



Review Article

ANTITUMOR ACTIVITY OF BERBERINE AGAINST BREAST CANCER: A REVIEW

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ABSTRACT

As the prevalence of breast cancer has been increasing day by day in almost every part of the world, there is need to develop alternative therapeutic measures for breast cancer control. To fulfill this need, chemoprevention is a novel approach. Efforts have been made to identify synthetic or natural products that can prevent the pre-neoplastic events preceding the occurrence of detectable cancer. Berberine (quaternary ammonium salt from the protoberberine group of isoquinoline alkaloids) is one such compound. In this review *in vitro* and *in vivo* anticancer activities of berberine have been summarized. The mechanisms of action of berberine include; inhibition of tumorigenic microorganisms, regulation of oncogene, interaction with DNA and RNA, inhibition of carcinogenesis related enzymes and induction of apoptosis. Berberine has synergistic activity of when given in combined medication while it is also responsible for reduction of multidrug resistance in breast cancer treatment.

Keywords: Berberine - breast cancer - *in vitro* - *in vivo* - multidrug resistance

INTRODUCTION

Cancer is a set of disorders characterized by unrestrained growth of abnormal cells which spread out throughout the body. If this spread is not limited, death may occur. Breast cancer mainly originates in lobules and ducts of breast tissues. Lobules are joined to nipples by ducts; however, the remaining major parts of the breast are lymphatic and connective tissues. The international agency for research on cancer (IARC), a focused agency for cancer of the world health organization (WHO), has provided the latest information regarding occurrence, death rate and frequency of cancer worldwide on December 12, 2013. According to IARC report, the most frequently diagnosed cancer globally were those of the lungs affecting 1.8, 1.7 and 1.4 million people respectively and their percentage was recorded to be 13.0, 11.9 and 9.7 % respectively. According to this report there was a sharp rise in breast cancer worldwide. Studies have revealed that since 2008, breast tumor occurrence has enhanced by more than 20 %, however mortality has augmented by 14 %. Breast sarcoma was found to be the tumor that was mostly diagnosed in females of 140 out of 184 countries of the world. Furthermore, this type of cancer also proved to be the cause of death in under developed countries worldwide¹. Breast cancer is mainly caused by the mutations in BRCA1 and BRCA2 genes; however family history, obesity and hormone therapies also participate in pathogenesis of breast tumors. Enhanced levels of estrogen are mainly responsible for breast cancer in females. Chemotherapy and radiation therapy are mostly used in the treatment of breast cancer along with adjuvant and neoadjuvant therapies. Recent studies have shown that monoclonal antibodies are also used in the treatment of breast tumors². From the previous studies it is obvious that the medicines obtained from the plant extracts have played a significant role in health care of ancient and current cultures. In Indian Ayurveda system mostly plant origin drugs are used to treat various diseases including cancer. In the treatment of sarcoma's about 60 % of natural origin drugs are used, such as vinca alkaloid and paclitaxel, etc³. The latest treatment for different types of cancers includes gene therapy⁴. Berberine is basically a quaternary ammonium salt from the protoberberine group of isoquinoline alkaloids and It is isolated from rhizome, stem

bark and roots of a various plant species including *Berberis aristata*, *Berberis vulgaris*, *Berberis aquifolium*, *Coptis chinensis*, *Hydrastis canadensis* and *Arcangelisia flava*⁵. In this review we will review such studies to give an updated status on anti-tumor activity of berberine with reference to breast cancer.

Mechanisms of action of Berberine

From recent research it is obvious that berberine possesses both *in vivo* and *in vitro* antitumor activity. Berberine exerts anticancer activity through following mechanisms.

Inhibition of tumorigenic microorganisms

Different experiments depicted berberine has inhibitory effects on propagation and duplication of some tumorigenic microbes and viruses like hepatitis B-virus and *Helicobacter pylori*⁶. There is etiological close relationship between tumorigenesis and pathogenic microorganisms; for example, *Helicobacter pylorus* is a source of peptic ulcer, gastric cancer and chronic gastritis^{7,8}. Therefore the antimicrobial activity of berberine may be responsible for its anticancer potential.

Regulation of oncogene

In many recent studies it was revealed that berberine is responsible for increased AMP- activated protein kinase. This increased activity due to berberine causes phosphorylation of tumor suppressor gene p53 in vascular smooth muscle cells (VSMCs)⁹. Transcription factors like nuclear factor-kB (NF-kB), nuclear factor E2-related factor 2 (Nrf2) and activated protein-1 (AP-1) mediate cellular signaling cascades. These factors play a significant role in tumor initiation, promotion, and propagation¹⁰. In a study it was observed that berberine has inhibitory potential for AP-1 activity in human hepatoma cells, hence, this inhibitory potential is dose and time dependent¹¹. Moreover, a latest study has discovered that berberine induces apoptosis and growth inhibition in lung cancer cells of human *in vitro*¹².

Interaction with DNA and RNA

Berberine interacts with DNA and RNA to form the complexes with them. This complex formation might be responsible for its antitumor mechanism¹³. Several analytical techniques like fluorescence, absorption, electroscopy ionization mass spectrometries and nuclear magnetic resonance and have been used to study berberine binding affinities with DNA or RNA¹⁴. Liu¹⁵ conducted a study which showed that berberine therapy is effective for the treatment of normal osteoblasts and osteosarcoma cells via the activation of p53 gene (tumor suppressor gene) and p53 dependent cellular responses which are responsible for cell cycle capture and cell death.

Inhibition of Carcinogenesis related Enzymes

Inhibition of N-acetyltransferase

The environmental and occupational chemicals play a pivotal role in causation of chemical carcinogenesis. Cytosolic arylamines N-acetyl transferase (NAT) metabolize arylamines and forms reactive carcinogenic metabolite^{16,17}. NAT has important role in drug detoxification and carcinogen activation¹⁸. In many studies it was observed that berberine has inhibitory effect on NAT activity of several cancerous cells like human bladder carcinoma cells (T24) dose dependently¹⁹, human colon tumor cells²⁰, HL-60 human promyelocytic leukemia cells²¹, human malignant astrocytoma (G9T/VGH)²², and mouse lymphocytic leukemia cells (L1210)²³. Moreover, berberine also inhibited the NAT genes expression *in vitro* in a dose and time dependent manner^{22,24}.

Inhibition of cyclooxygenase-2(COX-2)

The COX-2 plays a pivotal role in prostate²⁵, lung²⁶, colon²³, and skin²⁷ tumorigenesis. It may be a new potential target for cancer therapy²⁸⁻³⁰. Therefore the compounds that inhibit COX-2 transcriptional activity can be important for chemoprevention against cancer. Accumulate evidence suggests that berberine has inhibitory effect on transcriptional activity of COX-2 in cancer cells of colon³¹, oral cancer cell line OC2 and KB cells³², MCF-7 cells of breast cancer³³. Berberine reduced the prostaglandin E2 production in a dose dependent manner, due to the effect of direct inhibition of AP-1 binding, resulting in reduction of COX-2 protein and transcriptional suppression of COX-2³⁴. This influence of berberine on activity and expression of COX-2 was due to its anti-inflammatory potential³².

Inhibition of telomerase

Telomeres prevent degradation and aberrant recombination of DNA. In this way telomeres maintain genome stability and cell viability. Continuous cell growth is the hallmark of advanced malignancies due to reactivation of telomerase³⁵. Telomerase is a novel therapeutic target because it is the requirement of all cancerous cells for their immortalization including stem and tumor cells³⁶. Berberine is responsible for dose dependently inhibition of telomerase activity in human nasopharyngeal carcinoma (NPC) CNE-2 cells and HL-60 cells^{37,38}.

Inhibition of topoisomerase

Tops are novel molecular targets for anticancer drugs. Berberine inhibits Top-1 by stabilizing the enzyme mediated DNA cleavable complex³⁹.

Induction of apoptosis

Chemopreventive cancer agents might be classified as suppressing agents that suppress the propagation and promotion of cancerous cells or blocking agents that hamper the initiation stage, most probably by disturbing fundamental factors which control propagation of cells, differentiation or cell death⁴⁰. Proapoptotic effects of berberine have been shown in many cell lines of cancer

and non-tumor cells, like HL 60^{37,41}, Balb/c 3T3 cells⁴², HeLa and L1210 cells, prostate cancer cells⁴³.

Alteration of pro-apoptotic and anti-apoptotic gene expression

Studies have shown that in tumor cell lines, berberine increases Fas protein expression dose and time dependently⁴⁴. Berberine also enhances the protein expression of proapoptotic gene p53 *in vitro* and increases phosphorylation^{9,41}.

Role of reactive oxygen species (ROS)

ROS are recognized to have vast biological properties; some of them are cell propagation, activation, cell survival and death⁴⁵. Two important ROS derived sources; lipoxygenase and xanthine oxidase⁴⁶ are inhibited by berberine, signifying its anti oxidative potential. Different experiments have concluded that berberine has the ability to prevent Low-density lipoprotein (LDL) oxidation induced by Copper (Cu²⁺) and can protect cellular dysfunction⁴⁷. It is also observed that berberine significantly enhances the superoxide dismutase level and reduces malondialdehyde (MDA) formation⁴⁸. There are many *in vivo* studies in which anti oxidative potential of berberine has been studied⁴⁸⁻⁵⁰.

Effect on mitochondria transmembrane potential, cytochrome c release and caspase activation

Mitochondria release cytochrome c and cause cell apoptosis which is considered to be a pivotal step in apoptosis because this is the main stimulus for cell death. In many tumor cell lines, for example, SNU-5, Hep G2, carcinoma cells of human prostate^{41,43} and liver mitochondria isolated from rat⁵¹; the drop or loss of mitochondrial trans-membrane potential was observed after berberine therapy.

Effect on NF-κB activation

Berberine is responsible for inhibition of NF-κB expression induced by different carcinogenic substances and inflammatory agents like PMA, TNF-α, okadiac acid (OA) and condensate of cigarette smoke. This inhibition of NF-κB results in reduced expression of regulated gene products of NF-κB which is involved in anti-apoptosis (Bcl-xL, CFLIP, surviving, IAP1 and IAP2), inflammation (COX-2), invasion (MMP-9) and proliferation (cyclin D1)⁵². The possible mechanism that underlies this inhibitory process could be different for cancerous and non-cancerous cells. In tumor cells, mechanism responsible for NF-κB inhibition by berberine involves activation by time dependent phosphorylation of p38 MAPK and JNK and inactivation of ERK genes.

In Vitro anticancer studies

In various cell culture studies on normal cells as well as cell lines of multiple tumors, the anticancer activity of berberine has been comprehensively observed. The results of these studies can be summarized in various unique characteristics including: First, the anticancer potentials of berberine are different in various cells. As an example, B16 cell line of murine tumor cells was more receptive for berberine therapy than U937 cells of human promonocytic⁵³. In another study it was also observed that the growth of L1210 cells of murine leukemia in suspension was more receptive to berberine treatment in comparison to human cervical carcinoma⁴². Second, berberine therapy has proved to be better in inhibiting propagation of tumor cell; however, studies have also shown that along with cytoprotective effects of berberine, it is also associated with minor cytotoxic potentials to the normal body cells. Cytoprotective activity of berberine against cancer cell line HepG2 of human liver has also been investigated⁵³⁻⁵⁵. Third, for the same cell type, different laboratories provided different IC₅₀ values, which may be due to different cultural conditions and detection methods^{20,22,43,49,51,52,54,56,57}. Fourth, berberine exerts its effect slowly and smoothly which means it usually produces its effects after 24

hour treatment⁵⁸. Fifth, moreover berberine has capability to capture cell cycle in both tumor and non tumor cells. Berberine produces G2/M phase arrest in non-tumor Balb/c 3T3 cells⁴². This observation has also been recorded in leukemia cells of SNU-5 cell line in gastric carcinoma⁴¹. Berberine also has the potential to induce G1-phase cell cycle capture in human epidermoid carcinoma A431 cells⁴², human HSG-3 oral cancer cells⁵⁹, murine leukemia L1210 cell lines⁶⁰ and T98G cells⁶¹.

In Vivo anticancer studies

Berberine exhibited significant cytoprotective activity against sarcoma-180 ascities⁶². A study has also demonstrated the effectiveness of Berberine therapy against chemical carcinogenesis induced by 20-Methyl-cholanthrene or N-nitrosodiethyl-amine⁶³. Some animal studies have shown that the combined therapy of berberine with anticancer drugs (carmustine and cyclophosphamide) is more effective in comparison to monotherapy⁶⁴⁻⁶⁶. Moreover this synergistic effect of berberine has been reported in both *in vitro* and *in vivo* lung cancer models when it was used in combination with irradiation⁶⁷. In male F344 rats, berberine inhibited the formation of colon putative pre-neoplastic lesions and azoxymethane (AOM)-induced aberrant crypt foci (ACF). This is because berberine inhibits COX-2 activity. Berberine administration improved the carbohydrates bound to proteins, anti oxidative status in rats and lipid per oxidation induced by AOM. Berberine treatment reduced the tumor size and tumor incidence in a murine xeno graft model implanted with tumor cell CC-4⁶⁹. In a study conducted by Manoharan⁷⁰ oral administration of berberine @ 75 mg/kg body weight completely cured the tumor incidence in buccal pouch in DMBA-treated hamsters. In Swiss albino mice, administration of berberine completely prevented the skin cancer induced by DMBA⁷⁰.

Effect on tumor metastasis

Previous studies have shown that berberine drastically inhibits the Matrix metalloproteinases (MMPs) expression of proteins and angiogenesis in multi cellular DU-145 prostate tumor spheroids cultures and embryoid bodies⁷¹. Moreover berberine also reduced TPA-induced MMP-9, UV-induced MMP-1 and basal expression and activity in normal keratinocytes and dermal fibroblasts in humans^{72,73}. The decreased intracellular ROS levels might be responsible for this MMP inhibition (free radical scavengers, like vitamin E also exhibits same results). Inhibition of MMP-2 expression by berberine was due to regulation of the tissue inhibitor of metalloproteinases-2 in human lung cancer A549 cells⁷⁴. This suppression of MMPs by berberine is responsible for the inhibitory potentials on the movement and invasive capability of tumor cells to some extent⁷⁵. SDF-1 and NM23-H1 genes are concerned with motility and movement of tumor cells. Berberine might considerably enhance NM23-H1 and decrease SDF-1 protein expression, which significantly reduces the migration of leukemic stem cells⁷⁶. Hypoxia- inducible factor (HIF)-1 α and vascular endothelial growth factor (VEGF) are two important factors that mediate tumor angiogenesis. In a study berberine inhibited the potential of hypoxic SC-M1 cells to potentiate the human umbilical vein endothelial cells movement; however this inhibitory effect of berberine was due to its regulatory effects on these two factors⁵⁵.

Application in combined medication

In a study conducted by Yount⁷⁷ Glioblastoma (GBM) cells were treated with safe dose of berberine. Results of study demonstrated that the GBM cells became more susceptible as compared to vehicle treated control cells, however, this susceptibility was not found in primary glial cultures of humans. To promote the death of remaining GBM tumor cells, it is suggested that berberine should be used in combination with postoperative radiotherapy. Another study was conducted for determination of the synergistic activity of berberine along with estrogen receptor antagonists. It was observed that

estrogen receptor antagonists have antitumor potential for MCF-7 cells of human breast cancer due to berberine through down regulating expression of HER2, EGFR, COX-2 and Bcl-2 and up-regulating of p21 and IFN- β ³³. These results indicate that combined treatment of berberine should be used with other treatments in chemotherapy of tumors.

Improvement of multidrug resistance

Chemo resistance is caused by ATP-binding cassette (ABC)-super family efflux pumps of multidrug. Resistant protein of breast cancer (ABCG2), MRP1 (ABCC1) and P-glycoprotein (ABCB1) have major role in physiology because these transporters protect tissues from noxious xenobiotics⁷⁸. ABCG2 acts as multidrug transporter which is responsible for resistance in tumor cells⁷⁹. Berberine is responsible for reduction in MCF-7 breast cancer cells as it decreases the ABCG2 expression⁸⁰.

CONCLUSION

This review provides an evidence that berberine has anticancer potential in both *in vitro* and *in vivo* conditions. It affects the tumor cells by different mechanisms, while it synergistic activity of berberine along with estrogen receptor antagonists when given in combined medication. Berberine is also responsible for reduction of multidrug resistance in breast cancer treatment.

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