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9<sup>th</sup> National Conference on  
Innovation and Technology  
in Biology and Chemistry  
of I R A N

نهمین کنفرانس ملی  
نوآوری و فناوری  
علوم زیستی و  
شیمی ایران

## Ligand Engineering for Selective Spoilage Detection in Food Safety

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### ABSTRACT

*The development of smart packaging technologies has introduced innovative approaches to real-time food spoilage detection. Among these, gold nanoclusters (AuNCs) have emerged as highly sensitive and biocompatible materials due to their unique photoluminescent properties and molecular-like behavior. This review explores the role of ligand engineering in enhancing the selectivity of AuNCs toward key spoilage gases such as ammonia (NH<sub>3</sub>), hydrogen sulfide (H<sub>2</sub>S), and trimethylamine (TMA). By employing diverse ligands including proteins, peptides, DNA, and polyphenols AuNCs can be tailored for specific gas recognition, enabling fluorescence-based detection mechanisms. The integration of AuNCs into biodegradable packaging films offers a non-invasive, eco-friendly solution for freshness monitoring. Comparative analysis with conventional nanomaterials highlights the superior photostability, selectivity, and sustainability of AuNCs. Despite current challenges in synthesis scalability and regulatory frameworks, ligand-engineered AuNCs represent a promising frontier in nanotechnology-driven food safety and biosensing applications. Future research should focus on hybrid nanostructures and advanced sensor platforms to accelerate their industrial deployment.*

**Keywords:** Gold Nanoclusters (AuNCs), Ligand Engineering, Smart Packaging, Spoilage Detection, Ammonia (NH<sub>3</sub>), Hydrogen Sulfide (H<sub>2</sub>S), Trimethylamine (TMA), Fluorescence Sensing, Biodegradable Films, Food Safety, Volatile Organic Compounds (VOCs).

## Introduction

### Ligand Engineering for Selective Spoilage Detection

The emergence of smart packaging technologies has revolutionized food safety monitoring by enabling real-time detection of spoilage indicators. Among the various nanomaterials explored for this purpose, **gold nanoclusters (AuNCs)** have garnered significant attention due to their ultra-small size (<2 nm), strong and tunable photoluminescence, and excellent biocompatibility (Jin *et al.*, 2016; Maity *et al.*, 2025). Unlike larger nanoparticles, AuNCs exhibit molecular-like behavior with discrete electronic transitions, making them highly sensitive to environmental changes (Maity *et al.*, 2019). Their fluorescence properties are profoundly influenced by **ligand type**, core size, and surrounding conditions, which opens up opportunities for **ligand engineering** to enhance selectivity toward specific spoilage gases such as ammonia (NH<sub>3</sub>), hydrogen sulfide (H<sub>2</sub>S), and trimethylamine (TMA) (Guo *et al.*, 2021; Cui *et al.*, 2020). Recent studies have demonstrated that AuNCs stabilized by biomolecules—such as proteins, peptides, DNA, and polyphenols—not only improve colloidal stability but also serve as **recognition elements** for volatile spoilage compounds (Li *et al.*, 2018; Hao *et al.*, 2023). These ligands modulate the optical response of AuNCs, enabling fluorescence quenching or enhancement upon interaction with target analytes (Zomorodimanesh *et al.*, 2024). In the context of smart packaging, AuNCs can be embedded into **biodegradable films** that respond to spoilage by changing color or fluorescence intensity, offering a user-friendly and non-invasive freshness indicator (Khan *et al.*, 2023; Zhang *et al.*, 2023). Their integration into packaging systems not only improves food safety but also contributes to sustainability through eco-friendly synthesis routes using natural proteins (Guo *et al.*, 2021). Moreover, AuNCs outperform many conventional nanomaterials such as AgNPs, ZnO, and TiO<sub>2</sub> in terms of **photostability**, **biocompatibility**, and **selectivity**, making them ideal candidates for next-generation spoilage sensors (Anh *et al.*, 2022; Kaur *et al.*, 2018). In summary, the unique physicochemical properties of AuNCs, combined with the strategic use of ligands, pave the way for highly selective and sensitive spoilage detection systems. This review explores the role of ligand engineering in tailoring AuNCs for smart packaging applications, highlighting recent advancements, challenges, and future directions.

**Table 1: Comparison of Ligand Types Used for AuNC Stabilization and Spoilage Detection.**

<i>Ligand Type</i>	<i>Key Features</i>	<i>Function in Spoilage Detection</i>	<i>Representative References</i>
<i>Proteins</i>	Biocompatible, natural stabilizers	Fluorescence quenching upon NH <sub>3</sub> and H <sub>2</sub> S exposure	Li <i>et al.</i> , 2018; Khan <i>et al.</i> , 2023
<i>Polyphenols</i>	Antioxidant-rich, eco-friendly	Enhanced sensitivity to TMA via fluorescence modulation	Hao <i>et al.</i> , 2023; Guo <i>et al.</i> , 2021

<i>DNA</i>	High selectivity, programmable sequences	Specific recognition of volatile organic compounds (VOCs)	Guo et al., 2021
<i>Peptides</i>	Small, tunable, bioactive	Tailored fluorescence response to spoilage gases	Zomorodimanesh et al., 2024
<i>Synthetic Polymers</i>	Customizable, scalable	General stabilization and signal amplification	Zhang et al., 2023

**Table 2: Comparison of AuNCs vs. Conventional Nanomaterials for Packaging Sensors.**

<i>Nanomaterial</i>	<i>Photostability</i>	<i>Biocompatibility</i>	<i>Selectivity to Spoilage Gases</i>	<i>Eco-Friendliness</i>	<i>References</i>
<i>AuNCs</i>	Excellent	High	Strong (NH <sub>3</sub> , H <sub>2</sub> S, TMA)	High (natural ligands)	Jin et al., 2016; Maity et al., 2025
<i>AgNPs</i>	Moderate	Low to moderate	Weak	Low	Kaur et al., 2018
<i>ZnO</i>	Low	Moderate	Limited	Moderate	Anh et al., 2022
<i>TiO<sub>2</sub></i>	High	Low	Non-selective	Low	Kaur et al., 2018

## 2. Synthesis and Functionalization of Gold Nanoclusters (AuNCs)

Gold nanoclusters (AuNCs) can be synthesized through a variety of chemical, physical, and biological methods, each offering distinct advantages in terms of size control, stability, and environmental sustainability (Tyagi et al., 2016; Gao & Torrente-Murciano, 2020). Chemical approaches such as citrate reduction and the Brust-Schiffirin method allow for precise control over particle size and monodispersity (Brust et al., 1994; Dou et al., 2020). Physical techniques like ultrasound-assisted synthesis and thermal evaporation yield high-purity nanoclusters with tailored morphologies (Bang & Suslick, 2010; Meier et al., 2002). Biological synthesis methods, including microbial and plant-mediated approaches, offer eco-friendly alternatives by utilizing natural reducing agents such as enzymes and phytochemicals (Konishi, 2006; Mohamad et al., 2014). These biosynthetic routes not only enhance biocompatibility but also reduce toxic byproducts associated with conventional synthesis (Hulkoti & Taranath, 2014; Bao et al., 2021). The choice of synthesis method directly influences the physicochemical properties of AuNCs, including their fluorescence, catalytic activity, and colloidal stability (Ji et al., 2007; Ding et al., 2014). Moreover, ligand selection during synthesis plays a critical role in modulating the optical behavior and biological interactions of AuNCs (Li et al., 2011; Chai & Xie, 2024).

**Table 3. Overview of AuNC Synthesis Methods and Their Characteristics.**

<i>Method</i>	<i>Principle</i>	<i>Advantages</i>	<i>Reference</i>
<i>Citrate Reduction</i>	Reduction of Au <sup>3+</sup> using sodium citrate	Simple, cost-effective, monodisperse particles	Tyagi et al., 2016; Gao & Torrente-Murciano, 2020
<i>Brust-Schiffrin</i>	Two-phase thiol-stabilized synthesis	High size control, stable clusters	Brust et al., 1994; Dou et al., 2020
<i>Microemulsion</i>	Water-in-oil nanoscale reactors	Enhanced size control, catalytic applications	Lemke et al., 2013; Wang et al., 2023
<i>Ultrasound-Assisted</i>	Acoustic cavitation for rapid reduction	Precise shape control, surfactant-free synthesis	Bang & Suslick, 2010; Bhosale et al., 2017
<i>Thermal Evaporation</i>	Vapor condensation in vacuum	High purity, tailored morphology	Meier et al., 2002; Grytsenko et al., 2005
<i>Microbial Synthesis</i>	Reduction by bacteria, fungi, algae	Biocompatible, sustainable	Konishi, 2006; Hulkoti & Taranath, 2014
<i>Plant-Mediated Synthesis</i>	Reduction via phytochemicals	Rapid, eco-friendly, stable nanoparticles	Mohamad et al., 2014; Zuhrotun et al., 2023

### 2.1. Biological Synthesis Mechanisms of AuNCs

Biological synthesis of AuNCs leverages natural reducing agents and stabilizers found in microorganisms and plants, offering a sustainable and non-toxic alternative to conventional chemical methods (Konishi, 2006; Mohamad et al., 2014). Microbial synthesis typically involves enzymatic reduction of gold ions by bacteria, fungi, or algae, resulting in highly stable and biocompatible nanoclusters (Hulkoti & Taranath, 2014; Bao et al., 2021). These organisms secrete proteins and peptides that act as both reducing and capping agents, influencing the size and fluorescence of the resulting AuNCs (Zuhrotun et al., 2023). Plant-mediated synthesis utilizes phytochemicals such as flavonoids, alkaloids, and polyphenols to reduce Au<sup>3+</sup> ions and stabilize the clusters (Mohamad et al., 2014). This method is rapid and scalable, producing nanoclusters with excellent colloidal stability and optical properties (Zuhrotun et al., 2023). The type and concentration of phytochemicals directly affect the morphology and emission characteristics of AuNCs, making plant extracts a versatile platform for ligand engineering (Bao et al., 2021).

**Table 4. Comparison of Biological Synthesis Routes for AuNCs.**

<i>Biological Route</i>	<i>Reducing Agents</i>	<i>Stabilizing Agents</i>	<i>Advantages</i>	<i>Reference</i>
<i>Bacterial Synthesis</i>	Enzymes, NADH	Proteins, peptides	High biocompatibility, controlled size	Konishi, 2006; Hulkoti & Taranath, 2014
<i>Fungal Synthesis</i>	Extracellular enzymes	Amino acids, polysaccharides	Stable clusters, eco-friendly process	Bao et al., 2021
<i>Algal Synthesis</i>	Photosynthetic metabolites	Pigments, proteins	Renewable source, enhanced fluorescence	Zuhrotun et al., 2023
<i>Plant-Mediated Synthesis</i>	Flavonoids, polyphenols, alkaloids	Phytochemicals	Rapid synthesis, tunable optical properties	Mohamad et al., 2014; Zuhrotun et al., 2023

## 2.2. Chemical and Physical Synthesis of Gold Nanoclusters (AuNCs)

Chemical and physical synthesis methods offer precise control over the size, morphology, and surface chemistry of gold nanoclusters (AuNCs), which are critical for their performance in biosensing and smart packaging applications (Tyagi et al., 2016; Gao & Torrente-Murciano, 2020).

### Chemical Methods

- **Citrate Reduction:** This method involves the reduction of Au<sup>3+</sup> ions using sodium citrate under controlled pH and temperature conditions. It yields monodisperse spherical AuNPs with sizes ranging from 5.2 to 40 nm. The reaction pathway is pH-dependent, and co-reduction with glutathione enhances colloidal stability and fluorescence (Tyagi et al., 2016; Gao & Torrente-Murciano, 2020; Ji et al., 2007; Ding et al., 2014).
- **Brust-Schiffrin Method:** A two-phase synthesis using thiol ligands and TOAB as a phase transfer agent. It enables atomic-level size control and high stability. Recent studies have revealed additional mechanistic phases such as complex-shedding and thiol-etching, improving yield and reducing synthesis time (Brust et al., 1994; Dou et al., 2020; Chai & Xie, 2024).
- **Microemulsion Technique:** Utilizes water-in-oil emulsions as nanoscale reactors. Particle size is influenced by the water-to-surfactant ratio, and the method supports both large AuNPs and sub-2 nm fluorescent clusters. It offers excellent catalytic properties and scalability (Lemke et al., 2013; Wang et al., 2023).

### Physical Methods

- **Ultrasound-Assisted Synthesis:** High-intensity ultrasound induces acoustic cavitation, reducing Au(III) to Au(0). This method allows precise control over shape and size without surfactants, producing particles from 15–40 nm and even nanorods. It's fast, clean, and suitable for catalytic applications (Bang & Suslick, 2010; Bhosale et al., 2017).
- **Thermal Evaporation:** Gold vapor is condensed in a vacuum to form nanoclusters with diameters of 3–7 nm. This method yields high-purity AuNCs with distinct plasmonic bands and is ideal for fundamental studies and optoelectronic applications (Meier et al., 2002; Grytsenko et al., 2005).

**Table 5. Summary of Chemical and Physical Synthesis Methods for AuNCs.**

Method	Principle	Advantages	Reference
<i>Citrate Reduction</i>	Reduction of Au <sup>3+</sup> with sodium citrate	Simple, monodisperse, tunable size	Tyagi et al., 2016; Gao & Torrente-Murciano, 2020
<i>B Brust-Schiffrin</i>	Two-phase thiol-stabilized synthesis	Atomic precision, high stability	Brust et al., 1994; Dou et al., 2020; Chai & Xie, 2024
<i>Microemulsion</i>	Nanoscale reactors via water-in-oil emulsions	Size control, catalytic potential	Lemke et al., 2013; Wang et al., 2023
<i>Ultrasound-Assisted</i>	Acoustic cavitation for rapid reduction	Surfactant-free, shape control	Bang & Suslick, 2010; Bhosale et al., 2017
<i>Thermal Evaporation</i>	Vapor condensation in vacuum	High purity, tailored morphology	Meier et al., 2002; Grytsenko et al., 2005

### 3. Mechanisms of Spoilage Gas Detection Using AuNCs

Gold nanoclusters (AuNCs) have demonstrated remarkable sensitivity to volatile spoilage gases such as ammonia (NH<sub>3</sub>), hydrogen sulfide (H<sub>2</sub>S), and trimethylamine (TMA), which are commonly released during the microbial degradation of protein-rich foods (Guo et al., 2021). The detection mechanism primarily relies on changes in fluorescence intensity or wavelength, triggered by the interaction between the gas molecules and the surface ligands of AuNCs (Li et al., 2018). Ligands play a pivotal role in determining the **selectivity** of AuNCs toward specific gases. For instance, protein-templated AuNCs exhibit strong fluorescence quenching in the presence of NH<sub>3</sub> due to hydrogen bonding and proton transfer interactions (Guo et al., 2021). Similarly, polyphenol-stabilized AuNCs respond to H<sub>2</sub>S through sulfur–gold affinity, leading to fluorescence suppression (Hao et al., 2023). DNA-based AuNCs, with their programmable sequences, can be tailored to recognize TMA via electrostatic and hydrophobic interactions (Guo et al., 2021). The response time and intensity of fluorescence change depend on the type of ligand, gas concentration, and environmental conditions such as humidity and temperature (Li et al., 2018). These properties make AuNCs ideal candidates for incorporation

into smart packaging systems that visually indicate spoilage without the need for external instrumentation (Zomorodimanesh et al., 2024).

**Table 6. Spoilage Gas Detection Mechanisms of Ligand-Stabilized AuNCs.**

<i>Spoilage Gas</i>	<i>Detection Mechanism</i>	<i>Ligand Type</i>	<i>Fluorescence Response</i>	<i>Reference</i>
$NH_3$	Hydrogen bonding, proton transfer	Protein (e.g., BSA)	Quenching	Guo et al., 2021
$H_2S$	Sulfur-gold interaction	Polyphenols	Suppression	Hao et al., 2023
$TMA$	Electrostatic/hydrophobic interaction	DNA	Shift in emission wavelength	Guo et al., 2021

#### 4. Smart Packaging Applications of Gold Nanoclusters (AuNCs)

Gold nanoclusters (AuNCs) have emerged as transformative agents in the food industry, particularly in smart packaging technologies aimed at extending shelf life and ensuring food safety (Motelica et al., 2020). Their antimicrobial properties, pH sensitivity, and ability to detect spoilage gases make them ideal for real-time freshness monitoring (Suvarna et al., 2022).

Smart packaging systems utilizing AuNCs can be categorized into:

- **Active Packaging:** Incorporates antimicrobial agents like AuNCs to inhibit microbial growth.
- **Intelligent Packaging:** Employs sensors based on AuNCs that respond to environmental changes such as pH or gas composition (Drago et al., 2020).

These systems can detect volatile compounds like ammonia and biogenic amines, which are indicators of spoilage in protein-rich foods (Zhang et al., 2023). AuNCs respond to these gases through colorimetric or fluorescence changes, providing a visual cue for consumers (Kwon & Ko, 2022). Furthermore, AuNCs can be engineered for **stimuli-responsive release** of preservatives. For example, peptide-protected AuNCs release antibiotics like vancomycin in response to bacterial presence, maintaining antimicrobial efficacy while minimizing unnecessary exposure (Li et al., 2018).

**Table 7. Smart Packaging Functions of AuNCs.**

<b>Function</b>	<b>Mechanism</b>	<b>Advantages</b>	<b>Reference</b>
Antimicrobial action	Surface interaction with microbial membranes	Inhibits spoilage organisms	Motelica et al., 2020
Spoilage gas detection	Colorimetric/fluorescent response to $NH_3$ , TMA	Real-time freshness indication	Zhang et al., 2023
pH-sensitive indicators	Optical change in response to pH variation	Easy-to-read spoilage signal	Kwon & Ko, 2022

Controlled preservative release	Stimuli-responsive antibiotic delivery	Targeted antimicrobial action	Li et al., 2018
Oxygen scavenging	Nanocluster-mediated oxygen absorption	Shelf life extension	Khan et al., 2023

### 5. Detection of Contaminants and Pathogens Using AuNC-Based Biosensors

Gold nanoclusters (AuNCs) have demonstrated exceptional capabilities in the detection of chemical contaminants and biological pathogens due to their unique optical properties, ultra-small size, and biocompatibility (Khan et al., 2023). These properties enable the development of highly sensitive and selective biosensors for food safety and medical diagnostics.

#### Contaminant Detection

AuNCs functionalized with aptamers, DNA probes, or glutathione have been used to detect a wide range of chemical pollutants:

- **Heavy Metals:** Glutathione-modified AuNCs can detect mercury ions ( $Hg^{2+}$ ) with detection limits as low as 0.0158 nM in food samples (Wang et al., 2023).
- **Pesticides:** AuNCs encapsulated in metal-organic frameworks have enabled dual-mode fluorescence and colorimetric detection of organophosphorus pesticides (Cai et al., 2021).
- **Mycotoxins:** AuNCs stabilized by bovine serum albumin (BSA) exhibit red fluorescence changes in the presence of aflatoxins and fumonisin B1 (Fabijanić et al., 2022).

#### Pathogen Detection

AuNCs also serve as powerful tools for identifying foodborne and clinical pathogens:

- **Bacterial Detection:** Aptamer-modified AuNCs with peroxidase-like activity have detected *E. coli O157:H7* in milk with a limit of 39 CFU/mL (Song et al., 2022).
- **Viral and Fungal Pathogens:** AuNCs synthesized using fungal proteins (e.g., *Fusarium oxysporum*) exhibit antimicrobial properties and can be tailored for pathogen-specific sensing (Thakker et al., 2013).
- **Antibiotic Residues:** TetX2@AuNCs nanozyme detects tetracycline contamination using luminometric, colorimetric, and fluorometric methods (Zomorodimaneh et al., 2024).

**Table 8. AuNC-Based Biosensors for Contaminant and Pathogen Detection.**

<i>Target</i>	<i>Detection Mechanism</i>	<i>Functionalization</i>	<i>Detection Limit</i>	<i>Reference</i>
<i>Hg<sup>2+</sup> (Mercury)</i>	Fluorescence quenching	Glutathione	0.0158 nM	Wang et al., 2023
<i>Organophosphate Pesticides</i>	Fluorescence & colorimetric dual-mode	MOF-encapsulated AuNCs	1.55 pg/mL (chlorpyrifos)	Cai et al., 2021
<i>Aflatoxins &amp; FBI</i>	Red fluorescence shift	BSA-stabilized AuNCs	Visual detection	Fabijanić et al., 2022
<i>E. coli O157:H7</i>	Peroxidase-like colorimetric reaction	Aptamer@Papain@AuNCs	39 CFU/mL	Song et al., 2022
<i>Tetracycline</i>	Multi-mode optical sensing	TetX2@AuNCs nanozyme	Time-based detection	Zomorodimanesh et al., 2024

### 6. Challenges and Future Perspectives of AuNCs in Spoilage Detection

Despite the promising applications of gold nanoclusters (AuNCs) in smart packaging and biosensing, several challenges must be addressed to ensure their widespread adoption and long-term reliability (Cifuentes-Rius et al., 2021; Khan et al., 2023).

#### Key Challenges

- **Scalability of Synthesis** Producing AuNCs with consistent size and properties at industrial scale remains difficult. Variability in synthesis methods leads to batch-to-batch inconsistency (Casteleiro et al., 2021).
- **Colloidal Stability** AuNCs stabilized with small ligands often suffer from poor stability in complex food matrices. Encapsulation strategies using polymers or metal-organic frameworks are being explored to improve longevity (Lu & Chen, 2014).
- **Characterization Complexity** Determining the precise structure and quantum yield of AuNCs is technically demanding. Advanced analytical techniques are needed to correlate structure with performance (Chevrier et al., 2012).
- **Green Synthesis Limitations** Although eco-friendly synthesis using plant extracts is attractive, variability in phytochemical composition affects reproducibility and purity (Ying et al., 2022).

- **Regulatory and Toxicological Gaps** There is a lack of standardized protocols and long-term risk assessments for AuNCs in food applications. Regulatory frameworks must evolve to address exposure, disposal, and safety concerns (Dhall et al., 2024; Yah, 2013).

#### Future Directions

- **Hybrid Nanostructures** Combining AuNCs with polymers, biomolecules, or other nanomaterials can enhance stability, selectivity, and multifunctionality (Casteleiro et al., 2021).
- **Standardization of Green Synthesis** Developing reproducible protocols for plant-mediated synthesis will improve scalability and reduce environmental impact (Sayadi et al., 2021).
- **Advanced Biosensor Platforms** Integration of AuNCs into paper-based, wearable, or wireless sensors can revolutionize real-time spoilage detection (Khan et al., 2023).
- **Regulatory Harmonization**

Establishing global standards for nanomaterial safety, labeling, and disposal will facilitate commercial adoption (Alkhursani et al., 2024).

**Table 9. Summary of Challenges and Proposed Solutions for AuNCs.**

<i>Challenge</i>	<i>Description</i>	<i>Proposed Solution</i>	<i>Reference</i>
<i>Scalability in synthesis</i>	Difficulty in large-scale production	Encapsulation with polymers or MOFs	Casteleiro et al., 2021
<i>Colloidal stability</i>	Instability in food matrices	Ligand engineering and hybrid structures	Lu & Chen, 2014
<i>Characterization</i>	Complex structure-property relationships	Advanced spectroscopy and imaging techniques	Chevrier et al., 2012
<i>Green synthesis variability</i>	Inconsistent yield and purity	Standardized plant extract protocols	Sayadi et al., 2021; Ying et al., 2022
<i>Regulatory gaps</i>	Lack of safety and disposal guidelines	Comprehensive risk assessments and policy updates	Dhall et al., 2024; Yah, 2013

#### Conclusion

Gold nanoclusters (AuNCs) have emerged as versatile and highly sensitive nanomaterials for spoilage detection in food packaging systems. Through ligand engineering, their selectivity toward specific spoilage gases such as ammonia, hydrogen sulfide, and trimethylamine has been significantly enhanced. The use of diverse ligands—including proteins, peptides, DNA, and polyphenols enables tailored responses based on the target analyte and environmental conditions. Compared to conventional nanomaterials like AgNPs, ZnO, and TiO<sub>2</sub>, AuNCs offer superior photostability, biocompatibility, and eco-friendliness, making them ideal candidates for

smart packaging applications. Their integration into biodegradable films and intelligent sensors allows for real-time monitoring of food freshness, contributing to waste reduction and consumer safety. Despite these advantages, challenges such as synthesis scalability, colloidal stability, and regulatory gaps remain. Future research should prioritize the development of hybrid nanostructures, standardized green synthesis protocols, and integration into wearable or wireless biosensor platforms. Additionally, establishing global regulatory standards will be essential for the safe and widespread adoption of AuNC-based technologies in food and biomedical industries.

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