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Appraisal of folate functionalized bosutinib cubosomes against hepatic cancer cells: *In-vitro*, *In-silico*, and *in-vivo* pharmacokinetic study

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ABSTRACT

Targeted therapies enhance the efficacy of tumour screening and management while lowering side effects. Multiple tumours, including liver cancer, exhibit elevated levels of folate receptor expression. This research attempted to develop surface-functionalised bosutinib cubosomes against hepatocellular carcinoma. The novelty of this work is the anti-hepatic action of bosutinib (BST) and folic acid-modified bosutinib cubosomes (BSTMF) established through proto-oncogene tyrosine-protein kinase (SrC)/ focal adhesion kinase (FAK), reactive oxygen species (ROS), mitochondrial membrane potential (MMP), and cell cytotoxicity. Later, the *in-vivo* pharmacokinetics of BSTMF were determined for the first time. The strong affinity of folic acid (FA) for folate receptors allows BSTMF to enter cells via FA receptor-mediated endocytosis. The particle size of the prepared BSTMF was 188.5 ± 2.25 nm, and its zeta potential was −20.19 ± 2.01 mV, an encapsulation efficiency of 90.31 ± 3.15 %, and a drug release rate of 76.70 ± 2.10 % for 48 h. The surface architecture of BSTMF was identified using transmission electron microscopy (TEM) and Atomic force microscopy (AFM). Cell-line studies demonstrated that BSTMF substantially lowered the viability of Hep G2 cells compared to BST and bosutinib-loaded cubosomes (BSTF). BSTMF demonstrated an elevated BST concentration in tumour tissue than in other organs and also displayed superior pharmacokinetics, implying that they hold potential against hepatic cancers. This is the first study to show that BSTMF may be effective against liver cancer by targeting folate receptors and triggering SrC/ FAK-dependent apoptotic pathways. Multiple parameters demonstrated that BSTMF enhanced anticancer targeting, therapeutic efficacy, and safety in NDEA-induced hepatocellular carcinoma.

1. Introduction

Hepatocellular carcinoma (HCC) is a very prevalent malignant tumour that accounts for a significant portion of cancer-related deaths worldwide. HCC incidences continue to rise each year, with a mortality rate of about 0.6 million annually. Rapid progression, severe malignancy, an inadequate probability of early diagnosis, and a poor prognosis are all hallmarks of HCC. Chemotherapy is the primary HCC treatment (Kong et al., 2019). For HCC therapy, numerous conventional chemotherapy drugs have been used, but these traditional methods have not been effective in lowering the total mortality rate. Currently, the USFDA (US- Food Drug and Administration) has only approved the drug for systemic injection in advanced HCC management sorafenib (Nexavar), but it has numerous disadvantages like dose-related side effects (alopecia, hand-foot syndrome), resistance (within 3–6 months) and high cost (Liang et al., 2019). These shortcomings, thus, limit the use of sorafenib as an anticancer agent to treat HCC.

Consequently, it is necessary to investigate novel drug entities and molecular targets that may have enhanced anti-HCC potential. Bosutinib (BST), a second-generation 2012 USFDA-approved tyrosine kinase inhibitor, inhibits both SrC (a non-receptor tyrosine kinase) and FAK (Focal Adhesion Kinases) for the treatment of chronic myeloid leukemia

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