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P0222 Chitosan-betulinic acid as a novel nanoformulation against resistant *Leishmania major*

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Background: Betulinic acid (B) is an antileishmanial agent and its clinical use is limited due to low water solubility and toxicity. In this study we aimed to evaluate the antileishmanial effect of B which loaded into nanochitosan (K) synthesized by phase separation method (which performed for the first time) and novel solvent and using this compound for treatment of leishmania major-infected Balb/c mice.

Materials/methods: First Betulinic acid-nanochitosan (BK) compound was synthesized. The formulation was characterized by using AFM, DLS, FTIR, HNMR, SEM and TEM methods. The nanodrug toxicity was measured in vitro by MTT assay. In addition, the formulation efficacy was determined in vitro by measurement of killing effects of this formulation against promastigotes and amastigotes. Furthermore, in vivo toxicity of formulation was measured by using enzymatic evaluation, pathological studies and mortality rate. Then, the in vivo efficacy was determined by measurement the lesion size, pathological effects, parasite burden and number.

Results: The therapeutic effects of betulinic acid were improved through increasing the effective dose due to using a novel solvent and phase separation method for nanochitosan synthesis which in turn increased the drug solubility rate to 80%, drug loading efficiency to 93%, cellular uptake to 97.5% and resulted to the pattern of slow drug release. This loading produced a non-toxic noformulation in vitro by 100% and also BK showed inhibition effects of 86% against promastigotes and amastigotes in dosage of 20mg/ml. Besides, the results of toxicity assays showed that BK was nontoxic without any tissues side effects and mortality rate. Then, BK20 mg/kg was used in the treatment of parasite infected mice. Measurement of lesion size of footpad infected with parasite performed and confirmed by pathological evaluation. Our findings showed wound complete recovery. Moreover, the results of parasite burden demonstrated that BK20 mg/kg significantly inhibited leishmania major number by 86% (significantly more potent than glucantime).

Conclusions: Promising results of BK20 mg/kg in preclinical trial (in vitro and in vivo) confirmed that BK can be considered as an alternative medicine for leishmania major treatment.