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Fabrication of Imatinib Mesylate-Loaded Lactoferrin-Modified PEGylated Liquid Crystalline Nanoparticles for Mitochondrial-Dependent Apoptosis in Hepatocellular Carcinoma

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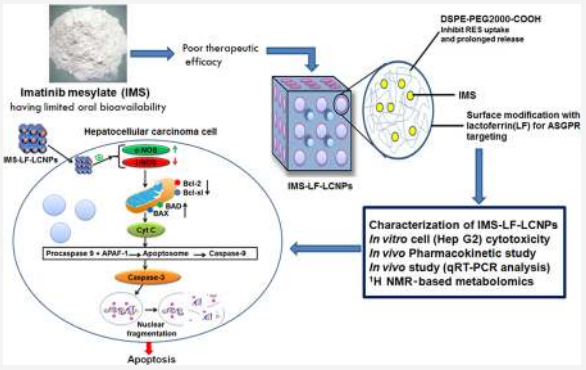
ABSTRACT: Hepatocellular carcinoma (HCC) is a major cause of concern as it has substantial morbidity associated with it. Previous reports have ascertained the antiproliferative activity of imatinib mesylate (IMS) against diverse types of carcinomas, but limited bioavailability has also been reported. The present study envisaged optimized IMS-loaded lactoferrin (LF)-modified PEGylated liquid crystalline nanoparticles (IMS-LF-LCNPs) for effective therapy of IMS to HCC via asialoglycoprotein receptor (ASGPR) targeting. Results displayed that IMS-LF-LCNPs presented an optimum particle size of 120.40 ± 2.75 nm, a zeta potential of +12.5 ± 0.23 mV, and 73.94 ± 2.69% release. High-resolution transmission electron microscopy and atomic force microscopy were used to confirm the surface architecture of IMS-LF-LCNPs. The results of cytotoxicity and 4,6-diamidino-2-phenylindole revealed that IMS-LF-LCNPs had the highest growth inhibition and significant apoptotic effects. Pharmacokinetics and biodistribution studies showed that IMS-LF-LCNPs have superior pharmacokinetic performance and targeted delivery compared to IMS-LCNPs and plain IMS, which was attributed to the targeting action of LF that targets the ASGPR in hepatic cells. Next, our in vivo experiment established that the HCC environment existed due to suppression of BAX, cyt *c*, BAD, e-NOS, and caspase (3 and 9) genes, which thus owed upstream expression of Bcl-xl, iNOS, and Bcl-2 genes. The excellent therapeutic potential of IMS-LF-LCNPs began the significant stimulation of caspase-mediated apoptotic signals accountable for its anti-HCC prospect. ^{1}H nuclear magnetic resonance (serum) metabolomics revealed that IMS-LF-LCNPs are capable of regulating the disturbed levels of metabolites linked to HCC triggered through *N*-nitrosodiethylamine. Therefore, IMS-LF-LCNPs are a potentially effective formulation against HCC.



KEYWORDS: *HCC, ^{1}H NMR-based metabolomics, lactoferrin, LCNPs, IMS*

1. INTRODUCTION

Hepatocellular carcinoma (HCC) is the sixth prevailing global health problem and the third cancer-related cause of death worldwide each year.[1] In India, the total cases of men and women suffering HCC accounts for 0.7 to 7.5 and 0.2 to 2.2, respectively, per 1 lakh person per annum.[2] It is believed that surgical resection is the only optimal treatment for HCC, as it is not always feasible since most of the patients are diagnosed with the disease in an advanced or intermediate stage of hepatic cancer. Also, traditional chemotherapy has a helpless endurance rate with extreme reactions due to lack of tumor selectivity, dose-dependent toxicity, low selectivity, and resistance development.[3] Besides sorafenib, the first choice of drug for HCC therapy has limited potency due to low solubility, high dose toxicity, multidrug resistance, etc.[4] Therefore, more efforts are necessary to identify new drug moieties and molecular targets to improve treatment regimens.

Imatinib mesylate (IMS) is an inhibitor of tyrosine protein kinase approved by the FDA for treating chronic myeloid leukemia (CML) and gastrointestinal stromal tumor.[5] IMS is also used as an important targeted therapy candidate for inhibition of tumor growth in numerous malignancies, including thyroid, ovarian, pancreatic, osteosarcoma, prostate, and other solid tumors.[6] Numerous investigations proposed that the anticancer property of IMS is predominantly because of mitochondrial apoptotic pathway activation, with the involvement of various antiapoptotic proteins (Bcl-2, Bcl-xl),

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