformulation of silver nanoparticles (AgNPs) showed enhancing cytotoxicity against breast cancer cells and decreasing drug loss during their circulation in the blood [128]. Moreover, berberine-loaded disulfide-bridged mesoporous organosil-
ica nanoparticles (ss-MONs) could enhance its accumulation in liver cancer tissue, avoid rapid blood clearance, and surmount several other obstacles from using berberine alone, such as poor gastrointestinal absorption and poor targeting abilities [131]. In addition, PEG-PE/TPGS-mixed micelles, which was made of 1,2-distearoyl-sn-glycero-3-phosphoethanolamine-N-(methoxy(polyethylene glycol)2000) (PEG-PE) mixed with d-a-tocopheryl polyethylene glycol 1000 succinate (TPGS) in a 3:1 M ratio, could increase berberine solubilization by 300% and enhance the cytotoxic effectiveness of berberine against prostate cancer cells [132]. Furthermore, berberine-loaded selenium nanoparticles (SeNPs) were more easily taken up by cells because of the nano-size of the SeNPs [133].

5. Safety of Berberine

Several studies showed that berberine had low toxic effects on human beings. For example, a phase I clinical trial showed that berberine was safe at excessive doses [134]. Another study found that berberine showed low toxicity towards healthy cells [135]. Although berberine could contribute to some adverse events, such as constipation and nausea, these adverse effects are not serious. The most common event, constipation, disappeared once berberine was discontinued [136,137].

6. Conclusions and Perspectives

Cancer is a severe public health problem in the world. Berberine showed anticancer activities in various cancers, such as breast, lung, gastric, liver, colorectal, prostate, and ovarian cancers. The potential mechanisms include inhibiting cell proliferation, suppressing metastasis, inducing cell apoptosis, activating autophagy, regulating gut microbiota, and enhancing the effects of other antitumor drugs. Moreover, different nanomaterials have been developed, such as AgNPs, ss-MONs, and SeNPs, in order to improve berberine bioavailability and enhance its anticancer activities. In addition, berberine is safe and tolerable for human beings, although some side effects were observed, such as constipation and nausea. In the future, effects of berberine against more cancers should be evaluated, and the relative mechanisms should be studied. Furthermore, the effects and mechanisms of berberine inhibiting migration of cancers should be further explored from the perspective of intratumoral microbes inhibition or gut microbiota regulation. Additionally, more methods or techniques should be developed to improve the bioavailability and anticancer activity of berberine. More clinical trials should be carried out to confirm effects of berberine on human beings, and adverse effects should also be observed.

Author Contributions: Conceptualization, R.-G.X., Y.-J.Z., R.-Y.G. and H.-B.L.; writing—original draft preparation, R.-G.X., S.-Y.H., S.-X.W., D.-D.Z., Z.-J.Y., A.S. (Adila Saimaiti), C.-N.Z. and A.S. (Ao Shang); writing—review and editing, Y.-J.Z., R.-Y.G. and H.-B.L.; supervision, Y.-J.Z., R.-Y.G. and H.-B.L.; funding acquisition, R.-Y.G. and H.-B.L. All authors have read and agreed to the published version of the manuscript.

Funding: This research was funded by Local Financial Funds of National Agricultural Science and Technology Center, Chengdu (No. NASC2021KR01), and the Key Project of Guangdong Provincial Science and Technology Program (No. 2014B020205002).

Acknowledgments: We thank Hang-Yu Li in Department of Nutrition, School of Public Health, Sun Yat-sen University, for collecting some materials for this paper.

Conflicts of Interest: The authors declare no conflict of interest.

References

1. Sung, H.; Ferlay, J.; Siegel, R.L.; Laversanne, M.; Soerjomataram, I.; Jemal, A.; Bray, F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J. Clin. 2021, 71, 209–249. [CrossRef] [PubMed]

2. Farha, A.K.; Gan, R.Y.; Li, H.B.; Wu, D.T.; Atanasov, A.G.; Gul, K.; Zhang, J.R.; Yang, Q.Q.; Corke, H. The anticancer potential of the dietary polyphenol rutin: Current status, challenges, and perspectives. Crit. Rev. Food Sci. Nutr. 2022, 62, 832–859. [CrossRef] [PubMed]
3. Grivennikov, S.I.; Karin, M. Inflammatory cytokines in cancer: Tumour necrosis factor and interleukin 6 take the stage.

4. Li, Y.; Li, S.; Zhou, Y.; Meng, X.; Zhang, J.J.; Xu, D.P.; Li, H.B. Melatonin for the prevention and treatment of cancer. Oncotarget 2017, 8, 39896–39921. [CrossRef] [PubMed]

5. Saimaiti, A.; Zhou, D.D.; Li, J.; Xiong, R.G.; Gan, R.Y.; Huang, S.Y.; Shang, A.; Zhao, C.N.; Li, H.Y.; Li, H.B. Dietary sources, health benefits, and risks of caffeine. Crit. Rev. Food Sci. Nutr. 2022, in press. [CrossRef]

6. Xu, X.Y.; Zhao, C.N.; Cao, S.Y.; Tang, G.Y.; Gan, R.Y.; Li, H.B. Effects and mechanisms of tea for the prevention and management of cancer. An updated review. Crit. Rev. Food Sci. Nutr. 2020, 60, 1693–1705. [CrossRef]

7. Zhao, C.N.; Li, Y.; Meng, X.; Li, S.; Liu, Q.; Tang, G.Y.; Gan, R.Y.; Li, H.B. Insight into the roles of vitamins C and D against cancer: Myth or truth? Cancer Lett. 2018, 431, 161–170. [CrossRef]

8. Zheng, J.; Zhou, Y.; Li, S.; Xu, D.P.; Li, S.; Li, H.B. Spices for prevention and treatment of cancers. Nutrients 2016, 8, 495. [CrossRef]

9. Zhou, Y.; Zheng, J.; Li, Y.; Xu, D.P.; Li, S.; Chen, Y.M.; Li, H.B. Natural polyphenols for prevention and treatment of cancer. Nutrients 2016, 8, 515. [CrossRef]

10. Wang, K.; Feng, X.C.; Chai, L.W.; Cao, S.J.; Qiu, F. The metabolism of berberine and its contribution to the pharmacological effects. Drug Metab. Rev. 2017, 49, 139–157. [CrossRef] [PubMed]

11. Imenshahidi, M.; Hosseinzaadeh, H. Berberine and barberry (Berberis vulgaris): A clinical review. Phytother. Res. 2019, 33, 504–523. [CrossRef] [PubMed]

12. Kong, W.; Wei, J.; Abidi, P.; Lin, M.; Inaba, S.; Li, C.; Wang, Y.; Wang, Z.; Si, S.; Pan, H.; et al. Berberine is a novel cholesterol-lowering drug working through a unique mechanism distinct from statins. Nat. Med. 2004, 10, 1344–1351. [CrossRef] [PubMed]

13. Kumar, A.; Ekavali; Chopra, K.; Mukherjee, M.; Pottabathini, R.; Dhull, D.K. Current knowledge and pharmacological profile of berberine: An update. Eur. J. Pharmacol. 2015, 761, 288–297. [CrossRef]

14. Neag, M.A.; Mocan, A.; Echeverria, J.; Pop, R.M.; Bocsan, C.I.; Crisgan, G.; Buzoianu, A.D. Berberine: Botanical occurrence, traditional uses, extraction methods, and relevance in cardiovascular, metabolic, hepatic, and renal disorders. Front. Pharmacol. 2018, 9, 357. [CrossRef] [PubMed]

15. Chen, Z.; Vallega, K.A.; Chen, H.Y.; Zhou, J.; Ramalingam, S.S.; Sun, S.Y. The natural product berberine synergizes with osimertinib preferentially against MET-amplified osimertinib-resistant lung cancer via direct MET inhibition. Pharmacol. Res. 2022, 175, 105998. [CrossRef]

16. Gan, R.Y. Bioactivities of berberine: An update. Int. J. Med. Biol. Med. 2012, 1, 48–81.

17. Ortiz, L.M.G.; Lombardi, P.; Tillhon, M.; Scovassi, A.I. Berberine, an epiphany against cancer. Molecules 2014, 19, 12349–12367. [CrossRef]

18. Wang, N.; Tan, H.Y.; Li, L.; Yuen, M.F.; Feng, Y.B. Berberine and Coptidis rhizoma as potential anticancer agents: Recent updates and future perspectives. J. Ethnopharmacol. 2015, 176, 35–48. [CrossRef]

19. Xia, Y.Y.; Chen, S.Z.; Cui, J.F.; Wang, Y.; Liu, X.C.; Shen, Y.L.; Gong, L.; Jiang, X.W.; Wang, W.F.; Zhi, Y.F.; et al. Berberine suppresses bladder cancer cell proliferation by inhibiting JAK1-STAT3 signaling via upregulation of miR-17-5p. Biochem. Pharmacol. 2021, 188, 114575. [CrossRef]

20. Khan, S.; Hussain, A.; Attar, F.; Bloukh, S.H.; Edis, Z.; Sharifi, M.; Balali, E.; Nemati, F.; Derakhshankhah, H.; Zeinabad, H.A.; et al. A review of the berberine natural polysaccharide nanostructures as potential anticancer and antibacterial agents. Biomed. Pharmacother. 2022, 146, 112531. [CrossRef]

21. Zhang, C.; Sheng, J.; Li, G.; Zhao, L.; Wang, Y.; Yang, W.; Yao, X.; Sun, L.; Zhang, Z.; Cui, R. Effects of berberine and its derivatives on cancer: A systems pharmacology approach. Front. Pharmacol. 2019, 10, 1461. [CrossRef]

22. Rauf, A.; Abu-Izneid, T.; Khalil, A.A.; Imran, M.; Shah, Z.A.; Emran, T.B.; Mitra, S.; Khan, Z.; Alhumaydi, F.A.; Aljohani, A.S.M.; et al. Berberine as a potential anticancer agent: A comprehensive review. Molecules 2021, 26, 7368. [CrossRef] [PubMed]

23. Wang, Y.; Liu, Y.; Du, X.; Ma, H.; Yao, J. The anti-cancer mechanisms of berberine: A review. Cancer Manag. Res. 2020, 12, 695–702. [CrossRef]

24. Li, Y.; Li, S.; Meng, X.; Gan, R.Y.; Zhang, J.J.; Li, H.B. Dietary natural products for prevention and treatment of breast cancer. Nutrients 2017, 9, 728. [CrossRef]

25. Sun, Y.; Wang, W.T.; Tong, Y.W. Berberine inhibits proliferative ability of breast cancer cells by reducing metadherin. Med. Sci. Monit. 2019, 25, 9086–9066. [CrossRef] [PubMed]

26. Yao, M.J.; Fan, X.D.; Yuan, B.; Takagi, N.; Liu, S.; Han, X.; Ren, J.G.; Liu, J.X. Berberine inhibits NLRP3 inflammasome pathway in human triple-negative breast cancer MDA-MB-231 cell. BMC Complement. Altern. Med. 2019, 19, 216. [CrossRef] [PubMed]

27. Grivennikov, S.I.; Karin, M. Inflammatory cytokines in cancer: Tumour necrosis factor and interleukin 6 take the stage. Ann. Rheum. Dis. 2011, 70, 1104–1108. [CrossRef]

28. Sefidabi, R.; Mortazavi, P.; Hosseini, S. Antiproliferative effect of berberine on canine mammary gland cancer cell culture. Biomed. Rep. 2017, 6, 95–98. [CrossRef]

29. Khalki, L.E.; Maire, V.; Dubois, T.; Zyad, A. Berberine impairs the survival of triple negative breast cancer cells: Cellular and molecular analyses. Molecules 2020, 25, 506. [CrossRef]

30. Lin, Y.S.; Chiu, Y.C.; Tsai, Y.F.; Tsai, Y.H.; Tsai, Y.F.; Wang, J.Y.; Teng, L.M.; Chiu, J.H. Different mechanisms involved in the berberine-induced antiproliferation effects in triple-negative breast cancer cell lines. J. Cell. Biochem. 2019, 120, 13531–13544. [CrossRef]
31. Ahmadiankia, N.; Moghaddam, H.K.; Mishan, M.A.; Bahrami, A.R.; Meshkin, H.N.; Bidkhori, H.R.; Moghaddam, M.; Mirfeizy, S.J.A. Berberine suppresses migration of MCF-7 breast cancer cells through down-regulation of chemokine receptors. *Int. J. Basic Med. Sci.* 2016, 15, 125–131. [PubMed]

32. Zhu, C.Y.; Li, J.P.; Hua, Y.M.; Wang, J.L.; Wang, K.; Sun, J.Q. Berberine inhibits the expression of SCT through miR-214-3p stimulation in breast cancer cells. *Evid. Based Complement. Altern. Med.* 2020, 2020, 2817147. [CrossRef][PubMed]

33. Jeong, Y.; You, D.; Kang, H.G.; Yu, J.; Kim, S.W.; Nam, S.J.; Lee, J.E.; Kim, S. Berberine suppresses fibronectin expression through inhibition of c-Jun phosphorylation in breast cancer cells. *J. Breast Cancer* 2018, 21, 21–27. [CrossRef][PubMed]

34. Ouyang, L.; Shi, Z.; Zhao, S.; Wang, F.T.; Zhou, T.T.; Liu, B.; Bao, J.K. Programmed cell death pathways in cancer: A review of apoptosis, autophagy and programmed necrosis. *Cell Prolif.* 2012, 45, 487–498. [CrossRef]

35. Pan, Y.; Zhang, F.; Zhao, Y.W.; Shao, D.; Zheng, X.; Chen, Y.J.; He, K.; Li, J.; Chen, L. Berberine enhances chemosensitivity and induces apoptosis through dose-dependent AMPK signaling in breast cancer. *J. Cancer* 2017, 8, 1679–1689. [CrossRef]

36. Sakaguchi, M.; Kitaguchi, D.; Morinami, S.; Kurashiki, Y.; Hashida, H.; Miyata, S.; Yamaguchi, M.; Sakai, M.; Murata, N.; Tanaka, S. Berberine-induced nucleolar stress response in a human breast cancer cell line. *Biochem. Biophys. Res. Commun.* 2020, 528, 227–233. [CrossRef]

37. Tak, J.; Sabarwal, A.; Shyanti, R.K.; Singh, R.P. Berberine enhances posttranslational protein stability of p21/cip1 in breast cancer cells via down-regulation of Akt. *Mol. Cell. Biochem.* 2019, 458, 49–59. [CrossRef]

38. Gao, X.J.; Wang, J.; Li, M.Q.; Wang, J.; Lv, J.; Zhang, L.; Sun, C.F.; Ji, J.M.; Yang, W.B.; Zhao, Z.N.; et al. Berberine attenuates XRCC1-mediated base excision repair and sensitizes breast cancer cells to the chemotherapeutic drugs. *J. Cell. Mol. Med.* 2019, 23, 6797–6804. [CrossRef]

39. Pronusamy, L.; Kothandan, G.; Manoharan, R. Berberine and Emodin abrogates breast cancer growth and facilitates apoptosis through inactivation of SIK3-induced mTOR and Akt signaling pathway. *BBA Mol. Basis Dis.* 2020, 1866, 165897. [CrossRef]

40. Chen, Y.; Zhang, H.Y. Berberine and chemotherapeutic drugs synergistically inhibits cell proliferation and migration of breast cancer cells. *Int. J. Clin. Exp. Med.* 2018, 11, 13243–13250.

41. Zhao, Y.W.; Jing, Z.L.; Li, Y.; Mao, W.F. Berberine in combination with cisplatin suppresses breast cancer cell growth through induction of DNA breaks and caspase-3-dependent apoptosis. *Oncol. Rep.* 2016, 36, 567–572. [CrossRef]

42. Qian, K.; Tang, C.Y.; Chen, L.Y.; Zheng, S.; Zhao, Y.; Ma, L.S.; Xu, L.; Fan, L.H.; Yu, J.D.; Tan, H.S.; et al. Berberine reverses breast cancer multidrug resistance based on fluorescence pharmacokinetics in vitro and in vivo. *ACS Omega* 2021, 6, 10645–10654. [CrossRef][PubMed]

43. Nejman, D.; Livyatan, I.; Fuks, G.; Gavert, N.; Zwang, Y.; Geller, L.T.; Rotter-Maskowitz, A.; Weiser, R.; Mallel, G.; Gigi, E.; et al. The human tumor microbiome is composed of tumor type-specific intracellular bacteria. *Science* 2020, 368, 973–980. [CrossRef][PubMed]

44. Fu, A.; Yao, B.; Dong, T.; Chen, Y.; Yao, J.; Liu, Y.; Li, H.; Bai, H.; Liu, X.; Zhang, Y.; et al. Tumor-resident intracellular microbiota promotes metastatic colonization in breast cancer. *Cell* 2022, 185, 1356–1372.e1326. [CrossRef][PubMed]

45. Deng, H.; Muthupalani, S.; Erdman, S.; Liu, H.; Niu, Z.; Wang, T.C.; Fox, J.G. Translocation of *Helicobacter hepaticus* synergizes with myeloid-derived suppressor cells and contributes to breast carcinogenesis. *Oncoinmunology* 2022, 11, 2057399. [CrossRef]

46. Wolf, P.G.; Devendran, S.; Doden, H.L.; Ly, L.K.; Moore, T.; Takei, H.; Nittono, H.; Murai, T.; Kurosawa, T.; Chlipala, G.E.; et al. Berberine alters gut microbial function through modulation of bile acids. *BMC Microbiol.* 2021, 21, 24. [CrossRef]

47. Zheng, H.; Zhu, F.; Miao, P.; Mao, Z.; Redfearn, D.P.; Cao, R.Y. Antimicrobial natural product berberine is efficacious for the treatment of atrial fibrillation. *BioMed Res. Int.* 2017, 2017, 3146791. [CrossRef][PubMed]

48. Huang, X.X.; Yi, Y.L.; Yong, J.Y.; Sun, J.Y.; Song, Z.; Li, D.M.; Li, Y. Inhibitory effect of berberine hydrochloride against Candida albicans and the role of the HOG-MAPK pathway. *J. Antibiot.* 2021, 74, 807–816. [CrossRef]

49. Kocic, B.D.; Dimitrijevic, M.V.; Miladinovic, L.C.; Markovic, M.S.; Rankovic, G.Z.; Miladinovic, D.L. In vitro anti-*Helicobacter pylori* activity of berberine and barberry extracts: A preliminary report. *Nat. Prod. Commun.* 2019, 14, 1934578X19857905. [CrossRef]

50. Li, Y.; Wen, H.L.; Ge, X.Z. Horseness effect of berberine against klebsiella pneumoniae is mediated by up-regulation of the efflux pump kmarA. *J. Nat. Prod. Med.* 2021, 84, 2885–2892. [CrossRef]

51. Tan, J.; Wang, J.; Yang, C.; Zhu, C.; Guo, G.; Tang, J.; Shen, H. Antimicrobial characteristics of berberine against prosthetic joint infection-related Staphylococcus aureus of different multi-locus sequence types. *BMC Complement. Altern. Med.* 2019, 19, 218. [CrossRef][PubMed]

52. Cao, S.Y.; Li, Y.; Meng, X.; Zhao, C.N.; Li, S.; Gan, R.Y.; Li, H.B. Dietary natural products and lung cancer: Effects and mechanisms of action. *J. Funct. Foods* 2019, 52, 316–331. [CrossRef]

53. Duma, N.; Santana-Davila, R.; Molina, J.R. Non-small cell lung cancer: Epidemiology, screening, diagnosis, and treatment. *Mayo Clin. Proc.* 2019, 94, 1623–1640. [CrossRef][PubMed]

54. Chen, J.; Huang, X.F.; Tao, C.; Wang, L.; Chen, Z.D.; Li, X.P.; Zeng, Q.; Ma, M.; Zhang, R.; Wu, Z.Z. Berberine chloride suppresses non-small cell lung cancer by deregulating Sin3A/TOP2B pathway in vitro and in vivo. *Cancer Chemother. Pharmacol.* 2020, 86, 151–161. [CrossRef]

55. Li, J.; Liu, F.; Jiang, S.L.; Liu, J.; Chen, X.H.; Zhang, S.N.A.; Zhao, H.B. Berberine hydrochloride inhibits cell proliferation and promotes apoptosis of non-small cell lung cancer via the suppression of the MMP2 and Bcl-2/Bax signaling pathways. *Onco. Lett.* 2018, 15, 7409–7414. [CrossRef]
56. James, M.A.; Fu, H.; Liu, Y.; Chen, D.R.; You, M. Dietary administration of berberine or Phellodendron amurense extract inhibits cell cycle progression and lung tumorigenesis. Mol. Carcinog. 2011, 50, 1–7. [CrossRef]

57. Ni, L.L.; Li, Z.J.; Ren, H.L.; Kong, L.Z.; Chen, X.; Xiong, M.R.; Zhang, X.Q.; Ning, B.B.; Li, J.A. Berberine inhibits non-small cell lung cancer cell growth through repressing DNA repair rather than through apoptosis. Clin. Exp. Pharmacol. Physiol. 2022, 49, 134–144. [CrossRef]

58. Chen, Q.Q.; Shi, J.M.; Ding, Z.; Xia, Q.; Zheng, T.S.; Ren, Y.B.; Li, M.; Fan, L.H. Berberine induces apoptosis in non-small-cell lung cancer cells by upregulating miR-19a targeting tissue factor. Cancer Manag. Res. 2019, 11, 9005–9015. [CrossRef]

59. Chen, Q.Q.; Hou, Y.Q.; Li, D.; Ding, Z.; Xu, X.; Hao, B.J.; Xia, Q.; Li, M.; Fan, L.H. Berberine induces non-small cell lung cancer apoptosis via the activation of the ROS/ASK1/JNK pathway. Ann. Transl. Med. 2022, in press. [CrossRef]

60. Chen, P.; Bai, C.H.; Shi, Z.H.; Wang, Y.; Wu, J.N.; Chen, K.; Su, J.Y.; Li, J. Synergistic inhibitory effect of berberine and icotinib on non-small cell lung cancer cells via inducing autophagic cell death and apoptosis. Apoptosis 2021, 26, 639–656. [CrossRef]

61. Zheng, F.; Li, J.; Ma, C.J.; Tang, X.J.; Tang, Q.; Wu, J.J.; Chai, X.S.; Xie, J.H.; Yang, X.B.; Hann, S.S. Novel regulation of miR-34a-5p.

62. Mao, Q.Q.; Xu, X.Y.; Shang, A.; Gan, R.Y.; Wu, D.T.; Atanasov, A.G.; Li, H.B. Phytochemicals for the prevention and treatment of gastric cancer: Effects and mechanisms. Int. J. Mol. Sci. 2021, 21, 570. [CrossRef]

63. Smyth, E.C.; Nilsson, M.; Grabsch, H.I.; van Grieken, N.C.T.; Lordick, F. Gastric cancer. Lancet 2020, 396, 635–648. [CrossRef]

64. Yang, Y.H.; Zhang, N.; Li, K.D.; Chen, J.; Qiu, L.; Zhang, J.F. Integration of microRNA-mRNA profiles and pathway analysis of plant isoquinoline alkaloid berberine in SGC-7901 gastric cancers. Drug Des. Dev. Ther. 2018, 12, 393–408. [CrossRef]

65. Wang, M.; Sun, L.T.; Wang, L.; Sun, Y.N. Effects of berberine on circular RNA expression profiles in human gastric cancer cells. Evid. Based Complement. Altern. Med. 2021, 2021, 6688629. [CrossRef]

66. Kou, Y.Y.; Tong, B.D.; Wu, W.Q.; Liao, X.Q.; Zhao, M. Berberine improves chemo-sensitivity to cisplatin by enhancing cell apoptosis and repressing PI3K/AKT/mTOR signaling pathway in gastric cancer. Front. Pharmacol. 2020, 11, 616251. [CrossRef]

67. You, H.Y.; Xie, X.M.; Zhang, W.J.; Zhu, H.L.; Jiang, F.Z. Berberine improves cisplatin sensitivity of human gastric cancer cells by upregulation of miR-203. In Vitro Cell Dev. Biol. Anim. 2016, 52, 857–863. [CrossRef]

68. Llovet, J.M.; Kelley, K.K.; Villanueva, A.; Singal, A.G.; Pikarsky, E.; Roayaie, S.; Lencioni, R.; Koike, K.; Zucman-Rossi, J.; Finn, R.S. Hepatocellular carcinoma. Nat. Rev. Dis. Prim. 2017, 1, 2018. [CrossRef] [PubMed]

69. Zhou, Y.; Li, Y.; Zhou, T.; Zheng, J.; Li, S.; Li, H.B. Dietary natural products for prevention and treatment of liver cancer. Nutrients 2016, 8, 156. [CrossRef]

70. Zhang, P.C.; Wang, Q.C.; Lin, Z.B.; Yang, P.J.; Dou, K.F.; Zhang, R.H. Berberine inhibits growth of liver cancer cells by suppressing glutamine uptake. Oncotargets Ther. 2019, 12, 1751–1763. [CrossRef] [PubMed]

71. Mustafa, K.; Mohamed, H.; Shah, A.M.; Yu, S.X.; Akhlaq, M.; Xiao, H.F.; Li, S.Q.; Naz, T.; Nosheen, S.; Bai, X.Y.; et al. In vitro anticancer potential of Berberis lychnophora extracts against human hepatocarcinoma (HepG2) cells. BioMed Res. Int. 2020, 2020, 8256809. [CrossRef] [PubMed]

72. Liu, X.B.; Li, M.; Cao, Y.; Li, C.L.; Zhou, W.J.; Ji, G.; Zhang, L. Berberine alleviates non-alcoholic steatohepatitis through modulating gut microbiota mediated intestinal FXR activation. Front. Pharmacol. 2021, 12, 750826. [CrossRef]

73. Li, S.; Wang, N.; Tan, H.Y.; Chueng, F.; Zhang, Z.J.; Yuen, M.F.; Feng, Y.B. Modulation of gut microbiota mediates berberine-induced expansion of immuno-suppressive cells to against alcoholic liver disease. Clin. Transl. Med. 2020, 10, e112. [CrossRef]

74. Dekker, E.; Tanis, P.J.; Vleugels, J.L.A.; Kasi, P.M.; Wallace, M.B. Colorectal cancer. Lancet 2019, 394, 1467–1480. [CrossRef] [PubMed]

75. Tao, J.; Li, Y.; Li, S.; Li, H.B. Plant foods for the prevention and management of colon cancer. J. Funct. Foods 2020, 52, 110245. [CrossRef] [PubMed]

76. Niu, L.L.; Li, Z.J.; Ren, H.L.; Kong, L.Z.; Chen, X.; Xiong, M.R.; Zhang, X.Q.; Ning, B.B.; Li, J.A. Berberine inhibits non-small cell lung cancer.

77. Shu, X.B.; Li, M.; Cao, Y.; Li, C.L.; Zhou, W.J.; Ji, G.; Zhang, L. Berberine alleviates non-alcoholic steatohepatitis through modulating gut microbiota mediated intestinal FXR activation. Front. Pharmacol. 2021, 12, 750826. [CrossRef]

78. Li, S.; Wang, N.; Tan, H.Y.; Chueng, F.; Zhang, Z.J.; Yuen, M.F.; Feng, Y.B. Modulation of gut microbiota mediates berberine-induced expansion of immuno-suppressive cells to against alcoholic liver disease. Clin. Transl. Med. 2020, 10, e112. [CrossRef]

79. Dekker, E.; Tanis, P.J.; Vleugels, J.L.A.; Kasi, P.M.; Wallace, M.B. Colorectal cancer. Lancet 2019, 394, 1467–1480. [CrossRef] [PubMed]

80. Tao, J.; Li, Y.; Li, S.; Li, H.B. Plant foods for the prevention and management of colon cancer. J. Funct. Foods 2020, 52, 110245. [CrossRef] [PubMed]
83. Ruan, H.; Zhan, Y.Y.; Hou, J.; Xu, B.; Chen, B.; Tian, Y.; Wu, D.; Zhao, Y.; Zhang, Y.; Chen, X.; et al. Berberine binds RXR alpha to suppress beta-catenin signaling in colon cancer cells. Oncogene 2017, 36, 6906–6918. [CrossRef] [PubMed]

84. Li, P.F.; Hao, Z.F.; Liu, H.H.; Zhu, B.J.; Dang, L.Y.; Ma, C.; Xu, Y.T.; Zhang, Y.Y.; Fan, D.D.; Sun, S.S. Quantitative proteomics analysis of berberine-treated colon cancer cells reveals potential therapy targets. Biology 2021, 10, 250. [CrossRef]

85. Samad, M.A.; Saiman, M.Z.; Majid, N.A.; Karsani, S.A.; Yaacob, J.S. Berberine inhibits telomerase activity and induces cell cycle arrest and telomere erosion in colorectal cancer cell line, HCT 116. Molecules 2021, 26, 376. [CrossRef]

86. Liu, Y.X.; Hua, W.W.; Li, Y.; Xian, X.R.; Zhao, Z.; Liu, C.; Zou, J.J.; Li, J.; Fang, X.J.; Zhu, Y.B. Berberine suppresses colon cancer cell proliferation by inhibiting the SCAP/SREBP-1 signaling pathway-mediated lipogenesis. Biochem. Pharmacol. 2020, 174, 113776. [CrossRef]

87. Zhang, Y.R.; Liu, X.J.; Yu, M.; Xu, M.M.; Xiao, Y.P.; Ma, W.Y.; Huang, L.; Li, X.G.; Ye, X.L. Berberine inhibits proliferation and induces G0/G1 phase arrest in colorectal cancer cell by downregulating IGF2BP3. Life Sci. 2020, 260, 118413. [CrossRef]

88. Liu, Y.X.; Fang, J.X.; Li, Y.; Bing, L.; Li, Y.; Fang, J.; Xian, X.R.; Zhang, W.; Li, J.; Zhao, Z.; et al. Berberine suppresses the migration and invasion of colon cancer cells by inhibition of lipogenesis through modulation of prolymocytic leukemia zinc finger-mediated sterol-regulatory element binding proteins cleavage-activating protein ubiquitination. J. Pharm. Pharmacol. 2022, in press. [CrossRef]

89. Gong, C.X.; Hu, X.; Xu, Y.L.; Yang, J.H.; Zong, L.; Wang, C.; Zhu, J.; Li, Z.Y.; Lu, D.Z. Berberine inhibits proliferation and migration of colorectal cancer cells by downregulating of GRP78. Anti-Cancer Drugs 2020, 31, 141–149. [CrossRef]

90. Lü, Y.; Han, B.; Yu, H.; Cui, Z.; Li, Z.; Wang, J. Berberine regulates the microRNA-21-ITGB4-PDCD4 axis and inhibits colon cancer viability. Oncol. Lett. 2018, 15, 5971–5976. [CrossRef]

91. Dai, W.; Mu, L.Y.; Cui, Y.L.; Li, Y.Y.; Chen, P.; Xie, H.J.; Wang, X. Berberine promotes apoptosis of colorectal cancer via regulation of the long non-coding RNA (IncRNA) cancer susceptibility candidate 2 (CASC2)/AU-binding factor 1 (AUF1)/B-cell CLL/Lymphoma 2 (Bcl-2) axis. Med. Sci. Monit. 2019, 25, 730–738. [CrossRef] [PubMed]

92. Fu, T.; Coulter, S.; Yoshihara, E.; Oh, T.G.; Fang, S.; Cayabyab, F.; Zhu, Q.Y.; Zhang, T.; Leblanc, M.; Liu, S.H.; et al. FXR regulates intestinal cancer stem cell proliferation. Cell 2019, 176, 1098–1112.e1018. [CrossRef] [PubMed]

93. Tian, Y.; Cai, J.W.; Gwi, W.; Nichols, R.G.; Koo, I.; Zhang, J.T.; Anitha, M.; Patterson, A.D. Berberine directly affects the gut microbiota to promote intestinal farnesoid X receptor activation. Drug Metab. Dispos. 2019, 47, 86–93. [CrossRef] [PubMed]

94. Deng, J.; Zhao, L.; Yuan, X.; Li, Y.; Shi, J.; Zhang, H.; Zhao, Y.; Han, L.; Wang, H.; Yan, Y.; et al. Pre-administration of berberine exerts chemopreventive effects in AOM/DSS-induced colitis-associated carcinogenesis mice via modulating inflammation and intestinal microbiota. Nutrients 2022, 14, 726. [CrossRef]

95. Okuno, K.; Garg, R.; Yuan, Y.C.; Tokunaga, M.; Kinugasa, Y.; Goel, A. Berberine and oligomeric proanthocyanidins exhibit synergistic efficacy through regulation of PI3K-Akt signaling pathway in colorectal cancer. Front. Oncol. 2022, 12, 855860. [CrossRef]

96. Matulonis, U.A.; Sood, A.K.; Fallowfield, L.; Howitt, B.E.; Sehouli, J.; Karlan, B.Y. Ovarian cancer. Nat. Rev. Dis. Prim. 2016, 2, 16061. [CrossRef]

97. Li, J.; Zou, Y.L.; Pei, M.L.; Zhang, Y.; Jiang, Y. Berberine inhibits the Warburg effect through TET3/miR-145/HK2 pathways in ovarian cancer cells. J. Cancer 2021, 12, 207–216. [CrossRef]

98. Zhao, Y.W.; Yang, X.H.; Zhao, J.T.; Gao, M.H.; Zhang, M.; Shi, T.F.; Zhang, F.; Zheng, X.; Fan, Y.; Shao, D.; et al. Berberine inhibits chemotherapy-exacerbated ovarian cancer stem cell-like characteristics and metastasis through GLI1. Eur. J. Pharmacol. 2021, 895, 173887. [CrossRef]

99. Parashar, D.; Nair, B.; Geethadevi, A.; George, J.; Nair, A.; Tsaih, S.W.; Kadamberi, I.P.; Nair, G.K.G.; Lu, Y.L.; Ramchandran, R.; et al. Peritoneal spread of ovarian cancer harbors therapeutic vulnerabilities regulated by FOXM1 and EGFR/ERBB2 signaling. Cancer Res. 2020, 80, 5554–5568. [CrossRef]

100. Chuang, T.C.; Wu, K.H.; Lin, Y.Y.; Kuo, H.P.; Kao, M.C.; Wang, V.; Hsu, S.C.; Lee, S.L. Dual down-regulation of EGFR and ErbB2 by berberine contributes to suppression of migration and invasion of human ovarian cancer cells. Environ. Toxicol. 2021, 36, 737–747. [CrossRef]

101. Liu, L.; Fan, J.Y.; Ai, G.H.; Liu, J.; Luo, N.; Li, C.X.; Cheng, Z.P. Berberine in combination with cisplatin induces necroptosis and apoptosis in ovarian cancer cells. Biol. Res. 2019, 52, 37. [CrossRef] [PubMed]

102. Zhao, Y.W.; Cui, L.Z.; Pan, Y.; Shao, D.; Zheng, X.; Zhang, F.; Zhang, H.S.; He, K.; Chen, L. Berberine inhibits the chemotherapy-induced repopulation by suppressing the arachidonic acid metabolic pathway and phosphorylation of FAK in ovarian cancer. Cell Prolif. 2017, 50, e12393. [CrossRef] [PubMed]

103. Hou, D.; Xu, G.W.; Zhang, C.B.; Li, B.X.; Qin, J.C.; Hao, X.H.; Liu, Q.; Zhang, X.Y.; Liu, J.S.; Wei, J.J.; et al. Berberine induces oxidative DNA damage and impairs homologous recombination repair in ovarian cancer cells to confer increased sensitivity to PARP inhibition. Cell Death Dis. 2017, 8, e3070. [CrossRef] [PubMed]

104. Cohen, P.A.; Jiangran, A.; Oakinin, A.; Denny, L. Cervical cancer. Lancet 2019, 393, 169–182. [CrossRef]

105. Liu, L.P.; Sun, L.; Zheng, J.; Cui, I. Berberine modulates Keratin 17 to inhibit cervical cancer cell viability and metastasis. J. Recept. Signal Transduct. 2021, 41, 521–531. [CrossRef]

106. Chu, S.C.; Yu, C.C.; Hsu, L.S.; Chen, K.S.; Su, M.Y.; Chen, P.N. Berberine reverses epithelial-to-mesenchymal transition and inhibits metastasis and tumor-induced angiogenesis in human cervical cancer cells. Mol. Pharmacol. 2014, 86, 609–623. [CrossRef]
107. Zhang, Q.; Sun, Y.; Huang, Y.; Sun, J.; Zhao, C.; Song, Y.; Wu, J. Combination of berberine and matrine affects apoptosis and cellcycle in human cervical cancer cells. *Acta Pol. Pharm.* 2019, 76, 1089–1097. [CrossRef]

108. Zeng, X.; Wan, L.; Wang, Y.; Xue, J.; Yang, H.; Zhu, Y. Effect of low dose of berberine on the radioreistance of cervical cancer cells via a PI3K/HIF-1 pathway under nutrient-deprived conditions. *Int. J. Radiat. Biol.* 2020, 96, 1060–1067. [CrossRef]

109. Rebello, R.J.; Qings, C.; Knudsen, K.E.; Loeb, S.; Johnson, D.C.; Reiter, R.E.; Gillessen, S.; Van der Kwast, T.; Bristow, R.G. Prostate cancer. *Nat. Rev. Dis. Prim.* 2021, 7, 9. [CrossRef]

110. Li, X.N.; Zhang, A.H.; Sun, H.; Liu, Z.D.; Zhang, T.L.; Qiu, S.; Liu, L.; Wang, X.J. Metabolic characterization and pathway analysis of berberine protects against prostate cancer. *Onco Targets* 2017, 8, 65022–65041. [CrossRef]

111. Zenata, O.; Dvorak, Z.; Vrzal, R. Pharmacologically relevant concentrations of berberine transiently stimulate dihydrotestosterone-inducible androgen receptor-mediated luciferase activity in human prostate cancer cells. *Transl. Cancer Res.* 2018, 7, 383–390. [CrossRef]

112. Tian, Y.T.; Zhao, L.J.; Wang, Y.; Zhang, H.T.; Xu, D.; Zhao, X.J.; Li, Y.; Li, J. Berberine inhibits androgen synthesis by interaction with aldo-keto reductase 1C3 in 22Rv1 prostate cancer cells. *Asian J. Androl.* 2016, 18, 607–612. [CrossRef] [PubMed]

113. Huang, Z.H.; Zheng, H.F.; Wang, W.L.; Wang, Y.; Zhong, L.F.; Wu, J.L.; Li, Q.X. Berberine targets epithelial growth factor receptor signaling to suppress prostate cancer proliferation in vitro. *Mol. Med. Rep.* 2015, 11, 2125–2128. [CrossRef] [PubMed]

114. Liu, C.H.; Tang, W.C.; Sia, P.; Huang, C.C.; Yang, P.M.; Wu, M.H.; Lai, I.L.; Lee, K.H. Berberine inhibits the metastatic ability of prostate cancer cells by suppressing epithelial-to-mesenchymal transition (EMT)-associated genes with predictive and prognostic relevance. *Int. J. Med. Sci.* 2015, 12, 63–71. [CrossRef] [PubMed]

115. Zhang, Q.; Zhang, C.; Yang, X.; Yuan, B.; Wang, J.; Kang, Y.; Wang, Z.; Li, D.; Huang, G.; Ma, Z.; et al. Berberine inhibits the expression of hypoxia induction factor-1alpha and increases the radiosensitivity of prostate cancer. *Diagn. Pathol.* 2014, 9, 98. [CrossRef]

116. Gao, X.H.; Liu, J.K.; Fan, D.M.; Li, X.F.; Fang, Z.Q.; Yan, K.Q.; Fan, Y.D. Berberine enhances gemcitabine-induced cytotoxicity in bladder cancer by downregulating Rad51 expression through inactivating the PI3K/Akt pathway. *Oncl. Rep.* 2022, 47, 33. [CrossRef]

117. Zhuo, Y.M.; Chen, Q.B.; Chen, B.; Zhan, X.Y.; Qin, X.P.; Huang, J.; Lv, X.X. Berberine promotes antiproliferative effects of epirubicin in T24 bladder cancer cells by enhancing apoptosis and cell cycle arrest. *Int. J. Clin. Pharmacol. Ther.* 2017, 55, 32–40. [CrossRef]

118. Wang, Y.; Zhang, S.L. Berberine suppresses growth and metastasis of endometrial cancer cells via miR-101/COX-2. *Biomed. Pharmacother.* 2018, 103, 1287–1293. [CrossRef]

119. Liu, J.; Luo, X.; Guo, R.; Jing, W.; Lu, H. Cell metabolomics reveals berberine-inhibited pancreatic cancer cell viability and proliferation by regulating citrate metabolism. *J. Proteome Res.* 2020, 19, 3825–3836. [CrossRef]

120. Och, A.; Zalewski, D.; Komsta, Ł.; Kolodziej, P.; Kocki, J.; Bogucka-Kocka, A. Cytotoxic and proapoptotic activity of sanguinarine, berberine, and extracts of *Chelidonium majus* L. and *Berberis thunbergii* DC. toward hematopoietic cancer cell lines. *Toxins* 2019, 11, 485. [CrossRef]

121. Jiang, S.X.; Qi, B.; Yao, W.J.; Gu, C.W.; Wei, X.F.; Zhao, Y.; Liu, Y.Z.; Zhao, B.S. Berberine displays antitumor activity in esophageal cancer cells in vitro. *World J. Gastroenterol.* 2017, 23, 2511–2518. [CrossRef] [PubMed]

122. Ren, K.; Zhang, W.; Wu, G.; Ren, J.; Lu, H.; Li, Z.; Han, X. Synergistic anti-cancer effects of galangin and berberine through apoptosis induction and proliferation inhibition in oesophageal carcinoma cells. *Biomed. Pharmacother.* 2016, 84, 1748–1759. [CrossRef] [PubMed]

123. Naveen, C.R.; Gaikwad, S.; Agrawal-Rajput, R. Berberine induces neuronal differentiation through inhibition of cancer stemness and epithelial-mesenchymal transition in neuroblastoma cells. *Phytomedicine* 2016, 23, 736–744. [CrossRef] [PubMed]

124. Gao, X.; Zhang, C.; Wang, Y.; Zhang, P.; Zhang, J.; Hong, T. Berberine and cisplatin exhibit synergistic anticancer effects on osteosarcoma MG-63 cells by inhibiting the MAPK pathway. *Molecules* 2021, 26, 1666. [CrossRef]

125. Tong, M.F.; Liu, H.M.; Hao, J.Y.; Fan, D.M. Comparative pharmacoproteomics reveals potential targets for berberine, a promising therapy for colorectal cancer. *Biochem. Biophys. Res. Commun.* 2020, 525, 244–250. [CrossRef] [PubMed]

126. Liu, H.; Huang, C.; Wu, L.Y.; Wen, B. Effect of evodiamine and berberine on miR-429 as an oncogene in human colorectal cancer. *OncoTargets Ther.* 2016, 9, 4121–4126. [CrossRef]

127. Lin, J.P.; Yang, J.S.; Chang, N.W.; Chiu, T.H.; Su, C.C.; Lu, K.W.; Ho, Y.T.; Yeh, C.C.; Mei, D.; Lin, H.J.; et al. GADD153 mediates berberine-induced apoptosis in human cervical cancer Ca sk cells. *Anticancer Res.* 2007, 27, 3379–3386. [CrossRef]

128. Bhanumathi, R.; Vimala, K.; Shanthi, K.; Thangaraj, R.; Kannan, S. Bioformation of silver nanoparticles as berberine carrier cum anticancer agent against breast cancer. *New J. Chem.* 2017, 41, 14466–14477. [CrossRef]

129. Hu, S.W.; Zhao, R.C.; Liu, Y.H.; Chen, J.Z.; Zheng, Z.J.; Wang, S.S. Preventive and therapeutic roles of berberine in gastrointestinal cancers. *BioMed Res. Int.* 2019, 2019, 6831520. [CrossRef]

130. Paudel, K.R.; Mehta, M.; Yin, G.H.S.; Yen, L.L.; Malaya, V.; Patel, V.K.; Panneerselvam, J.; Madheswaran, T.; MacLoughlin, R.; Jha, N.K.; et al. Berberine-loaded liquid crystalline nanoparticles inhibit non-small cell lung cancer proliferation and migration in vitro. *Environ. Sci. Pollut. Res. Int.* 2022, 29, 46830–46847. [CrossRef] [PubMed]

131. Yue, J.; Wang, Z.; Shao, D.; Chang, Z.; Hu, R.; Li, L.; Luo, S.Z.; Dong, W.F. Cancer cell membrane-modified biodegradable mesoporous silica nanocarriers for berberine therapy of liver cancer. *RSC Adv.* 2018, 8, 40288–40297. [CrossRef] [PubMed]
132. Shen, R.; Kim, J.J.; Yao, M.; Elbayoumi, T.A. Development and evaluation of vitamin E d-α-tocopheryl polyethylene glycol 1000 succinate-mixed polymeric phospholipid micelles of berberine as an anticancer nanopharmaceutical. *Int. J. Nanomed.* 2016, 11, 1687–1700. [CrossRef]

133. Othman, M.S.; Obeidat, S.T.; Al-Bagawi, A.H.; Fareid, M.A.; Fehaid, A.; Moneim, A.E.A. Green-synthetized selenium nanoparticles using berberine as a promising anticancer agent. *J. Integr. Med.* 2022, 20, 65–72. [CrossRef] [PubMed]

134. Thomas, A.; Kamble, S.; Deshkar, S.; Kothapalli, L.; Chitlange, S. Bioavailability of berberine: Challenges and solutions. *Istamb. J. Pharm.* 2021, 51, 141–153. [CrossRef]

135. Och, A.; Podgorski, R.; Nowak, R. Biological activity of berberine—a summary update. *Toxins* 2020, 12, 713. [CrossRef] [PubMed]

136. Fang, S.; Guo, S.; Du, S.; Cao, Z.; Yang, Y.; Su, X.; Wei, W. Efficacy and safety of berberine in preventing recurrence of colorectal adenomas: A systematic review and meta-analysis. *J. Ethnopharmacol.* 2022, 282, 114617. [CrossRef]

137. Mirzaee, F.; Razmjouei, P.; Shahrahmani, H.; Vafisani, F.; Najafi, M.N.; Ghazanfarpour, M. The effect and safety of Berberine on polycystic ovary syndrome: A systematic review. *J. Obstet. Gynaecol.* 2021, 41, 684–689. [CrossRef] [PubMed]