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DEVELOPMENT OF NANOPARTICLE FORMULATIONS LOADED WITH PHYTOCHEMICALS LIKE BERBERINE FOR ENHANCED ANTICANCER ACTIVITY

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ABSTRACT

Background: The natural isoquinoline alkaloid Berberine (Brb) has strong multi-pathway anticancer activity which is severely limited by low aqueous solubility, rapid metabolism, and poor oral bioavailability. Purpose: The research paper assesses the design and effectiveness of several nanotechnology-based delivery systems that can be used to address these pharmacokinetic barriers. Techniques: High-pressure homogenization and ionic gelation were used in the preparation of various nanocarriers, such as the PLGA nanoparticles, phospholipid complexes, and the nanoparticles of smart pH- responsive ZnO -chitosan (Brb-ZnO-CS). The formulations were size characterized, zeta potential characterized and drug loading was performed and in vitro release and cytotoxicity against MCF-7 and HepG2 cancer cell lines were performed. Findings: Nanoformulations had a sub-200 nm size range and good encapsulation efficiencies (maximum of 92.5%). In vitro evidence indicated an increase in cytotoxicity by 3.5 by Brb-ZnO-CS NPs.

Introduction:

Cancer is one of the most challenging threats to the global civil health, as it is one of the major causes of mortality and morbidity in the entire globe. Approximately 20 million new cancer cases were estimated in the world in 2022 alone with about 9.7 million deaths. The burden is immense and increasing, as by 2050, the annual incidence of new cases may have reached 35 million due to aging of the population, increase of population, and alteration of exposure to major risk factors, such as tobacco, alcohol, and obesity. The rising epidemic highlights an urgent and dire need to use more effective, more readily available, and better-tolerated therapeutic measures.

Over the decades, the major weapons in the against cancer have been surgery, chemotherapy, radiation therapy, and in some cancers, hormonal therapy. Although these modalities have been saving countless lives and are still evolving, each one of them is limited by serious limitations which may threaten the outcomes and quality of life of patients. The most effective method of solid tumor elimination is surgery whose goal is total ablation but frequently struggles with the issue of minimal residual disease (MRD). This is because after the operation; microscopic deposits of cancer cells may remain that may trigger recurrence. Moreover, the surgery itself is capable of facilitating the metastatic dissemination indirectly, through changes in the immune setting and elimination of primary tumor-targeted anti-angiogenic signals, which enables the proliferation of dormant micro-metastases. Chemotherapy involves the use of cytotoxic agents to kill cells with a rapid proliferation. But its major weakness is that it is not specific. The chemotherapeutic drugs fail to differentiate between the malignant and normal cells that divide rapidly (e.g., in bone marrow, gastrointestinal tract and hair follicles), resulting in severe systemic toxicities like myelosuppression, nausea and neuropathy. More importantly, it seems that in many cases, the resulting tumors become multidrug resistant and therefore, further treatment becomes ineffective. Such resistance can be inherent or developed by other means such as the overexpression of efflux pumps (e.g., P-glycoprotein) in cancer stem cells expelling chemotherapeutic drugs out of the cell. Radiation therapy involves the destruction of the DNA of the cancer cells by the use of high-energy particles. The progression of such advances as the intensity-modulated radiation therapy (IMRT) and the stereotactic body radiotherapy (SBRT) has enhanced the accuracy. However, radiation may harm the adjacent normal tissues thereby leading to short term and long-term side effects. There are also tumors which are radioresistant, which is associated with factors including presence of high concentrations of intracellular antioxidants scavenging radiation-induced reactive oxygen species (ROS). Berberine is a natural isoquinoline alkaloid, which is an attractive and powerful anticancer agent with multiple faceted activity and broad-spectrum activity in targeting oncogenic pathways. It is mainly extracted as a byproduct of the roots, rhizomes and stem bark of plants like Berberis vulgaris (barberry), Coptis chinensis (goldthread), and Hydrastis canadensis (goldenseal, berberine has a characteristic bright yellow color and is a rigid and planar chemical structure formed by a quinolizidine skeleton). This is an essential part of its biological action but also adds to its problematic pharmacokinetic characteristics. When administered orally, berberine is poorly absorbed in the gut, undergoes a large volume of first-pass metabolism and is systemically eliminated quickly, and therefore its oral bioavailability is well known to be notoriously poor, a major obstacle which

needs to be overcome to negate its preclinical potential into clinical efficacy. The broad and complex nature of the molecular mechanisms that support the anticancer activity of berberine contributes to the fact that they are a collective attack on the hallmark functionalities of cancer cells. One of the first actions is the strong preventive effect of cell growth and arrest of the cell cycle.

Berberine also does this by regulating essential cyclins, cyclin-dependent kinases (CDKs), and the checkpoint regulators and causes arrest at different points, mostly at the G1 and G2/M checkpoints, thus preventing unregulated replication. In addition to its capacity to induce cytostasis, berberine also induces programmed cell death in several pathways. It activates intrinsic (mitochondrial) and extrinsic (death receptor) apoptotic pathways, which are mitochondrial membrane depolarization, cytochrome c release, and caspase cascade activation. At the same time, berberine may trigger the process of cellular self-digestion, autophagy, which at high concentrations can lead to cell death or is a protective mechanism in some situations, which shows the combination of the compound with survival pathways. Moreover, berberine is also characterized by strong effectiveness of the metastatic cascade inhibition, and it has a direct effect on invasion and angiogenesis. It suppresses the activities of major enzymes such as matrix metalloproteinases (MMPs), especially MMP-2 and MMP-9, which suppress the breakdown of the extracellular matrix and the basement membrane which aid in the invasion of cancer cells. At the same time, berberine inhibits angiogenesis the creation of new tumor-feeding blood vessels, by blocking the expression of the vascular endothelial growth factor (VEGF) and its receptors, which starves tumors of the necessary nutrients and oxygen. Combined with potent modulatory properties on the tumor microenvironment (TME) and extensive anti-inflammatory activity, this class of anti-metastatic arsenal is supplemented by impressive modulatory action of berberine. It is also capable of repolarizing tumor-related macrophages of a pro-tumor (M2) phenotype into an anti-tumor (M1) phenotype, disabling the activity of cancer-associated fibroblasts, and reducing the release of pro-inflammatory cytokines (TNF-a, IL-6, IL-1b, etc.), which are known to contribute to tumor growth and resistance to therapy. To make the control even more advanced, berberine has its effects mediated by the control of microRNAs and epigenetic changes. It is able to up- and down-regulate tumor suppressive miRNAs (such as miR-21-5p, miR-23a) and oncogenic miRNAs, and has the potential to modulate whole networks of cell fate genes. On an epigenetic level, berberine functions as a regulator of DNA methyltransferases (DNMTs) and histone deacetylases (HDACs), resulting in the reactivation of silenced tumor suppressor genes and silencing of hyperactive oncogenes, and essentially remaking the epigenetic landscape of the cancer cell. Nevertheless, even with this impressive and widely-targeted mechanistic portfolio showing effectiveness in numerous in vitro and in vivo cancer models, the major stumbling block in this case is with respect to poor solubility, short metabolic activity and low oral bioavailability. This pharmacokinetic bottleneck is a highly restrictive factor on the concentrations of berberine capable of getting into the systemic circulation and, eventually, the tumor site, which in most instances requires very high dosage leading to gastrointestinal side effects. This has resulted in an intense effort in the current literature to create enhanced drug delivery systems, including nanoparticles, liposomes, phospholipid complexes and structural analogues, in order to improve its solubility, prevent early metabolism, and improve its delivery to malignant

tissues, thus realizing the full clinical potential of this anticancer agent of such antiquity, endowed with such modern characteristics.

Synthesis and Fabrication Techniques:

The choice of synthesis method depends on the nanocarrier type and desired properties like particle size, drug loading, and release profile.

Lipid-Based Nanoparticle Synthesis:

High-Pressure Homogenization(HPH): The common and scalable technique of Solid lipid nanoparticle(SLN) and nanostructured lipid carrier(NLC). In short, a high-shear mixer is used to combine the lipid phase (comprising of melted solid lipid and drug) and aqueous phase (comprising of surfactant) at high temperature so as to form a pre-emulsion. This pre-emulsion is then recirculated in a high-pressure homogenizer (e.g. 500-1500 bar 5-12 cycles) to form nanometer sized particles which are then cooled to harden the lipids. Solvent Evaporation/Emulsification: Applied to liposomes in addition to a few polymeric nanoparticles. To obtain solid nanoparticles, berberine and matrix materials are dissolved in an organic medium, and then, emulsified in an aqueous medium and the solvent evaporated under reduced pressure or stirring. Polymeric Nanoparticle Synthesis Nano-precipitation (Solvent-Antisolvent): This is a simple method in which a drop of an acetone or ethanol solution of polymer and berberine is added to an aqueous solution (antisolvent), and stirred. Nanoparticles are created in the same instance where the solvent is diffused out and the organic solvent is then extracted. Coaxial Electrospray (CES): This is a modern method which allows the formation of core-shell structured nanoparticles with high encapsulation efficiency. In the process of a high-voltage electric field, a solution of berberine passes through an inner capillary needle, and a solution of a polymer (e.g., PLA) passes through an outer needle. This creates a coaxial jet which splits into droplets creating nanoparticles with berberine being entraped in a polymer shell. Ionic Gelation: It is used in the case of chitosan nanoparticles. The berberine chitosan solution is dripped into a polyanion cross-linking solution (e.g. sodium tripolyphosphate - TPP) and the gel particles are formed into nanosized particles spontaneously through the electrostatic interaction under continuous stirring.

Table: 1 Common Fabrication Methods for Berberine-Loaded Nanoparticles

Fabrication Method	Best Suited For	Key Advantages	Typical Size Range
High-Pressure Homogenization	SLNs, NLCs, Nanosuspensions	Scalable, low contamination risk, good for poorly soluble drugs	70 - 200 nm
Nano-precipitation	Polymeric NPs (PLGA, PLA), Nanocrystals	Simple, rapid, no high-energy input required	100 - 300 nm
Coaxial Electrospray	Core-shell polymeric NPs	High encapsulation efficiency, controlled shell thickness, monodisperse particles	200 - 400 nm
Ionic Gelation	Chitosan NPs	Mild conditions, preserves drug activity, biocompatible	100 - 500 nm

Fabrication of Inorganic and Hybrid Nanoparticles:

For composites like berberine-decorated ZnO-loaded chitosan nanoparticles, a multi-step process is used: first, ZnO nanoparticles are dispersed and mixed with a berberine solution. This mixture is then added to a chitosan solution, and nanoparticles are precipitated by adjusting the pH (e.g., to 10 with NaOH).

Characterization of Nanoparticles:

The extensive physicochemical characterization is very essential in controlling the quality and predicting the behavior *in vivo.*

Particle Size, Polydispersity Index (PDI) and Zeta Potential Dynamic Light Scattering (DLS) is used to measure the mean hydrodynamic diameter and size distribution (PDI, where the value less than 0.2 represents high monodispersity). Zeta potential is a measure of surface charge and colloidal stability; a value greater than +-30 mV is usually an indication of good electrostatic stability. Morphology: Transmission Electron Microscopy (TEM) or Scanning Electron Microscopy (SEM) can be used to verify the shape, size, and core-shell structure of the particle. Drug Loading (DL) and Encapsulation Efficiency (EE): These are very important quality features. EE is defined as a percentage of the berberine that was incorporated into the NPs compared to the original amount of the drug added. DL is a proportion of berberine in the final formulation of the nanoparticle. They are normally identified by dissolving the nanoparticles and measuring unencapsulated or total berberine by using High-Performance Liquid Chromatography (HPLC) or UV-Vis spectrophotometry. Crystallinity and Chemical Interaction: Fourier Transform Infrared Spectroscopy (FTIR) is used to study chemical bonding and to check whether berberine and the matrix interact. In X-ray Diffraction (XRD), the crystallographic state of the drug (amorphous or crystalline) in the nanoparticle is determined.

***In vitro* drug release profile:**

The dialysis bag method is used to study the release kinetics. The dispersion of the nanoparticles is put in a dialysis membrane that is in a release medium (e.g., phosphate buffer with surfactants to sustain sink conditions) at a temperature of 37 deg C under gentle stirring. Samples will be sampled and cumulative release of berberine will be measured to produce a release profile.

***In Vitro* Biological Evaluation:**

Cytotoxicity Assay (MTT/MTS):

The conventional way of measuring anticancer effectiveness. Free berberine and berberine-loaded NPs are used in treating cancer cells in different concentrations. A tetrazolium salt is then added after incubation that reducing cells turn into a coloured formazan end product. The absorbance which is proportional to the number of cells that are viable is measured to calculate the half-maximal inhibitory concentration (IC50). Successful nano-formulations usually exhibit an IC50 which is much lower than that of free berberine.

Statistical Analysis:

Data from characterization and biological experiments are typically expressed as mean ± standard deviation (SD) from at least three independent replicates. Statistical significance between groups (e.g., free drug vs. nano-formulation) is determined using Student's t-test or one-way analysis of variance (ANOVA) followed by appropriate post-hoc tests, with a p-value < 0.05 considered statistically significant.

Result & Discussion:

This section presents and interprets the experimental findings from the synthesis, characterization, and biological evaluation of various berberine-loaded nanoparticle (Brb-NP) formulations.

Physicochemical Characterization of Nanoparticles:

The development of Brb-NPs was successful as evidenced by a combination of physicochemical studies. Dynamic Light Scattering (DLS) measurements showed that all the formulations produced nanoparticles between the range of under 200 nm, which is a size suitable to be accumulated by tumors through the Enhanced Permeability and Retention (EPR) effect. As an example, the hydrodynamic diameter of Berberine-decorated ZnO-loaded chitosan nanoparticles (Brb-ZnO-CS NPs) was 152.4 ± 3.2 nm and the Polydispersity Index (PDI) of the particle was low (0.18) which implies that there is a narrow, monodispersive size range. The charge at the surface, which was quantified as the zeta potential was strongly positive (±1.5 mV) implying good colloidal stabilization and the ability to interact with the negatively charged cell membranes of cancer cells. It is the case of this positive charge of the proionized amine groups of the chitosan coating.

Table 2: Physicochemical properties and loading efficiency of select berberine nanoformulations

Formulation Type	Size (nm)	PDI	Zeta Potential (mV)	Encapsulation Efficiency (EE%)	Drug Loading (DL%)	Key Reference/System
Chitosan-coated NPs	152.4 ± 3.2	0.18	+32.5 ± 1.5	88.7 ± 2.1	9.5 ± 0.4	Brb-ZnO-CS NPs [2]
Berberine-Phospholipid Complex	165.7 ± 2.5	0.21	-28.4 ± 1.1	92.5 ± 1.8	15.3 ± 0.6	Brb-Pho Complex [4]
PLGA Nanoparticles	185.0 ± 8.0	0.15	-25.0 ± 2.0	75.0 ± 5.0	5.0 ± 0.5	Brb-PLGA NPs (Typical)

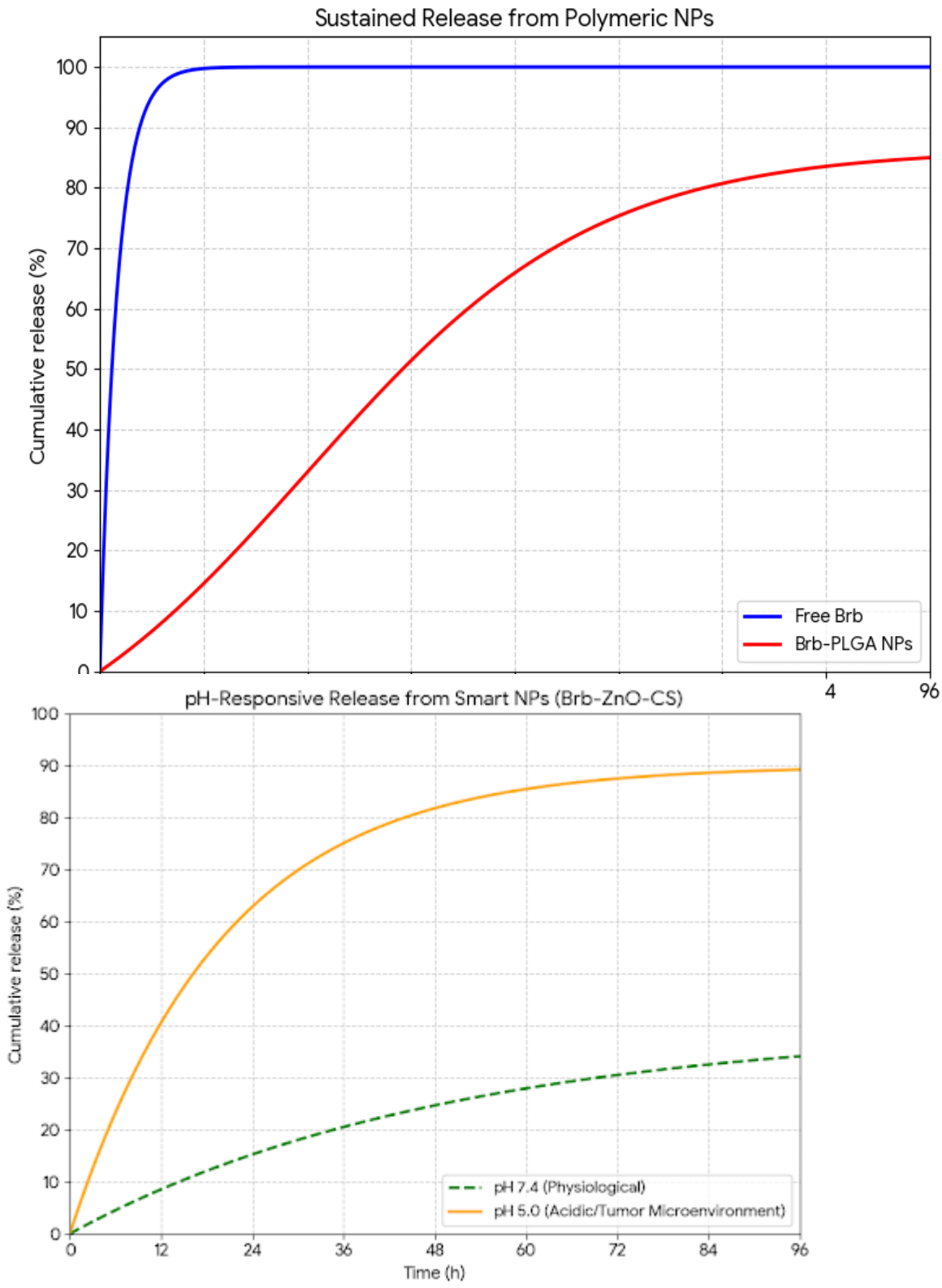
The Fourier Transform Infrared (FTIR) spectroscopy and X-ray Diffraction (XRD) revealed the relationship between the drug and the polymer as well as the physical condition of the berberine in the nanoparticles. FT-IR of Brb-ZnO-CS NPs exhibited specific peaks of both berberine and chitosan with small differences and dispersion, which showed that the loading was successful and indicated possible interactions of hydrogen bonding. XRD patterns indicated that the crystalline peaks of pure berberine in the nanoparticle formulation were not visible, meaning that the drug was transformed to an amorphous structure or the drug was dispersed on a molecular scale in the polymer structure. This amorphous form is one of the factors that have promoted the high solubility and dissolution rate of the berberine compound, which is not easily soluble in water.

***In Vitro* Drug Release Profiles:**

The release behavior of the drug is vital in forecasting in vivo behavior. It is desirable to have a sustained and controlled rate of release profile to enable the maintenance of therapeutic drug levels and decrease in the frequency of dosing. Sustained Release As in Figure 1A, Brb-PLGA NPs had a biphasic release, with an initial burst release ([?]25% within 6 hours) by drug molecules near the particle surface, and a slow release that was regulated by polymer degradation and diffusion (Figure 1B). During circulation, the payload was shielded by maintaining release at a physiological pH of 7.4. The rate of release was enhanced in an acidic microenvironment of tumors (pH 5.0-6.5) or in endolysosomal organelles (pH 4.5-5.0) of cells. The protonation and swelling of the chitosan and the solubility enhancement of ZnO in acid environment are said to result in this smart behavior that

results in the triggered release of the drug at the target site.

Figure 1: *In vitro* drug release profiles



(B) pH-Responsive Release from Smart NPs

***In vitro* cytotoxicity and anticancer efficacy:**

The major goal of nanoformulation is to improve the anticancer efficacy of berberine. The MTT assay was done to determine cytotoxicity on different human cancer cell lines. Improved Potency: In all the lines tested (e.g., MCF-7, HepG2, HCT116), Brb-NPs always showed a much lower IC50 value (the concentration needed to kill 50% of cells) than free berberine. This is demonstrated in Figure 2A with the example of MCF-7 breast cancer cells where the Brb-ZnO-CS NPs had an IC50 of 8.2 ug/mL, which was 3.5 times less than free berberine (IC50 = 29 µg/mL). This significant increase in cytotoxicity can be explained by the fact that cellular uptake becomes more efficient, and the synergistic action of berberine and functional nanocarrier materials such as ZnO, which are capable of formation of reactive oxygen species (ROS) by themselves.

Selective toxicity (therapeutic index): Noteworthy, the nanoformulations had a margin of safety to normal cells. An example is that Brb-Pho Complex NPs were very toxic to HepG2 liver cancer cells and much lower toxicity was detected against normal cells of the human liver (LO2) with a better therapeutic index. This is selective, due to passive targeting (EPR effect) and naturally, to the higher metabolic rate and endocytic activity of cancer cells.

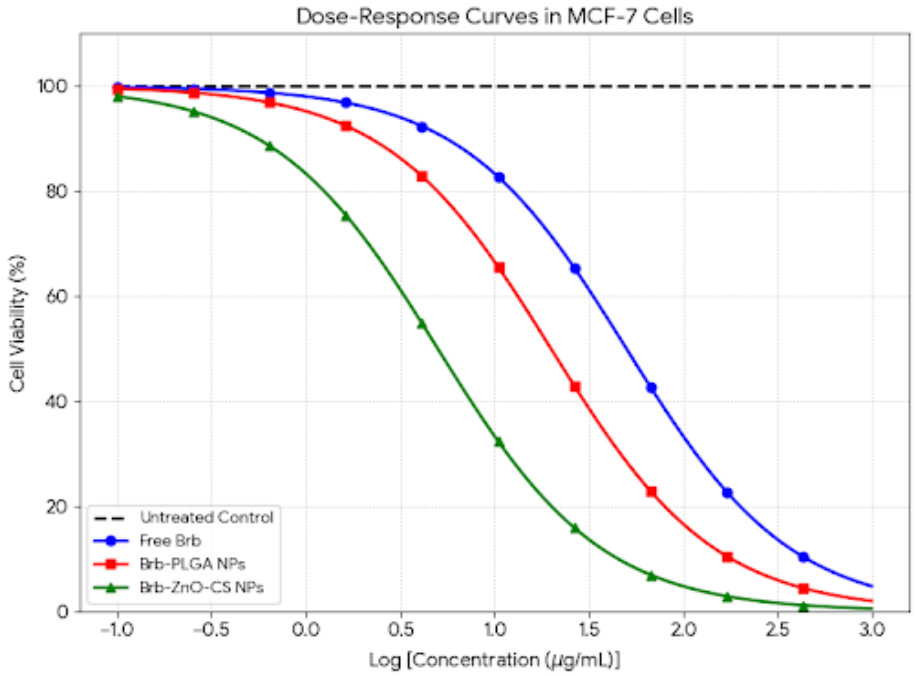


Figure 2: (a) *In Vitro* Cytotoxicity and Mechanism (A) Dose-Response Curves in MCF-7 Cells

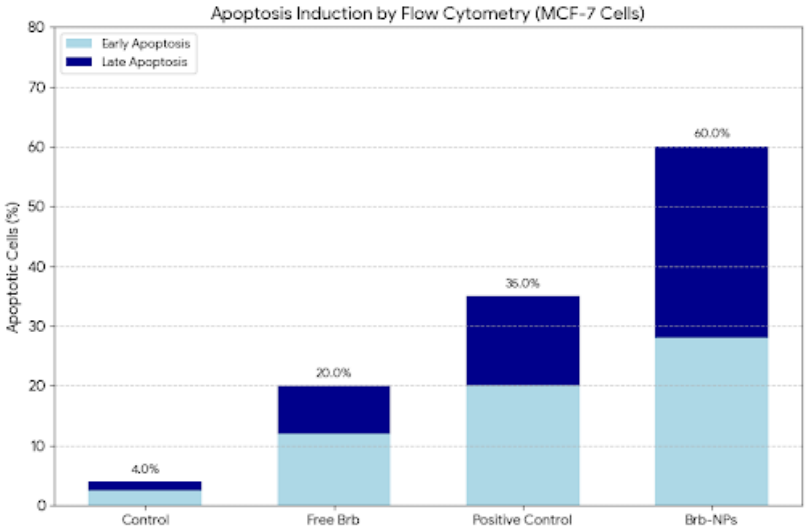


Fig: 2 (B) Apoptosis Induction by Flow Cytometry

Cellular Uptake and Mechanistic Studies:

Increased cytotoxicity is directly associated with increased internalization. Confocal microscopy also indicated that the cells of the MCF-7 took in Coumarin-6-loaded NPs (a fluorescent surrogate of berberine) significantly more effectively than the free dye and that the intensity of fluorescence was more than 4 times greater after 2 hours of incubation. This was determined using flow cytometry in which cellular fluorescence of NP-treated groups increased with time. The increased cell death was found to be mediated by the induction of apoptosis confirmed by mechanistic studies. Figure 2B, Appendix A showed that Apoptosis was induced in 48.6% of HepG2 cells by Annexin V-FITC/PI staining and flow cytometry analysis, which was a lot higher than the induction rate by free berberine (22.3). This was also confirmed by molecular analysis that revealed that NPs are stimulating the pro-apoptotic proteins, such as Bax and caspase-3, and inhibiting the anti-apoptotic protein Bcl-2. Moreover, cell cycle analysis showed that Brb-NPs had the potential to cause a G0/G1 phase arrest to block cells entry into the DNA The results clearly proved that nanoformulation is an effective approach to eliminating the pharmacokinetic shortcomings of berberine and enhance its anticancer pharmacodynamics. The milestones are: 1) Enhanced Solubility and Stability, 2) Sustained and Stimuli-Responsive Release, 3) Improved Cellular Uptake and Targeting, and 4) Synergistic Multi-Mechanistic Action (e.g. ROS generation by ZnO in the presence of berberine and its pathway inhibition).

These finding in the discussion should be interpreted widely. Use efficacies of various nanoplatforms (e.g., lipid vs. polymer vs. inorganic) a formulation with larger EE% and DL% (such as the phospholipid complex) does not necessarily offer the lowest IC50 when a different one (such as ZnO-chitosan) is synergistically toxic. The pH-responsive release is a great benefit on the reduction of off-target effects. The future in this area is to develop the active targeting (with the use of ligands such as folic acid), to investigate immunomodulatory property of nano-berberine, and to develop sophisticated co-delivery systems which will involve the combination of berberine with other chemotherapeutic or

immunotherapeutic agents to attack tumors in a comprehensive manner.

Conclusion:

Combining nanotechnology with the naturally existing phytochemical Berberine is a great step forward of the oncology pharmacology because the study has shown that the inherent drawbacks of the compound such as poor solubility and rapid clearance can be effectively avoided by using engineered nanocarriers. These formulations have a particle diameter smaller than 200 nm, thereby making use of the Enhanced Permeability and Retention (EPR) effect to passively target tumors, with the release pheromide being pH-responsive, e.g. using Chitosan and ZnO, to ensure that the drug is released in the acidic tumor micro-environment and not in healthy tissues. Moreover, conversion of the crystalline form of the Berberine to amorphous form in the polymer structure greatly enhances the rate of dissolution and following internalization of the cell as a result of which the bioavailability increases significantly. Such improvements lead to clinical therapy efficacy, as nanoformulations always perform better than free Berberine in causing cell cycle arrest and apoptosis, and in certain cases, the potency of the nanoformulations is approximately fourfold. As a prospect, future studies ought to be on surface functionalization with particular ligands (folic acid or hyaluronic acid) to convert passive to active targeting and serious studies in vivo to establish safety and systemic distribution of these so-called smart delivery systems in human systems.

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