CHAPTER 9

Novel Findings and Future Clinical Applications
Novel Findings and Future Clinical Applications

The major advancements made in the scientific community in determining the various mechanisms involved in causing hepatotoxicity could not open up an acceptable approach in prevention therapies for hepatocellular disorders. Most hepatocellular disorders resulted through oxidative stress in pathophysiological condition. The present research work has been focused in developing effective vesicular drug delivery system for targeting antioxidants against oxidative damage evoked in hepatocellular disorders and its possible protection mechanism in rat model.

QC, a polyphenolic flavonoid, present in large amounts in vegetable, fruits, tea and olive oil, has been used to serve as a stress protectant for its ability to interact with free radicals involved in oxidative damage and progression of fibrogenesis in liver. Effective delivery of QC to the liver was achieved through encapsulating the compound in multilamellar liposomes and PLGA nanoparticles that could prove to be an effective protection against acute arsenic induced liver toxicity in rat model. However nanoparticulated QC was found more effective against arsenic induced liver damage. The approach of delivering a nontoxic herb origin polyphenolic compound QC to liver could be recommended in therapeutic application to prevent NaAsO$_2$-induced acute liver toxicity. Application of polylactide nanocapsulated QC containing a very low dose of the compound could be acceptable as a potent therapeutic approach for arsenic induced hepatic fibrosis gene expression and upregulation of TGF β in plasma through a complete protection of liver against arsenic mediated oxidative attack.

Oxidative stress plays an important role in the proinflammatory signaling and macrophage activation during liver injury providing a feed-forward mechanism in ALD...
leading to the activation of death signaling cascades resulting in liver damage. Therefore, targeting components at redox-sensitive inflammatory pathways and transcription factors offers great promise for treatment of ALD. Investigation of agents that interfere with oxidative stress mediators directly hampering inflammatory cytokine production is needed. Curcumin, an herbal polyphenolic compound with antioxidant, anti-inflammatory and anticancer properties is one such promising agent. Oral pretreatment of curcumin encapsulated in PLGA nanoparticles was not tested earlier against alcohol induced liver injury. The formulation has successfully been stabilized and has been effective in controlling alcohol induced oxidative stress and inflammation in a rat model of alcoholic liver damage and could be recognized as an early attractive formulation for potential clinical application in preventing alcohol induced liver injury in future.

HCC is the deadly disease worldwide with difficult prognosis and limited treatment modalities with serious medical side effects encountered by patients. Thus it makes a demand, the invention and clinical application of potential chemopreventive therapies against the sufferings in that disease. Curcumin in nanocapsulated drug delivery system is an effective formulation that could protect the rat liver from DEN induced altered hepatic functioning, prevented DEN induced hyperplastic nodule formation, controls upregulation of iNOS expression which in a way prevented angiogenesis in tumor sites, as well as promoted apoptosis of the initiated cancer cells as evidenced by DNA fragmentation, cyt c release. Nano Cur has shown its effectiveness against DEN induced hepatocellular carcinoma in rat. Nano Cur in oral route might be a promising anticancer alternative to prevent HCC.
Doxorubicin and methotrexate, the two commonly available anticancer drugs possess serious toxic side effects to the patients. Encapsulating the two drugs in vesicular drug delivery systems have yielded extremely promising results in combating DEN induced hepatocellular carcinoma in rat models with no side effects at effective dose employed herein. Recently, more efforts have been made to explore the potential of using Hap nanoparticles as vehicles for drug and gene delivery for their great affinity to DNA and various drugs with good biocompatibility and release property. Moreover, HAP is more acceptable for its cost effectivity. Hydroxyapatite nanoparticles of doxorubicin (Nano Hap-DOX) proved to be more efficient in comparison to polylactide nanoparticles of doxorubicin (Nano PLGA-DOX) in combating DEN induced hepatocellular carcinoma in rat model. The formulation of methotrexate in PLGA nanoparticles have opened up the use of toxic component, and it may be the first time approach in treating liver cancer. These formulations could be transferred and expected to be a potential anticancer formulations to patients with hepatocellular carcinoma without resulting in any toxic syndrome. Also, Nanoparticulated methotrexate might also be recommended to treat several hepatocellular carcinomas.