A REVIEW OF BERBERINE BIOACTIVE COMPOUNDS AND ITS THERAPEUTIC POTENTIAL IN OVARIAN CANCER

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Abstract

Berberine, a secondary metabolite, basically an isoquinoline alkaloid, derived from various species of *Berberis* and *Coptis* has significant biochemical effects like anti-inflammatory and anti-cancerous at various sites of the human body. Its role is significant in ovarian cancer. As an anticancer agent, it can block the cell cycle, can hinder activity of topoisomerases, can upregulate the expression of proteins to activate apoptotic cascade in various cell lines. It can also inhibit metabolic process of tumor cells which leads to the death of tumor. Moreover, repopulation of tumor stem cells can also be inhibited by berberine therapy. Combined dose therapy enhances its efficacy against malignancy. However, poor absorption and efflux from digestive tract limit its benefit. This problem is overcome by the production of its derivatives or by the formulation of berberine Nano-carriers. Also, its specificity towards its target site is increased through Nano-formulation. So, this study explores the biochemical characteristics and effective chemotherapeutic pathways of berberine, also highlights the strategies that include using berberine in combination with other chemotherapeutic agents either to reduce toxic side effects or enhance their anticancer effects and determines the potential of various novel formulation approaches to enhance pharmacokinetics of berberine.

Introduction

Berberine a yellow extract can be extracted from variety of plants including *Hydrastis canadensis* (goldenseal), *Coptis Chinesis* (chinese goldthread), *Berberis aristata* (tree turmeric), *Berberis vulgaris* (barberry) *and Berberis darwinii* (Darwin barberry). It is a powerful antioxidizing agent having the potential to treat a variety of illnesses and hormonal imbalance. It shows numerous therapeutic activities including antimicrobial, anti-diabetic, anti-diarrheal, anti-hypertensive, anti-inflammatory and hypolipidemic activities [(1)]. As a chemotherapeutic agent berberine is cytotoxic to a large number of tumors cell lines of genital carcinoma, leukemia (acute myelocytic, lymphoblastic, myelogenous and non-lymphocytic), esophageal colorectal carcinoma as well as urothelial carcinoma [(2)]. The therapeutic potential of berberine is shown in figure 2. Ovarian cancer is one of the most prevalent malignancies of genital tract. It is termed a heterogeneous disorder

with a wide range of clinical and pathological characteristics. Its pathogenesis comprises several biological as well as molecular mechanisms, including genetic modifications, inflammation, apoptosis and the presence of ROS [3].

As an effective treatment for ovarian cancer, berberine has recently gotten a lot of interest. In ovarian cancer, berberine can influence some cancer related pathways and molecules summarized in figure 3. Evidence on berberine has also revealed that it can prevent spread of ovarian carcinoma cells through several mechanisms, either alone or in conjugation with other chemotherapeutic agents.

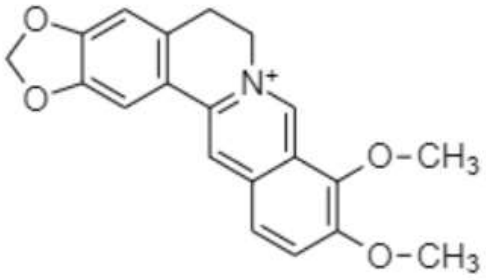

Fig1. Chemical structure of berberine

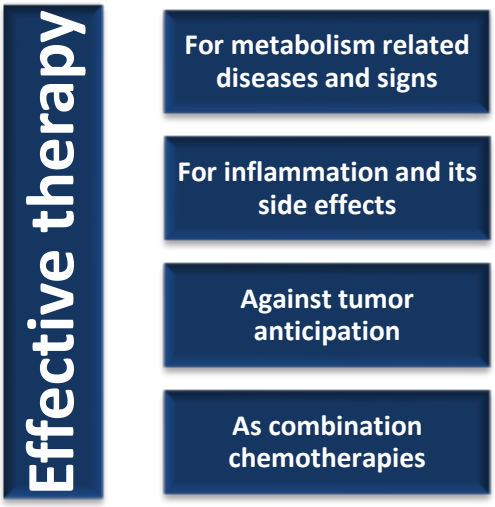

Fig 2. Therapeutic potential of berberine

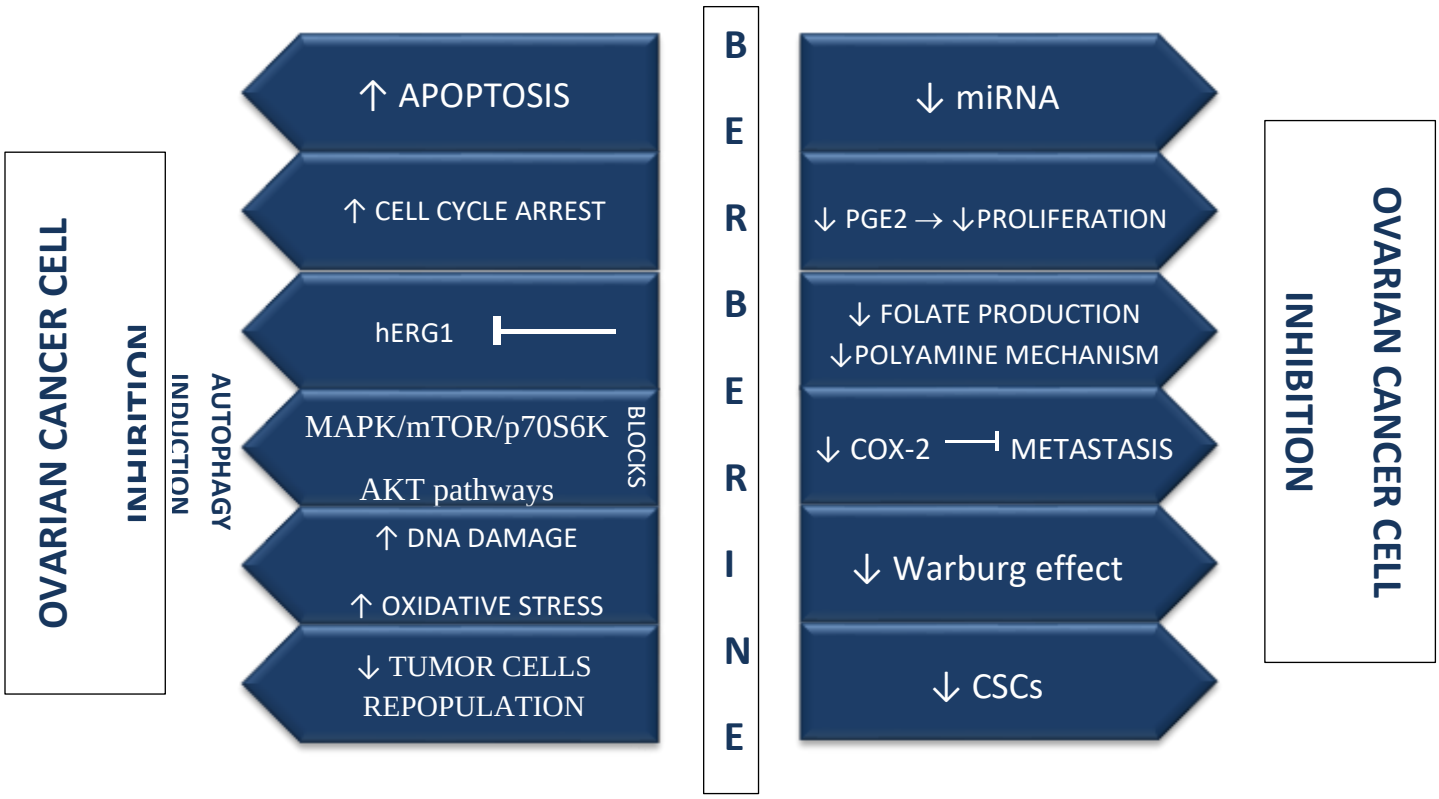

Fig 3. Chemotherapeutic Activities of Berberine in Ovarian Cancer

Apoptosis induction by berberine

Potential therapeutic approaches for the treatment of malignant ovary include medicinal drugs that direct toward the tumor cells and sensitize them to apoptotic signals. It has been demonstrated that berberine has pro-apoptotic effects in a number of malignancies .One of the key mechanisms in the ovary is that the berberine reduces the growth of tumors by boosting apoptosis, promoting tumor differentiation, and inhibiting metastasis and invasion. It has been demonstrated that a wide range of genetic as well as epigenetic occurrences can cause cancer cells to undergo apoptosis. In an investigational research berberine significantly slowed the proliferation of cancerous cells by promoting apoptotic cell death in ovary. Through suppressing the transcription of anti-apoptotic genes like BCL-2 and pro-survival protein and raising the expression of proapoptotic genes like BAX, berberine triggered apoptosis as summarized in figure 3. Additionally, cisplatin along with berberine had a cumulative influence on the growth of tumors [(3)].

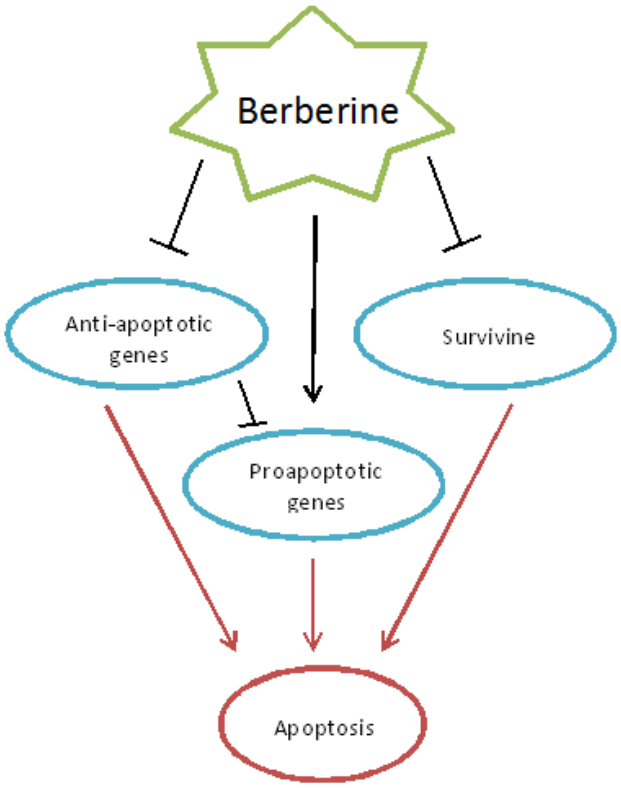

Fig3. Apoptotic induction pathway

A rise in the concentration of key proapoptotic proteins involved in apoptosis signaling pathways, including p53, Rb protein, Serine/Threonine Kinase), Caspase-8, Fas Death Receptor/Fas Ligand, BH3 Interacting-domain death agonist and proapoptotic member of the Bcl. In contrast, it was found that after exposure to berberine, the levels of the apoptosis inhibiting proteins such as cIAP1, XIAP (an X-linked antagonist of apoptotic protein), Bcl X, and Survival (an anti-apoptotic protein) decreases (2).

Induction of apoptosis via miRNAs is activated by Berberine

MicroRNAs (miRNAs), a class of epigenetic regulators, have become important participants in the regulation of many physiological activities. Every cell produces miRNAs, which are regarded as short RNAs. The target genes' expression is silenced by these noncoding RNAs. Its sequence will eventually interfere with the translation of proteins since it is directly complementary to the trailer sequence regions (3′UTRs) at mRNA strands.

Through the miR93/PTEN/PKB cascade, berberine improves the chemotherapeutic properties of cisplatin in ovarian cancer cells. By inhibiting miR93, berberine potentially makes human ovarian cancer cells more sensitive to cisplatin [(4)].

The increased miR-21 expression is also seen to be a significant factor in the resistance of tumor cells to cisplatin ovarian carcinoma. In meantime, chemoresistance to cisplatin in SKOV3 cell lines produced by miR21 are might be mediated by Programmed Cell Death 4, an effective as well as a key target of miR21. The miR21/PDCD4 axis offers a fresh insight into the mechanism underlying medication resistance and could aid in the creation of viable therapies for the treatment of ovarian cancer. In persistent SKOV-3 cell lines as compared to OVCAR-3 cell lines, miR21 was up-regulated while the proteins of proapoptotic i.e., PDCD4 knockdown. PDCD4 protein levels were related to the molecular relationship between miR21 deregulation and developing chemoresistance in SKOV3 cells [(5)].

Inhibition of Enzymes of PGE2 by Berberine

Prostaglandin E2 (PGE2) is a biologically active lipid that encourages tumor proliferation and cell division.

By raising the amount of free Arachidonic Acid in ovarian cancer, the chemotherapeutic medication VP16 encouraged the production of PGE2, which resulted in the growth of neighboring non-apoptotic cells. However, berberine prevented the phosphorylation of FAK, which prevented the process, by inhibiting the two major enzymes (calcium-independent phospholipase A2 and cyclooxygenase 2) involved in PGE2 synthesis in the tumor microenvironment [(6)].

Cell cycle arrest through berberine

For the cell cycle arrest brought on by berberine, cyclins appear to be a key target.

Low doses of berberine have been proven to stop cancerous cells in the G1 phase in humans, whereas large quantities have been demonstrated to stop cell division in the G2/M phase [(1, 7)]. In the G1 cell cycle phase, cyclin D1 was found to be downregulated following berberine treatment. Tumors can be halted in the G1 and G2 phases by berberine as it reduces the manifestation of Cyclins and G2/M phase checkpoint protein kinases. During berberine treatment, G0/G1 arrest was seen in genital cancer cell lines, mostly as a result of a drop in the quantity of the cell cycle regulating protein cyclin B1. The effect is dose-dependent [(1, 8)].

Because berberine interrupts the cell cycle, it prevents the proliferation of ovarian cancer cells. Experiments revealed that OVCAR-3 cells had a 7 percent rise in their genetic content in the G2 phase following berberine therapy, but SKOV-3 cells had a 9 percent rise in the genetic material in the S phase. Such findings support our data from immunoblotting, which show that berberine raises the levels of p27 in SKOV-3 as well as OVCAR-3 tumor cells. The response is in line with the discovery that division cycle arrest could impede cell proliferation. Moreover, it is also seen that berberine in other cell lines hinders the role of a CDK inhibitor and CDK cyclins complex as well as DNA topoisomerase II, while some investigations claim showed this could cause mouse lymphocytic leukemia cells to enter the G2/M-phase arrest and human leukemia cells to enter the G1 cell-cycle arrest. In some earlier research, it is discovered that berberine also inhibits breast

cancer growth by causing cell division blockage and apoptotic cell death. Further researches revealed about the expression of the protein p27, a well-known protein identified to have activity linked to cell division cycle blockage, is upregulated by berberine in both cell lines [9].

Berberine causes inhibition of hERG1

The human ether-a-go-go related potassium channel 1 (hERG1) is recognized as a crucial component in the development of ovarian cancers, and berberine treatment has been shown to reduce the high expression of this protein in ovarian cancer cells. A recent study revealed a novel mechanism for berberine's inhibitory action on ovarian cancer. According to this study, berberine inhibits the hERG1 protein channel, which in turn inhibits the proliferation of ovarian cancer cells [10].

Berberine Impairs Polyamine Mechanism

The ability of berberine to form effective complexes with adenine-thymine base-pair content of nucleic acid sequence, encourage DNA damage, and exert associated effects, such as inhibition of telomerase, topoisomerase poisoning, and gene transcription obstruction, appears to be the source of its anticancer activity. According to research, berberine preferentially binds to AT-rich DNA sequences that are also found to be in TS mRNA, explaining how it affects the production of folate enzymes and, in turn, causes cytotoxicity. Also disruption of the folate cycle appears to be a contributing factor to a decrease in the accumulation of folic acid in cell lines. Resistant cells exposed to berberine collect less folic acid than sensitive cells. Folate, a vitamin B family member, participates in the creation of nucleic acid and amino acids, which are crucial for cell life. Yet again, the slightly less stable accumulation of parent complex of purine and pyrimidine bases and amino acids helps to account for the cell lines' decreased tolerance to the isoquinoline alkaloid [11].

Autophagy Induction and Anti-metastatic Activity of Berberine

Uncertainty still exists regarding berberine's function in ovarian cancer autophagy induction and metastasis inhibition. However, berberine was said to promote autophagy and have anti-metastatic effects to other cancer.

In cancer cells, berberine has been shown to block the MAPK/mTOR/p70S6K and AKT pathways, leading to cytostatic autophagy and cell cycle arrest [12]. By suppressing matrix metalloprotease 3 (MMP-3) in cancer cell lines, berberine may prevent cell migration and demonstrate anti-metastatic properties [13]. Additionally, berberine reduced the production of COX-2 to prevent the metastasis of endometrial cells [14].

DNA Damage caused by Berberine

In ovarian cancer cells, berberine leads to oxidative stress and DNA damage. According to certain reports, berberine causes DNA damage and encourages the production of ROS in human cancer cells. In the process of repairing oxidative DNA damage, PARP1 is crucial. Additionally, PARP1 is hyperactivated in cells with a dysfunctional HRR, and cells with a dysfunctional HRR are particularly vulnerable to PARP inhibition. The well-known cause of PARP1 activation is oxidative stress. Increased PARP1 activation is connected to the downregulation of HRR. Berberine administration causes the downregulation of HRR as well as an increase in oxidative stress. So a very effective approach for the treatment of ovarian cancer is PARP inhibition [(15)].

Berberine Inhibits the Warburg effect

Aerobic glycolysis, often known as the Warburg effect, is a crucial energy metabolic trait for maintaining tumor cells' malignant nature. The mechanism by which berberine inhibits the Warburg effect has been linked to the route made up of miR-145, TET3, and HK2. By encouraging the production of TET3 and lowering the degree of methylation at initiator sequence site of the miR-145gene precursor, berberine boosted the regulation of miR-145. In addition to encouraging miR-145 expression, TET3 may prevent carcinoma cells from experiencing the Warburg effect in ovary. So, the potential therapeutic targets for the management of cancerous ovarian cells can be originated from the TET3/miR-145/HK2/berberine pathway's regulation of Warburg effect in cancerous ovarian cells [(16)].

Inhibition of tumor cells repopulation by berberine

Recurrence is thought to contribute to the failure of cancer treatments. Researchers have shown that the tumor cells that have undergone radiation treatment and gone into apoptosis may cause a few portions of living cancer cells to repopulate the tumor. To prevent the recurrence of cancer cells in ovary following chemotherapy, a natural component, berberine can play a significant role.

In investigation, both the VP16 and exogenous PGE2 treatment conditions resulted in increased PTK2 phosphorylation. More crucially, it was discovered that berberine prevented PTK2 from being more phosphorylated just after the inhibition of the Cyclo-oxygenase dependent Prostaglandin E2 biosynthetic pathway. Through primarily limiting these two rate-limiting enzymes COX-2 and iPLA2 in the failing cells, berberine managed to prevent a minor percentage of malignancy in ovaries from proliferating subsequently chemotherapy, in turn, which decreased the synthesis of PGE2 in the tumor microenvironment. Further PGE2-PTK2 inhibition in the cells of ovarian tumor through recurrence potential, however, correspondingly plays a significant effect in tumor regrowth [(6)].

Inhibition of cancer stem cells (CSCs) via controlling GLI1/PCGF4 signaling

Ovarian cancer is thought to be caused by the conjunction of CSCs having higher ability of rejuvenation and distinction and persistent forms of cells, based on the fact that it has diverse relapse and growth patterns. Investigation shows that berberine can control transcriptional element GLI1 in ovarian cancer, thereby inhibiting the chemotherapy-induced CSCs-related marker PCGF4. Additionally, studies have shown that PGE2 can control GLI1 by way of the cell surface-expressed integrin 1. Integrin 1 on the cell surface probably is how berberine controls GLI1/PCGF4 signaling [(17)].

Combination Chemotherapy

It was discovered that the mixture of BBR with DDP expressively withdraw the proliferation of OVCAR3 as well as POCCLs at the G0/G1 phase, along with a reduction in Cyclin D1 protein levels. Their combinational medicinal treatment significantly improves the decease of various cancerous cells of ovarian tumor by triggering apoptotic and necroptotic cell death in the OVCAR3 cell line of ovarian carcinoma and primary ovarian cancer cells, although the efficacy depends upon time and dose as well [(18)].

When used alone or in combination with DDP, berberine can cause ovarian cancerous cells to stop during the G1 phase by increasing the activity of proteins linked to cell death, such as caspase-8 and caspase-3, which encourages apoptosis and necrosis [(19)].

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By suppressing miR-93 and increasing its targeted gene expression, PTEN, berberine improved the susceptibility of tumor cells to cisplatin in ovary [(19)]. It was seen that berberine increased DNA damage and caused apoptosis while suppressing homologous recombination, making ovarian cancer cells more susceptible to PARP inhibitors [(15)].

Bio-delivery and availability

Berberine and its derivatives are not readily taken up in the human digestive tract from a pharmacokinetic perspective. Numerous investigations on the pharmacokinetic profile of berberine and its metabolic products have shown that they have a poor rate of diffusion through intestine when administered through mouth. These characteristics have made it much more difficult to distribute berberine to the desired tissue region. This problem is resolved because of progress in the field of nanotechnology. To boost berberine bio-delivery and availability at the directed site of the cancerous tissue, alkylated berberine, berberine-embedded lipid vesicles, pH-responsive liposomes nanoparticles, deacetylated chitosan nanocarriers, NISV or lipid based NISV nanoparticles forms, as well as magnetic or partially crystalline nanoparticles, phosphorous and lipid based nanocarriers, Ag-nanocarriers, and mitochondrion-directed nanocarrier have all been proposed by modern biotechnology to achieve the best results from this perspective biological substance To increase berberine stabilization and oral administration, Nano-formulations containing berberine have proven to be somewhat effective [(21)].

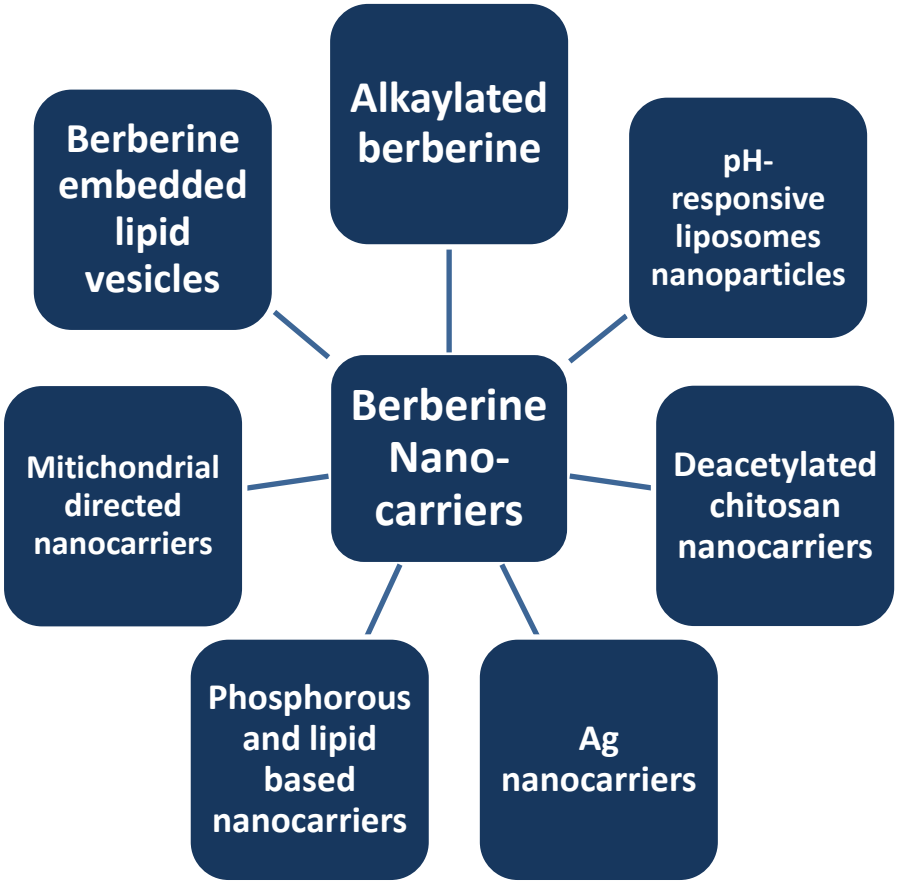

Fig4. Some of the proposed berberine Nano-carriers

Some other novel methods for preserving berberine and enhancing its absorption have been developed. This prompted the creation of innovative berberine products along with modifications

at several fundamental locations in its structure, including the Carbon no. 8, 9, 10, 12 and 13, for enhanced constancy and bioactivity. While the modification at the Carbon 9 site boosts the anticancer approaches of berberine, showed that such adjustments in it have increased the its antibacterial activity [22].

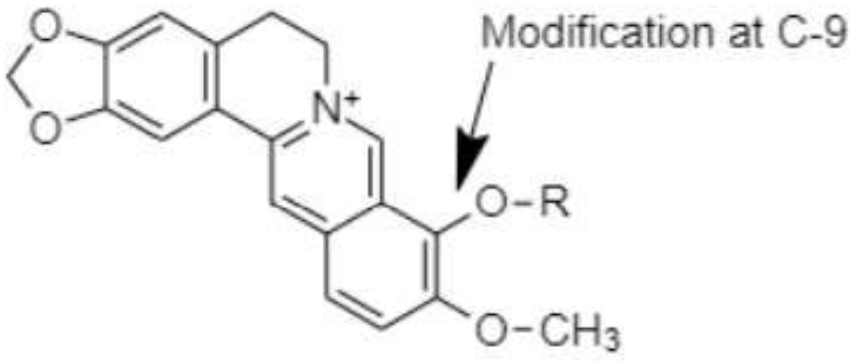

Fig5. Effective berberine derivative

Researchers also formulated several products of 9-O-substituted berberine derivatives with improved efficacy and bioavailability. Among them five compounds expressively inhibited the proliferation of human colon carcinoma cell lines. Also, these bioactive complexes showed the ability to induce autophagy [24].

Many C-13-substituted berberine derivatives have been produced and researched; some of these have proven to have unique anti-cancerous properties than berberine. Noticeably, advanced anti-tumor actions were seen by 13-alkyl berberine than by 13-benzyl berberine derivatives [23]. The antitumor activities of 8-alkyl-13-bromo-berberine derivatives were identified by Ding et al. according to them the tumor cell sensitivity is seen to be associated with the carbon chain length of derivative [25].

In another experiment a series of cycloberberine derivatives were identified [26]. Cycloberberine derivatives were evaluated for their anti-tumor activity in vitro. these, compounds exhibit the activity to strongly inhibit human hepatoma cells by blocking cells at the G2/M phase by inhibiting DNA Topoisomerase I [27].

Moreover, Triazolyl berberine derivatives were synthesized and proved to be novel anticancer agents; most of them exhibited stronger anticancer activity against human hepatoma cell line than berberine [28].

An innovative benzoazepinoisoquinolone with a seven-membered B-ring of oxyberberine has been demonstrated to possess anti-tumor action against cell lines originating from human lesions [29].

All these experiments show that derivatization enhances it activity against many cancer cell lines. Various experimentations can also be made to synthesize such novel derivatives having enhanced medicinal effects against ovarian cancer.

Conclusion and future perspectives

Following roles of berberine however, highlight its significance for clinical usage for chemotherapy as a safe molecule with low toxicity against normal cells. Berberine may be utilized as an adjuvant therapy alongside chemotherapy medications to prevent a recurrence of cancer. The nano-based formulation and derivatization can be an excellent choice to boost absorption percentage.

As it appears to be an effective natural compound for therapy further clinical trials and study can be made to broaden its use against cancer as well as other medical conditions through multiple targeting approaches.

Abbreviations

AKT (PK-B) Protein Kinase B
BAX BCL2 Associated X protein
BBR Berberine
BCL-2 B-Cell Lymphoma 2
COX-2 Cyclo Oxygenase 2
CSCs Cancer Stem Cells
DDP Cisplatin
GL1 Glioma associated oncogene 1
hERG1 Human Ether-a-go-go-Related Gene
HK-2 Hexokinase-2
HRR Homologous Recombinational Repair proteins
MAPK Mitogen Activated Protein Kinases
MMP Matrix Metalloproteinases
mTOR mammalian Target Of Rapamycin
NISV Non-ionic Surfactant Vesicles
OVCAR3 Ovarian cancer cell line
P70s6k Ribosomal protein S6 kinase beta-1, P70-S6 Kinase 1
PARP Poly ADP-Ribose Polymerase
PCGF4 Polycomb group RING finger protein 4
POCCLs Promary Ovarian Cancer Cell Lines
PTEN Phosphate and TENsin homolog
ROS Reactive Oxygen Specie
SKOV3 Ovarian cancer cell line
TET Ten-Eleven Translocation enzymes
TS mRNA Thymidylate Synthase mRNA
VP-16 Viral Protein Etoposide

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