Multiple molecular and cellular mechanisms of the antitumour effect of dihydromyricetin (Review)

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Abstract. Dihydromyricetin (DHM) is a natural flavonoid compound with multiple antitumour effects, including inhibition of proliferation, promotion of apoptosis, inhibition of invasion and migration, clearance of reactive oxygen species (ROS) and induction of autophagy. For example, DHM can effectively block the progression of the tumour cell cycle and inhibit cell proliferation. In different types of cancer cells, DHM can regulate the PI3K/Akt pathway, mTOR, and NF-κB pathway components, such as p53, and endoplasmic reticulum stress can alter the accumulation of ROS or induce autophagy to promote the apoptosis of tumour cells. In addition, when DHM is used in combination with various known chemotherapy drugs, such as paclitaxel, nedaplatin, doxorubicin, oxaliplatin and vinblastine, it can increase the sensitivity of tumour cells to DHM and increase the therapeutic effect of chemotherapy drugs. In the present review, the multiple molecular and cellular mechanisms underlying the antitumour effect of DHM, as well as its ability to increase the effects of various traditional antitumour drugs were summarized. Through the present review, it is expected by the authors to draw attention to the potential of DHM as an antitumour drug and provide valuable references for the clinical translation of DHM research and the development of related treatment strategies.

Contents

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1. Introduction

Cancer is the second most deadly disease worldwide after cardiovascular disease and one of the major threats to human health (1). According to recent estimates, the global cancer burden is expected to increase significantly in the coming decades (by 47% from 2023 to 2040) (2,3). Due to the various limitations regarding conventional treatment regimens, a growing number of researchers around the world are working to discover new anticancer agents and develop new effective modalities for cancer treatment (4). The vast majority of currently clinically approved chemotherapeutic agents are derived from a variety of natural sources, including microbes and terrestrial and marine plants (5). Commonly used anticancer drugs such as pergolide, vincristine, paclitaxel and podophyllotoxin are found in plants (6,7). Inspired by the recent success in drug development, an increasing number of research groups worldwide are working to isolate new structural leads from different plant species and to assess their potential anticancer activity.

Dihydromyricetin (DHM, PubChem compound ID: 161557), also known as ampelopsin, is a polyphenolic hydroxy-dihydroflavonol compound (8). It was first isolated from the plant *Ampelopsis meliaefolia Kudo* in 1940 (9); it is part of a class of active natural compounds widely present in a variety of plant families, including the *Umbelliferae*, *Asteraceae*, *Leguminosae*, *Rutaceae*, *Mulberry*, *Mucuna pruriens* and *Thymus* families (10). DHM has a wide range of pharmacological activities, such as anti-inflammatory, anticoagulant, antibacterial, antifungal, antiviral, anticancer and antihypertensive activities (11,12). DHM has poor water solubility and is only stable at low temperatures and in a weakly acidic environment (pH 6.0) (8,13). To improve the medicinal properties (for example, the solubility, permeability and stability) of DHM, researchers have developed numerous new formulations of DHM, such as nano-formulations (14), microemulsions (15), gels (16) and crystals (17).

Several preclinical studies have revealed that DHM can inhibit the growth of a variety of cancer cells by modulating various cellular signalling pathways; for example, DHM can

protect the cardiovascular system through the PI3K/Akt, Nrf2/HO-1 and SIRT3 signalling pathways (18-20) and can prevent or inhibit the growth of a variety of cancer cells through the ERK/Akt, AMPK/MAPK/XAF1, Akt-mTOR, ROS/NF-κB and mitochondrial apoptosis signalling pathways to prevent or inhibit hepatocellular carcinoma, lung cancer, colorectal cancer, breast cancer, leukaemia and melanoma (21-23). DHM can also prevent or inhibit neurodegenerative diseases through the TRL4/NF-κB and p53/p21 signalling pathways (24,25). In addition, DHM has anti-inflammatory, antibacterial, antiviral and skin-protective effects, thus it has great potential for the treatment of tumours (10). Previous studies have revealed that DHM can inhibit the proliferation of various types of tumour cells, induce apoptosis, and inhibit migration, invasion, and metastasis (12). In addition, treatment of malignant tumour cells with DHM has been shown to suppress drug resistance and increase the response to standard anticancer drugs such as adriamycin or doxorubicin (DOX), opening new avenues for cancer treatment (18,26). Therefore, in the present review, the multiple molecular and cellular mechanisms underlying the tumour-suppressive effects of DHM will be described in depth to provide ideas for the research and development of clinical treatments involving DHM.

Given that DHM has drawn widespread concern in recent years, its anticancer effects have been widely described (9,12,27), while there are few reviews that summarize the antitumour effects of DHM from the molecular mechanism level, and the reviews about the role of DHM in conventional antitumour drugs are less understood. In 2018 Zhang *et al* (28) suggested that DHM may be associated with several different molecules involved in cellular apoptosis, oxidative stress and inflammation. However, further research on DHM discovered that DHM is also associated with tumor cell proliferation (29), invasion and metastasis (30), and autophagy (31). To improve understanding of the antitumour mechanism of DHM, in the present review, four types of antitumour effects of DHM were summarized: Inhibition of tumour cell proliferation, promotion of apoptosis, inhibition of tumour cell invasion and migration, scavenging of tumour cell reactive oxygen species (ROS), and induction of autophagy. Relevant articles were screened from recent years and the results related to the molecular and cellular mechanisms were summarized. The present review also summarized the potential application of DHM in combination with conventional antitumour drugs, as well as the advantages and disadvantages of DHM as an antitumour drug.

2. Multiple molecular and cellular mechanisms of the antitumour activity of DHM

DHM induces tumour cell cycle arrest and inhibits cell proliferation. The process of the cell cycle is divided into interphase (G1 phase, S phase, G2 phase), division phase (M phase), and stationary phase (G0 phase), and the normal progression of the cell cycle is regulated by various mechanisms of action to ensure orderly cell division (32); if any of the related factors are dysregulated, the cell cycle is terminated (32,33). The central cell cycle regulation mechanism is the Cyclin-CDK-CDI mechanism, and CDK inhibitor (CKI) genes have positive regulators such as cyclin and p16 and negative regulators such as p53 and p21 (34,35). The overexpression of positive regulators or the absence of negative regulators results in the downregulation of the cell cycle threshold and weakening of cell cycle function, resulting in reduced sensitivity of cells to exogenous regulatory signals (32,35). CDC genes (cell division cycle genes) are a class of genes whose expression is cell cycle-dependent or directly involved in cell cycle regulation; these genes mainly include Cyclin genes, CDK genes and CKI genes (36,37). In addition, DNA polymerase and DNA ligase genes related to DNA replication are also part of the CDC gene family (38).

Several studies have reported that in some tumour cells, DHM can inhibit cell proliferation by blocking the G2/M phase and G1/S phase of the cell cycle (29,39,40). For example, DHM can inactivate the CDK1/cell cycle protein B1 complex by phosphorylating CDK1, thus inducing G2/M phase cell cycle arrest and inhibiting the growth of hepatocellular carcinoma cells (29). In SK-MEL-28 melanoma cells, DHM downregulates the expression of the CDC25A, CDC2, and phosphorylated (p-)CDC2 proteins to induce cell cycle arrest in the G1/S phase (39). DHM also induces G2-M arrest of the U2OS cell cycle in osteosarcoma cells by increasing the levels of p21 protein and RNA and inhibiting cell proliferation (40).

In addition to inhibiting the proliferation of tumour cells by blocking the cell cycle, DHM can also target the activation of ERK1/2 and Akt to inhibit the proliferative potential of fibroblasts in lung cancer cells (41) and upregulate the expression of p53 to inhibit the proliferation of hepatocellular carcinoma cells (42). In animal studies using an *in situ* prostate tumour model, Ni *et al* (43) reported that DHM inhibited the proliferation of PC-3 tumours in a dose-dependent manner, which was associated with a decrease in the CXCR4 protein. In BGC-823 gastric cancer cells, DHM induced a decrease in the expression of Cyclin D1, Cyclin E1 and N-cadherin; increased the expression of E-cadherin; inhibited the phosphorylation of Akt and STAT3; and downregulated the expression of HMGB1 in cells. Therefore, DHM inhibits BGC-823 cell proliferation and migration by regulating the activation of the Akt/STAT3 signalling pathway and the expression of HMGB1 (44). In cholangiocarcinoma (CAA) cells, DHM upregulated the expression of miR-455-3p, which in turn inhibited the expression of its downstream target ZEB1, thereby suppressing the proliferation of CAA cells (45). ZEB1 is a transcription factor that promotes metastasis and stem cell characteristics, and it is aberrantly expressed in CAA cells (46) (Fig. 1).

DHM induces the apoptosis of tumour cells and affects signalling pathways. The apoptotic pathway includes both exogenous and endogenous pathways, the former being mediated by receptors such as TNF-α and FAS-L, while the latter uses mitochondria as the main site of apoptosis induction by regulating the permeability of their outer membrane (47). When various stress responses, DNA damage and abnormal cell signalling occur, Bax is activated, and under the regulation of this protein, the permeability of the mitochondrial outer membrane increases, and Cytochrome C is released into the cytoplasm, where it binds to Apaf-1 in the presence of dATP, causing Apaf-1 to expose its Card structural domain and bind to the Card of Procaspase-9 to form an apoptotic complex; this

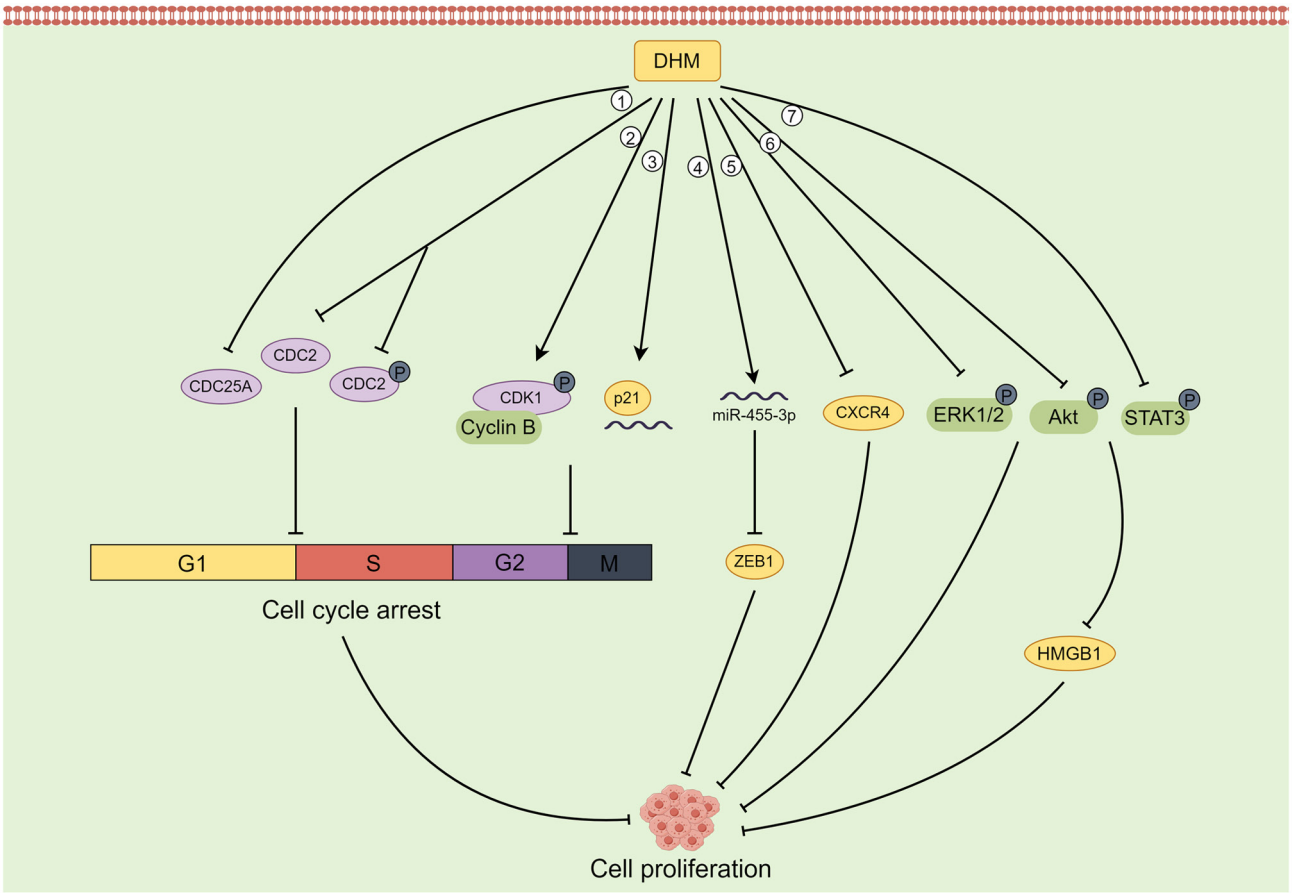

Figure 1. Mechanistically, DHM inhibits tumour cell proliferation. The numbers in the figure indicate the following: (1) DHM decreases the production of the CDC25A, CDC2 and phosphorylated CDC2 proteins, induces cell cycle arrest in the G1/S phase, and inhibits cell proliferation. (2) The phosphorylation of CDK1 by DHM inactivates the CDK1/cell cycle protein B1 complex, thereby inducing G2/M-phase cell cycle arrest and thus inhibiting the growth of hepatocellular carcinoma cells. (3) DHM increases the protein and RNA levels of p21, induces G2-M cell cycle arrest in U2OS osteosarcoma cells, and inhibits cell proliferation. (4) DHM upregulates the expression of miR-455-3p and inhibits the expression of the downstream target ZEB1, thereby inhibiting the proliferation of cholangiocarcinoma cells. (5) DHM decreases the protein expression of CXCR4 and inhibits the proliferation of PC-3 tumour cells. (6) DHM targets the activation of ERK1/2 and Akt to inhibit the proliferation of fibroblasts in lung cancer cells. (7) DHM regulates the activation of the Akt/STAT3 signalling pathway and the expression of HMGB1 to inhibit the proliferation of BGC-823 cells. DHM, dihydromyricetin; miR, microRNA.

complex in turn activates Caspase-9, which further activates Caspase-3, thus causing apoptosis (48-50). By contrast, Bcl-2 plays the opposite role as Bax in inhibiting Cytochrome C release, thus inhibiting the process of apoptosis; therefore, regulation of the expression of Bcl-2 has an important impact on the apoptosis of tumour cells (51). Because of the inverse effects of Bcl-2 and Bax, when cells are stimulated, the ratio of the two determines cell survival (52). Liu *et al* (42) discovered that DHM significantly increases p53 protein expression in four types of hepatocellular carcinoma cells (HepG2, QGY7701, Hepal-6, and MHcc97L), which activated Bax and Bak, and inhibited Bcl-2 expression, which in turn activated Caspase-3 and eventually led to the apoptosis of tumour cells; the regulatory effect was dose-dependent. Ji *et al* (53) revealed that DHM significantly ($P<0.05$) inhibited AGS cell proliferation and induced cell cytotoxicity in a dose- and time-dependent manner; DHM also regulated the expression of apoptosis-related genes such as p53 and Bcl-2 in a dose- and time-dependent manner in AGS cells treated with DHM, as determined by western blotting (53).

In addition to inducing the apoptosis in tumour cells through the p53-mediated signalling pathway, DHM is associated with the Nuclear Factor Kappa B Subunit 1(NF-κB) signalling pathway (22,23,54). Han *et al* (54) reported that in the leukemic cell lines HL60 and K562, DHM induced apoptosis through nuclear condensation, induced loss of mitochondrial membrane potential, increased ROS production, activated Caspase-9, Caspase-3 and poly ADP-ribose polymerase, and regulated the expression of Bcl-2 family members; these authors also reported that DHM induced apoptosis in the leukaemia cell lines HL60 and K562, possibly through the NF-κB signalling pathway. Li *et al* (22) examined the expression of phosphorylated nuclear factor kappa B kinase subunit β (p-IKKβ), phosphorylated nuclear factor kappa B kinase subunit α (p-IKKα), nuclear factor kappa Bα (IκB-α) inhibitor, and NF-κB/p65 in a nasopharyngeal carcinoma CNE-2 cell line via western blot analysis and confocal laser scanning microscopy; the observed nuclear translocation of NF-κB/p65 indicated that DHM promotes the inactivation of p-IKKβ and p-IKKα and blocks the nuclear translocation of the NF-κB subunit p65, promoting the apoptosis of CNE-2 cells in nasopharyngeal carcinoma. Guo *et al* (23) treated a rat model of fatty liver disease with DHM and found that DHM inhibited the protein expression of NF-κB, p53 and Bax, acting as hepatoprotective agent.

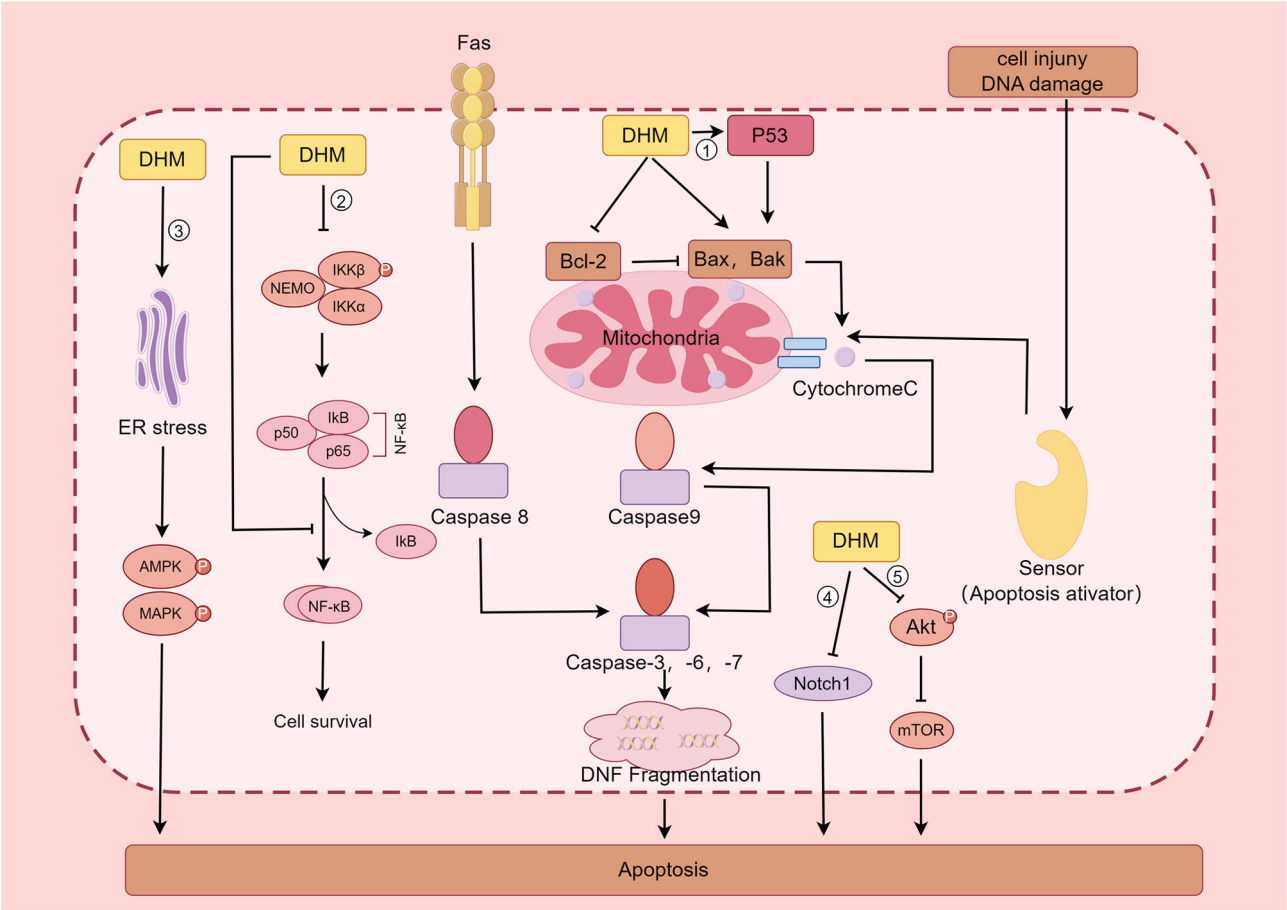

Figure 2. DHM induces apoptosis in tumour cells and induces the associated signalling pathway. The numbers in the figure indicate the following: (1) DHM upregulates p53, activates Bax and Bak, and inhibits Bcl-2 expression, thereby activating Caspase-3 and ultimately leading to tumour cell apoptosis. (2) DHM regulates tumour cell apoptosis via the NF-κB signalling pathway. (3) DHM induces ER stress to regulate tumour cell apoptosis. (4) DHM downregulates the expression of Notch1 to promote tumour cell apoptosis. (5) DHM inhibits the activation of Akt and inhibits the formation of mTOR complexes to promote tumour cell apoptosis. DHM, dihydromyricetin; ER, endoplasmic reticulum.

In addition, DHM promotes the apoptosis of tumour cells through several other pathways (55-59). For example, DHM inhibits the activation of Akt, which in turn inhibits the formation of the mTOR complex and promotes apoptosis in breast cancer cells (55). DHM is a biologically active natural chemopreventive agent and a potent mTOR inhibitor that may be a useful chemotherapeutic agent for breast cancer treatment (55). Lu *et al* (56) revealed that Notch1 is involved in the development of HCC and that DHM inhibits cell proliferation and promotes apoptosis by downregulating Notch1 expression. A study by Ye *et al* (57) demonstrated that in cisplatin-resistant nasopharyngeal carcinoma cell lines (Hone1/Cis and CNE1/Cis), cotreatment with DHM increased the growth-inhibitory effect of cisplatin by blocking the Wnt/β-catenin signalling pathway to increase the antitumour activity of cisplatin in nasopharyngeal carcinoma. In a mouse model of cerebral ischaemia-reperfusion injury, DHM inhibited oxidative stress and apoptosis in mouse hippocampal neuronal HT22 cells by activating the Nrf2/HO-1 signalling pathway (58). Treatment of colon cancer cells with DHM resulted in dose- and time-dependent apoptosis through the activation of endoplasmic reticulum (ER) stress, 5'-adenosine monophosphate-activated protein kinase (AMPK) and JNK/p38 MAPKs, and AMPK/MAPK/XAF1 signalling initiated by DHM through the ER stress pathway, which induces apoptosis in colon cancer cells (59) (Fig. 2).

The mechanisms by which DHM inhibits tumour cell invasion and metastasis. The invasion-migration cascade is a complex biological process that includes the following major events: (i) Cell migration and local invasion of the basement membrane, (ii) invasion of the vasculature and/or lymphatic system, (iii) survival in the circulation, (iv) arrest and extravasation at distant organ sites, and (v) colonization at metastatic sites (60,61). According to previous case reports, >80% of cancer patients succumb to tumour invasion/metastasis, making it one of the major causes of death in cancer patients. The decrease in 5-year survival upon metastasis is particularly severe in patients with osteosarcoma (62). DHM can suppress the invasion and metastasis of osteosarcoma cells by blocking the TNF-α/p38MAPK/MMP-2 signalling pathway (30). Moreover, Chou *et al* (63) reported that DHM regulates osteosarcoma metastasis through the ERK pathway; it also inhibits metastasis by suppressing the expression of the downstream urokinase plasminogen activator through the inhibition of SP-1 and NF-κB.

DHM inhibits the invasion and migration of human retinal pigment epithelial cells (ARPE-19) by decreasing

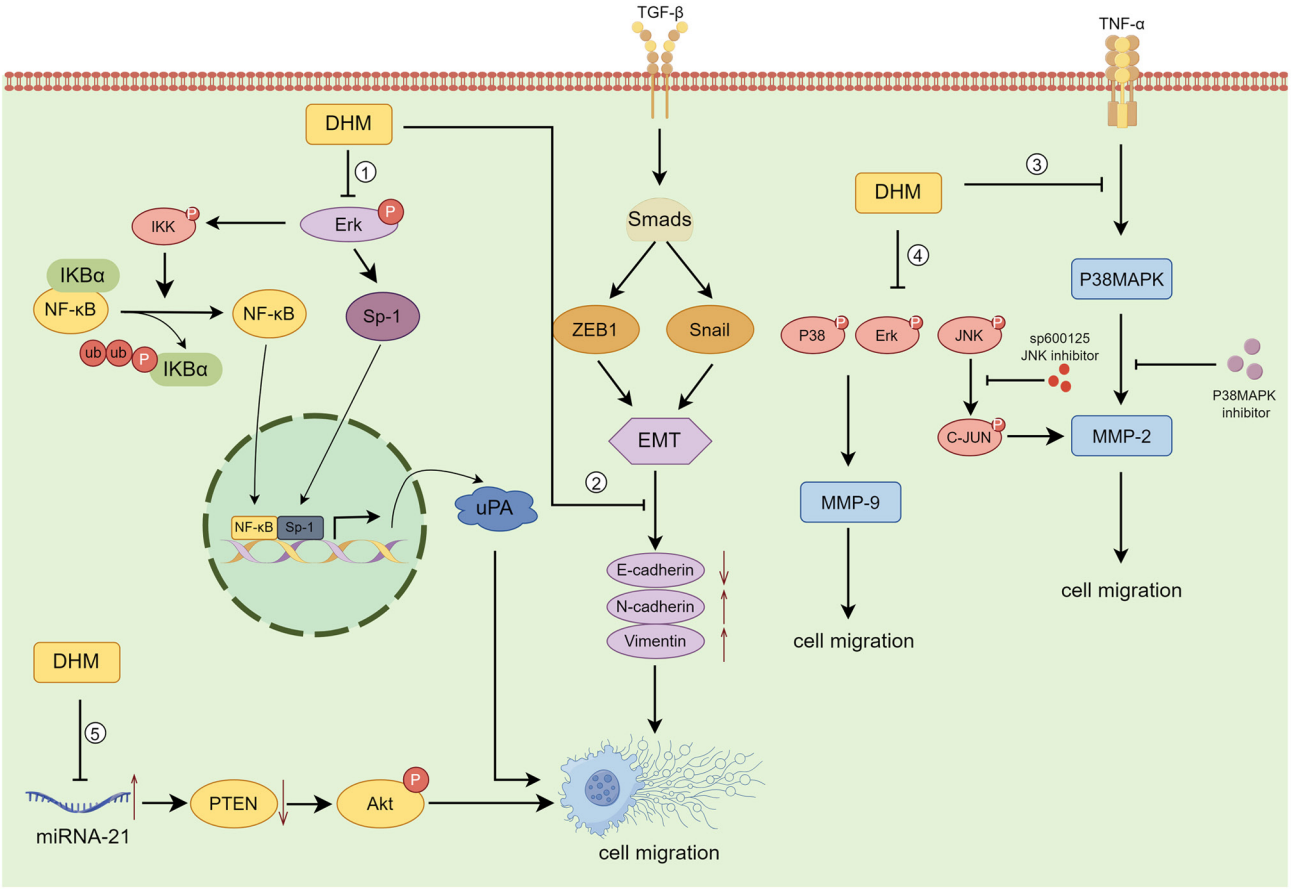

Figure 3. Mechanisms by which DHM inhibits tumour cell invasion and metastasis. The numbers in the figure indicate the following: (1) DHM inhibits metastasis via the NF-κB pathway. (2) DHM suppresses tumour cell invasion by regulating the Snail pathway. (3) DHM regulates tumour cell invasion and metastasis through the TNF-α/p38MAPK/MMP-2 signalling pathway. (4) DHM inhibits the phosphorylation of p38, ERK1/2 and JNK and decreases the levels of MMP proteins, thereby inhibiting tumour cell migration and invasion. (5) DHM inhibits tumour cell migration and invasion by regulating miR-21. DHM, dihydromyricetin.

the expression of MMP-2 (64). By contrast, Zhang *et al* (65) reported that DHM significantly inhibited the migration and invasion of SK-Hep-1 and MHCC97L hepatocellular carcinoma cells by decreasing MMP-9 protein expression, while downregulation of MMP-9 protein expression was closely associated with increased PKC-δ protein levels and decreased phosphorylation of p38, ERK1/2 and JNK in SK-Hep-1 and MHCC97L cells. In the ovarian cancer cell line A2780, DHM upregulated E-cadherin and downregulated N-cadherin and Vimentin in the Snail signalling pathway in a concentration- and time-dependent manner, inhibiting the nuclear translocation of NF-κB; these results suggested that DHM inhibits epithelial-mesenchymal transition (EMT) via the NF-κB/Snail pathway and suppresses ovarian cancer cell invasion (66). DHM also was also demonstrated to inhibit the migration and invasion of human gastric cancer MKN45 cells and reverse EMT through the downregulation of MMP-2 expression via the JNK signalling pathway (67). In an *in vivo* experiment on mice transplanted with B16 melanoma cells, Zheng *et al* (68) reported that mice given DHM at doses of 150, 200 and 250 mg/kg exhibited a significant reduction in the number of metastatic tumours compared with those in the control group, demonstrating the anti-invasive and anti-metastatic effects of DHM on B16 melanoma. Moreover, DHM inhibits the migration and invasion of nasopharyngeal carcinoma cells by suppressing the ERK1/2 signalling pathway and suppressing MMP-2 expression (69); it also inhibits the proliferation, migration and invasion of CAA HCCC9810 and TFK-1 cells by regulating miR-21 and promoting apoptosis (70) (Fig. 3).

DHM regulates intracellular ROS levels and induces autophagy in tumour cells. ROS are highly reactive substances containing oxygen radicals, and ROS are produced in various biochemical reactions in cellular organelles, such as the ER, mitochondria and peroxisomes, as a by-product of normal oxygen metabolism (71). ROS are cytotoxic molecules that stimulate apoptosis, but high levels of ROS can induce tumorigenesis, leading to uncontrolled cancer cell proliferation (72). Autophagy is an evolutionarily conserved catabolic mechanism by which eukaryotic cells recycle or degrade internal components through a membrane transport pathway (73). The process of autophagy is divided into four key steps: Initiation, nucleation, maturation and degradation (74). In cancer, autophagy plays a dichotomous role, that is, it inhibits tumorigenesis and supports tumour development (75).

DHM induces autophagy in head and neck squamous cell carcinoma (HNSCC) through the phosphorylation and activation of the STAT3 transcription factor (31). In HNSCC cells, the increase in ROS levels was proportional to the increase

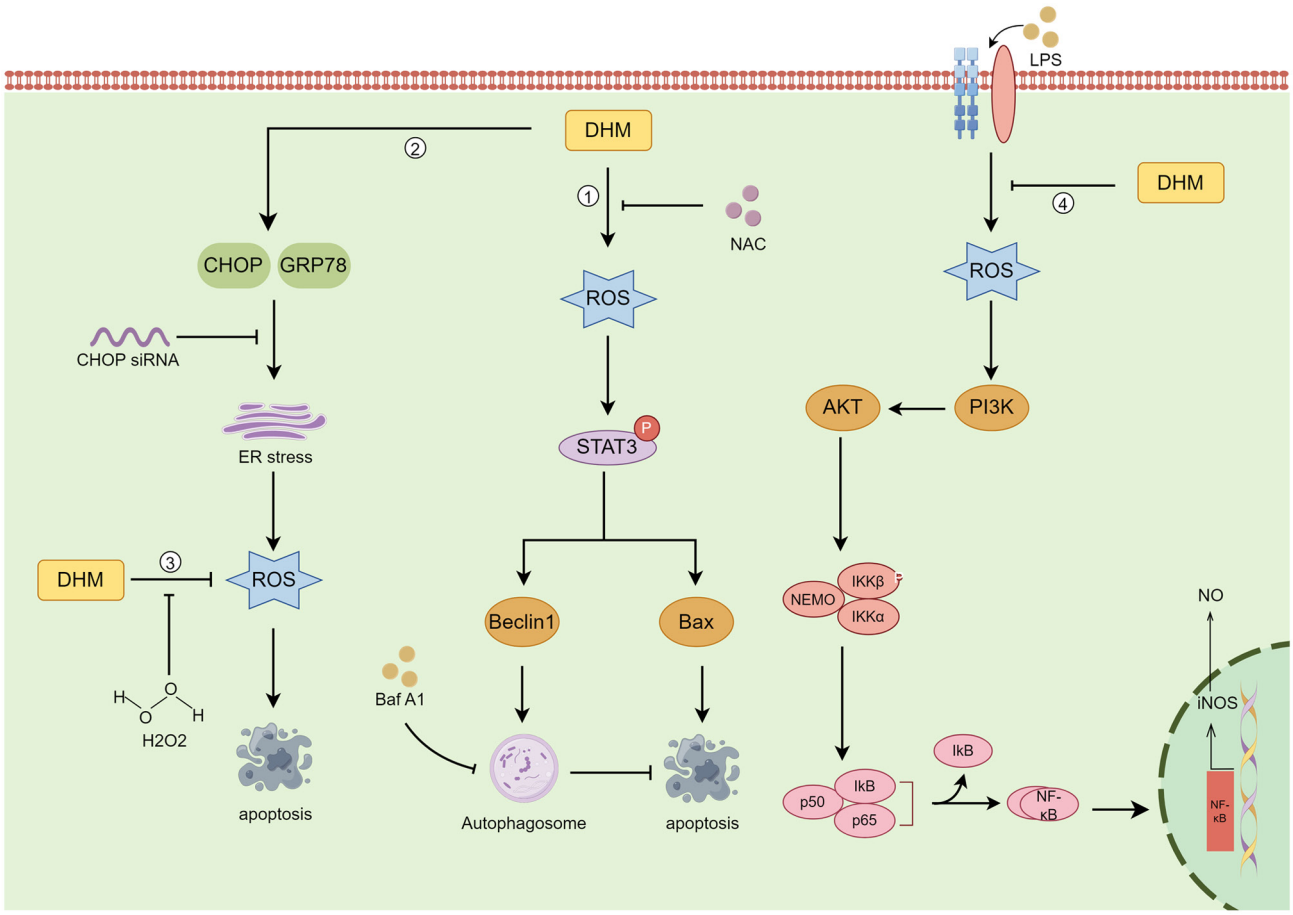

Figure 4. DHM regulates intracellular ROS and induces autophagy in tumour cells. The numbers in the figure indicate the following: (1) DHM activates phosphorylated STAT3-dependent autophagy by inducing ROS production in tumour cells. (2) DHM stimulates ROS production through ER stress to induce its antitumour effects. (3) DHM suppresses the accumulation of ROS and participates in tumour cell apoptosis. (4) DHM inhibits ROS accumulation and NF-κB activation to suppress lipopolysaccharide-induced inducible iNOS expression. DHM, dihydromyricetin; ROS, reactive oxygen species; ER, endoplasmic reticulum; NO, nitric oxide; iNOS, inducible NO synthase; siRNA, small interfering RNA.

in DHM concentration, and DHM activated p-STAT3-dependent autophagy through ROS production in HNSCC (31). Zhou *et al* (76) demonstrated that in the human breast cancer cell lines MCF-7 and MDA-MB-231, DHM had antitumour effects through ROS production, and the ER stress pathway had antitumour effects on breast cancer cells. However, in human melanoma cells, autophagy has a protective role in DHM-induced apoptosis, and pharmacological inhibition or genetic blockade of autophagy increases DHM-induced cell death and apoptosis (77). Liu *et al* (78) evaluated the effects of DHM on the induction of ROS accumulation and activation of mitochondrial signalling pathways in human hepatocellular carcinoma HepG2 cells. DHM reduced the accumulation of ROS in a concentration-dependent manner, while the expression of proteins involved in the apoptotic program increased in a concentration-dependent manner. This suggests that ROS can act as redox signalling messengers that regulate DHM-induced apoptosis (78). In a pharmacobiochemical study of the effect of DHM on inflammation in a RAW264.7 macrophage model, DHM was discovered to inhibit the accumulation of ROS, suppress the release of NO and the proinflammatory cytokines IL-1β, IL-6 and TNF-α, and suppress lipopolysaccharide-induced inducible nitric oxide synthase by inhibiting nuclear factor-κB (NF-κB) activation (79). In cutaneous squamous cell carcinoma (CSCC), DHM induced TFEB (Ser142) dephosphorylation, activated TFEB nuclear translocation, increased TFEB reporter activity, decreased lncRNA MALAT1 expression, and induced CSCC cell death by inducing excessive autophagy via the MALAT1-TFEB pathway (80) (Fig. 4).

3. DHM attenuates the drug resistance of tumour cells and increases their sensitivity to chemotherapeutic drugs

DHM is mainly extracted from the plant *Garcinia cambogia* and is an antitumour drug with high efficiency, low toxicity and few side effects (81). The focus of present review was mainly to explore its antitumour mechanism in combination with existing chemotherapeutic drugs (82-84). Several studies have demonstrated that the combination of DHM has a stronger antitumour effect than single drugs (85-91). Jiang *et al* (85) reported that DHM increases the chemosensitivity of hepatocellular carcinoma cell lines to nedaplatin (NDP) through the p53/Bcl-2 pathway while reducing the damage caused by NDP to normal hepatocytes and thus protecting normal hepatocytes. Another study revealed that DHM increases the chemosensitivity of leukemic NB4 cells to all-trans retinoic acid through modulation of the p38-STAT1

signalling pathway, thereby further inhibiting cancer cell growth (86). Wang *et al* (87) reported that DHM increased the chemosensitivity of CRC cells to oxaliplatin (OXA). DHM increased the chemosensitivity to OXA, promoted OXA-induced apoptosis, and suppressed the accumulation of 5(6)-carboxy-2,7-dichlorofluorescein in OXA-resistant HCT116/L-OHP CRC cells. DHM inhibited the growth of colorectal cancer cells by suppressing MRP2 expression and activity in the HCT116/OXA and HCT8/vincristine (VCR) colorectal cancer cell lines; these changes in MRP2 expression and promoter activity restored the chemosensitivity of these two cell lines to OXA and VCR (88). In a mouse model of AOM/DSS-induced colorectal cancer, DHM increased the therapeutic effect of irinotecan (CPT-11) (89).

Ovarian cancer is one of the leading causes of cancer-related death in gynaecologic malignancies, and resistance to chemotherapeutic agents remains a major challenge in ovarian cancer treatment (90). Xu *et al* (90) reported that DHM significantly increased the sensitivity of ovarian cancer cells to paclitaxel and DOX by inhibiting the expression of survivin, a member of the IAP family of apoptosis-inhibitory proteins. One of the most common treatments for gastric cancer is chemotherapy, but multidrug resistance often leads to the failure of anticancer therapy, and the combination of DHM and mitomycin increases the inhibitory effect of mitomycin on the proliferation of gastric cancer cells (91).

4. Advantages and challenges of DHM as an antitumour drug

The advantages of DHM as an antitumour drug for combination with chemotherapy are as follows: It has fewer toxic side effects than chemotherapy, it has multiple antitumour mechanisms, and it has a lower risk of drug resistance than chemotherapy alone (81-84). Several studies confirmed that DHM was not cytotoxic to the immortalized normal human hepatocyte line LO-2 (92), the normal prostate epithelial cell line PrEC (43), or the normal mammary epithelial cell line MCF-10A (76). Moreover, Dong *et al* (93) reported that DHM pre-treatment regulated APAP metabolism by regulating the expression of UDP-glucuronosyltransferase 1 and cytochrome P4502E1 to ameliorate APAP-associated hepatocyte necrosis and stimulate liver regeneration. DHM can be used in combination with a variety of known chemotherapeutic agents, such as DHM in combination with NDP, to regulate the balance of Bcl-2/Bax and Bcl-2/Bak ratios through the p53/Bcl-2 signalling pathway and inhibit NDP-induced ROS production, thereby increasing the chemosensitivity of hepatocellular carcinoma cells to NDP (85). DHM increases the antitumour activity of adriamycin (ADR) and prevents ADR-induced DIC in a p53-dependent manner by inhibiting MDM2-mediated degradation of ARC via ubiquitination (90).

Although DHM is a promising cancer treatment, its chemical instability and low bioavailability hinder its application (9). The phenolic hydroxyl structure of DHM makes it unstable (93). In particular, when DHM is exposed to light, pH buffers, pepsin and trypsin, it undergoes various chemical reactions, such as oxidation, hydrolysis, cleavage, reduction and decomposition, to produce metabolites (93). Pharmacokinetic studies have also shown that DHM is not readily absorbed into the bloodstream and is unstable in the intestinal environment (94). Therefore, the combination of DHM with other chemotherapeutic drugs requires consideration of differences in the physicochemical properties, absorption sites, pharmacokinetic behaviours, and effective doses of different drugs (95).

5. Conclusions and perspectives

The present review mainly summarized the molecular mechanism underlying the inhibitory effect of DHM on tumours. A total of four effects of DHM were described: It inhibits tumour cell proliferation, promotes apoptosis, inhibits invasion and migration, clears ROS, and induces autophagy. The effects of DHM were also summarized in combination with several traditional antitumour drugs, as well as the advantages and disadvantages of DHM as an antitumour drug. Currently, there are two reported clinical trials related to DHM: In a double-blind clinical trial, Chen *et al* (96) conducted a three-month follow-up observation on 60 adult patients with non-alcoholic fatty liver disease and it was identified that the serum levels of alanine, aspartate aminotransferase, γ-glutamyl transpeptidase, glucose, low-density lipoprotein-cholesterol and apolipoprotein B, and the homeostasis model assessment of insulin resistance index were significantly decreased in the DHM group compared with the placebo group, and DHM supplementation improves glucose and lipid metabolism as well as various biochemical parameters in patients with non-alcoholic fatty liver disease. Ran *et al* (97) conducted a follow-up experiment on 80 participants with type 2 diabetes mellitus (T2DM) and it was revealed that compared with the placebo group, the levels of fasting blood glucose, glycosylated albumin, cystatin C and retinol binding protein-4 in the DHM group significantly decreased, and DHM can effectively improve the blood sugar control in patients with T2DM. However, there are no studies reporting that DHM has been tested in any clinical trials for treating cancer. The antitumour mechanisms of DHM are diverse and not limited to these four aspects, and the antitumour effects of DHM on different tumour cells may be the result of a combination of mechanisms.

With advances in diagnostic and treatment technology, the mortality rate of cancer patients is gradually decreasing. However, innovative and more effective drugs are needed to further suppress the progression of cancer. Natural herbal medicines are attracting increasing attention because they offer clear advantages in terms of research and development and medical costs. DHM, a flavonoid extracted from the stem and leaves of buttercups, has promising anticancer effects. In the present review, different molecular and cellular mechanisms by which DHM induces antitumour effects were described. DHM has been demonstrated to be highly effective and to have low toxicity and few side effects. The combination of DHM with other existing anticancer drugs could increase the inhibitory effects on tumour cells. Thus, the present review provided a comprehensive reference for the development of DHM as an anticancer drug.

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Authors' contributions

RZ and TX designed the study. TX collected the information and wrote the manuscript. RZ was responsible for handling the revisions. All authors contributed to the article and approved the submitted version. Data authentication is not applicable. All the authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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