ROZWADOWSKA, Patrycja, BATOR, Piotr, RAZIK, Michał, RAMIAN, Jan, RYBAK, Jakub, MAGIERA, Barbara, MAGIERA, Karol and RAZIK, Wiktor. Anticancer properties of berberine - analysis of the latest reports. Journal of Education, Health and Sport. 2024;61:73-86. eISSN 2391-8306. https://dx.doi.org/10.12775/JEHS.2024.61.005
https://apcz.umk.pl/JEHS/article/view/48332
https://zenodo.org/records/10672439

The journal has had 40 points in Minister of Science and Higher Education of Poland parametric evaluation. Annex to the announcement of the Minister of Education and Science of 05.01.2024 No. 32318. Has a Journal's Unique Identifier: 201159. Scientific disciplines assigned: Physical culture sciences (Field of medical and health sciences); Health Sciences (Field of medical and health sciences).
Punkty Ministerialne 40 punktów. Załącznik do komunikatu Ministra Nauki i Szkolnictwa Wyższego z dnia 05.01.2024 Lp. 32318. Posiada Unikatowy Identyfikator Czasopisma: 201159. Przypisane dyscypliny naukowe: Nauki o kulturze fizycznej (Dziedzina nauk medycznych i nauk o zdrowiu); Nauki o zdrowiu (Dziedzina nauk medycznych i nauk o zdrowiu).© The Authors 2024;
This article is published with open access at Licensee Open Journal Systems of Nicolaus Copernicus University in Torun, Poland

The authors declare that there is no conflict of interests regarding the publication of this paper.
Received: 25.01.2023. Revised: 12.02.2024. Accepted: 16.02.2024. Published: 16.02.2024.

Anticancer properties of berberine - analysis of the latest reports

Patrycja Rozwadowska, Piotr Bator, Michał Razik, Jan Ramian, Jakub Rybak, Barbara Magiera, Karol Magiera, Wiktor Razik

Patrycja Rozwadowska
patrycja.roz98@gmail.com
Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
ORCID: 0000-0001-8541-2108

Piotr Bator
piotrbator9@icloud.com
Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
ORCID: 0009-0009-3300-0078

Michał Razik
michrazik@gmail.com
Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
ORCID: 0009-0005-8930-8961

Jan Ramian
ramianjann@gmail.com
Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
ORCID: 0009-0002-1956-241X

Jakub Rybak
rybakjak@gmail.com
Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
ORCiD 0009-0005-0481-1569

Barbara Magiera
barbaramgra@gmail.com
Prof. K. Gibiński University Clinical Center of the Medical University of Silesia in Katowice, Medyków 14, 40-752 Katowice
ORCiD 0009-0001-9180-9942

Karol Magiera
magierakarol0@gmail.com
Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland, ORCiD: 0009-0004-8621-9755

Wiktor Razik
wiktor.razik@onet.pl
Faculty of Medical Sciences in Katowice, Medical University of Silesia, Katowice, Poland
ORCID: 0009-0005-7370-7933

ABSTRACT

Introduction and purpose:

Berberine is a plant alkaloid that naturally occurs in the fruits of common barberry (Berberis vulgaris). This alkaloid has long been used in natural medicine. It exhibits a range of bioactivities, such as antioxidant, anti-inflammatory, antidiabetic, anti-edema, and antimicrobial actions. Through the promising therapeutic effects of berberine in metabolic syndrome, as well as its impact on carcinogenesis, this compound is beginning to play a significant role in preventive medicine. Recently, particular attention has been paid to the anticancer properties of berberine, which are based on many biochemical pathways, particularly its pro-apoptotic and anti-inflammatory action. The study aimed to review the anticancer mechanisms of berberine and summarize them about individual cancers.

State of knowledge:

The article reviews the current literature on the anticancer properties of berberine for individual cancers, focusing primarily on its molecular mechanisms of action. In addition, the potential of berberine as a promising candidate forming the basis for drug production and its use in preventive medicine was analyzed.

Summary:

In summary, many studies have shown that berberine exhibits anticancer activity in many types of cancers, including breast, lung, stomach, liver, colorectal, ovarian, cervical, and prostate cancers. Berberine inhibits the growth of cancer cells, limits metastases, induces apoptosis, stimulates autophagy, and enhances the effectiveness of anticancer drugs. Despite its potential as a promising candidate for drug production, there are currently no approved pure berberine preparations for the treatment of specific ailments. Research on its effectiveness and safety is still ongoing.

KEYWORDS: berberine, anticancer properties, anticancer medications, cancer

INTRODUCTION

Berberine is a plant metabolite belonging to the group of isoquinoline alkaloids with strong biological and pharmacological activity [1]. Berberine naturally occurs in the fruits of common barberry (Berberis vulgaris). This alkaloid has been used in natural medicine for many years. Currently, berberine is attracting great interest due to its anticancer activity based on many biochemical pathways, especially its pro-apoptotic and anti-inflammatory action [1]. In addition to anticancer properties, the alkaloid may also be useful in the treatment of other diseases such as diabetes, obesity, hyperglycemia, and hyperlipidemia. Inhibition and control of metabolic syndrome is particularly important due to the significant increase in the number of patients struggling with it recently [2]. However, its oral bioavailability is limited by P-glycoprotein (P-gp), a membrane transporter that removes berberine from intestinal cells [3]. Therefore, berberine is currently being intensively studied, and its anticancer activity, reflected in the pro-apoptotic effect, seems to be the most promising direction of research [1].

ANTICANCER PROPERTIES

Berberine is a natural compound that exhibits many bioactivities, such as antioxidant, anti-inflammatory, antidiabetic, anti-edema, and antimicrobial actions. Studies have shown that berberine has anticancer effects on various types of cancers, such as breast, lung, stomach, liver, colon, ovarian, cervical, and prostate cancer [4].

1.1. Breast Cancer

TNBC is a triple-negative breast cancer, which is an aggressive subtype of breast cancer. Berberine was shown to exhibit toxic properties against all TNBC cell lines such as MDA-MB-231, MDA-MB-468, HCC1937, HCC70, HCC38, BT-20, HCC1143 and BT-549. The alkaloid not only induced cell cycle arrest in the first (G1) and second growth phase (G2)/medium, but also induced significant apoptosis. In addition, berberine did not affect normal breast cells (MCF10) [5]. In cultures of MDA-MB-468 cells, the compound reduced the expression of proliferating cell nuclear antigen (PCNA) and cyclin D1 proteins, blocking their progression to the G1 phase of the cell cycle [6]. The role of berberine against the MDA-MB-231 malignant breast cancer cell line was also investigated, and the compound was shown to reduce cell migration capacity, provoke inhibition of phosphorylation, reduce overexpression of tumor necrosis factor α (TNF-α) and interleukin 6 (IL-6), and induce suppression of the nuclear factor kappa light chain enhancer of activated β cells (NF-Kβ) [7]. Berberine also showed synergistic effects with TRAIL on the MDA-MB-231 breast cancer cell line, which is sensitive to TRAIL, and the MDA-MB-468 breast cancer cell line, which is resistant to TRAIL. Berberine not only interacted with TRAIL but also increased the sensitivity of resistant cells, as confirmed by markers of this process, such as caspase-3, PARP 9 cleavage of poly (ADP-ribose) polymerase 1, and p53. Additionally, despite berberine's moderate cytotoxicity, when combined with anti-DR5, it inhibits primary growth and reduces lung metastasis in the 4T1 breast cancer cell line [8,9]. Berberine has also been shown to reduce the deleterious effects of doxorubicin, and the berberine/doxorubicin nanocomposite acted synergistically to reduce tumor growth and metastasis in breast cancer xenograft models [10]. The findings presented here demonstrate that berberine may show promise in developing a breast cancer drug in the future.

1.2. Colon Cancer

In a study by Chen et al, patients with confirmed colorectal adenomas who underwent polypectomy were treated with berberine or placebo. Berberine proved effective in reducing the risk of adenoma

recurrence, with no side effects except constipation. Colorectal adenomas are benign but can undergo malignant transformation into cancer, especially in patients with metabolic syndrome and inflammation. Therefore, berberine may be helpful in the prevention of these cancers. Importantly, none of the study participants developed cancer during follow-up [11]. The alkaloid was shown to inhibit the transformation of colorectal adenoma into colorectal cancer via pyruvate kinase isozyme type M2 (PKM2) and by inhibiting the Warburg effect [12]. In addition, berberine has been shown to inhibit STAT3, which reduces MMP2/9 expression and inhibits colorectal cancer metastasis [13]. The alkaloid also exerts anti-cancer effects by inhibiting cell activity, and apoptosis, and increasing CASC2 lncRNA expression [14,15]. Liu and colleagues conducted studies on colorectal cancer (CRC) stem cells, which showed that berberine inhibits CRC cell invasion and metastasis via prostaglandin-endoperoxide synthase 2/prostaglandin E2, whose action is mediated by the Janus kinase 2 pathway [16]. Berberine treatment has also been shown to inhibit colon cancer cell viability, induce apoptosis, and activate caspase-3 activity in the human colon cancer cell line HCT116 [17].

1.3. Pancreatic Cancer

One study evaluated the effects of berberine and its modified NAX compounds, metformin, and chemotherapeutic drugs on four pancreatic adenocarcinoma cell lines (AsPC-1, BxPC-3, MIA-PaCa-2, and PANC-28). It was shown that both berberine and its modified compounds enhanced the effects of metformin and were involved in inhibiting the expression of key molecules for cell growth. Thus, such combined treatment may help inhibit the proliferation of pancreatic cancer cells [18]. In human pancreatic cancer cells (BxPC-3 cells), berberine has been studied to inhibit tumor cell growth and mediate caspase-independent cell death [19]. In one study, berberine also showed the ability to suppress Rad51 expression and increase PARP expression in pancreatic cancer cells (PANC-1, AsPC-1, and MIA-PaCa-2) compared to control pancreatic cancer cells. The joint action of olaparib (a PARP inhibitor) and berberine synergistically inhibited cellular activity and led to the induction of apoptosis in experimental pancreatic cancer cells [20]. Berberine, by affecting the expression of miR-17-5p, which is a poor prognostic indication for pancreatic cancer, may also have additional implications for the treatment of this cancer [21]. In addition, this alkaloid also plays an important role in inhibiting metastasis and limiting the viability of pancreatic cancer cells by deregulating their energy metabolism. Berberine also affects citrate metabolism, which may prove to be a promising target when developing drugs for pancreatic cancer [22].

1.4. Gastric Cancer

Gastric cancer is associated with matrix metalloproteinases (MMP-1,-2,-7,-9), which contribute to malignant cell invasion and metastasis. Berberine exhibits anti-tumor properties in these cancer cells by inhibiting the expression of MMP-1,-2, and -9 genes [23, 24]. The alkaloid also acts by inhibiting STAT3 activity, which is induced by EGFR, making gastric cancer more sensitive to EGFR inhibitors such as cetuximab and erlotinib [25]. This compound also reverses gastric cancer resistance to cisplatin [26]. Studies conducted on both cellular samples (in vitro) and living organisms (in vivo) have shown that berberine can inhibit the growth of BGC-823 gastric cancer cells by causing autophagy, a process that stops cell growth, by suppressing the MAPK/mTOR/p70S6K and Akt signaling pathways [27]. Therefore, researchers suggest that berberine hydrochloride could be a potential treatment for gastric cancer because it affects MAPK signaling pathways [28].

1.5. Liver Cancer

In berberine-treated Huh-7 and HepG2 cells, cell cycle arrest at the G1 stage was observed, demonstrating that berberine also has anticancer properties in hepatocellular carcinoma (HCC) cells [29]. In addition, the use of this alkaloid inhibits cell viability in the liver cancer cell lines SNU-182, Hep3B, and HepG2, due to its modulating effect on the expression of many tumor-associated gene proteins [30]. In one study, simultaneous administration of berberine and sorafenib was shown to synergistically inhibit the proliferation of human liver cells (HepG2 and SMM-7721) in a concentration-dependent manner [31]. In contrast, berberine 9-/13-dodecyl derivatives were responsible for destabilizing mitochondrial membrane potential and increasing ROS production, along with cell cycle arrest and apoptosis in liver cancer cells [32].

1.6. Oral Cancer

Berberine also exhibits anticancer properties against KB oral cancer cells by leading to genomic DNA fragmentation, changes in cell morphology, and nuclear condensation. The alkaloid has also been shown to increase the expression of the death receptor ligand FasL and increase the activity of caspase-3 and -7, which play an important role in apoptosis. Due to the actions of berberine, the expression of proapoptotic factors is increased, while anti-apoptotic factors are decreased [33].

1.7. Bone Cancer

The positive effect of berberine was also demonstrated by its administration to osteosarcoma cells both in vitro and in vivo. By reducing the expression of caspase-1 and interleukin-1 (IL-1), there was an inhibition of tumor cell growth [34]. Berberine has also been shown to downregulate integrin v3 mediated by protein kinase C (PKC) and the protooncogene tyrosine-protein kinase c-Src, thereby inhibiting the migration and invasion of human chondrosarcoma cells [35]. To induce PDCD4 expression, berberine downregulates miR-21, which in turn contributes to multiple myeloma apoptosis by suppressing p53 [36].

1.8. Cancer of the Glioblastoma

Blocking the AMPK/mTOR/ULK1 pathway involving berberine leads to reduced tumor growth in polymorphic glioblastoma multiforme (GBM) cells in vivo [37]. The glioma microenvironment is characterized by inflammation, so special attention is paid to IL-1 and other neuroinflammatory cytokines that play a role in tumor initiation and progression [38]. Berberine through ERK1/2 signaling inhibits the activation of the inflammatory cytokine caspase-1 and later also the development of IL-1 and IL-18 in glioma cells. Moreover, berberine has been studied to have the potential to reverse the mechanism of epithelial-mesenchymal metastasis [39]. In addition, berberine has been shown to reverse temozolomide resistance in glioma [40].

1.9. Skin Cancer

Berberine administration induced morphological changes in cells and reduced the number of viable cells in human cutaneous melanoma cells (A375.S2 and A375.S2/PLX). Berberine treatment of A375.S2 cells led to the inhibition of SOS-1, p-AKT, MMP-1, NF-κB, Ras, p-FAK, and MMP-13 gene expression, as well as an increase in PI3K and PKC levels [41]. In addition, the treatment induced various biochemical changes, such as loss of mitochondrial membrane potential, release of cytochrome C into the cytosol, and cleavage of poly (ADP) ribose polymerase, which induced apoptotic conditions and inhibited the development of cutaneous squamous cell carcinoma [42]. By molecular analysis, berberine was shown to bind STAT3 directly. This mechanism results in decreased IL-10 expression, reprogramming of tumor-associated M2 macrophages to an M1 tumor suppressor phenotype, and increased recognition of tumor cells by T cells. These mechanisms have been shown to reduce tumor burden in mice with melanoma [43].

1.10. Uterus and Endometrium Cancer

According to the results of both in vitro and in vivo studies by Wang and Zhang, berberine inhibited proliferation, migration, and invasion, as well as metastasis in endometrial cancer. The researchers showed that berberine inhibits tumor cells through COX-2/PGE2 signaling pathways [44]. The alkaloid also engages the PI3K/Akt pathway, which also plays a role in the prevention and treatment of endometrial cancer [45]. In one study, berberine or placebo was also administered to patients treated for seminoma, lymphoma, and cervical cancer. Despite the small study group, the study showed that berberine significantly delayed and reduced the incidence of radiation-induced acute abdominal syndrome. Based on the results, it was concluded that berberine may have a protective role in patients treated with radiation therapy [46].

1.11. Prostate Cancer

The LNCaP cell line that was xenografted into nude mice was treated with berberine. This alkaloid improved the sensitivity of prostate cancer cells and xenografts to radiation in a dose-dependent manner by inhibiting the expression of HIF-1 and VEGF [47]. Berberine was also shown to reduce the proliferation of human prostate cancer epithelial cell line 22Rv1 and decrease cellular testosterone synthesis [48]. The action of berberine leads to a significant decrease in the expression of a set of mesenchymal genes responsible for the development of EMT. High expression levels of BMP7, NODAL, and Snail genes in metastatic prostate cancer tissues are associated with shorter survival in patients. Therefore, downregulation of gene expression by berberine may be a potential therapeutic target [49].

1.12. Thyroid Cancer

Two thyroid cancer cell lines, 8505C, and TPC1, showed a dose-dependent decrease in growth after berberine treatment. 8505C cells showed a marked increase in apoptosis, while TPC1 cells showed cell cycle arrest in the G0/G1 phase [50]. Besides, berberine also inhibited RET expression in medullary thyroid carcinoma (MTC) cells by more than 90% [51].

SUMMARY

Berberine's mechanisms of action include inhibition of tumor cell proliferation, suppression of metastasis, induction of apoptosis, activation of autophagy, regulation of the gut microbiota, and

enhancement of anticancer drug effects [4]. Despite advances in currently used chemotherapy, resistance and non-response to many chemotherapeutics is still a significant problem. Therefore, cancer immunotherapy has recently received considerable attention as a treatment option for certain cancers. Natural plant-derived compounds have been shown to have anti-cancer properties by modulating traditional cancer pathways as well as immunity [52]. Berberine is also beneficial at early stages of tumor development by downregulating the expression of epithelial-mesenchymal transition proteins [2]. Despite its importance as a potentially promising drug candidate, there are currently no approved pure preparations of berberine for the treatment of specific ailments [2]. Despite its potential, berberine is not yet widely used in anticancer therapy, and its efficacy and safety are still under investigation [1,2].

Author's contribution:

Conceptualization: P.R., P.B.; methodology: P.R., P.B.: software: P.R., M.R., P.B., J.R.; formal analysis: P.R., M.R., P.B., J.R.; investigation: P.R. ,M.R., P.B., J.R., J.R., B.M., K.M, W.R.; resources: P.R. ,M.R., P.B., J.R.; data curation: P.R. ,M.R., P.B., J.R., B.M., K.M., W.R.; writing - rough preparation:
P.R. ,M.R., P.B., J.R., J.R., B.M., K.M, W.R.; writing - review and editing:
P.R. ,M.R., P.B., J.R., J.R., B.M., K.M, W.R. ; visualization: P.R., M.R.;
supervision: P.R., P.B. project administration: P.R., M.R.

Supplementary Materials: They have not been provided.

Funding statement: This research received no external funding.

Institutional Review Board Statement: Not applicable.

Informed Consent Statement: Not applicable.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest. All authors have read and agreed to the published version of the manuscript.

REFERENCES

1. Och A, Podgórski R, Nowak R. Biological Activity of Berberine—A Summary Update. Toxins. 2020;12, 713. doi: 10.3390/toxins12110713.
2. Rauf A, Abu-Izneid T, Khalil AA, Imran M, Shah ZA, Emran TB, et al. Berberine as a potential anticancer agent: A comprehensive review. Molecules. 2021;26(23):7368. doi: 10.3390/molecules26237368.
3. Kim JB, Ko E, Han W, Shin I, Park SY, Noh DY. Berberine diminishes the side population and ABCG2 transporter expression in MCF-7 breast cancer cells. Planta Med. 2008;74(14):1693-700. doi: 10.1055/s-0028-1088313.
4. Xiong RG, Huang SY, Wu SX, et al. Anticancer Effects and Mechanisms of Berberine from Medicinal Herbs: An Update Review. Molecules. 2022;27(14):4523. DOI: 10.3390/molecules27144523. PMID: 35889396; PMCID: PMC9316001.
5. El Khalki L, Maire V, Dubois T, Zyad A. Berberine impairs the survival of triple-negative breast cancer cells: Cellular and molecular analyses. Molecules. 2020;25:506.
6. Lin YS, Chiu YC, Tsai YH, Tsai YF, Wang JY, Tseng LM, Chiu JH. Different mechanisms involved in the berberine-induced antiproliferation effects in triple-negative breast cancer cell lines. J Cell Biochem. 2019;120:13531–13544.
7. Zhao L, Zhang C. Berberine Inhibits MDA-MB-231 Cells by attenuating their inflammatory responses. BioMed Res Int. 2020;2020:3617514.
8. Farooqi AA, Qureshi MZ, Khalid S, Attar R, Martinelli C, Sabitaliyevich UY, Nurmurzayevich SB, Taverna S, Poltronieri P, Xu B. Regulation of Cell Signaling Pathways by Berberine in Different Cancers: Searching for Missing Pieces of an Incomplete Jig-Saw Puzzle for an Effective Cancer Therapy. Cancers. 2019;11:478. doi: 10.3390/cancers11040478.
9. Refaat A, Abdelhamed S, Yagita H, Inoue H, Yokoyama S, Hayakawa Y, Saiki I. Berberine Enhances Tumor Necrosis Factor-related Apoptosis-inducing Ligand-mediated Apoptosis in Breast Cancer. Oncol Lett. 2013;6:840–844. doi: 10.3892/ol.2013.1434.
10. Zheng X, Zhao Y, Jia Y, Shao D, Zhang F, Sun M, et al. Biomimetic co-assembled nanodrug of doxorubicin and berberine suppresses chemotherapy-exacerbated breast cancer metastasis. Biomaterials. 2021;271:120716. doi: 10.1016/j.biomaterials.2021.120716.
11. Chen YX, Gao QY, Zou TH, Wang BM, Liu SD, Sheng JQ, et al. Berberine versus placebo for the prevention of recurrence of colorectal adenoma: A multicentre, double-blinded, randomised controlled study. Lancet Gastroenterol Hepatol. 2020;5(3):267–75. doi: 10.1016/S2468-1253(19)30409-1.

12. Yan SH, Hu LM, Hao XH, Liu J, Tan XY, Geng ZR, et al. Chemoproteomics reveals berberine directly binds to PKM2 to inhibit the progression of colorectal cancer. iScience. 2022;25(8):104773. doi: 10.1016/j.isci.2022.104773.
13. Liu X, Ji Q, Ye N, Sui H, Zhou L, Zhu H, et al. Berberine inhibits invasion and metastasis of colorectal cancer cells via COX-2/PGE2 mediated JAK2/STAT3 signaling pathway. PloS One. 2015;10(5):e0123478. doi: 10.1371/journal.pone.0123478.
14. Dai W, Mu L, Cui Y, Li Y, Chen P, Xie H, Wang X. Berberine promotes apoptosis of colorectal cancer via regulation of the long non-coding RNA (lncRNA) cancer susceptibility candidate 2 (CASC2)/AU-binding factor 1 (AUF1)/B-cell CLL/lymphoma 2 (Bcl-2) axis. Med Sci Monitor. 2019;25:730.
15. Hu S, Zhao R, Liu Y, Chen J, Zheng Z, Wang S. Preventive and therapeutic roles of berberine in gastrointestinal cancers. BioMed Res Int. 2019;2019:6831520.
16. Liu H, Huang C, Wu L, Wen B. Effect of evodiamine and berberine on miR-429 as an oncogene in human colorectal cancer. Onco Targets Ther. 2016;9:4121.
17. 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.
18. Akula SM, Candido S, Libra M, Abrams SL, Steelman LS, Lertpiriyapong K, Ramazzotti G, Ratti S, Follo MY, Martelli AM, et al. Abilities of berberine and chemically modified berberines to interact with metformin and inhibit proliferation of pancreatic cancer cells. Adv Biol Regul. 2019;73:100633.
19. Pinto-Garcia L, Efferth T, Torres A, Hoheisel JD, Youns M. Berberine inhibits cell growth and mediates caspase-independent cell death in human pancreatic cancer cells. Planta Med. 2010;76:1155–1161.
20. Zhang C, Yang T, Chen X, Xu J, Liang D, Yi H, Chen S, Huang L, Liu N, Lin S. A preliminary study on the synthetic lethal effect of berberine and olaparib on pancreatic cancer cells and its mechanism. In IE3S Web of Conferences. 2020;130:01013. doi: 10.1051/ie3sconf/202013001013.
21. Bobbili MR, Mader RM, Grillari J, Dellago H. OncomiR-17-5p: alarm signal in cancer? Oncotarget. 2017;8(41):71206–22. doi: 10.18632/oncotarget.19331.
22. Liu J, Luo X, Guo R, Jing W, Lu H. Cell metabolomics reveals berberine-inhibited pancreatic cancer cell viability and metastasis by regulating citrate metabolism. J Proteome Res. 2020;19:3825–3836.
23. Shapiro SD. Matrix metalloproteinase degradation of extracellular matrix: Biological consequences. Curr Opin Cell Biol. 1998;10:602–608.

24. Lin J, Yang J, Wu C, Lin S, Hsieh W, Lin M, Yu F, Yu C, Chen G, Chang Y, et al. Berberine induced down-regulation of matrix metalloproteinase-1, -2 and -9 in human gastric cancer cells (SNU-5) in vitro. In Vivo. 2008;22:223–230.
25. Wang J, Yang S, Cai X, Dong J, Chen Z, Wang R, et al. Berberine inhibits EGFR signaling and enhances the antitumor effects of EGFR inhibitors in gastric cancer. Oncotarget. 2016;7(46):76076–86. doi: 10.18632/oncotarget.12589.
26. Kou Y, Tong B, Wu W, Liao X, 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. doi: 10.3389/fphar.2020.616251.
27. You HY, Xie XM, Zhang WJ, Zhu HL, Jiang FZ. Berberine modulates cisplatin sensitivity of human gastric cancer cells by upregulation of miR-In Vitro. Cell Dev Biol Anim. 2016;52:857–863.
28. Zhang Q, Wang X, Cao S, Sun Y, He X, Jiang B, Yu Y, Duan J, Qiu F, Kang N. Berberine represses human gastric cancer cell growth in vitro and in vivo by inducing cytostatic autophagy via inhibition of MAPK/mTOR/p70S6K and Akt signaling pathways. Biomed Pharmacother. 2020;128:110245.
29. Li F, Dong X, Lin P, Jiang J. Regulation of Akt/FoxO3a/Skp2 axis is critically involved in berberine-induced cell cycle arrest in hepatocellular carcinoma cells. Int J Mol Sci. 2018;19:327.
30. Chuang TY, Wu HL, Min J, Diamond M, Azziz R, Chen YH. Berberine regulates the protein expression of multiple tumorigenesis-related genes in hepatocellular carcinoma cell lines. Cancer Cell Int. 2017;17:1–8.
31. Huang Y, Wang K, Gu C, Yu G, Zhao D, Mai W, Zhong Y, Liu S, Nie Y, Yang H. Berberine, a natural plant alkaloid, synergistically sensitizes human liver cancer cells to sorafenib. Oncol Rep. 2018;40:1525–1532.
32. Lin HJ, Ho JH, Tsai LC, Yang FY, Yang LL, Kuo CD, et al. Synthesis and In vitro photocytotoxicity of 9-/13-Lipophilic substituted berberine derivatives as potential anticancer agents. Molecules. 2020;25(3):677. doi: 10.3390/molecules25030677.
33. Kim JS, Oh D, Yim MJ, Park JJ, Kang KR, Cho IA, Moon SM, Oh JS, You JS, Kim CS. Berberine induces FasL-related apoptosis through p38 activation in KB human oral cancer cells. Oncol Rep. 2015;33:1775–1782.
34. Jin H, Jin X, Cao B, Wang W. Berberine affects osteosarcoma via downregulating the caspase-1/IL-1β signaling axis. Oncol Rep. 2017;37:729–736.

35. Hsu HK, Hsu KH, Cheng YM, Suen HY, Peng SF. Development and in vitro evaluation of linear PEI-shelled heparin/berberine nanoparticles in human osteosarcoma U-2 OS cells. Molecules. 2018;23:3121.
36. Luo X, Gu J, Zhu R, Feng M, Zhu X, Li Y, et al. Integrative analysis of differential miRNA and functional study of miR-21 by seed-targeting inhibition in multiple myeloma cells in response to berberine. BMC Syst Biol. 2014;8:82. doi: 10.1186/1752-0509-8-82.
37. Wang J, Qi Q, Feng Z, Zhang X, Huang B, Chen A, Prestegarden L, Li X, Wang J. Berberine induces autophagy in glioblastoma by targeting the AMPK/mTOR/ULK1-pathway. Oncotarget. 2016;7(41):66944–58. doi: 10.18632/oncotarget.11396. PMID: 27531889; PMCID: PMC5342793.
38. Nasrollahzadeh E, Razi S, Keshavarz-Fathi M, Mazzone M, Rezaei N. Pro-tumorigenic functions of macrophages at the primary, invasive and metastatic tumor site. Cancer Immunol Immunother. 2020;69:1673–1697.
39. Tong L, Xie C, Wei Y, Qu Y, Liang H, Zhang Y, Xu T, Qian X, Qiu H, Deng H. Antitumor effects of berberine on gliomas via inactivation of caspase-1-mediated IL-1β and IL-18 release. Front Oncol. 2019;9:364.
40. Qu H, Song X, Song Z, Jiang X, Gao X, Bai L, et al. Berberine reduces temozolomide resistance by inducing autophagy via the ERK1/2 signaling pathway in glioblastoma. Cancer Cell Int. 2020;20(1):592. doi: 10.1186/s12935-020-01693-y.
41. Liu JF, Lai KC, Peng SF, Maraming P, Huang YP, Huang AC, Chueh FS, Huang WW, Chung JG. Berberine inhibits human melanoma AS2 cell migration and invasion via affecting the FAK, uPA, and NF-κB signaling pathways and inhibits PLX4032 resistant AS2 cell migration in vitro. Molecules. 2018;23:2019.
42. Li DX, Zhang J, Zhang Y, Zhao PW, Yang LM. Inhibitory effect of berberine on human skin squamous cell carcinoma A431 cells. Genet Mol Res. 2015;14:10553–10568.
43. Shah D, Challagundla N, Dave V, Patidar A, Saha B, Nivsarkar M, et al. Berberine mediates tumor cell death by skewing tumor-associated immunosuppressive macrophages to inflammatory macrophages. Phytomedicine. 2022;99:153904. doi: 10.1016/j.phymed.2021.153904.
44. Wang Y, Zhang S. Berberine suppresses growth and metastasis of endometrial cancer cells via miR-101/COX-2. Biomed Pharmacother. 2018;103:1287–1293.
45. Kuo HP, Lee YJ, Hsu CY, Lee SL, Hsu SC, Chuang TC, Liu JY, Kuo CL, Ho CT, Kao MC. Growth-suppressive effect of berberine on endometrial carcinoma cells: Role of mitochondrial and PI3K/Akt pathway. J Funct Foods. 2015;17:600–609.

46. Li Gh, Wang Dl, Hu Y, Pu P, Li Dz, Wang Wd, et al. Berberine inhibits acute radiation intestinal syndrome in human with abdomen radiotherapy. Med Oncol. 2010;27(3):919–25. doi: 10.1007/s12032-009-9307-8.
47. Zhang Q, Zhang C, Yang X, Yang B, Wang J, Kang Y, Wang Z, Li D, Huang G, Ma Z. Berberine inhibits the expression of hypoxia induction factor-1alpha and increases the radiosensitivity of prostate cancer. Diagn Pathol. 2014.
48. Tian Y, Zhao L, Wang Y, Zhang H, Xu D, Zhao X, 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.
49. Liu CH, Tang WC, Sia P, Huang CC, Yang PM, Wu MH, Lai IL, Lee KH. 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 Biol Med Sci. 2015;12:63.
50. Park KS, Kim JB, Bae J, Park SY, Jee HG, Lee KE, Youn YK. Berberine inhibited the growth of thyroid cancer cell lines 8505C and TPC. Yonsei Med J. 2012;53:346–351.
51. Kumarasamy VM, Sun D. Demonstration of a potent RET transcriptional inhibitor for the treatment of medullary thyroid carcinoma based on an ellipticine derivative. Int J Oncol. 2017;51:145–157.
52. Bernitsa S, Dayan R, Stephanou A, Tzvetanova ID, Patrikios IS. Natural biomolecules and derivatives as anticancer immunomodulatory agents. Front Immunol. 2023;DOI:10.3389/fimmu.2022.1070367.