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Understanding curcumin-induced modulation of protein aggregation

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ABSTRACT

Curcumin, a diarylheptanoid compound, found in spice turmeric is known to alter the aggregation of proteins and reduce the toxicity of the aggregates. This review looks at the molecular basis of modulating protein aggregation and toxicity of the aggregates. Foremost, we identify the interaction of curcumin and its derivatives with proteins/peptides and the effect of their interaction on the conformational stability and unfolding/folding pathway(s). The unfolding/folding processes generate partially folded/unfolded intermediate, which serve as aggregation precursor state. Secondly, we discuss the effect of curcumin binding on the kinetics parameters of the aggregation process, which give information about the mechanism of the aggregation inhibition. We describe, in addition, that curcumin can accelerate/promote fibril formation by binding to oligomeric intermediate(s) accumulated in the aggregation pathway. Finally, we discuss the correlation of curcumin-induced monomeric and/or oligomeric precursor states with aggregate structure and toxicity. On the basis of these discussions, we propose a model describing curcumin-induced inhibition/promotion of formation of amyloid-like fibrils.

1. Curcumin structure and its medicinal usage

Turmeric (*Curcuma longa*) is a rhizomatous plant of the ginger family Zingiberaceae. This rhizome (underground stems capable of producing the shoot and root systems of a new plant) when dried and grounded is used as a spice and imparts yellow colour found in most of the cuisine and curries of Indian subcontinents. Turmeric has also been used in South Asia to treat many human diseases for thousands of years and is the main constituent of many Ayurvedic and Unani medicine preparations [1,2]. Exactly two hundred years ago in 1815, Vogel and Pelletier isolated the yellow colouring material of turmeric and named it as curcumin [3]. The curcumin ((1*E*, 6*E*)-1,7-Bis(4-hydroxy-3-methoxyphenyl)-1,6-heptadiene-3,5-dione) is a bioactive diphenylheptanoid and contains a variety of functional groups (Fig. 1). The structure of curcumin consists of two o-methoxy phenolic groups linked by a seven carbon linker consisting of an α,β-unsaturated β-diketone moiety. The α,β-unsaturated β-diketone group exhibits keto-enol tautomerism due to strong intramolecular hydrogen bonding in the 1,3-diketone functionality [4,5]. Thus, the naturally occurring curcumin exists as an equilibrium mixture of two tautomeric forms in solution (Fig. 1) [5]. The enol form is the most dominant structure of curcumin in solution as it is stabilized by intramolecular H-bonding [6]. These functional groups can be used by the molecule to interact with different kind of pathogen targets such as proteins, nucleic acid and/or membrane [7]. The aromatic moiety is involve in π-π interaction, whereas, phenolic moiety and keto-enol group participate in hydrogen bonding interactions [6,7]. Due to flexibility provided by seven carbon linker, the molecule can easily adopt a conformation suitable for overall hydrophobic interaction [6]. Biomolecules mainly interact with curcumin through these non-covalent forces and induce a specific biological activity. Curcumin is known to bind many proteins and peptides and modulate their conformation, dynamics and stability. The modulation in conformation and dynamics and stability of the protein molecules are thought to be main cause of protein aggregation or inhibition of aggregation [8–11].

The biological activity of curcumin is due to different functional groups, which provide different types of interaction forces [5–7]. However, the limitation associated with the structure is its poor solubility and bioavailability. These limitations can be overcome by use of new curcumin delivery systems, new curcumin analogues or synthesis of new derivatives. Development of new biocompatibles such as liposomes, polyethylene glycols, biopolymers, hydrogels etc. have shown improved water solubility and increased curcumin bioavailability [4,12]. Khodarahmi et al. have

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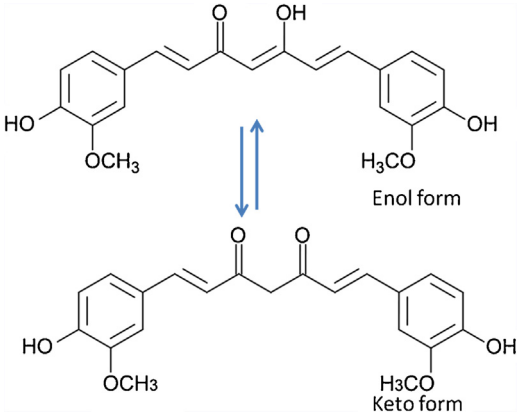

Fig. 1. Structure of curcumin. Keto form is the predominant specie in water.

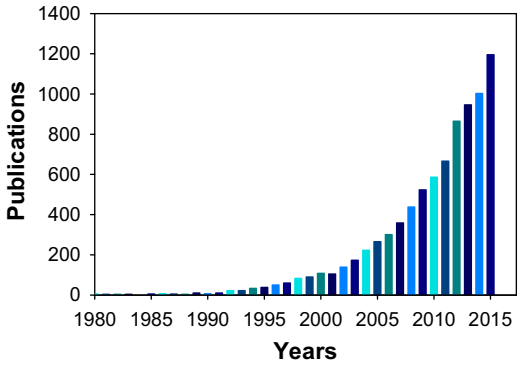

Fig. 2. A time course of no. of publications in Pub Med with key word curcumin.

shown that curcumin-bovine serum albumin complex formation enhanced both stability and the bioavailability of curcumin [13]. The glycosylated derivatives have been found to improve water solubility of curcumin [4]. Moreover, exploiting different types of functional groups and involved interaction forces in curcumin, such as hydrophobic interaction, aromatic π-stacking and hydrogen bonds, Nagahama et al. recently created curcumin-based multi-functional nano-biomaterials for use in cancer theranostics [14].

The modern research on different aspects of curcumin is a really hot issue over the last decade. There are about 8300 papers in PubMed dedicated to the different aspects of curcumin-related research, with ~7000 papers being published in the last 10 years, and with 1100 papers published only in 2015 (Fig. 2). The rising interest in the curcumin research is principally due to several recent discoveries on the potential anti-disease effect and improved bioavailability of curcumin in humans. Besides its well-known anti-inflammatory, anticancer, anti-microbial and anti- psychiatric effects, recent researches also show its potential ability to become a therapeutic drug for angiostenosis [15] and to promote lipid processing, disposal and removal hence supporting cholesterol homeostasis [16], therefore, could possibly manifest an anti-atherosclerotic effect as well. The biological relevance of curcumin nanoparticles and a possibility of its development as new neutraceutical agent have also been at the core of research involving interactions of plasma proteins with curcumin nano-formulation [17]. On the basis of these results, as of November 2015, there are 125 clinical trials registered with the US National Institutes of Health evaluating the effect of curcumin against several human diseases [18]. Among these, there are nine clinical trials evaluating the effect of curcumin against age-related disorders like Alzheimer's and Parkinson's diseases [18] which are directly linked to the relevant theme of protein aggregation.

2. General mechanism of fibrils formation by proteins and peptides

Protein aggregation is the process by which native proteins get misfolded and cling to each other to form structurally altered stacks of monomers often referred to as protein aggregates. On the basis of morphology and structural rearrangements, the protein aggregates are generally classified as amorphous or fibrillar. Amorphous aggregates include various types of assemblies without ordered intermolecular interactions and are common to most of the proteins [19]. The amorphous aggregation of proteins is associated with many phenomena, ranging from the formation of protein wine haze to the development of cataract in the eye lens and the precipitation of recombinant proteins during their expression and purification [20–22]. Also it is becoming increasingly apparent that it may be the prefibrillar aggregates, often amorphous, that are the most toxic species *in-vivo* than the fibrillar aggregates [23,24]. The protein aggregation leading to formation of insoluble structured fibrils is the most studied process and a generic property of proteins and peptides [25]. The fibrillar aggregates are commonly referred to as amyloid fibrils or simply, protein fibrils. The fibril is characterized by an extended cross-β structure and the ability to bind with specific dyes such as Thioflavin T (ThT) and Congo red (CR) [25,26]. From a biological point of view, the formation of extracellular amyloid fibrils, or intracellular inclusions is associated with a large number of human diseases. These include Alzheimer's disease, Parkinson's disease, Creutzfeld-Jakob disease and different types of amyloidoses [26]. Since these diseases affect millions of people every year, preventing aggregation is a public health priority. Curcumin is known to modulate protein fibril formation by binding to different monomeric and/or oligomeric species formed in the fibrillation pathway and by tailoring inter- and/or intramolecular interactions between polypeptides chains. Therefore, a thorough understanding of the curcumin-induced modulation of fibrillar aggregation is necessary to explain the underlying mechanism of amyloid-like fibril formation and to characterize various pathway(s) of the protein aggregation process [27].

2.1. Initiation of fibrillar aggregation

The fibrillar aggregation of both globular and intrinsically disordered proteins (IDPs) is known to cause many human diseases [26]. One of the key issues to elucidate the pathogenesis of protein deposition diseases is the process which initiates fibrillar aggregation. Till date, two ways are known which can trigger the onset of formation of fibrils from native proteins (Globular or IDPs)[16,18]. The formation of partially folded intermediates (PFI) is the most common mechanism to initiate the fibril formation [26,28,29]. The PFI is formed either by partial folding of IDPs or partial unfolding of globular proteins. Thus, the formation of PFI states requires a partial unfolding/folding of the native structure across the major free energy barrier for unfolding/folding. This unfolding/folding event leads to the exposure of aggregation-prone segments of the protein, which are capable of forming intermolecular interactions, thus triggering aggregation. The second mechanism of aggregation initiation is the interactions between different conformational states that are directly accessible from native states via thermal fluctuations [30]. Thermal fluctuations are random deviations of a native state from its average structure that is determined by X-ray crystallography. This means native state of a protein is in equilibrium with many native-like states. Many of these native-like states have high aggregation propensity. They stick to each other to form native-like aggregated species, which ultimately reorganize into amyloid-like fibrils [28,30]. The aggregation prone native-like states can either