p53 protein plays a major role in maintaining the integrity of the genome. It serves as a tumor suppressor, inducing cell cycle arrest or apoptosis, leading to elimination of cancer cells. However, p53 is often lost or mutated in human malignancies. TAp73 protein is a functional and structural homolog of p53. In stress conditions TAp73 can be activated, bind to p53-responsive genetic targets and induce cell death. Therefore, TAp73 can serve as an alternative target for pharmaceutical intervention in cells lacking functional p53.

Plants are a rich source of biologically active compounds that can be used as therapeutic drugs. *Withania somnifera* leaf and root extracts have been used throughout the years in Indian traditional medicine – Ayurveda. Scientific studies on their activity led to identification of a number of compounds, among them anti-cancer steroidal lactone - withaferin A (WA). Further studies proved that WA inhibits tumor progression through inhibiting Akt and NF-$_{\kappa}$B signaling pathways, altering cytoskeleton proteins, inducing reactive oxygen species (ROS) formation and blocking proteasome activity. These activities were confirmed in studies carried out *in vitro* and *in vivo*.

This study was focused on unraveling the mechanism leading to TAp73 stabilization upon WA in cancer cells lacking functional p53 protein. Preliminary experiments confirmed that WA inhibits proliferation and causes cell death in studied cell lines. Western blot analysis showed elevated TAp73 protein level upon WA treatment. Furthermore, PUMA, pro-apoptotic TAp73 target was up-regulated on protein and mRNA level. Oxidative stress activated upon WA triggers JNK-mediated TAp73 phosphorylation and stabilizes phase II anti-oxidant response element NQO1 (NADPH quinone oxidoreductase). WA treatment facilitates NQO1 binding to TAp73 and prevents its proteasomal degradation. Immunoprecipitation experiment revealed that WA disrupts TAp73-MDM2 inhibitory complex. JNK inhibitor and ROS scavenger N-acetylcysteine (NAC) abrogated WA activity in investigated cell lines. Presented data demonstrate the mode of action of 20S proteasome inhibitor WA, that stabilizes and activates TAp73, causing apoptosis of cells lacking functional p53.