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Molecular Mechanisms of Berberine Action on Tumor Cells

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ABSTRACT

Malignant tumors remain one of the leading causes of mortality worldwide, highlighting the urgent need to develop novel and effective therapeutic strategies. In recent years, the scientific community has actively pursued agents that combine high efficacy with minimal adverse effects and offer the potential to induce complete remission. In this context, berberine is a natural phytochemical derived from various Berberis species. It has garnered considerable interest due to its diverse pharmacological properties. Berberine, known as a nutraceutical, exhibits a broad spectrum of biological activity, including anti-inflammatory, antioxidant, and antitumor effects. *In vitro* and *in vivo* studies have shown that berberine exerts inhibitory activity against several cancer types, including breast, lung, liver, and colorectal cancers. Its antitumor properties are associated with several key molecular mechanisms through which it exerts effects on tumor cells. This review provides a detailed overview of the molecular pathways through which the antitumor effects of berberine are mediated. In particular, berberine activates the caspase cascade, leading to the induction of apoptosis in tumor cells, and inhibits cell proliferation by blocking key signaling pathways such as PI3K/Akt/mTOR. It also modulates the expression of genes involved in cell migration and invasion, including matrix metalloproteinases and E-cadherin, highlighting its potential as a promising therapeutic candidate. Additionally, berberine's anti-inflammatory effects may contribute to cancer prevention by protecting cells from oxidative stress and chronic inflammation associated with tumor development. These pharmacological properties make berberine a promising agent for further investigation and clinical application, both as monotherapy and in combination with standard anticancer therapies. Thus, berberine represents a promising subject for further investigation of its molecular mechanisms of action and potential use in oncology, which may lead to the development of more effective and safer therapeutic strategies for patients with malignant tumors.

Keywords: oncology; berberine; alkaloids; plant metabolites; autophagy; apoptosis.

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Молекулярные механизмы влияния берберина на опухолевые клетки

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АННОТАЦИЯ

Злокачественные опухоли остаются одной из основных причин смертности во всём мире, что подчёркивает необходимость разработки новых и эффективных терапевтических стратегий для их лечения. В последние годы научное сообщество активно занимается поиском лекарственных средств с минимальными нежелательными явлениями и высокой эффективностью, которые могут привести к полной ремиссии у пациентов. В этом контексте берберин, природный фитохимический компонент, получаемый из различных видов барбариса, привлекает всё большее внимание благодаря своим многообразным фармакологическим свойствам. Берберин, известный как нутрицевтик, демонстрирует широкий спектр биологической активности, включая противовоспалительные, антиоксидантные и противоопухолевые эффекты. Исследования *in vitro* и *in vivo* показали, что берберин обладает ингибирующим действием на несколько типов рака, включая рак молочной железы, лёгких, печени и кишечника. Его противоопухолевые свойства связаны с несколькими ключевыми молекулярными механизмами, через которые он воздействует на опухолевые клетки. В данном обзоре мы подробно рассмотрели различные молекулярные пути, через регуляцию которых опосредованы противоопухолевые эффекты берберина. В частности, берберин активирует каспазный каскад, что приводит к индукции апоптоза в опухолевых клетках, а также ингибирует пролиферацию клеток, блокируя ключевые сигнальные пути, такие как PI3K/Akt/mTOR. Кроме того, берберин модулирует экспрессию генов, связанных с клеточной миграцией и инвазией, включая матриксные металлопротеиназы и E-cadherin, что делает его многообещающим кандидатом для разработки новых терапевтических подходов. Также стоит отметить, что берберин обладает противовоспалительными свойствами, что может способствовать предотвращению канцерогенеза, защищая клетки от окислительного стресса и воспалительных процессов, связанных с развитием рака. Эти свойства делают берберин перспективным средством для дальнейших исследований и клинического применения как в качестве монотерапии, так и в комбинации с другими противоопухолевыми препаратами. Таким образом, берберин представляет собой интересный объект для дальнейшего изучения его молекулярных механизмов действия и потенциала использования в онкологии, что может привести к созданию более эффективных и безопасных терапевтических стратегий для пациентов со злокачественными опухолями.

Ключевые слова: онкология; берберин; алкалоиды; растительные метаболиты; аутофагия; апоптоз.

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BACKGROUND

Over the years, despite the improvement in the prognosis for patients with cancer treated with modern therapies, cancer remains a leading cause of mortality worldwide [1–3]. Chemotherapy, surgery, and radiotherapy are the most common modern cancer treatment methods. Advances in molecular biology, genetics, and immunology have led to the understanding of the molecular mechanisms involved in cancer development, which has resulted in the development of new treatment methods such as gene therapy, targeted therapy, and immunotherapy [4].

Compounds that can act on several targets can be used as an alternative to drugs that target a defined target, having fewer side effects and being effective against different tumors [5, 6]. These include several plant-based products that attract increased interest [7]. According to recent literature, various plant-based compounds play a crucial role in inhibiting proteins, enzymes, and signaling pathways of tumor cells, such as alkaloids, flavonoids, lignans, saponins, terpenes, taxanes, and other primary or secondary plant metabolites (SPMs) [8–10].

Clinical studies are being conducted to assess the potential effect of alkaloids when they are included in the treatment of patients with cancer (ClinicalTrials.gov NCT03281096, NCT03333265, NCT02226185, and NCT03486496).

Berberine—an SPM and natural isoquinoline alkaloid obtained from various plants—has attracted considerable attention from several authors. It was found in the rhizome of *Coptidis* and in many species of *Berberis* (*Berberis aquifolium*, *Berberis vulgaris L.*, and *Berberis aristata DC*), *Coptis* (*Coptis chinesis Franch*. and *Coptis japonica Makino*), and *Hydrastis* (*Hydrastis canadensis L.*) [11, 12]. Berberine is a benzyltetraisoquinoline alkaloid and a derivative of 5,6-dihydro-dibenzo[a,g]quinolizinium with the chemical formula $C_{20}H_{18}NO_4$+. In vivo experiments showed that berberine undergo rapid metabolism, resulting in the formation of over 20 metabolites in the body [13]. Current studies have evaluated berberine in hypertension, coronary heart disease, gastroenteritis, hyperlipidemia, fatty liver disease, obesity, diabetes, metabolic syndrome, polycystic ovary disease, and Alzheimer's disease [14–16]. Recent in vitro studies have revealed the cytotoxic effect of berberine by inhibiting tumor cell migration and proliferation through induction of apoptosis and cell cycle arrest [17–20].

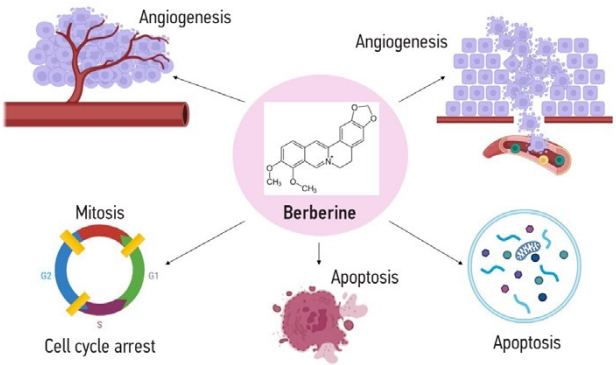

Fig. 1. Some mechanisms of berberine influence on tumor growth.

Based on a review of modern publications, the present study presents the processes that are significant for carcinogenesis and tumor growth and affected by berberine (Fig. 1).

The antitumor properties of berberine can be associated with its anti-inflammatory effect, inhibition of angiogenesis, metastasis, invasion, induction of apoptosis and autophagy, and elimination of drug resistance [21–23].

ANTI-INFLAMMATORY EFFECT OF BERBERINE

During inflammation, the tumor microenvironment is characterized by an influx of immune cells, including macrophages, neutrophils, and lymphocytes, which release inflammatory mediators that promote tumor cell proliferation, survival, and migration [24]. Moreover, the inflammatory environment can induce genetic changes that lead to tumor progression and trigger NF-κB, STAT3, and COX-2 signaling pathways [25]. These pathways regulate the expression of genes involved in cell proliferation and angiogenesis. Berberine can inhibit the transcription of *IL-1*, *IL-6*, *IL-8*, *IL-17*, and *TNF-α* genes by regulating NF-κB, MAPK, and PPAR signaling pathways. These factors contribute to the development of inflammation and tumor progression. By reducing the levels of the inflammatory proteins *IL-1*, *IL-6*, and *TNF-α*, berberine can create an environment that is less favorable for tumor growth and survival [26]. In 2019, Luo et al. investigated the mechanisms and therapeutic prospects of berberine in mice with hepatocellular carcinoma and found that berberine reduced the incidence of tumors. The study showed that berberine suppressed the expression of genes associated with lipogenesis, inflammation, fibrosis, angiogenesis, p38MAPK and ERK phosphorylation, and COX2 expression, reducing hepatocellular carcinoma cells proliferation [27].

INHIBITION OF ANGIOGENESIS

Angiogenesis is the development of new blood vessels through the migration, growth, and differentiation of endothelial cells that line the inner walls of blood vessels [28]. Matrix metalloproteinases (*MMPs*) are crucial in tumor angiogenesis, with *MMP-2* promoting endothelial cell migration and *MMP-9* and other metalloproteinases promoting vascular endothelial growth factor (VEGF) expression [29].

When B16F-10 melanoma cells were treated with berberine, tumor cell metastasis slowed down through the effect of berberine on *MMP-2* and *MMP-9-mediated angiogenesis*, as well as the proliferation of various tumor cell types through downregulation of transcription factors such as VEGF [30].

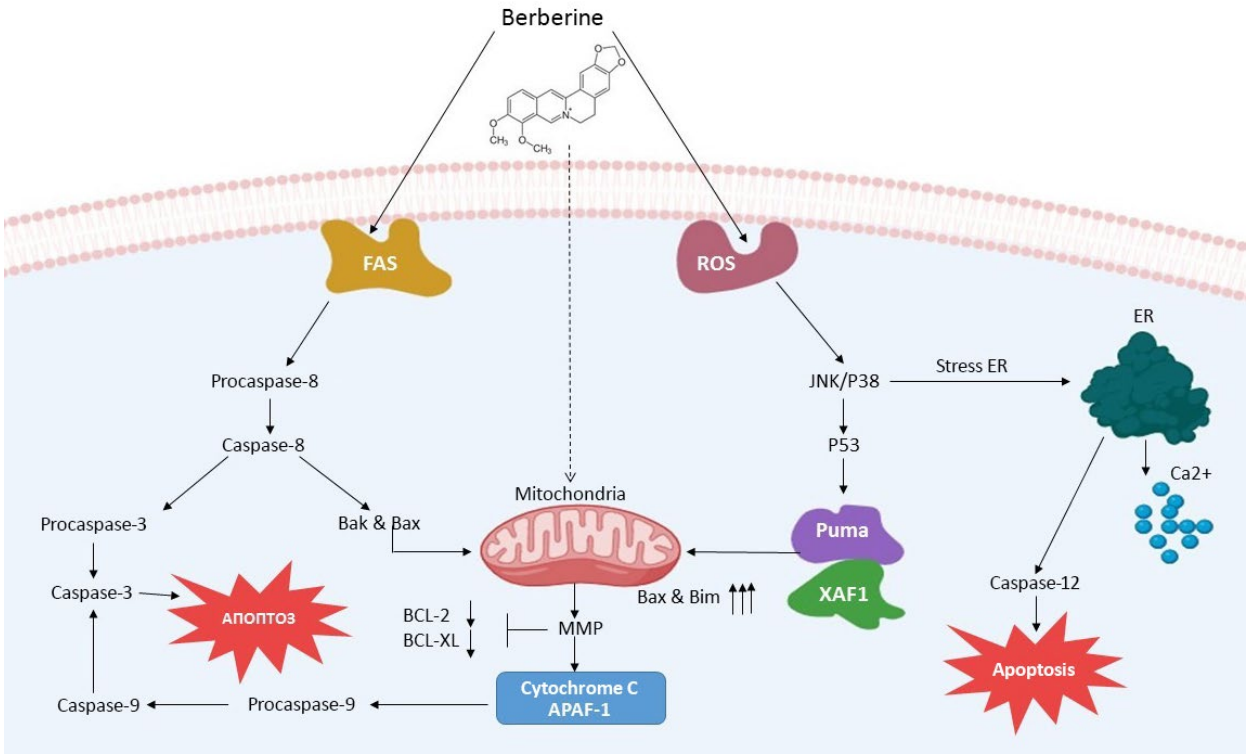

Fig. 2. Proapoptotic effect of berberine. *APAF-1*, apoptotic protease-activating factor 1; *Bak*, BCL-2 homologous antagonist/killer; *Bax*, X-associated with BCL2; *BCL-2*, B-cell lymphoma protein family; *BCL-XL*, BCL-2 homolog; *BIM*, BCL-2-like protein 11; *Ca2+*, calcium ion; *ER*, endoplasmic reticulum; *JNK*, c-Jun N-terminal kinase; *MMP*, mitochondrial membrane potential; *PUMA*, p53-activated apoptosis modulator; *ROS*, reactive oxygen species; *XAF1*, XIAP-associated factor 1.

EFFECT OF BERBERINE ON APOPTOSIS

Apoptosis involves the activation of a sequence of molecular interactions that cause cell death [31]. In tumor cells, berberine can induce cell death by activating intrinsic and extrinsic apoptotic pathways [32]. Activation of the extrinsic apoptotic pathway is mediated by the induction of Fas (a member of the tumor necrosis factor receptor superfamily) and subsequent cleavage of caspase-8, caspase-9, and caspase-3 [33]. Moreover, berberine altered the mitochondrial membrane potential through stimulating cytochrome C release from the mitochondria and inhibiting the expression of the antiapoptotic proteins BCL-2 and BCL-XL. In turn, the release of cytochrome C triggers caspase activation, which eventually leads to apoptosis. Additionally, berberine can promote the formation of reactive oxygen species (ROS), resulting in the activation of ER protein in response to stress [34]. Chen et al. and Yip et al. showed that berberine induced apoptosis in non-small cell lung cancer and liver cancer cells by activating procaspase-9 and its effector caspases, namely, procaspase-3 and procaspase-7 [35, 36].

Agnarelli et al. studied caspase expression in MIA PaCa-2 pancreatic adenocarcinoma cells and U343 glioblastoma cells treated with 50 μM of berberine for 48 h and found differing effects depending on the cell line: caspase-3 activity decreased in U343 cells and increased in MIA PaCa-2 cells [37]. Moreover, treatment of HCT-15 colorectal adenocarcinoma cell line with berberine increased the expression of spliced caspase-3 and Bax, which significantly decreased BCL-2 expression and caused apoptosis (Fig. 2) [37].

Fig. 2 shows that the activation of the extrinsic apoptotic pathway is related to the induction of FAS expression and subsequent cleavage of caspase-8, caspase-9, and caspase-3. When the intrinsic pathway is activated, increased ROS production yields more intracellular calcium, which promotes caspase-12 activation and influences the expression of BCL-2 family proteins. Furthermore, berberine can alter mitochondrial membrane potential, thus stimulating the release of cytochrome C from the mitochondria and inhibiting the expression of antiapoptotic proteins BCL-2 and BCL-XL. The release of cytochrome C triggers caspase activation, which eventually leads to apoptosis.

A study by Li et al. showed that berberine inhibited CD4+ T-cell proliferation and suppressed the production of pro-inflammatory cytokines TNF-α and IL-1 [38]. Additionally, according to Wang et al., berberine suppressed the phosphorylation of signal transducer and activator of transcription 1, inhibiting IDO1 expression caused by IFN-γ [39–42].

Recent studies have shown that berberine exhibited cytotoxicity and induced apoptosis in a human leukemia cell line [43, 44]. For example, when HL-60 and WEHI-3 acute myeloid leukemia cells were treated with berberine, apoptosis was induced by caspase-3 activation and mitochondrial membrane depolarization [43, 44]. Moreover, berberine was associated with increased ROS levels and decreased *MMP* expression in

Table 1. Effect of berberine on autophagy signaling pathways in tumor cell cultures

Tumor	Cell line	Effect	Reference
Liver carcinoma	HepG2	Inhibition of mTOR signaling	[49]
	MHCC97-L	GRP 78 increase	
		ATF6 activation	
Pancreatic cancer	MIA PaCa-2	Increased Becline-1 and LC3 levels	[37]
		Autophagosome formation	
Colorectal adenocarcinoma	HCT-116	GRP 78 increase	[49]
	DLD1	ATF6 activation	
	HCT-15	Activation of the p38 signaling pathway	[37]
		Increased ATG5 and LC3 levels	
Glioblastoma	U251	Increased AMPK	[50]
	U87	Inhibition of mTOR signaling	
	U343	Increased Becline-1 and LC3 levels	[37]
Mesothelioma	NCI-H2452	Decreased p62 expression	[48]
		Increased LC3-II	
Leukemia	Jurkat	Inhibited expression of MDM2	[44]
	U937		
	EU-6	Inhibition of AKT/mTORC1 signaling	[43]
	SKW-3	Increased LC3-I, LC3-II and Becline-1	
Gastric cancer	BGC-823	Inhibition of MAPK/mTOR/p70S6K and Akt signaling	[51]
		Increased LC3-II and Becline-1	
		Decreased p62 expression	

Note: *mTOR*, mammalian target of rapamycin; *GRP78*, regulated glucose 78; *ATF6*, activating transcription factor 6; *Becline-1*, cellular autophagy system protein; *LC3*, autophagy marker; *ATG5*, activating transcription factor 5; *AMPK*, AMP-activated protein kinase; *MDM2*, regulator of p53 degradation; *AKT/mTORC1*, serine/threonine protein kinase/TORC1 complex, which consists of Kog1, Lst8, and Tco89 proteins and may include either TOR1 or TOR2; *MAPK/mTOR/p70S6K*, mitogen-activated protein kinase/mammalian target of rapamycin/ribosomal protein kinase S6; p62, multifunctional protein that binds ubiquitin and regulates activation of the nuclear factor kappa B (NF-kB) signaling pathway.

both cell lines with a dose-dependent effect. In addition, berberine at 5–60 μM concentrations increased cytochrome C, Bax, and Bad levels and decreased BCL-2 levels in both cell lines [43, 44].

A study by Liu et al. demonstrated that berberine suppressed the proliferation of the OVCAR3 continuous cell line and primary ovarian cancer cell culture in a dose- and time-dependent manner [45]. The combination of berberine and cisplatin revealed a pronounced inhibitory effect on tumor cell growth and caused G0/G1 cell cycle arrest in vitro. Further, berberine and cisplatin suppressed the expression of proliferating cell nuclear antigen and Ki67 and enhanced the expression and activation of caspase-3, caspase-8, RIPK3, and MLKL [45].

Considering the results of the studies, notably, berberine has a potential antitumor effect mediated through the stimulation of intrinsic and extrinsic apoptotic pathways by increasing the expression of the proapoptotic molecules BAX, BAD, and BIM and inhibiting the expression of the antiapoptotic molecules BCL-2, resulting in the death of tumor cells.

EFFECT OF BERBERINE ON AUTOPHAGY

Autophagy is an evolutionarily conservative mechanism that acts as a form of type II programmed cell death or as cell survival under certain conditions [46]. This is a lysosomal degradation system, wherein long-lived proteins and nonfunctional or old organelles are encapsulated in a double-membrane vesicle (autophagosome) and degraded by lysosomal hydrolases under physiological conditions to maintain cellular homeostasis [47]. Recently, evidence has emerged that autophagy is crucial in carcinogenesis, tumor growth, and tumor growth suppression [21, 31]. A study by Yao et al. showed that the cell death rate of NCI-H2452, a human pleural mesothelioma cell line, treated with 3-MA and berberine significantly increased compared to that of cells treated with berberine alone. The expression of LC3-II, a marker of autophagy, and the rate of cell death increased in a concentration- and exposure-dependent manner with berberine. Based on these results, Yao et al. hypothesized that berberine induced autophagy could be one of the mechanisms

Table 2. Effect of berberine on invasion and metastasis signaling pathways in tumor cell cultures

Tumor	Cell line	Effect	Reference
Tongue squamous cell carcinoma	SCC-4	Inhibition of FAK, IKK, NF-KB, uPA, *MMP-2*, and *MMP-9*	[55]
Melanoma	B16F-10	Stimulation of AMPK signaling	[56]
		Decreased ERK activity and COX-2 and *MMP* expression	
	A375.S2	Inhibition of FAK, RhoA, ROCK1, p-AKT, NF-κB, and uPA	[57]
		Inhibition of *MMP-1* and *MMP-13*	
Chondrosarcoma	JJ012	Suppression of integrin αvβ3 by protein kinase C (PKCδ), c-Src, and AP-1	[58]
Prostate cancer	PC-3	Inhibition of TGF-β-related signaling molecules: BMP7, NODAL → inhibition of EMT	[59]
Colorectal adenocarcinoma	LOVO SW620	Downregulation of the COX-2/PGE2-JAK2/STAT3 signaling pathway	[60]
Gastric carcinoma	AGS SGC7901	Inhibition of *MMP-3*	[61]

Note*: AMPK*, AMP-activated protein kinase; *ERK*, extracellular signal-regulated kinase; *COX-2*, cyclooxygenase 2; *MMP*, metalloproteinase; *FAK*, focal adhesion kinase; *RhoA*, transforming protein RhoA, also known as a member of the Ras homolog A family; *ROCK1*, protein serine/threonine kinase, also known as rho-associated, coiled-coil-containing protein kinase 1; *p-AKT*, phosphorylated Akt enzyme; *NF-κB*, intracellular signaling pathway whose central component is a transcription factor; *uPA*, urokinase plasminogen activator, a human serine protease; *MMP-1*, metalloproteinase 1; *MMP-13*, metalloproteinase 13; *TGF-β*, transforming growth factor beta; *BMP7*, bone morphogenetic protein 7; *NODAL*, nodular growth differentiation factor; *EMT*, epithelial–mesenchymal transition; *IKK*, IκB kinase; *MMP-2*, metalloproteinase 2; *MMP-9*, metalloproteinase 9; *PKCδ*, protein kinase C, delta-type; *c-Src*, proto-oncogene tyrosine-protein kinase phosphorylates specific tyrosine residues in other tyrosine kinases; *AP-1*, transcription factor activating protein; *PGE2*, prostaglandin E2; *JAK2*, Janus kinase 2; *STAT3*, signal transducer and activator of transcription 3; *MMP-3*, metalloproteinase 3.

underlying the antitumor activity leading to autophagic cell death and used the autophagy inhibitor 3-methyladenine (3-MA) in vitro to confirm this hypothesis. In the presence of berberine and 3-MA, the cell death rate of NCI-H2452 cells increased [48]. La et al. reported that berberine exposure on colon cancer HCT-116, DLD1, and liver carcinoma HepG2 cell lines could induce autophagy [49]. Their findings showed that berberine increased glucose-regulated protein 78 (GRP78) levels by suppressing the ubiquitination/proteasomal degradation of GRP78 and stimulation of activating transcription factor 6. Moreover, berberine induced autophagy by inhibiting the mTOR signaling pathway and activating Beclin-1 in MHCC97-L and HepG2 cells.

In another study, berberine was shown to suppress mTOR levels and increase AMP -activated protein kinase levels in U251 and U87 glioblastoma cells; the authors indicated that berberine induced mTOR-dependent autophagy in these cell lines [50]. Li et al. showed that berberine prevented colon cancer cell proliferation, suppressed epidermal growth factor receptor expression, stimulated apoptosis and autophagy via the p38 signaling pathway, and reduced the growth of human colorectal adenocarcinoma HCT-15 cells [38].

Some studies found that berberine induced time-dependent autophagy in the BGC-823 gastric cancer cell line and inhibited the MAPK/mTOR/p70S6 K and Akt pathways, which was also associated with the inhibition of culture growth [51]. Furthermore, berberine induced autophagy in the acute lymphoblastic leukemia cell lines EU-6 and SKW-3b, inhibited the AKT/mTORC1 signaling pathway, and caused cell death [43].

Table 1 summarizes the effects of berberine on the autophagy-related signaling pathways in the cells of various tumor lines.

Based on the presented studies, it can be deduced that berberine acted as a potential autophagy modulator and induced or suppressed autophagy in various tumor cell cultures.

EFFECT OF BERBERINE ON INVASION AND METASTASIS

Tumor cell invasion and metastasis are key signs of malignant tumors. In patients with malignant tumors, these factors are the main causes of death [9]. Studies have shown that tumor cells can migrate and penetrate into various tissues of the body through the bloodstream or lymphatic system, forming new tumors [25, 29, 52]. The extracellular matrix (ECM) functions as a mechanical barrier to cell movement; therefore, ECM loss is critical in the metastatic cascade. Thus, *MMPs* can cause degradation of the ECM, in particular *MMP-3*, which controls metastasis, angiogenesis, and invasion (Table 2) [53, 54].

A study in human tongue squamous cell carcinoma SCC-4 cells showed that berberine inhibited NF-κB, focal adhesion kinase (FAK), urokinase-type plasminogen activator (u-PA), IκB kinase, *MMP-2*, and *MMP-9* and reduced in vitro

migration [55]. Hamsa et al. demonstrated the potential antimetastatic and anti-invasive effects of berberine using in vitro and in vivo models in C57BL/6 mice with B16F-10 melanoma cells. The survival of animals with metastatic tumors increased after berberine administration [56]. The expression of various pro- and antimetastatic genes was evaluated after berberine administration to understand the mechanism of action of berberine in inhibiting lung metastasis at the molecular level. Metastasis-induced expression of prometastatic genes such as genes encoding *MMP*, *ERK 1/2*, prolyl hydroxylase, and lysyl oxidase in the lungs was decreased after berberine administration, indicating its in vitro antimetastatic activity [56].

In 2018, a study by Hu et al. showed that berberine had a strong effect on the inhibition of MMP-3 protein and mRNA sequences in SGC7901 and AGS gastric cancer cell cultures. In an in vitro experiment using the Transwell method, increased levels of berberine were associated with a significantly decreased number of invasive and metastasizing gastric cancer cells [61].

Berberine caused downregulation of integrin αvβ3 c-Src, protein kinase C (PKCδ), and AP-1, demonstrating the suppression of human chondrosarcoma JJ012 cell invasion and migration [58]. A similar effect was found in PC-3 prostate cancer cells, where berberine inhibited TGF-β-related signaling molecules that induce epithelial–mesenchymal transition, such as bone morphogenetic protein 7 and nodular differentiation factor ligand [59].

In another study, berberine inhibited the invasion and metastasis of colorectal cancer cells (i.e., SW620 and LoVo cells) by inhibiting the COX-2/PGE2-JAK2/STAT3 signaling pathway [60].

Berberine significantly inhibited the motility, invasion, and migration of human melanoma A375.S2 cells by inhibiting metastasis-associated proteins such as ROCK1, FAK, Ras Homolog Family Member A (RhoA), NF-κB, and u-PA, which resulted in the inhibition of *MMP-1* and *MMP-13* in vitro [57]. Therefore, several recent studies showed that berberine inhibits the metastatic and migratory potential in the cells of various tumor cultures, affecting p38 MAPK, PPAR, JNK, AKT/mTORC1, COX-2/PGE2-JAK2/STAT3, MAPK/mTOR/p70S6K, and NF-kB signaling pathways and suppressing the action of *MMPs*.

CONCLUSION

Berberine is a natural isoquinoline alkaloid that can control molecular mechanisms in tumor cells through modulating signaling pathways involved in proliferation, apoptosis, invasion, metastasis, and autophagy, which substantiates its known properties and indicates antitumor properties.

Although the exact mechanism underlying the action of berberine as an antitumor agent remains unclear, nonclinical studies with the identification of molecular targets are crucial for developing new treatment approaches and establishing berberine's role in antitumor therapy protocols.

ADDITIONAL INFORMATION

Authors' contribution. S.V.T.—conceptualization, analysis of literary sources, creation of a draft, creation of figures for the manuscript; E.Yu.Z.—editing the manuscript, general supervision; L.N.V.—editing the manuscript; Ya.S.E.—resource support for the study; E.M.I.—approval of the final version of the article. Thereby, all authors made a substantial contribution to the conception of the work, acquisition, analysis, interpretation of data for the work, drafting and revising the work, final approval of the version to be published and agree to be accountable for all aspects of the work.

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Competing interests. The authors declare that they have no competing interests.

ДОПОЛНИТЕЛЬНАЯ ИНФОРМАЦИЯ

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