CURRICULUM VITAE

Personal Details:

Name : **KRITI DUBEY SHARMA**
Date of Birth : 07 Oct 1985
Marital status : Married
Gender : Female
Current Address : A-319, Pragati Vihar Hostel, Lodhi Road, New Delhi (India)
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Academic Qualifications:

Ph. D.
Year : 2013-2017
Institute : Indian Institute of Technology Jodhpur, Rajasthan (India)
Subject : Protein Biophysics
Title of Thesis : Biophysical approach to develop inhibitors against protein aggregation

M. Tech.
Year : 2008-2010
Institute : Maulana Azad National Institute of Technology, Bhopal (M.P.)
Subject : Bioinformatics
CGPA : 9.34/10

B. Tech.
Year : 2004-2008
College/University : S.R.I.T.S. Datia (M.P.), Affiliated by R.G.P.V. Bhopal (M.P.)
Subject : Biotechnology
Percentage : 79.34%

Work Experience

DBT-Research Associateship (DBT-RA)
Year : 2020- present
Agency : DBT
Host Institute : Jawaharlal Nehru University, New Delhi (India)
Department : School of Life Science
Project Title : Designing nanoformulation for age-related bone pathology

National Post-Doctoral Fellow (NPDF-SERB)
Year : 2017- 2019
Agency : DST-SERB
Project Cost : INR 19,11,505
Host Institute : Jawaharlal Nehru University, New Delhi (India)
Department : School of Life Science
Project Title : Organized peptidic nanostructures as potential wound healing biomaterial

Assistant Professor

Year	: 2011-2013
Institute	: National Institute of Technology Jalandhar (India)
Department	: Department of Biotechnology

Research Interests

I am mainly interested in understanding the underlying principle of protein assemblies, especially which are associated with amyloid formation. I am also interested in investigating potential small molecules that can inhibit aggregation process in proteins that are related to sever pathologies. Beside this, I want to explore the phenomenon of protein aggregation to develop nanoscale devices/biomaterial which may be seems useful for future biomedical and social applications.

Experimental Tools/Techniques:

Experimental Systems	: Supramolecular-assemblies of proteins/peptides
Spectroscopic Techniques	: UV-Visible Spectroscopy, Fluorescence Spectroscopy, Circular Dichroism Spectroscopy
Microscopic Techniques	: Atomic Force Microscopy
Molecular Biology Techniques	: Polyacrylamide Gel Electrophoresis, *in vitro* cell culture
***In silico* Techniques**	: Molecular docking and simulation.

Academic achievements

- DBT-Research Associateship Awarded by Department of Biotechnology during January, 2020- December, 2021.
- National Post-Doctoral Fellowship Award, DST-Science and Engineering Research Board during 2017-2019.
- Senior Research Fellow (SRF), IIT Jodhpur during 2015-2017.
- Junior Research Fellow (JRF), IIT Jodhpur during 2013-2015.
- Student Trainee, BTISNET - Centre of Excellence**,** Apex Bioinformatics Center, DBT, New Delhi, during Dec-Jan, 2010.
- Second position holder in M.Tech. Bioinformatics, during 2008-2010.
- **Silver Medalist** for being **Second rank holder** in B.E. Biotechnology, RGPV Bhopal (India), 2009.

Research Publications

Published Manuscripts

1. ***Kriti Dubey*** and Karunakar Kar, **(2014)**. "Type I collagen prevents amyloid aggregation of hen egg white lysozyme." **Biochemical and Biophysical Research Communication.** 448, 480-484.

2. Sathaimurthi Perumal*, ***Kriti Dubey****, Rahul Badhwar, Kodimattah Joesph George, Rakesh Kumar Sharma, Ganesh Bagler, Balaraman Madhan, and Karunakar Kar. **(2015)**. "Capsaicin inhibits collagen fibril formation and increases the stability of collagen fibers." **European Biophysics Journal**. 76, 44-69. (*Equal contribution)

3. ***Kriti Dubey***, Bibin G. Anand, Mayur Temgire, and Karunakar Kar. **(2014).** "Evidence of rapid coaggregation of globular proteins during amyloid formation." **Biochemistry**. 53, 8001-8004.

4. ***Kriti Dubey***, Bibin G. Anand, Rahul Badhwar, Ganesh Bagler, P.N. Navya, Hemant Kumar Daima and Karunakar Kar. **(2015)**. "Tyrosine- and Tryptophan-coated gold nanoparticles inhibit amyloid aggregation of insulin." **Amino Acids**. 47(12), 2551-2560.

5. Bibin G Anand, ***Kriti Dubey***, Dolat Singh Shekhawat, and Karunakar Kar. **(2016).** "Capsaicin-coated silver nanoparticles inhibit amyloid fibril formation of serum albumin."**Biochemistry**. 55, 3345-3348.

6. ***Kriti Dubey***, Bibin G. Anand, Dolat Singh Shekhawat, and Karunakar Kar. **(2017).** "Eugenol prevents amyloid formation of proteins and inhibits amyloid-induced hemolysis." **Scientific Reports**. 7(40744).

7. Bibin G. Anand*, ***Kriti Dubey****,* Dolat Singh Shekhawat and Karunakar Kar. **(2017).** "Intrinsic property of phenylalanine to trigger protein aggregation and hemolysis has a direct relevance to phenylketonuria." **Scientific Reports.** 7(11146). (*Equal contribution)

8. Bibin G. Anand, Dolat Singh Shekhawat, ***Kriti Dubey*** and Karunakar Kar. **(2017). "**Uniform, polycrystalline, and thermostable piperine coated gold nanoparticles to target insulin fibril assembly." **ACS Biomaterials Science & Engineering.** 3(6), 1136-1145.

9. Bibin G. Anand, ***Kriti Dubey,*** Dolat Singh Shekhawat, Kailash Prasad Prajapati and Karunakar Kar. **(2017).** "Strategically designed antifibrotic gold nanoparticles to prevent collagen fibril formation." **Langmuir.** 33(46), 13252-13261.

10. Bibin G. Anand, Kailash Prasad Prajapati, ***Kriti Dubey***, Naseem Ahamad, Dolat Singh Shekhawat, Pramod Chandra Rath, Kodimattah Joesph George and Karunakar Kar. **(2019)** "Self-assembly of artificial sweetener aspartame yields amyloid-like cytotoxic nanostructures." **ACS Nano**. 13, 6033-6049.

11. Paramita Chaudhuri, Kailash P. Prajapati, Bibin G. Anand, ***Kriti Dubey***, Karunakar Kar. **(2019)**. "Amyloid cross-seeding raises new dimensions to understanding of amyloidogenesis mechanism". **Ageing Research Reviews.** 56:100937.

12. Kailash P. Prajapati, Akhilesh P. Singh, ***Kriti Dubey***, Masihuzzaman Ansari, Mayur Temgire, Bibin G. Anand, Karunakar Kar. **(2020)**. "Myricetin inhibits amyloid fibril formation of globular proteins by stabilizing the native structures". **Colloids and Surface B: Biointerfaces.** 186:110640.

Published Book Chapters

1. Karunakar Kar, Bibin G. Anand, ***Kriti Dubey***, and Dolat Singh Shekhawat. **(2019).** "Protein aggregation, related pathologies, and aging". Models, Molecules and Mechanisms in Biogerontology. **Springer Nature.**

List of Papers presented in Conferences:

1. ***Dubey, K.***, Pant, B., Pardasani, K.R., Amino acid based SVM for prediction of polyproteins of Dengue virus. **1st IFIP International Conference on Bioinformatics,** 2010, Sardar Vallabhbhai National Institute of Technology, Surat (India). (**Oral)**
2. ***Dubey, K.***, Kar, K., Co-aggregation and cross-seeding among globular proteins during amyloid formation, **Biotech Express,** Conference on Recent Advances in Biomedical Research: Strategies and Innovantion, SYSCON 2016, AIIMS, New Delhi (India). (**Oral)**
3. Anand B.G., ***Dubey, K.***, Shekhawat D.S., Kar, K., Targeting protein aggregation through nanoparticles based inhibitors. **National Science Day**, 2017, Jawaharlal Nehru University, New Delhi (India). (**Poster)**
4. **Nanobioteck- 2018, 3rd Annual Conference of ISNM**, 24th-27th Oct. 2018, AIIMS New Delhi (India). (Attended)

References

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Myricetin inhibits amyloid fibril formation of globular proteins by stabilizing the native structures

Kailash P. Prajapati[1], Akhilesh P. Singh[1] , Kriti Dubey[1], Masihuzzaman Ansari[1], Mayur Temgire[2], Bibin G. Anand[1†]*bibin.anand276@gmail.com and Karunakar Kar[1]* karunakarkar@gmail.com

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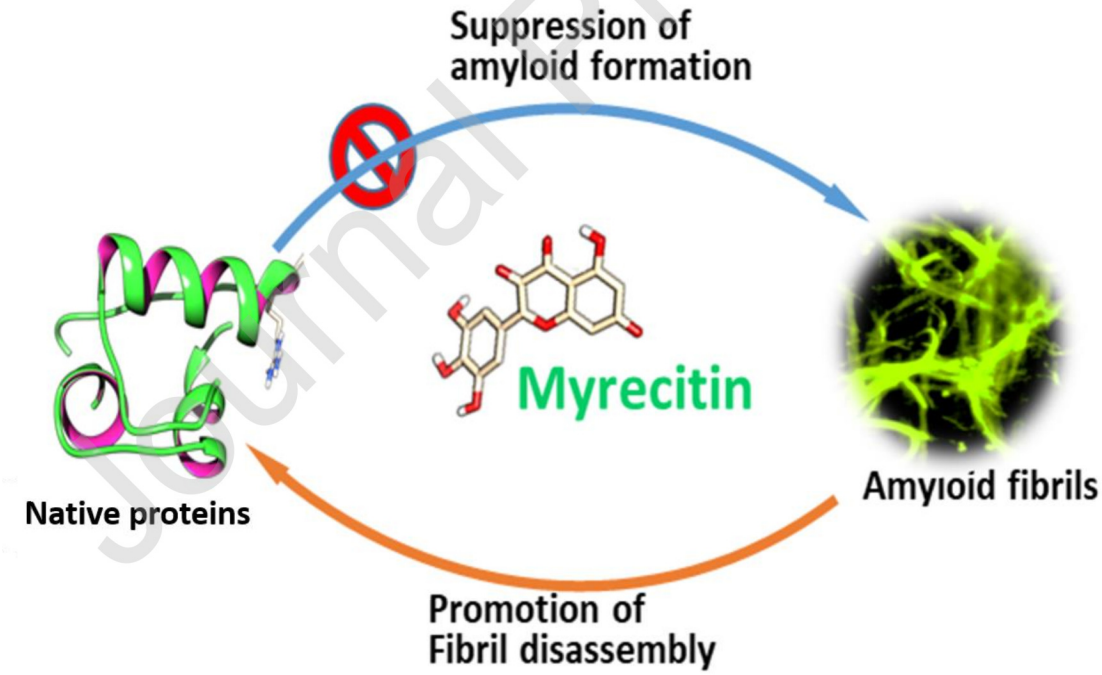
Graphical abstract



HIGHLIGHTS:

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ARTICLE

Self-Assembly of Artificial Sweetener Aspartame Yields Amyloid-like Cytotoxic Nanostructures

Bibin Gnanadhason Anand,[‡] Kailash Prasad Prajapati,[†] Kriti Dubey,[†] Naseem Ahamad,[†] Dolat Singh Shekhawat,[‡] Pramod Chandra Rath,[†] George Kodimattam Joseph,[‡] and Karunakar Kar*[,†]

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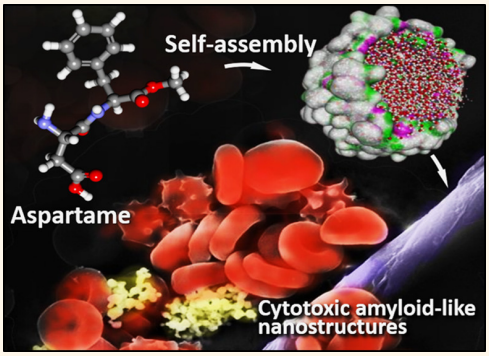
Supporting Information

ABSTRACT: Recent reports have revealed the intrinsic propensity of single aromatic metabolites to undergo self-assembly and form nanostructures of amyloid nature. Hence, identifying whether aspartame, a universally consumed artificial sweetener, is inherently aggregation prone becomes an important area of investigation. Although the reports on aspartame-linked side effects describe a multitude of metabolic disorders, the mechanistic understanding of such destructive effects is largely mysterious. Since aromaticity, an aggregation-promoting factor, is intrinsic to aspartame's chemistry, it is important to know whether aspartame can undergo self-association and if such a property can predispose any cytotoxicity to biological systems. Our study finds that aspartame molecules, under mimicked physiological conditions, undergo a spontaneous self-assembly process yielding regular *β*-sheet-like cytotoxic nanofibrils of amyloid nature. The resultant aspartame fibrils were found to trigger amyloid cross-seeding and become a toxic aggregation trap for globular proteins, A*β* peptides, and aromatic metabolites that convert native structures to *β*-sheet-like fibrils. Aspartame fibrils were also found to induce hemolysis, causing DNA damage resulting in both apoptosis and necrosis-mediated cell death. Specific spatial arrangement between aspartame molecules is predicted to form a regular amyloid-like architecture with a sticky exterior that is capable of promoting viable H-bonds, electrostatic interactions, and hydrophobic contacts with biomolecules, leading to the onset of protein aggregation and cell death. Results reveal that the aspartame molecule is inherently amyloidogenic, and the self-assembly of aspartame becomes a toxic trap for proteins and cells, exposing the bitter side of such a ubiquitously used artificial sweetener.



KEYWORDS: *aspartame, artificial sweetener, amyloid-like nanostructures, cross-seeding, amyloid aggregates, cytotoxicity*

Current evidence substantiates the propensity of single metabolites to undergo a self-assembly process that can yield toxic nanostructures of amyloid nature.[1−4] Since the aggregation-promoting factor aromaticity[5] is inherent to aspartame (Figure 1a), identifying whether this universally consumed artificial sweetener is inherently aggregation prone becomes an important area of inquiry. Aspartame is chemically recognized as a dipeptide consisting of aspartic acid and the methyl ester form of phenylalanine, and several reports based on *in vivo* studies have revealed diverse side effects of aspartame consumption (Table S1). The self-assembly of single aromatic metabolites such as phenylalanine and tyrosine has already been reported, and furthermore, it is observed that aromatic molecules, under physiological buffer conditions, can form amyloid structures that can effectively initiate amyloid cross-seeding, resulting in cytotoxic fibrils made up of proteins and metabolites.[1−4] Many studies have proposed direct links between neurophysiological symptoms and aspartame usage, suggesting that aspartame may be responsible for adverse neurobehavioral health issues,[6,7] most of which are also seen in amyloid-linked pathologies. Although a number of aspartame-linked adverse side effects[7−11] have been reported (Table S1), the fundamental mechanism that mediates these complications is poorly understood. Furthermore, it is also unknown whether such problems are arising from amyloid-linked consequences. It remains important to know whether aspartame is inherently amyloidogenic because recent reports have revealed phenylalanine's surprising ability to form hemolytic and cytotoxic

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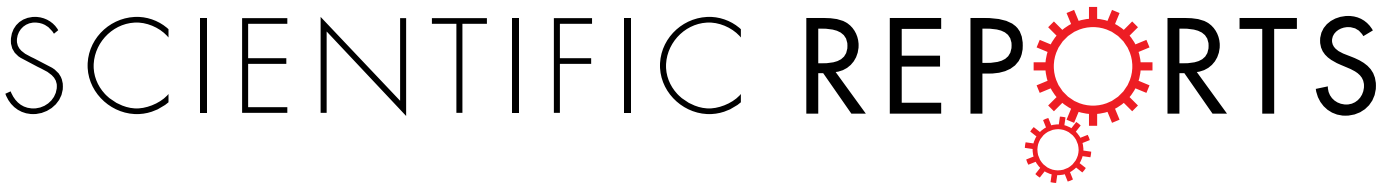

OPEN

Eugenol prevents amyloid formation of proteins and inhibits amyloid-induced hemolysis

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Kriti Dubey[1], Bibin G. Anand[1], Dolat Singh Shekhawat[1] & Karunakar Kar[1,2]

Eugenol has attracted considerable attention because of its potential for many pharmaceutical applications including anti-inflammatory, anti-tumorigenic and anti-oxidant properties. Here, we have investigated the effect of eugenol on amyloid formation of selected globular proteins. We find that both spontaneous and seed-induced aggregation processes of insulin and serum albumin (BSA) are significantly suppressed in the presence of eugenol. Isothermal titration calorimetric data predict a single binding site for eugenol-insulin complex confirming the affinity of eugenol for native soluble insulin species. We also find that eugenol suppresses amyloid-induced hemolysis. Our findings reveal the inherent ability of eugenol to stabilize native proteins and to delay the conversion of protein species of native conformation into β-sheet assembled mature fibrils, which seems to be crucial for its inhibitory effect.

Eugenol (4-Allyl-2-methoxyphenol) is a phenolic natural compound which has gained a lot of attention in recent years because of its versatile pharmacological applications[1] which include its anti-inflammatory, anti-tumorigenic and anti-oxidant properties[2]. Eugenol is mostly found in the essential oils extracted from clove, basil, cinnamon and bay leaf[3,4]. Eugenol is known to interact with different proteins as well as DNA molecules[5–7] and to influence their functional properties. Antiasthmatic effect of eugenol has been recently reported in a mouse model where eugenol was shown to influence Vitamin D3 upregulated protein 1/NF-κB pathway[8]. Recently, the inhibition effect of eugenol on key enzymes related to diabetes and hypertension[2] was reported in a study that involved both *in vitro* and *in vivo* model systems. Furthermore, it has been shown that eugenol suppresses the activity of Cl^- Channel TMEM16A[9].

Neuroprotective nature of eugenol has been already reported using both *in vitro* and cellular model systems[10,11]. Since eugenol has the potential to interact with a wide range of proteins and reports on the effect of eugenol on amyloid formation of proteins are limited in literature, the question of what effect eugenol would have on the amyloid formation of proteins stands very significant. Some studies on cell models, however, have indicated that eugenol can protect PC12 cells from toxic amyloids[12,13]. Further, eugenol is also known to suppress the occurrence of dopamine depression and lipid peroxidation inductivity, which are directly linked to Parkinson's disease[14]. Considering such neuroprotective nature of eugenol against toxic amyloids, elucidation of the effect of eugenol on amyloid formation of proteins becomes very important. The formation of amyloids is a fundamental process in biology and[15,16] more than 35 different proteins are known to be associated with several amyloid-linked diseases[16,17]. Targeting the onset of amyloid formation is considered to be one of the critical strategies to prevent amyloid linked diseases and its associated medical severities.

Here, we demonstrate the inhibition of temperature induced amyloid formation of two selected globular proteins, insulin and serum albumin (BSA), in the presence of eugenol. The process of amyloid formation of both insulin and serum albumin is known to cause many complications[18–21], and these globular proteins are also known to form amyloid fibrils under *in vitro* conditions[22–25]. The process of insulin aggregation is also a great concern for its storage as therapeutic agents[26,27]. Hence, we have selected these two proteins as convenient model systems to elucidate the anti-amyloid activity of eugenol. This study has mainly focused on two key issues. First, we have investigated eugenol's inhibitory effect on both spontaneous and seed-induced amyloid formation of proteins, under *in vitro* conditions. Second, we have explored the protective effect of eugenol on amyloid-induced

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SCIENTIFIC REPORTS

OPEN

Intrinsic property of phenylalanine to trigger protein aggregation and hemolysis has a direct relevance to phenylketonuria

Received: 2 May 2017
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Bibin G. Anand[2], Kriti Dubey[2], Dolat S. Shekhawat[2] & Karunakar Kar[1]

Excess accumulation of phenylalanine is the characteristic of untreated Phenylketonuria (PKU), a well-known genetic abnormality, which triggers several neurological, physical and developmental severities. However, the fundamental mechanism behind the origin of such diverse health problems, particularly the issue of how they are related to the build-up of phenylalanine molecules in the body, is largely unknown. Here, we show cross-seeding ability of phenylalanine fibrils that can effectively initiate an aggregation process in proteins under physiological conditions, converting native protein structures to β-sheet assembly. The resultant fibrils were found to cause severe hemolysis, yielding a plethora of deformed erythrocytes that is highly relevant to phenylketonuria. Unique arrangement of zwitterionic phenylalanine molecules in their amyloid-like higher order entities is predicted to promote both hydrophobic and electrostatic interaction, sufficient enough to trap proteins and to preferentially interact with the membrane components of RBCs. Since the prevalence of hemolysis and amyloid related psychoneurological severities are mostly observed in PKU patients, we propose that the inherent property of phenylalanine fibrils to trigger hemolysis and to induce protein aggregation may have direct relevance to the disease mechanism of PKU.

The multitude of health problems associated with phenylketonuria (PKU) includes disorders such as anemia, rickets, atopic dermatitis, coronary heart disease, diabetes mellitus and arthritis[1–3] (Supplementary data Table S1). Though several biologically relevant inherent properties of phenylalanine have been reported including its ability to generate β-sheet structured higher order entities and cytotoxic fibrils[4–8], the question of how these diverse PKU-linked severities arise from a single defect of uncontrolled build-up of phenylalanine in the blood remains largely unanswered. Since PKU symptoms include the occurrence of hemolysis[3] and the prevalence of amyloid-linked psychoneurological severities such as seizures, hyperactivity and mental retardation[9,10], it is very important to understand whether both amyloid fibril formation and hemolysis have any connection with the process of phenylalanine accumulation. We have attempted to gain insight into this fundamental question by testing whether phenylalanine fibrils would drive aggregation of globular proteins that are commonly found in the blood and by exploring what damaging effect such aggregation process would do to the RBCs whose abnormality is highly relevant to PKU.

Results

Formation of Phenylalanine fibrils in PBS at 37 °C. We generated phenylalanine fibrils by incubating ~6 mM of phenylalanine under physiological conditions of buffer and temperature[4]. The selection of this concentration was based on previous reports that have suggested the amyloid aggregation of Phenylalanine molecules under *in vitro* conditions[4,11,12]. Further, it has also been reported that millimolar concentration of phenylalanine can accumulate in the plasma, cerebrospinal fluid and brain tissue[13,14]. Significant rise in the fluorescence intensity of Thioflavin T, a dye that detects amyloid formation[15], and increase in the turbidity of the sample were observed (Fig. 1a,e), revealing the conversion of soluble phenylalanine molecules into self-assembled amyloid like

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ACS Biomaterials SCIENCE & ENGINEERING

Article

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Uniform, Polycrystalline, and Thermostable Piperine-Coated Gold Nanoparticles to Target Insulin Fibril Assembly

Bibin G. Anand,[‡] Dolat S. Shekhawat,[‡] Kriti Dubey,[‡] and Karunakar Kar*[,†]

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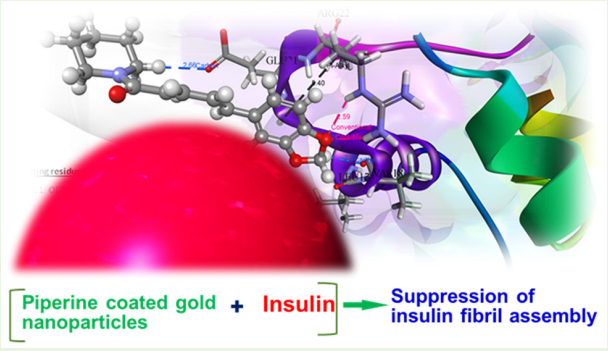
Supporting Information

ABSTRACT: Because the process of insulin fibril assembly is linked to a multitude of medical problems, finding effective and biocompatible inhibitors against such an aggregation process could be beneficial. Targeting the aggregation-prone residues of insulin may perhaps work as an effective strategy to prevent the onset of insulin fibril assembly. In this work, we have synthesized uniform sized, thermostable gold nanoparticles ($AuNPs^{piperine}$) surface-functionalized with piperine to target amyloid-prone residues of insulin. We found that the process of both spontaneous and seed-induced amyloid formation of insulin was strongly inhibited in the presence of $AuNPs^{piperine}$. Surface functionalization of piperine was found to be critical to its inhibition effect because no such effect was observed for free piperine as well as for uncoated control gold nanoparticles. Fluorescence quenching data revealed binding of $AuNPs^{piperine}$ with insulin's native structure which was further validated by docking studies that predicted viable H-bond and CH-π interactions between piperine and key aggregation-prone residues of insulin's B-chain. Our hemolysis assay studies further confirmed that these piperine coated nanoparticles were hemocompatible. Data obtained from both experimental and computational studies suggest that the retention of native structure of insulin and the ability of the piperine molecule to interact with the aggregation-prone residues of insulin are the key factors for the inhibition mechanism. The findings of this work may help in the development of nanoparticle-based formulations to prevent medical problems linked to insulin aggregation.



KEYWORDS: *piperine, gold nanoparticles, insulin, amyloids, thioflavin T, hemocompatible*

1. INTRODUCTION

The process of amyloid fibril formation of proteins is considered as one of the foundational events that trigger the onset of a number of pathologies including several neurodegenerative diseases.[1,2] About 40 amyloidogenic proteins have been identified to be responsible for several diseases such as Aβ-linked Alzheimer's disease, huntingtin-linked Huntington's disease, and α-synuclein-linked Parkinson's disease.[3] Aggregation of normal functional proteins such as insulin into amyloid fibrils has also been reported to cause many medical severities.[4−6] Insulin fibril assembly is known to be directly linked to type 2 diabetes.[7] The storage of insulin as therapeutic agent is also a big concern because of the tendency of insulin molecules to form toxic amyloid aggregates.[8,9] Formation of amyloid like aggregates of insulin has been reported in the artery walls located at the site of injection.[6] Hence, one of the effective strategies to target these aggregation linked severities could be the prevention of the process of protein aggregation. Successful designing of effective inhibitors of protein aggregation process has gained much attention in recent years. Several candidates including single molecules, amino acids, natural compounds, peptides, and proteins have been reported to act as inhibitors of amyloid fibril formation of different proteins.[8,10−15] Over the past decade much research has also focused on the surface functionalization of metallic nanoparticles with potential compounds to target amyloid formation of proteins.[15−18] Different properties of the nanoparticles, such as their size and thermal stability as well as their biocompatibility, are considered as critical factors for their inhibition effect against amyloid fibril formation of proteins.[19−22] Few studies of our group under in vitro conditions have found that the antiamyloid activity of inhibitors is greatly enhanced when these inhibitor molecules are surface functionalized with the nanoparticles.[15,23]

On the basis of this information, we chose piperine, a natural compound known for its multiple health benefits (see Table S1), to target the process of insulin fibril assembly. The piperine molecule has a unique structure (Figure 1a), which is already known to interact with proteins and DNA molecules through viable H-bonds mediated through its C═O and −O− functional groups.[24−27] Formation of strong H-bonds between piperine and

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