Anticancer Mechanism And Nanoparticulate Delivery System Of Berberine Hydrochloride

Bushra Ahmad[1], Farina Mujeeb[2], Arbab Husain[3], Ahamad Faiz Khan[4*]

[1]*Department of Bioengineering, Integral University, Lucknow, Uttar Pradesh 226026, India, Email: bushraahmad76@gmail.com*

[2]*Department of Biosciences, Faculty of Science, Integral University, Lucknow, Uttar Pradesh 226026, India, Email: farinam@iul.ac.in*

[3]*Department of Biotechnology & Life Sciences, Faculty of Sciences, Mangalayatan University, Aligarh, Uttar Pradesh 202146, India, Email: arbabhusain1@gmail.com*

[4*]*Department of Bioengineering, Integral University, Lucknow, Uttar Pradesh 226026, India, Email: faizkhan@iul.ac.in*

Author for correspondence:

Ahamad Faiz Khan

Department of Bioengineering, Integral University, Lucknow, Uttar Pradesh 226026, India, Email: faizkhan@iul.ac.in

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ABSTRACT

Berberine hydrochloride is a prominent constituent in traditional Chinese medicine, and it has a lot of different effects on the body. However, berberine hydrochloride was hard to use for a long time because it was unstable and not bioavailable because it doesn't like water. Recently, the medicinal form of berberine hydrochloride has gotten better, which means it has a good chance of being used in humans. This is especially true for new nanoparticle delivery methods. Also, anticancer activity and new processes have been looked into. It looks like there is more possibility than ever to control the metabolism of glucose and fats in cancer cells. So, the huge potential for anticancer activity should be able to be used with the right pharmaceutical methods, which should lead to new ideas about how to make anticancer drugs in Chinese medicine.

As more study is done on how berberine hydrochloride affects the metabolism of cancer cells and problems with nanoparticle delivery preparation are fixed, berberine hydrochloride is probably going to be a natural component of cancer treatment with nanoparticle delivery systems.

Additionally, the established effects of berberine hydrochloride include reducing multidrug resistance and enhancing the efficacy of chemotherapeutic agents, as well as improving patients' quality of life, could help us learn more about how cancer cells work and how to make nanoparticles that can deliver drugs.

Keywords: Berberine hydrochloride, nanoparticulate drug delivery system, anticancer mechanism.

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INTRODUCTION

There is an isoquinoline alkaloid called berberine hydrochloride (Figure 1) derived from many Chinese plants, including Coptidis rhizoma, Phellodendron chinense schneid, and Phellodendron amurense, exhibiting various pharmacological effects. It has effects that lower blood sugar levels and prevent lipid peroxidation, as well as effects that prevent atherosclerosis and preserve nerves. It also helps with polycystic ovarian syndrome (1-5). Berberine hydrochloride is a common antibacterial, antifungal, and anti-inflammatory medication. In China, it has been used as a treatment for gastrointestinal issues for thousands of years (6,7).

Table 1 shows some physicochemical properties of berberine hydrochloride. Berberine hydrochloride's antiproliferative activities and sensitivity improvement in numerous cancer cell lines (8-14) have sparked increased scientific interest in this chemical (15,17). It has antineoplastic capabilities that include causing apoptosis and stopping the cell cycle, as well as stopping cell migration and invasion via controlling several pathways (18-21). Reactive oxygen species production, mitochondrial activity, DNA topoisomerase inhibition, DNA or RNA binding, the estrogen receptor, matrix metalloproteinase modulation, p53 activation, and NF-kappa B signal activation are among the possible targets of berberine hydrochloride (22-26). However, due to a quarternary amine that causes poor water solubility, it has a low effective concentration and restricted absorption in the gastrointestinal system, which severely restricts its usage and advancement as a pharmaceutical preparation. Additionally, a unique drug delivery mechanism to increase the solubility and bioavailability of berberine hydrochloride has become urgent due to the possibility of side effects associated with intramuscular and IV administrations, such as anaphylactic shock and drug rash.

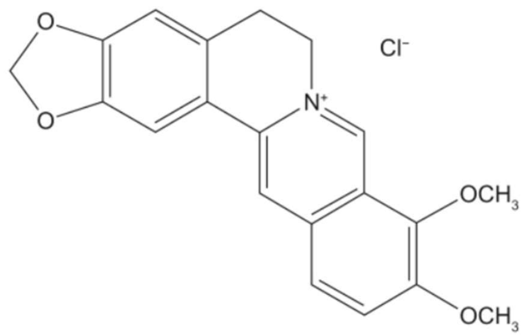

Fig. 1 Chemical structure of Berberine hydrochloride

Nanoparticulate medication delivery technologies have received more interest since nanotechnology has developed quickly. Polymeric nanoparticles, nanocapsules, liposomes, solid lipid nanoparticles, and nanoemulsions are examples of modern nanoparticulate dosage forms that can enhance drug solubility (27-29). While avoiding physical and chemical degradation, nanoparticulate drug delivery generally improves solubility and bioavailability, pharmacological activity, and tissue macrophage dispersion (30,31). Consequently, we created a promising anticancer agent by combining the good anticancer effectiveness of berberine hydrochloride with a unique nanoparticulate drug delivery technology.

This article aims to provide new insights into Chinese medicine preparations with anticancer potential by describing a unique drug delivery strategy for berberine hydrochloride and discussing anticancer mechanisms, particularly with regard to regulation of glucose and lipid metabolism (32,33).

Table 1 Physicochemical properties of Berberine

Properties	Berberine
Chemical name	7,8,13,13a-tetradehydro-9,10-dimethoxy-2,3-methylenedioxyberberinium
Chemical formulae	$C_{20}H_{18}O_4N^+$
Molecular weight (ion)	336.36
Crystal color	Yellow
Solubility	Water
Melting point (°C)	210
IC_{50} value in mice	27.5 mg/Kg

Berberine hydrochloride's anticancer mechanisms

The prospective anticancer efficacy of berberine hydrochloride has always been of significant interest due to its proven potential to interact with nucleic acids. Its antiproliferative action is explained by its capacity to bind selectively to oligonucleotides and to stabilize DNA triplexes or G-quadruplexes by inhibiting telomerase and topoisomerase. Berberine hydrochloride and double-stranded or single-stranded DNA mostly interacts electrostatically, which can be measured using the Hill model of cooperative interactions. Autophagy and autophagic regulators are more prevalent in recent new processes. Wang et al. (2010) discovered that in the human hepatic cancer cell lines HepG2 and MHCC97-L, berberine hydrochloride caused autophagic cell death, which was reduced by 3-methyladenine, a cell death inhibitor, by activating beclin-1 and blocking the mTOR signaling pathway. Additionally, after berberine hydrochloride was administered to the human A549 lung cancer cell line, the autophagic marker microtubule-associated protein-1 light chain 3 (LC3) changed, and in a Lewis lung carcinoma model in mice, the tumor volume shrank. These findings suggest that autophagy may play a role in cancer cell death (34-36).

Moreover, the hypoglycemic and hypolipidemic properties of berberine hydrochloride, alongside its role in autophagy and nucleic acid interaction, suggest a correlation between adipose tissue/adipocytes and tumorigenesis, evidenced by the upregulation of mRNA and protein levels in adipose tissue, including peroxisome proliferator-activated receptors (PPAR) α, β, and γ, CDK9, and cyclin T1. Adipocytes and adipose tissue play an important aspect in the environment around tumors (37,38). Nagaraju and Sharma (2011) suggested that SPARC, a secreted protein acidic and rich in cysteine, could be a powerful anticancer molecule (39). Human adipose tissue-derived stem cells are known to be a source of carcinoma-associated fibroblasts when transforming growth factor β1 is present (40). Additionally, leptin and vascular endothelial growth factor generated from adipose tissue stimulate adipogenesis to preserve the microenvironment of tumor (41). Hirano et al. (2008) have proposed the presence of unspecified factors originating from cancer cells that facilitate adipogenesis, so suggesting a possible correlation between adipogenesis and cancer progression (42). In clinical lipofilling operations for breast cancer patients, it is imperative to elucidate the relationship between cancer recurrence and adipogenesis (43). The adipogenesis positive regulator, PPARγ, is overexpressed in ERBB2-positive breast cancer cells, facilitating fatty acid production primarily to meet energy requirements and ensure cell survival (44). Thus, less toxic PPARγ agonists or antagonists, such as berberine hydrochloride, are thought to be promising treatments for enhancing adipose breast tissue, lowering the risk of breast cancer, and inhibiting the growth and invasion of cancer cells (45). It has been shown that berberine hydrochloride can improve insulin resistance caused by free fatty acids in myotubes, stop adipogenesis in human white preadipocytes, and lower insulin resistance in the liver of diabetic hamsters (46-49). It does this by blocking PPARγ protein production and increasing PPARα mRNA levels. Berberine hydrochloride also inhibited the loss of epididymal adipose tissue and improved cancer cachexia in mice with colon 26/clone 20 cells and colon 26/clone 20 cells (50). This shows how this compound is good for adipose tissue in the tumor microenvironment.

Berberine hydrochloride is a possible natural substance for cancer therapy due to its interaction with nucleic acids, regulation of cancer cells, and induction of autophagy. It enhances the effects of chemotherapy and radiotherapy and has demonstrated promising possibilities in the treatment of cancer (51,52). The effectiveness and potential uses of berberine hydrochloride were highlighted after the novel methods by which it disrupts the growth of adipose tissue and adipocyte metabolism in the tumor microenvironment were examined. Furthermore, berberine hydrochloride's widespread distribution in a variety of plant species and low toxicity indicate that it may eventually prove to be a successful anticancer drug.

Nanoparticulate delivery mechanisms

Studies on nanoparticulate delivery systems for berberine hydrochloride can be categorized into three types: solid lipid nanoparticles, nanoemulsions, and liposomes. This report summarizes preparation, characterisation, experimental design methodologies, as well as in vivo and in vitro investigations.

The initial nanoparticulate delivery device used a standard rotary-evaporated film-ultrasonication technique to produce solid lipid nanoparticles of berberine hydrochloride (BH-SLN). The average size is 60.5 nm, they have a zeta potential of 29.7 mV, 8.69% of the drug is loaded, and 97.58% of the drug is entrapped, and exhibit commendable stability. The actual quantity and quality of liposome entrapment are directly influenced by a number of additional parameters, including as manufacturing and preparation techniques, excipient types, and particle size. The percentage of the original solution that remains inside the liposomes is known as entrapment, and it is crucial for therapeutic use. Wang et al. (2009) developed the coagulation centrifugation method to assess BH-SLN entrapment efficiency (53). High-pressure liquid chromatography was used to determine a saturated aqueous solution of sodium chloride 0.05 mL in BH-SLN 0.5 mL. The supernatant was then obtained by centrifuging the mixture at 12,000 rpm for 10 minutes. The findings indicate that coagulation centrifugation was both fast and accurate.

The secondary delivery system is a nanoemulsion of berberine hydrochloride, formulated with isopropyl myristate, EL40, and glycerin utilizing pseudoternary phase diagrams. The nanoemulsion is a clear, transparent liquid with particles that are 56.8 nm in diameter on average. Under electron microscopy, small spherical droplets exhibit constant content and consistent diameter, even in settings of elevated humidity and temperature, specifically at 92.5% humidity, a temperature range of 40°C–60°C, and illumination of (4500 ± 500) LX (54).

The final system is a liposomal one, and there are a few different procedures that may be utilized in order to produce berberine hydrochloride liposomes. These methods include the thin film evaporation method, the active loading method, and a combination of the thin film evaporation method and the active loading method. The thin film evaporation process can attain enhanced the efficiency of encapsulation, with optimal manufacturing parameters defined by a temperature of 60°C, a duration of 30 minutes, and a cholesterol concentration of 3.3 mg/mL (55). An active loading method is superior than passive loading, exhibiting enhanced entrapment efficiency. Several aspects must be considered, including the addition sequence, incubation duration, incubation temperature, pH of the external aqueous phase, and the particle size of the liposome. Altering the adding sequence can yield varying entrapment efficiencies, as can extend incubation duration and temperature, as well as reducing particle size. To determine the ideal conditions of preparation for berberine hydrochloride liposomes, Chen et al. (2007) employed an orthogonal design and a variety of individual factors, such as incubation time and temperature, proportionate drug and lipid weights, soybean phosphatidylcholine, and cholesterol (56). The improved liposome had an average encapsulation effectiveness of 78.51% ± 2.45%, with a size range of 2.2–3.5 μm, according to the data. Berberine hydrochloride liposomes were made using thin film evaporation and an active loading technique based on the uniform design. A perfect formulation was found, and a drug loading ratio of 30.21 and a size range of 2.2–3.8 μm led to a high encapsulation efficiency of 79.33% (57). In vivo and in vitro investigations were conducted to examine the mechanism of action of liposomal berberine hydrochloride. Gou et al. investigated the impact of berberine hydrochloride liposomes on the combination between reduced glucose tolerance and hyperlipidemia, indicating that glucose and lipid metabolism were disrupted, and the development from hyperlipidemia to type 2 diabetes was mitigated (58,59).

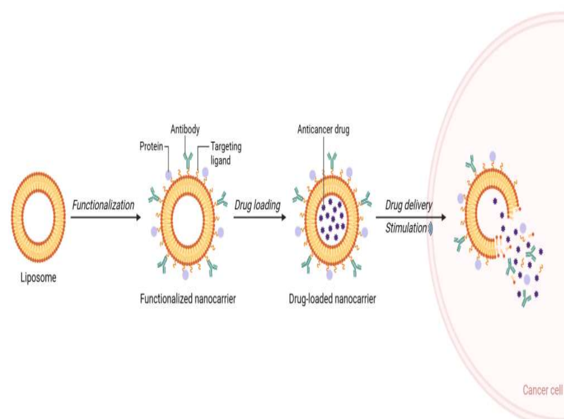

Fig. 2 Smart Drug Delivery System of Liposome for Cancer Treatment (56)

CONCLUSION

Research on the molecular effects of berberine hydrochloride on lipid and glucose metabolism necessitates more scrutiny. At the same time, there is more interest in changing the way cancer cells metabolize nutrients by targeting glycolysis, changing how mitochondria work, and limiting biosynthesis. These changes could be used to fight cancer that doesn't work properly. It might work to inhibit the growth and spread of cancer cells by stopping the formation of cell membranes, lowering the production of macromolecules, and finally stopping the proliferation of cancer cells.

Blocking a number of metabolic pathways may also help berberine hydrochloride improve important clinical characteristics. For example, it might make chemotherapy drugs work better, lower the risk of drug resistance, and make patients' lives better. This shows that it might be a helpful (adjuvant) drug for fighting cancer.

There are still problems with it, though. For example, it doesn't like water, isn't very stable, and isn't very bioavailable. Researchers are working on nanoparticle-based delivery systems to make treatments more effective and fix these issues. More research in this area could not only make berberine hydrochloride more useful in the clinic, but it could also lead to new ways to make cancer-curing drugs in traditional Chinese medicine.

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Conflict of interest

The authors declare that there is no conflict of interest.

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