7. FUTURE DIRECTIONS

Present investigation provided the selection of suitable derivative from the no. of synthesized betulinic acid derivatives. This investigation reduced the time of the discovery and development of betulinic acid derivative as anti cancer drugs considerably using suitable set of studies. Though the lead compound showed the acceptable pharmacokinetics and potent in vitro cytotoxicity which was later validated in the study itself in the form of marginal efficacy, a detailed set of studies needs to be further conducted in order to develop this as drug. The future scope of the work pertaining to this is summarized below

- Complete pharmacokinetic study in one non rodent species like in dog and minipigs should be performed and also to establish toxicity and safety of DRF-4012 in same species.
- Inter-scaling pharmacokinetic correlation need to be established between different species.
- Combining the methods — chemotherapy and anti-angiogenesis / chemotherapy and vascular disrupting agents / anti-angiogenesis and vascular disrupting agents — can be another way to kill cancer cells.
- As DRF 4012 showing poor bioavailability so better formulation strategy should be adopted to increase the oral bioavailability of DRF 4012.
- Since the permeability of the NCE was not clear from the PAMPA assay, so permeability has to be checked by Caco-2 and MDCK cells.
- Plasma protein binding assay has to be performed at higher concentration of the NCE.
- More detailed in vivo efficacy study with various study design pertaining to doses and dose regime need to be performed.
- The future prospective that the other matrix of rat like bile should be used to identify the possible metabolite formation in bile.
- The metabolite identification needs to be further confirmed by other spectroscopic techniques like NMR, IR etc.
- To elucidate the molecular mechanism of DRF-4012.

Betulinic acid when combined with anticancer drugs like taxol, doxorubicin, cisplatin etc. was found to induce apoptosis in different human tumor cell lines, including P53
mutant cells, and also in primary tumor cells, but not in normal human fibroblasts (Fulda et al., 2005). These findings indicate that betulinic acid acts as a sensitizer in chemotherapy-based combination regimens may be a novel strategy to enhance the efficacy of anticancer therapy. Further studies may be carried out to test whether any of the potent derivatives identified as a result of this study could be used in combination regimens.

Within the worldwide research of betulinic acid and betulin in the field of anti-tumor agents, number of structural modifications and derivatization has been studied. Some studies demonstrate that derivatization of 3-β-hydroxy group with lower diacids or amino acids that resulted in highly polar compounds. Future derivatives could be synthesized that make more polar derivatives of betulinic acid.

Finally, for the development of betulinic acid derivatives for clinical assessment, detailed pharmacology and toxicology, including genotoxicity and reproductive toxicology studies need to be performed in order to generate data on the potential short and long term toxicities, other pharmacological actions etc. for submission to the regulatory authorities for initiation of Phase-I clinical trials.

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