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Novel peptide inhibitors of human tumor necrosis factor-α: Molecular modelling and *in-vitro* assays

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TNF-α plays a very important role in the progression of various inflammatory diseases including rheumatoid arthritis. This study aims towards the designing, synthesis and evaluating the effects of the peptide inhibitors of TNF-α. Trimerized form of TNF-α is the active one, which can bind to receptor resulting in the progression of inflammatory cascade. The phenomenon of trimer formation was targeted for designing the inhibitors. The peptides were designed in silico using various bioinformatic tools and synthesized by solid phase peptide synthesis (SPPS) process. The anti-TNF activity of four different peptides (peptide 1, 2, 3 and 4) was checked in-vitro. Effect of peptide-2 was found to show the most significant anti-TNFα activity. TNF-α induced cell death of Wehi-164 cells was evaluated through MTT assay. The peptide-induced inhibition of TNF-α resulted in reduced cell death and increased viability. The TNF-α induced nuclear translocation of NF-κB was visualized using immune cytochemical analysis using A549 cells. The Western blotting of the nuclear lysate showed under expression of NF-κB in the TNF-stimulated cells with peptide inhibition as compared to the cells untreated with peptides. This result was fairly corroborated with the Electrophoretic Mobility Shift Assay (EMSA) test of the nuclear lysates of the experimental cells. Peptide-2 showed a dose dependent inhibition on the TNF-α activity with maximum effect at 200 μM of the peptide concentration ($p<0.05$). No significant cytotoxicity was observed when stimulated with the peptides with the concentrations ranging between 50 and 400 μM. To conclude, peptide-2 showed the highest anti- TNF activity among all the peptides tested and this peptide-2 appears to have potential of being a peptide drug, for which in-vivo studies and further trials are required.

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