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Andrographolide inhibits human serum albumin fibril formations through site-specific molecular interactions

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Protein misfolding and fibrillation are the fundamental traits in degenerative diseases like Alzheimer's, Parkinsonism, and diabetes mellitus. Bioactives such as flavonoids and terpenoids from plant sources are known to express protective effects against an array of diseases including diabetes, Alzheimer's and obesity. Andrographolide (AG), a labdane diterpenoid is prescribed widely in the Indian and Chinese health care systems for classical efficacy against a number of degenerative diseases. This work presents an in depth study on the effects of AG on protein fibrillating pathophysiology. Thioflavin T fluorescence spectroscopy and DLS results indicated concentration dependent inhibition of human serum albumin (HSA) fibrillation. The results were confirmed by electron microscopy studies. HSA fibril formations were markedly reduced in the presence of AG. Fluorescence studies and UV-Vis experiments confirmed further that AG molecularly interacts with HSA at site. *In silico* molecular docking studies revealed hydrogen bonding and hydrophobic interactions with HSA in the native state. Thus AG interacts with HSA, stabilizes the native protein structure and inhibits fibrillation. The results demonstrated that the compound possesses anti-amyloidogenic properties and can be promising against some human degenerative diseases.

1. Introduction

Proteins are complex yet exquisitely arranged molecules which carry out well defined biological functions. Three dimensional macromolecule structure and spatial arrangement of functional groups are major determinants for protein bio-functions. Physiological stress conditions such as oxidative imbalances, enhanced cellular degradation or dominant negative mutation often initiate a biochemical cascade. This leads to molecular self-association of proteins which can result in amyloidogenesis. Self-associated fibrils of α-synuclein, HSA and insulin are predominantly cytotoxic.[1–3] Similar molecular disposition brings about cell death and persistent physiological abnormalities.[4] Protein misfolding and fibrillation are some of the underlying causes in a number of degenerative conditions such as Alzheimer's disease, parkinsonism, type 2 diabetes, atherosclerosis and others.[5] Therapeutic stratagems to mitigate or prevent amyloidogenic diseases include stabilization of native protein structures and increased clearance of already misfolded protein aggregates.[6,7]

Different bioactive principles derived from natural sources have been explored recently as fibrillation inhibitors.[8] Andrographolide (AG) is a labdane diterpenoid extracted from *Andrographis paniculata* Nees herb. AG has been traditionally used in Indian and Chinese health care systems for contending a myriad of ailments and degenerative diseases. AG demonstrated pronounced efficacy as hepatoprotective, antimalarial, antitumor agent, in cognitive improvement, immunomodulation, and several others.[9–13] AG is an effective molecule in a multitude of amyloidogenic diseases such as diabetes, rheumatoid arthritis, and Aβ neurotoxicity.[14–16] A comprehensive molecular mechanism underlying the therapeutic effects of AG has not yet been explored.

In the present work, we have studied the effect of different concentrations of andrographolide on HSA fibrillation at an elevated temperature. The process of fibrillation has been monitored using a combination of dynamic light scattering techniques, Thioflavin T fluorescence spectroscopy and electron microscopy. Further efforts have been made to interpret the interactions between andrographolide and HSA protein through multi-spectroscopic and *in silico* molecular docking techniques. This study reveals an insight into the protective mechanism of AG against amyloid formations and protein misfolding disease conditions.

Human serum albumin (HSA) is the most abundant, soluble, single chained protein containing 585 amino acids. The protein remains stabilized by 17 disulfide bridges in heart-like self-assembly formations. It contributes to storage and transportation of endogenous and exogenous substances such as

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