Azadiradione ameliorates neurodegenerative diseases in mouse and fly models by potentiating DNA binding activity of heat shock factor 1

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Toxicity associated with protein aggregation in the brain underlies various neurodegenerative diseases (NDs) such Parkinson's diseases, and polyglutamine based diseases such as Huntington's diseases, and spinocerebeller ataxias. It has been shown that heat shock response (HSR) that maintains cellular protein homeostasis in response to protein unfolding is defective in these diseased conditions. Consistently, upregulation of activity of heat shock factor (HSF1), the central regulator of HSR and expression of its target protein chaperone genes through small molecule or overexpression, respectively yielded promising results in both cell and animal disease models. However, all small molecule activators of HSF1 reported thus far functions indirectly. We have isolated azadiradione (AZD) by HSF1-sensitive cell based reporter screening of extracts of seeds of Azadirachta indica, a plant known for its many medicinal properties. We show that AZD, a triterpinoid ameliorates toxicity due to protein aggregation and associated disease pathologies and symptoms in cell, mouse and fly models with all these activities correlating with activation of HSF1 function and expression of its target protein chaperone genes. Notably, HSF1 activation by AZD we report here is independent of cellular HSP90 chaperone or proteasome function. Furthermore, we show that AZD directly interacts with purified HSF1 with high specificity facilitating its binding to its recognition sequence with higher affinity. These unique findings qualify AZD as an ideal lead molecule for consideration for drug development against NDs that affect millions worldwide.

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