Abstract

Withania somnifera is a predominant medicinal herb having economically valuable secondary metabolites and high reduction potential. Apart from being medicinal, *W. somnifera* also has hyper accumulation capability especially with heavy metals. Initially, metal bioaccumulation and metal reduction capability of field grown shoot tissues of *W. somnifera* was analysed using elemental analysis and extract based green synthesis of silver nanoparticles. The capability of *W. somnifera* to grow under the influence of heavy metal stress and accumulation of secondary metabolites is studied using *in vitro* shoot cultures. On confirmation of metal reduction capability, 45-days old *in vitro* shoot cultures were treated with different concentrations of silver nitrate and lead acetate salts at acute and chronic conditions. An Increase in biomass, primary and secondary metabolites (withanolides) was found to be accumulated in considerable amounts in metal salts treated *in vitro* shoots compared to *in vitro* control. Among the metal treated shoots, 1mM $AgNO_3$ treatment for 12 days period and 0.8mM PbAc treatment for 12 days period was selected as the optimum treatment conditions and selected for the further studies. Optimum $AgNO_3$ and PbAc treated shoots along with control shoots were analysed for its respective metal content using ICP MS analysis. The concentration of Ag in optimum $AgNO_3$ treated shoot is 50.8ppm and Pb in optimum PbAc treated shoot is 405ppm. The nature of Ag and Pb within the shoot was analysed by TEM with EDAX analysis. The presence of Ag and Pb nanoparticles in spherical and rod shape was confirmed. In addition, the neuroprotective activity of metal treated IVS along with field grown tissues of *W. somnifera* was studied using Parkinson's disease cell model (SH-SY5Y cells). Compared to field grown tissues, $AgNO_3$ treated IVS exhibited increased neuroprotective activity against rotenone toxicity. Molecular docking study was conducted to analyse the binding site of rotenone and selected withanolides in mitochondrial complex I protein. Multiple ligand simultaneous docking revealed a binding of rotenone with withaferin A leaves complex I protein uninhibited. Thus, from the current study, we conclude that $AgNO_3$ treated IVS along with increased withaferin A content has higher neuroprotective activity which may be used as a potential drug for toxins induced PD.