BRM270 targets cancer stem cells and augments chemo-sensitivity in cancer (Review)

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Abstract. Over the past decade, a number of studies have demonstrated the resistance of cancer cells to conventional drugs and have recognized this as a major challenge in cancer therapy. While attempting to understand the underlying mechanisms of chemoresistance, several studies have suggested that the presence of cancer stem cells (CSCs) in tumors is one of the major pathways contributing toward resistance. Chemoresistance leads to cancer treatment failure and worsens the prognosis of patients. Natural herbal compounds are gaining attention as an alternative treatment strategy for cancer. These compounds may be effective against chemoresistant cells either alone or synergistically alongside conventional drugs, sensitizing cancer cells and enhancing the therapeutic efficacy. BRM270 is a natural compound made from seven herbal plant (*Saururus chinensis, Citrus unshiu Markovich, Aloe vera, Arnebia euchroma, Portulaca oleracea, Prunella vulgaris var. lilacina* and *Scutellaria bacicalensis*) extracts used in Asian traditional medicine and has the potential to target CSCs. Several studies have demonstrated the positive effects of BRM270 against chemoresistant cancer and its synergy alongside existing cancer drugs, including paclitaxel and gefitinib. These effects have been observed against various cancer types, including resistant non-small cell lung cancer (NSCLC), glioblastoma, multi-drug resistant osteosarcoma, cervical cancer, pancreatic cancer and hepatocarcinoma. The present review discusses the effects of BRM270 treatment against CSC-associated chemoresistance in common types of cancer.

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1. Introduction

Emergence of primary and acquired resistance to existing conventional chemotherapies is one of the major challenges to overcome in the clinical management of cancer (1,2). Patients with chemoresistant cancer do not respond to conventional drugs, which results in a poor prognosis and is often associated with the reoccurrence of malignancies following treatment (3,4). Therefore, understanding the underlying molecular mechanisms of chemoresistance is necessary to improve the survival of these patients. The cancer stem cell (CSC) phenotype is one of the favored molecular mechanisms of chemoresistance (1). However, eradication of CSC populations to increase the therapeutic response of cancer cells to existing chemotherapies remains a challenge (5). Therefore, novel strategies to eliminate

CSC populations and overcome chemoresistance are key for the successful clinical treatment of certain cancer types.

Herbal remedies have been used in traditional Asian medicine for centuries to treat various diseases. Recently, they have attracted global attention as potential strategies for overcoming the chemoresistance of cancer cells, without any observable side effects (1,6). Medicinal plant extracts have the potential to treat human cancer either alone or synergistically with existing chemotherapeutic drugs to inhibit resistance (7-11). BRM270 (BRM*Life*) is a formulated extraction from seven medicinal plants used in Asian medicine, including *Saururus chinensis, Citrus unshiu Markovich, Aloe vera, Arnebia euchroma, Portulaca oleracea, Prunella vulgaris var. lilacina* and *Scutellaria bacicalensis* (Fig. 1) (1). Recently, the effectiveness of BRM270 was demonstrated as an alternative treatment to chemotherapy on non-small cell lung cancer (NSCLC) stem cells, which were resistant to EGFR-TKIs (epidermal growth receptor-specific tyrosine kinase inhibitors) (1). Similarly, previous studies have reported that BRM270 has the potential to downregulate tumorigenesis via the following mechanisms: Suppression of NF-κB signaling in multidrug resistance (MDR)-induced stem-like cells, inhibition of cervical CSC proliferation via SOX2 restriction, suppression of the recurrence and stem cell properties of glioblastoma, suppression of pancreatic CSC proliferation, and prevention of inflammation-promoted hepatocarcinogenesis (12-14).

Previous studies have also demonstrated the individual effects of the seven plant extract constituents of BRM270 (15-18). The present review discusses our current understanding of the individual and synergistic effects of BRM270 and highlights the important role of this compound in disrupting the CSC phenotype and overcoming the chemoresistance of cancer.

2. BRM270 overcomes chemoresistance by targeting cancer stem cells

BRM270 targets EGFR-TKI-resistant NSCLC stem cells. NSCLC includes adenocarcinomas, squamous cell carcinomas and large-cell carcinomas, accounting for ~85% of all lung cancer cases (19,20). The main treatment strategies for NSCLC are chemotherapy and radiotherapy, which fail to improve the survival rates of patients owing to primary and acquired resistance; therefore, only 15% of patients with NSCLC have a 5-year survival rate (21,22). Inhibition of the EGFR tyrosine kinase pathway decreases NSCLC tumorigenesis, and EGFR-TKIs, including gefitinib and paclitaxel, are first-line treatments (1). However, the majority of patients with initial responses to EGFR-TKI treatment become resistant after 10-16 months (1). Resistance to the first generation of EGFR-TKIs has led to the development of novel drug generations and combination therapies (1,22,23).

Due to the high resistance of NSCLCs to EGFR-TKIs, studies aiming to understand the mechanisms of resistance and to identify potential anti-resistance approaches remain necessary. Our recent study suggested a safe and effective alternative treatment involving the use of BRM270 for patients with EGFR-TKI-resistant NSCLC (1). The therapeutic efficacy of BRM270 against both non-resistant and EGFR-TKI-resistant lung adenocarcinoma cells was demonstrated (1). Resistance

was derived from repeated exposure of lung adenocarcinoma cells to gefitinib and paclitaxel (1). It was demonstrated that BRM270 induced the apoptosis of chemoresistant NSCLC cells and caused G_2/M cell cycle arrest via the inhibition of NF-κB/Bcl2 signaling, thereby suppressing cell proliferation. Furthermore, it was demonstrated that BRM270 was capable of suppressing chemoresistant NSCLC stem cells by inhibiting epithelial-mesenchymal transition (EMT), metastasis and stemness (1). BRM270 was also reported to induce the expression of microRNA-128 (miR-128) in chemoresistant NSCLC (1). MicroRNA (miR)-128 is considered a tumor suppressor in various types of cancer (24-26), and acts against NSCLC cells by directly regulating vascular endothelial growth factor C (VEGF-C) (27). MiR-128 also induces lung cancer cell apoptosis by directly targeting NIMA (never in mitosis gene A)-related kinase 2 (28). Our previous study reported the tumor suppressive role of miR-128 in paclitaxel-resistant NSCLC by targeting MUC1-C and BMI-1 in CSCs (19). Furthermore, our previous study has suggested that miR-128 targets the c-met/PI3K/AKT pathway in lung CSCs and reverses gefitinib resistance (29). Therefore, BRM270 serves an important role in the prevention of the CSC phenotype, the inhibition of cancer progression and tumor growth, and the suppression of malignant behaviors in chemoresistant NSCLC through the induction of miR-128 overexpression (Fig. 2A) (1). Therefore, BRM270 is an effective compound that may be used to overcome chemoresistance in lung cancer as an alternative or addition to existing conventional drugs.

BRM270 suppresses the proliferation of cervical CSCs by inhibiting SOX2. Cervical cancer (CC) is the fourth most common cause of cancer-associated mortality in females worldwide (30). Surgical resection alone or in combination with adjuvant radiotherapy is commonly used to treat advanced stages of CC. However, this approach only decreases the risk of CC progression and is associated with irreversible morbidity (31). Due to the aggressive nature of CC, multimodality treatments are commonly used, including concurrent chemoradiotherapy or neoadjuvant chemotherapy (NACT) followed by surgery (32,33). However, the application of these approaches, especially NACT, is restricted by the chemoresistance of CC cells to cisplatin, paclitaxel and taxel-based chemotherapies (31). Therefore, increasing the chemotherapeutic efficiency by targeting the underlying mechanisms of chemoresistance is essential for the successful clinical management of CC.

Previous studies have suggested that CC stem cells serve a crucial role in the resistance to conventional therapies (34-36). Our recent study reported that BRM270 inhibited CC stem cells by targeting SRY (sex determining region Y)-box 2 (SOX2) (37). SOX2 is a transcription factor that serves a crucial role in the maintenance of CSC stemness and the development of resistance to existing conventional therapies (38-41). As BRM270 has the potential to inhibit SOX2 expression, it can block the maintenance of the CSC phenotype from interfering with the emerging chemoresistance (37). BRM270 also negatively affects the progression and metastasis of CC, the EMT and sphere formation of CC stem cells, and tumor initiation (37). It also promotes the apoptosis of CC cells by inhibiting cell proliferation. Furthermore, in CC stem cells,
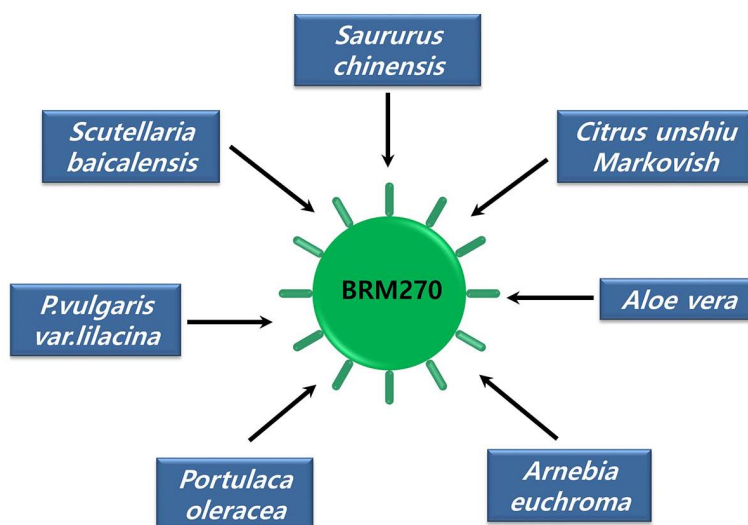
Figure 1. BRM270 consists of seven medicinal plant extracts. *Saururus chinensis, Citrus unshiu Markovish, Aloe vera, Arnebia euchroma, Portulaca oleracea, Prunella vulgaris var. lilacina* and *Scutellaria baicalensis* are the seven medicinal plants used in the BRM270 formulation.

BRM270 downregulates the Wnt/β-Catenin pathway, which is essential to sustain the CSC phenotype (Fig. 2B) (37,42).

Therefore, BRM270 represents an effective alternative to the existing conventional therapies for cervical cancer by targeting CSCs to overcome chemoresistance, thereby improving clinical management.

BRM270 disrupts stem cell properties and synergizes with CCRT to prevent glioblastoma recurrence. Glioblastoma multiforme (GBM) is the most common and aggressive type of primary brain malignancy in adults (43). Vigorous multimodality treatments, including surgeries, concurrent temozolomide chemo-irradiation and post-radiotherapy adjuvant temozolomide are currently used to treat patients with glioblastoma (44). Despite these treatments, patient prognosis is poor and the 5-year survival rate is less than 10% following the initial diagnosis. Furthermore, the median survival time is ~14.6 months owing to the infiltrative behavior and extreme resistance of cells to radiation and chemotherapy (45). This resistance also leads to the recurrence of glioblastoma following standard cancer therapy. Accumulating evidence suggests that glioblastoma stem cells are the major cause of chemo- and radio-resistance and are largely responsible for tumor recurrence (46-49). Therefore, the glioblastoma stem cell population is an important target for the successful clinical management of progressive and recurrent malignant glioblastoma.

A previous study demonstrated that BRM270 targets glioblastoma stem cells, suppressing growth and viability through the induction of apoptosis without affecting normal astrocytes (13). The sub-G_0 cell population was significantly increased following the BRM270 treatment, indicating an expanded population of dead cells. Notably, BRM270 treatment did not cause any difference in G_1, S or G_2/M subpopulations. Furthermore, the stemness properties of glioblastoma stem cells were also suppressed by treatment with BRM270. While BRM270 administration alone targeted the properties of glioblastoma stem cells, combined treatment with concurrent chemoradiotherapy (CCRT) successfully decreased the number of CD15-expressing stem cells and decreased the chance of glioblastoma recurrence (Fig. 2C).

Therefore, BRM270 alone and as a combined treatment with CCRT is effective in suppressing the CSC phenotype, overcoming resistance to radiotherapy and chemotherapy, and preventing the recurrence of malignant glioblastoma.

Pancreatic CSC proliferation is inhibited by BRM270 via the downregulation of sonic hedgehog signaling. Pancreatic ductal adenocarcinoma (PDAC) is considered one of the deadliest types of carcinoma, with a median survival time of less than 5-8 months (11). Gemcitabine is used as the first-line drug for PDAC, though intrinsic and acquired resistances remain major challenges. CSCs have been identified in previous studies as crucial players in the resistance of PDAC to existing conventional chemotherapy (11,50).

Our recent study established that BRM270 was capable of inhibiting malignancy and the self-renewal capacity of CD44$^+$ PDAC cells (14). CD44 is a marker of the CSC population and the initiation of cancer, suggesting that BRM270 is able to inhibit CSC populations and stem-like properties of PDAC (51). BRM270 treatment also suppresses PDAC CSC-derived tumor growth via the downregulation of sonic hedgehog signaling in PDAC stem cells (14). The aberrant activation of the sonic hedgehog pathway is one of the major fundamental drivers of PDAC stem cell self-renewal and is associated with decreased survival rates in patients (Fig. 2D) (52-54).

Therefore, BRM270 is an effective treatment for PDAC and has the potential to reduce its resistance to existing chemotherapies by inhibiting PDAC stem cells, a crucial player in chemoresistance.

BRM270 inhibits tumorigenesis by suppressing NF-κB signaling in MDR-induced osteosarcoma stem cells. Osteosarcoma is an aggressive malignant tumor that primarily affects the skeletal system, and leads to a 5-year survival rate below 20% (55). It remains a challenge for current therapeutic strategies to effectively treat osteosarcoma due to the MDR of cancer cells to existing chemotherapeutic drugs, including doxorubicin and
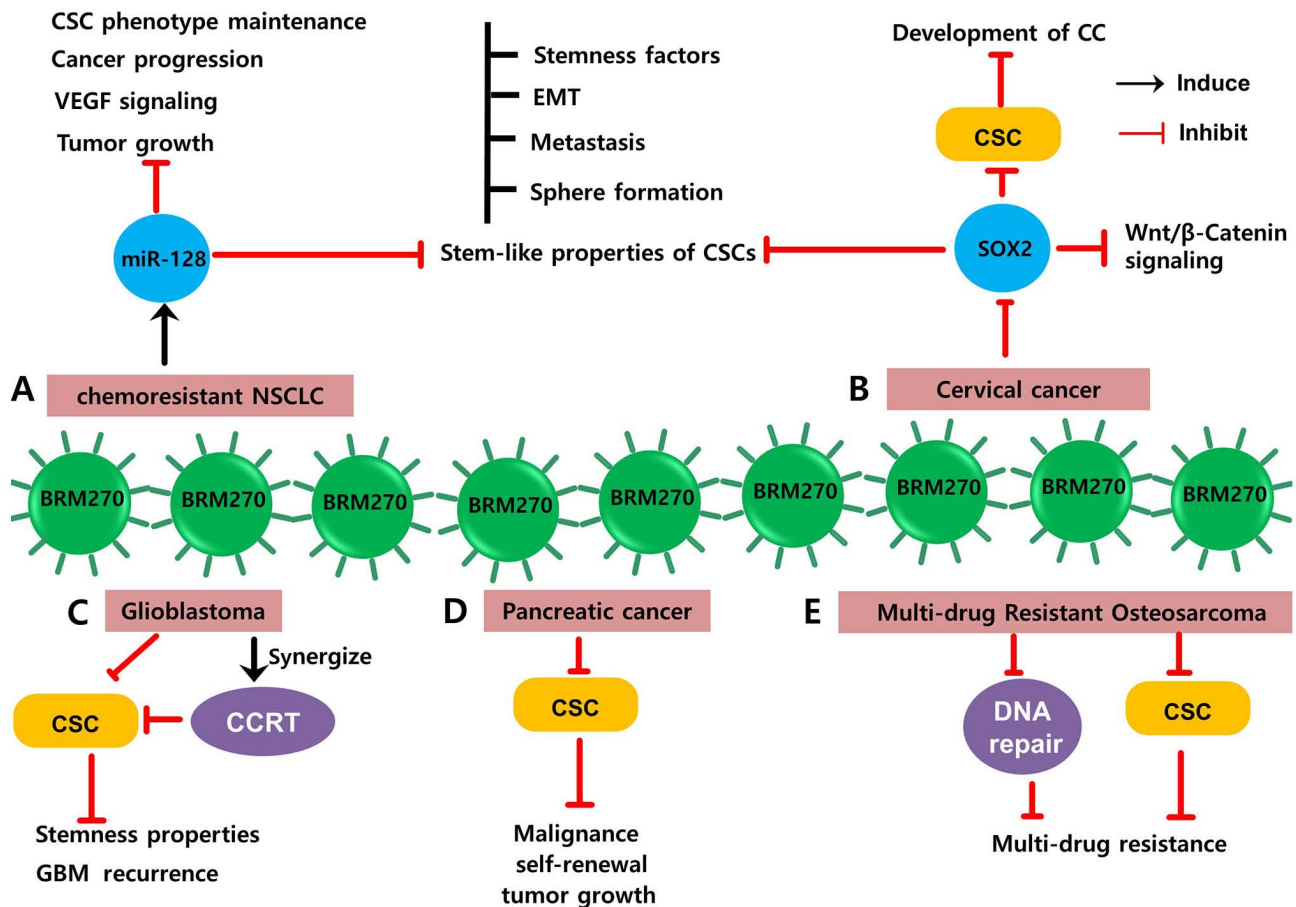
Figure 2. BRM270 acts against chemoresistance by inhibiting CSCs. BRM270 impacts gefitinib- and paclitaxel-resistant (A) NSCLC, (B) cervical cancer, (C) glioblastoma, (D) pancreatic cancer, and (E) multi-drug resistant osteosarcoma to overcome chemoresistance through the inhibition of CSC populations and stem-like characteristics. The CSC phenotype is one of the major underlying mechanisms in the chemoresistance of cancer cells. CSC, cancer stem cell; CC, cervical cancer; NSCLC, non-small cell lung cancer; VEGF, vascular endothelial growth factor; EMT, epithelial-mesenchymal transition; GBM, glioblastoma multiforme; CCRT, concurrent chemoradiotherapy; miR, microRNA; SOX2, SRY (sex determining region Y)-box 2.

cisplatin (56,57). The presence of stem cell populations and altered DNA repair mechanisms have been identified as the major underlying methods of MDR in osteosarcoma (57,58). Therefore, targeting these mechanisms would likely inhibit MDR and sensitize osteosarcoma cells to existing drugs.

The capability of BRM270 to circumvent MDR with minimal adverse side effects has been reported (12). BRM270 impacts osteosarcoma MDR by damaging DNA repair mechanisms and negatively affecting CSC populations (12). Our previous study demonstrated that BRM270 disrupts the formation of the microtubule cytoskeleton in doxorubicin-resistant osteosarcoma stem cells, inducing chromosomal condensation and nuclear fragmentation (12). BRM270 also induces programmed cell death and mitotic catastrophe in osteosarcoma stem cells by promoting irreversible DNA damage in the premature apoptosis stage and inhibiting cell proliferation selectively, without affecting the functions of normal cells (12). BRM270 treatment also induces the expression of key pro-apoptotic proteins, including structural maintenance of chromosome 2 (SMC2), Caspase-8, Interleukin-6 (IL-6), Cyclin-dependent kinase 6 (CDK6) and p65 (Fig. 2E) (12).

Therefore, BRM270 is a safe and effective natural compound to treat MDR osteosarcoma by promoting unrepairable DNA damage and cytotoxicity in osteosarcoma stem cells.

BRM270 prevents inflammation-induced hepatocarcinogenesis. Hepatitis B virus (HBV), hepatitis C virus (HCV), non-alcoholic fatty liver disease, alcoholism or aflatoxin exposure are common causes of chronic hepatic injury (59). Persistent inflammation, as a result of chronic liver injury, is strongly associated with hepatocarcinogenesis, leading to the development of hepatocellular carcinoma (HCC) after years of inflammation (59). For example, the inability to clear HCV leads to chronic hepatitis C infection, resulting in inflammation-induced lesions in the liver, hepatic fat accumulation, and progressive fibrosis followed by HCC or cirrhosis (60-63). Chronic liver inflammation includes phorbal-12-myristate-13-acetate (PMA)-induced inflammation, which promotes hepatocarcinogenesis and HCC progression. This inflammation induces the expression of numerous inflammatory cytokines, including tumor necrosis factor alpha (TNFα), Interleukin 1 (IL-1), IL-23, IL-6, cyclooxygenase-2 (COX-2), and lymphotoxins (LT) α and β (59,64).

Our recent study reported that this enhanced BRM270 prevents PMA-induced inflammation through suppression of signal transducer and activator of transcription 3 (STAT3) signaling (14). As PMA is a COX-2 inducer and a mediator of inflammation, inhibition of PMA-induced inflammation by BRM270 decreases the expression of IL-6 and COX-2, leading to the suppression of hepatocarcinogenesis progression (14).
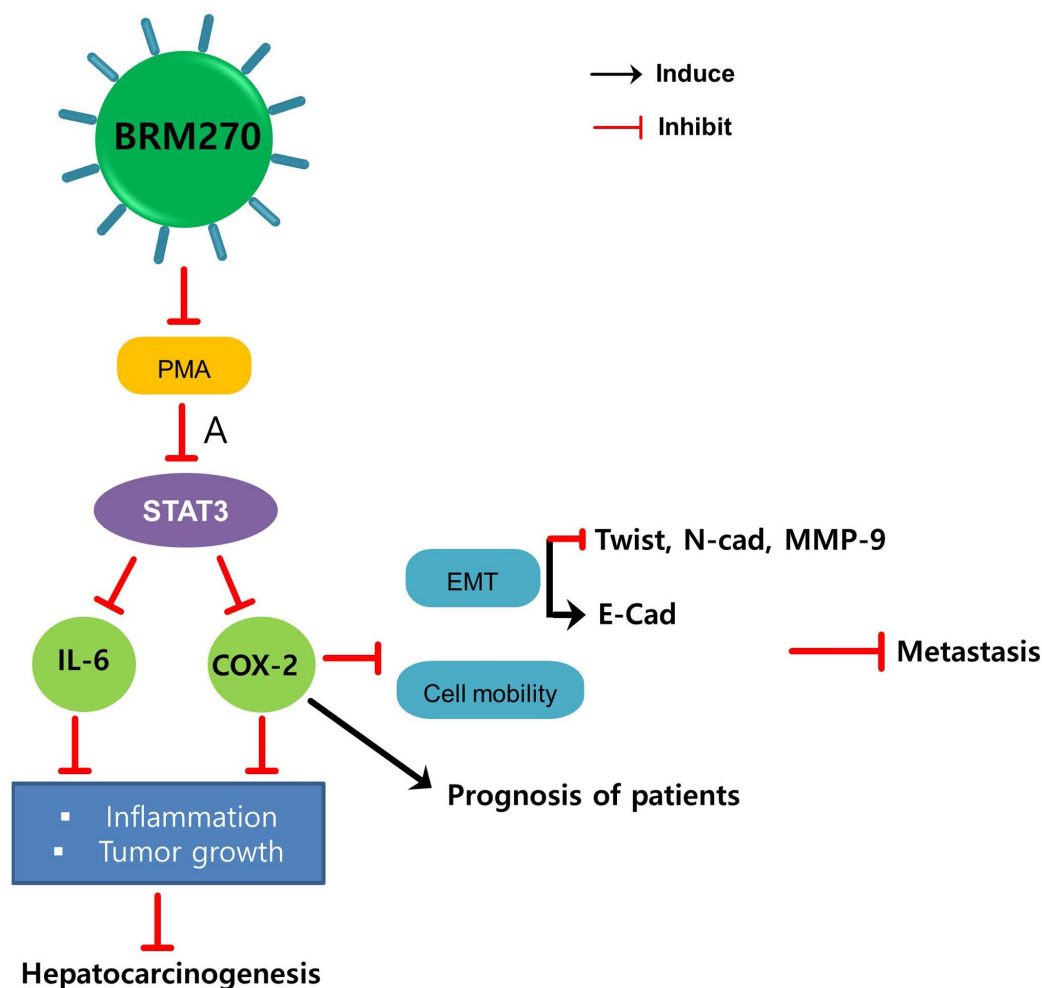
Figure 3. BRM270 suppresses inflammation-induced hepatocarcinogenesis by targeting the IL-6/STAT3/COX-2 axis. BRM270-induced PMA inhibits the phosphorylation of STAT3 at the tyrosine 705 site, thereby inhibiting IL-6 and COX-2 expression. IL-6 and COX-2 are essential for tumor growth and inflammation-induced hepatocarcinogenesis. BRM270 also inhibits cell metastasis via the suppression of COX-2 and the reduction of EMT and cell mobility. PMA, phorbal-12-myristate-13-acetate; EMT, epithelial-mesenchymal transition; IL-6, interleukin 6; E/N-Cad, E/N-cadherin; COX-2, cyclooxygenase-2; MMP-9, matrix metallopeptidase 9.

BRM270 also inhibits hepatic tumor growth and HCC cell metastasis and improves the prognosis of patients with HCC via the inhibition of IL-6 and COX-2 expression (Fig. 3) (14).

Therefore, BRM270 is a natural compound treatment that has the potential to prevent hepatocarcinogenesis induced by inflammation through the downregulation of the IL-6/STAT3/COX-2 axis.

3. Conclusions

BRM270, a compound made of seven herbal plant extracts, is capable of negatively regulating the resistance of cancer cells to existing conventional therapies by inhibiting the CSC phenotype. BRM270 exerts its antitumor effects against chemoresistance via the suppression of CSC populations and the stem-like properties of CSCs. The compound can be used either as a standalone treatment or synergistically with existing drugs. Furthermore, the functionally enhanced product of BRM270 prevents inflammation-induced hepatocarcinogenesis. BRM270 does not cause any adverse side effects and does not affect normal human cells, but selectively targets cancer cells. Future studies should focus on further understanding the effects of BRM270 on CSCs and chemoresistance and investigate the possibility of BRM270 in clinical use.

Availability of data and materials

Not applicable.

Authors' contributions

NC, HK and TK contributed toward the conception of the study, writing the manuscript and performing the literature search. JK, JL and YHP conducted analysis and revised the manuscript. HNS and TK performed analysis and the quality assessment of the study. All authors 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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