ABSTRACT

Index No. 49/17/Chem./25

Thesis Title: Investigating the anti-amyloidogenic activities of functionalized polyphenolic compounds and metal oxide nanoparticles on the structure and the fibrillation of β-lactoglobulin.

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When proteins misfold, they can form amyloid fibrils, which are linked to severe diseases like Alzheimer's, Parkinson's, and Huntington's. Recent research has focused on stopping fibril formation. Amyloid fibrils are characterized by cross β-structures, and their morphological features are not directly linked to the specific proteins involved. Studies have found that compounds like pyrroloquinoline quinone (PQQ), nitrophenols, epicatechin gallate, biocompatible nanogels, benzofurans, baicalein, and curcumins can inhibit amyloid formation.

β-lactoglobulin is a type of protein made up of 162 building blocks called amino acids. It is part of a group of proteins called lipocalins. This protein can carry small, water-repelling molecules like fatty acids and retinol. When heated at an acidic pH or in the presence of certain substances at a neutral pH, β-lactoglobulin easily forms amyloid fibrils. Serum albumins are blood proteins that mainly transport fatty acids, hormones, and other substances in the body. They also help maintain blood pressure and can clump together at low pH and when heated. Several proteins, including β-lactoglobulin, α-lactalbumin, immunoglobulin, bovine serum albumin, lysozyme, and insulin, exhibit pH-dependent conformational changes during thermal aggregation, which ultimately leads to the formation of amyloid fibrils.

In the context of my research, I have selected bovine β-lactoglobulin (β-lg) as a model transport protein due to its pH-dependent conformational changes, encapsulation properties, acidic pH sensitivity, and bioavailability. The protein exhibits a core structural motif comprising an α-helix and eight antiparallel β-sheets. Notably, a free, highly reactive -SH group is situated at the Cys-121 position, embedded within the protein's hydrophobic core. Furthermore, the protein features two tryptophan residues (Trp-19 and Trp-61) responsible for its fluorescent properties. To explore the influence of functionalized polyphenolic compounds and metal oxide nanoparticles on the thermal aggregation and structural alterations of bovine β-lactoglobulin, several chalcone derivatives were utilized in the study.

Chapter 1 presents a concise overview of the origin, isolation, purification, structural characteristics, chemical modification, and biological functions of bovine β-lactoglobulin. This

protein holds significance in the field of structural biology as it serves as an exemplary model protein system due to its well-defined crystal structure. Additionally, the chapter encompasses an examination of amyloid fibril formation, a phenomenon implicated in various neurodegenerative diseases, and explores the diverse factors influencing amyloid fibrillation resulting from aggregation. **Chapter 2** contains a thorough literature review of polyphenolic compounds, specifically chalcones analogues. In **Chapter 3**, an investigation was carried out involving the synthesis of four distinct chalcone derivatives denoted as SC1, SC2, SC3, and SC4, each featuring varying substituents positioned relative to the chalcone nucleus. Subsequently, an assessment was made regarding the impact of these chalcone derivatives on the structural and aggregation properties of β-lactoglobulin through the application of multispectroscopic and morphological (AFM and TEM) analyses. The observed efficacy of the synthesized compounds in promoting β-lg aggregation exhibited the following order: SC3 > SC2 > SC1 > SC4. In **Chapter 4**, an extensive literature review is presented, focusing on nanoparticles and nanotechnology, and their diverse impact on the structural modifications of protein aggregation and inhibition. **Chapter 5** undertakes an examination of the potential chaperone-like activity exhibited by synthesized zinc oxide nanoparticles (ZnO NPs) when confronted with alkaline unfolded bovine beta-lactoglobulin at pH 11.0. This exploration entails a comprehensive analysis employing multispectroscopic and morphological methodologies to elucidate the intricate interactions between the nanoparticles and the protein. **Chapter 6** delves into the impediment of amyloid aggregates of thermally incubated bovine beta-lactoglobulin by highly dispersed copper oxide nanoparticles (CuO NPs) prepared via a rapid precipitation method. This inhibition was scrutinized through diverse spectroscopic and morphological experiments conducted at physiological pH. In **Chapter 7**, the focus is on the self-assembly formation and the accelerated thermal aggregation of bovine β-lactoglobulin. This occurs in the presence of synthesized zinc oxide nanoparticles. The phenomena are studied extensively through a variety of spectroscopic and morphological experiments conducted under physiological pH conditions.

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