Journal of Metals, Materials and Minerals, 34(4), 2145, 2024

Recent advances in synthesis and bio-applications of natural stabilizers for metal nanoparticles

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Received date:
9 Setember 2024
Revised date:
4 November 2024
Accepted date:
27 November 2024

Keywords:
Metal nanoparticles;
Natural stabilizer;
Cellulose;
Alginate;
Starch

Abstract

Due to their exceptional physicochemical properties, the synthesis and application of metal nanoparticles gained significant traction and a grip in industries and scientific fields or regions. However, the thermodynamic instability of metal nanoparticles poses or leads to challenges in their controlled synthesis and stabilization. To address this stability and the immobilization strategies, natural polymers such as cellulose, starch, alginate, chitosan, and hyaluronic acid have been explored for their non-toxic, biodegradable, and environmentally friendly characteristics. Recent advances in nanotechnology have led to an increased focus on these natural polymer's utilization as effective stabilizers for diverse metal nanoparticles. This review comprehensively examines recent advances in utilizing these natural polymers as stabilizers for metal nanoparticles. Synthesis methods, stabilization mechanisms, and applications spanning catalysis, sensing, drug delivery, and biomedical imaging are discussed. Challenges such as scalability and reproducibility are addressed, alongside future directions for research and development. In this review, our goal is to encourage continued research and creativity in sustainable nanomaterials. By doing so, we hope to advance the development of adaptable and environmentally friendly nanoparticles that find applications across various industries.

1. Introduction

In recent years, the synthesis and application of metal nanoparticles (MNPs) have gathered significant attention in various scientific and industrial domains because of their unique physicochemical properties [1,2]. MNPs exhibit thermodynamic instability, leading to a propensity or a tendency for aggregation as they seek to minimize their surface area, ultimately causing a substantial decline in catalytic activities [3,4]. However, the controlled synthesis and stabilization of metal NPs remain critical challenges to tackle their full potential [5,6]. To address this challenge, the strategy of immobilization and stability of MNPs emerges as a promising approach [7].

In the past few years, various solid substrates, including magnetic materials, silica, and carbon nanotubes, have been developed to stabilize MNPs, with their applicability in catalytic systems being extensively explored [8,9]. Among these support materials, polysaccharides have garnered greater focus compared to their synthetic alternatives because of their non-toxic, biodegradable, cost-effective, as well as eco-friendly characteristics [10,11]. Furthermore, the exploration of envirnmentally friendly and sustainable materials to synthesize and stabilize MNPs has gained noteworthy momentum [12,13]. The escalating concerns over the environmental impact and toxicity associated with traditional stabilizers have prompted researchers to shift their focus toward the implementation of biocompatible and biodegradable materials [14]. Among these, cellulose, alginate, starch, chitosan, and hyaluronic acid have emerged as promising candidates owing to their inherent properties such as abundance, biocompatibility, and facile processability [15,16].

Cellulose, an universal polysaccharide found in plant cell walls, has garnered attention for its exceptional mechanical strength and biodegradability [17]. Alginate, derived from brown seaweeds and bacterial sources, possesses a unique gel-forming ability, making it a versatile stabilizer for metal nanoparticles [18]. Starch, another widely available polysaccharide, offers a cost-effective and sustainable alternative due to its renewable nature and ease of modification [19,20]. Chitosan, derived from chitin, the second most common natural polymer, has attracted considerable interest because of its antimicrobial properties and film-forming capabilities. Hyaluronic acid as a main constituent of extra-cellular matrix in animals, offers excellent biocompatibility and water retention properties [21].

In the pursuit of sustainable nanomaterials, researchers have developed various synthesis strategies that support the unique properties of cellulose, alginate, starch, chitosan, and hyaluronic acid [22]. The synthesis methods enclose a spectrum of techniques, including green synthesis routes, co-precipitation, electrochemical methods, and template-assisted approaches. These methods ensure the controlled synthesis of metal nanoparticles and facilitate the functionalization of natural polymers for enhanced stability and modified properties [15]. Understanding the stabilization mechanisms underlying the

interactions between these natural polymers and metal nanoparticles is crucial for optimizing their performance [23]. Cellulose, for instance, exhibits strong affinity through its hydroxyl groups, providing an effective stabilizing environment for metal nanoparticles [24]. Alginate, with its carboxyl groups, forms stable coordination complexes with metal ions, preventing particle aggregation. Starch, chitosan, and hyaluronic acid contribute to stabilization through a combination of electrostatic interactions, hydrogen bonding, and encapsulation, ensuring the uniform dispersion and long-term stability of metal nanoparticles [25].

The versatility of cellulose, alginate, starch, chitosan, and hyaluronic acid as stabilizers has led to their widespread application in diverse fields. In catalysis, these stabilized metal nanoparticles serve as efficient catalysts, offering enhanced reactivity and selectivity. In sensing applications, the tailored properties of the nanomaterials enable sensitive and selective detection of various analytes [26]. Moreover, in the domain of drug delivery and biomedical imaging, the biocompatibility and controlled release properties of these stabilized nanoparticles hold great promise for advancing therapeutic and diagnostic modalities [27]. While significant strides have been made in the application of these natural polymers for stabilizing metal nanoparticles, challenges such as scalability, reproducibility, and standardization persist. Addressing these challenges will be crucial for the widespread adoption of these materials in industrial applications [28]. Moreover, exploring novel combinations of natural polymers and metal nanoparticles, as well as integrating these stabilized nanoparticles into advanced nanocomposite materials, opens avenues for further innovation and discovery [29].

The subsequent sections of this review will immerse into the synthesis methods employed for the preparation of metal nanoparticles using these natural polymers, elucidate the mechanisms underlying their stabilization, and highlight the diverse applications ranging from catalysis, and sensing to drug delivery and biomedical imaging [30]. By synthesizing and presenting the collective knowledge in this rapidly evolving field, this review aims to inspire further research and innovation, ultimately contributing to the advancement of sustainable nanomaterials with reduced environmental impact. The exploration of these natural polymers as stabilizing agents not only addresses the environmental concerns associated with traditional stabilizers but also opens avenues for the development of novel, sustainable materials with diverse applications[31].

In conclusion, this comprehensive review aims to highlight the recent advances in utilizing cellulose, alginate, starch, chitosan, and hyaluronic acid as natural stabilizers for metal nanoparticles [32]. By examining synthesis strategies, elucidating stabilization mechanisms, and exploring diverse applications, this review contributes to the growing body of knowledge in sustainable nanomaterials. The collective efforts in this field not only underscore the potential of natural polymers as stabilizers but also pave the way for the development of environmentally friendly and versatile nanomaterials with a broad range of applications [33].

2. Motivation and purpose of this study

The burgeoning field of nanotechnology, with its uncountable applications across industries, necessitates a reevaluation of nanoparticle stabilization methods, steering towards sustainability and biocompatibility. This review paper is motivated by the escalating demand for eco-friendly alternatives to conventional stabilizers in metal nanoparticle synthesis. Cellulose, alginate, starch, chitosan, and hyaluronic acid, as naturally derived polymers, has emerged as promising candidates for this role. The purpose of this review is to dissect and consolidate the latest advancements in the application of cellulose, alginate, starch, chitosan, and hyaluronic acid as stabilizers for diverse metal nanoparticles. By delving into synthesis techniques, morphological effects, and stabilization mechanisms, the paper seeks to provide insights into the unique attributes of each polymer and their combined impact on nanoparticle stability. Furthermore, the review aims to assess the practical implications by exploring the applications of these stabilized metal nanoparticles in various sectors, emphasizing their role in biomedicine, catalysis, electronics, and environmental remediation. Through a critical analysis of biocompatibility and environmental considerations, the paper strives to offer a holistic perspective, guiding future research endeavors toward the development of sustainable nanotechnologies with versatile applications and minimizing environmental impact.

3. Role of stabilizers

In the dynamic region of nanotechnology, the synthesis and stabilization of metal nanoparticles stand as critical or vital challenges that shape the efficiency and applicability of these nanomaterials [34]. The inherent tendency of metal nanoparticles to aggregate and undergo unwanted transformations demands the use of stabilizers to maintain their desired properties [35]. In recent years, there has been a paradigm shift towards exploring natural polymers as stabilizers, steering away from conventional synthetic agents with potential ecological concerns. This review delves into the contemporary landscape of nanoparticle stabilization, focusing on the recent advance made in harnessing cellulose, alginate, starch, chitosan, and hyaluronic acid as natural stabilizers for an array of metal nanoparticles [36].

The role of stabilizers in nanoparticle synthesis is vitally acting as guardians against the clump and providing a stable environment for controlled growth and assembly (Figure 1). Traditional stabilizers often give rise to challenges related to toxicity and environmental impact, necessitating a transition toward sustainable alternatives [37]. Cellulose, alginate, starch, chitosan, and hyaluronic acid, being abundant and biocompatible natural polymers, have emerged as promising candidates for nanoparticle stabilization [38]. Their unique physico-chemical properties not only address the need for stability but also offer added functionalities and applicability in diverse fields [35]. This review critically examines recent advancements in employing these natural stabilizers, shedding light on their synthesis techniques,

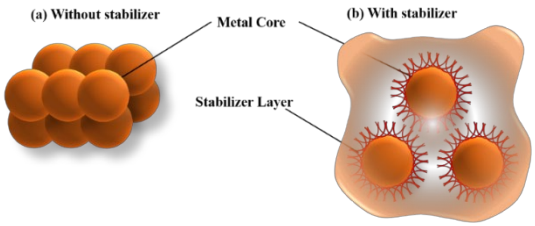

Figure 1. The effect of capping on metal nanoparticles' dispersion. (a) The aggregation of MNPs without a stabilizer layer. (b) The better dispersion of MNPs with stabilizer capping.

synergistic effects with metal nanoparticles, and applications across various industries [36]. The exploration of the role played by cellulose, alginate, starch, chitosan, and hyaluronic acid as stabilizers unveils a promising avenue for the development of sustainable nanotechnologies with wide-ranging applications and reduced environmental impact [39].

4. Natural and synthetic stabilizers

Stabilizing metal nanoparticles is a critical aspect of harnessing and exploiting their unique properties for diverse applications, and the choice between synthetic and natural stabilizers involves careful consideration of their distinct attributes [40]. Synthetic stabilizers, such as surfactants, polymers, and ionic liquids, provide precise control over nanoparticle characteristics, allowing tailoring for specific applications like catalysis and drug delivery [41]. Their adaptability and reproducibility make them suitable for scaled-up industrial production [42]. In contrast, natural stabilizers, including biopolymers and plant extracts, offer inherent biocompatibility and eco-friendliness, aligning with sustainable practices and reducing environmental impact [43]. The bioactive properties of some natural stabilizers, particularly those derived from plant extracts, open avenues for applications in biomedical fields [44]. However, the choice often hinges on application-specific requirements, with biocompatible natural stabilizers being favored in biomedical contexts, while the precision of synthetic stabilizers is advantageous in industrial applications [45]. Recent research explores hybrid approaches that combine the strengths of both types, aiming to create stabilizer systems that lift the synthetic precision and natural eco-friendliness or bioactivity [46]. Future developments may involve the design of responsive stabilizers, providing dynamic control over nanoparticle stability for advanced applications [47]. As the field evolves, the nuanced decision between synthetic and natural stabilizers continues to shape the synthesis and application of stabilized metal nanoparticles [48].

The preference for natural stabilizers over synthetic counterparts in stabilizing metal nanoparticles arises from several compelling factors, often dictated by the specific requirements of the intended applications [49]. One of the primary reasons is the inherent bio-compatibility of natural stabilizers, commonly derived from biopolymers or plant extracts [50]. This biocompatibility is critical in applications such as drug delivery or biomedical imaging, where minimizing adverse effects on living organisms is a paramount consideration [51]. Additionally, the use of natural stabilizers aligns with the growing emphasis on eco-friendly and sustainable practices in nanoparticle synthesis [52]. Biopolymers and plant extracts, being renewable resources, contribute to environmentally responsible processes, reducing the ecological footprint of nanoparticle production [53]. Furthermore, natural stabilizers are often comprehended and perceived as having lower toxicity compared to certain synthetic counterparts, enhancing safety profiles, particularly in applications involving contact with biological systems or the environment [54]. The bioactive properties inherent in some natural stabilizers, especially those derived from plant extracts, provide an additional advantage in applications where nanoparticles are intended to have therapeutic effects, such as targeted drug delivery [55]. Ongoing research often explores hybrid approaches that aim to combine the benefits of both natural and synthetic stabilizers, creating versatile systems with enhanced properties for specific applications [56].

Natural stabilizers, drawn from a spectrum of sources including plant extracts, microbial polysaccharides, and bio-based polymers, emerge as vital solutions in ensuring the enduring stability of these nanoparticles. Surfactants derived from plant extracts, exemplified by saponins and flavonoids, exhibit amphiphilic characteristics, forming a protective layer around metal nanoparticles and reducing the mass [57]. Microbial polysaccharides, sourced from bacteria and fungi, create stable coatings on metal surfaces, imparting resilience against external factors. Biopolymers or polysaccharides, including cellulose, chitosan, and alginate, sourced from living organisms and plants, show unique physicochemical properties in favor of binding with metal surfaces, thereby preventing undesirable particle aggregation [58]. Natural antioxidants such as polyphenols and flavonoids, inherent in fruits and vegetables, contribute to stabilization by inhibiting oxidation processes [59]. Marine polysaccharides, rich in sulfate groups, effectively interact with metal surfaces, forming stable complexes that enhance nanoparticle stability [60]. Additionally, natural polymers like gum arabic and pectin provide long-term stability through their hydrophilic and adhesive properties [61,62]. Essential oils, extracted from aromatic plants, bring antimicrobial and antioxidant qualities to stabilize metal nanoparticles effectively. Furthermore, bio-based polymers derived from renewable sources, such as corn starch and sugarcane, present a sustainable alternative for stabilizing metal nanoparticles, aligning with contemporary environmental considerations in materials science [63]. The strategic selection of these natural stabilizers be subject to on the specific requirements of the intended applications and the desired characteristics of the stabilized metal nanoparticle system [64].

Natural polysaccharides, a significant category of biopolymers, exhibit exceptional properties due to their chemical and structural diversity. variations in charge, chain lengths, monosaccharide sequences, and stereochemistry provide a robust foundation for developing advanced functional materials and biomedicines [65,66]. Notably, the hydrophilic nature of polysaccharides facilitates non-covalent bonding having tissue cells, contributing to cell-cell recognition and devotion. In addressing complex diseases like cancer, diabetes, and cardiovascular conditions, polysaccharides offer a more selective approach, avoiding the limitations of a single-target strategy and preventing over or under-dosing in outdated delivery systems [67,68]. Acting through mechanisms such as steric hindrance and electrostatic repulsion, polysaccharides effectively prevent the quantity, enhancing the stability of metal nanoparticles. Their inherent reducing capabilities further simplify the synthesis process by facilitating the reduction of metal ions. The environmentally friendly nature of polysaccharides, aligned with green chemistry principles, contributes to a sustainable approach to nanoparticle synthesis [69].

5. Polysaccharide as a natural stabilizer

Widely utilized in medical, agricultural, and environmental industries, biopolymers boast renewability, sustainability, and non-toxicity [70]. The Food and Agriculture Organization reports an annual harvest of natural fibers of approximately 35 million tons, a fundamental resource for biopolymer production [71]. In recent decades, various

biopolymers, including proteins, nucleic acids, and polysaccharides derived from plants, animals, and microorganisms, have found applications in packaging resources, drug delivery, and resynthesizing medicine [72].

5.1 Polysaccharides as stabilizer for MNPs

In recent years, the quest for sustainable and biocompatible natural stabilizers has led to a significant exploration of various polysaccharides as key players in this domain. Polysaccharides, abundant in nature and exhibiting inherent biocompatibility, present an attractive alternative to conventional or synthetic stabilizers [73]. This introduction sets the stage for a comprehensive exploration of the role of different polysaccharides as stabilizers for MNPs [74]. The diverse chemical and structural characteristics of polysaccharides, ranging from cellulose and alginate to starch, chitosan, and hyaluronic acid, offer a versatile toolkit for tailoring the stability and functionality of MNPs (Figure 2). As we embark on this exploration, the potential of polysaccharide-stabilized MNPs to revolutionize nanotechnological applications becomes evident, promising advances that are both sustainable and effective [72].

5.1.1 Cellulose: Molecular structure, properties, and bio-applications

Cellulose, a complex polysaccharide, serves as a stabilizer for metal nanoparticles due to its unique and hierarchical structural characteristics [75,76]. The basic building block of cellulose has a linear polymer consisting of repetition glucose units linked together by β-1,4-glycosidic bonds. Cellulose molecules aggregate into microfibrils, which further assemble into larger structures, forming the macroscopic cellulose fibers observed in plant cell walls [77]. The hydroxyl groups (–OH) present along the cellulose chains contribute to its hydrophilic nature and play a crucial role in stabilizing metal nanoparticles [78]. When cellulose is used as a stabilizer, these hydroxyl groups can interact with the metal nanoparticle surface through hydrogen bonding, electrostatic interactions, or other adsorption mechanism [79]. This interaction helps create a protective coating around the metal nanoparticles, preventing their mass and cluster and providing stability in various solvents or matrices [80,81].

In recent years, cellulose has emerged as a versatile and effective natural stabilizer for metal nanoparticles, presenting a promising avenue in nanotechnology and materials science [82]. Cellulose, derived from plant sources, is available in various forms such as cellulose-nanocrystals (CNCs), microcrystalline cellulose (MCC), micro-fibrillated cellulose (MFC), bacterial cellulose (BC), and nano-fibrillated cellulose (NFC) [83]. The unique structural and chemical characteristics of cellulose, both at the micro- and nanoscale, offer exceptional properties for stabilizing metal nanoparticles. With applications spanning from drug delivery to catalysis, cellulose-based stabilizers play a vital role in preventing nanoparticle clumps and enhancing their dispersion [84]. This introduction explores the diverse forms of cellulose and their applications as stabilizers, shedding light on the intricate mechanism by which cellulose interacts with various metal nanoparticles to impart stability and advance the field of nanomaterials [85].

Tehseen *et al.* synthesized Cu NPs stabilized with carboxymethyl cellulose using a rapid and effective microwave heating technique. To provide a high surface area substrate for the nanoparticles, they employed bacterial cellulose (BC). The catalytic efficacy of both CMC-Cu-BC and CMC-Cu was evaluated for the degradation of pollutants (4-nitrophenol and methylene blue dye) using $NaBH_4$. The results revealed that CMC-Cu exhibited a significantly faster catalytic activity compared to the supported CMC-Cu-BC. However, the supported CMC-Cu-BC demonstrated convenient recovery, in contrast to the suspended CMC-Cu which required high-speed centrifugation for retrieval. Notably, during recyclability testing, the suspended catalyst exhibited superior performance compared to the supported catalyst [86].

Maja Radetic *et al.* synthesized copper-based nanoparticles for potent antimicrobial efficacy, readily stabilized on cellulose fibers like cotton, viscose, or lyocell. Various in-situ synthesis methods on cellulose fabrics were developed (Figure 3), overcoming low ion exchange capacity by introducing specific groups [87]. The choice of reducing agent significantly influences nanoparticle size, form, and stability during washing. While effective, caution is advised in Cu-based nanoparticle use due to limited data on environmental impact and potential misuse in non-medical applications, unlike silver nanoparticles [88].

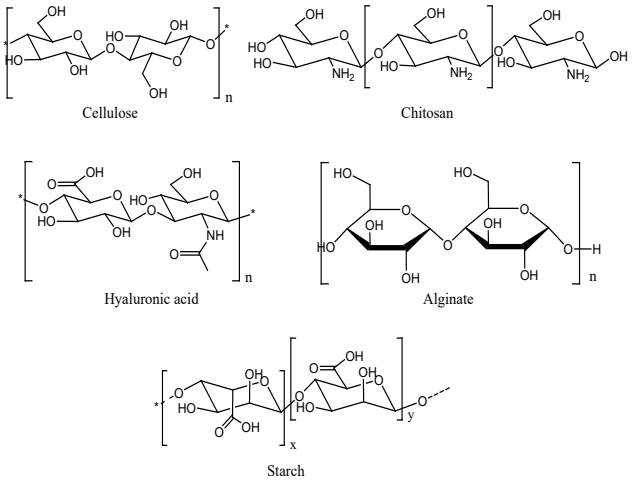

Figure 2. Chemical structure of natural polymers used commonly for nanoparticle synthesis.

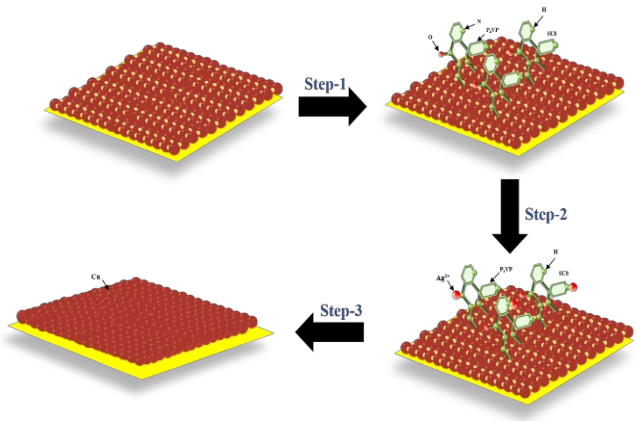

Figure 3. Schematic illustration of the process of electroless deposition of copper nanoparticles on cotton fabric with the assistance of polymer brushes.

Feng He *et al.* discovered that aluminium oxide and iron oxide enhance ZVI deposition on sand media by promoting particle-collector interactions and reducing electrostatic repulsion. Their study introduces a modified modelling approach, distinguishing a specific adsorption rate law, and offering insights into particle adsorption's role in contrast to overall filtration removal. Adsorption becomes more significant at higher flow velocities, with lower CMC-stabilized ZVI retention at higher influent particle concentrations due to blocking. Natural organic matter (NOM) minimally affects nanoparticle transport, and CaCl2 introduction does not alter behaviour significantly. CMC proves a stronger stabilizer than starch, but starch-coated ZVI shows increased retention, useful for establishing reactive ZVI zones [89].

Juan C. Noveron *et al.* present sodium rhodizonate as an innovative agent with dual functions of reduction and stabilization in the synthesis of Au NPs. The size of these NPs is contingent on the synthesis temperature. These gold nanoparticles, stabilized by sodium rhodizonate, effectively bind to cellulose fibers, creating stable NCs characterized by remarkable catalytic activity. The nanocomposites display consistent catalytic efficacy and cyclic stability in the reduction of 4-nitrophenol, as well as organic dyes like methyl orange and methylene blue. Furthermore, they demonstrated the continuous catalytic reduction of methyl orange, 4-nitrophenol, and methylene blue using a glass column packed with these nanocomposites over multiple cycles [90].

Nuray Yılmaz Baran *et al.* developed a palladium nanocatalyst on a chitosan/cellulose composite (Figure 4) for Suzuki coupling reactions, employing a rapid and eco-friendly microwave method. The catalyst showed exceptional performance, yielding high biphenyl yields, easy separation, and sustainability. Its advantages over other catalysts underscore its potential for future studies exploring diverse metallic nanoparticles on carbohydrate polymer composites as economically viable supports, promising catalytic activity across various reactions due to favourable metal-support interactions [91].

Candace K. Chan *et al.* introduced a method for synthesizing fullerene-stabilized gold nanoparticles (AuNPs) bound to titanium dioxide (TiO_2), resulting in enhanced photocatalytic activity. The TiO_2-supported AuNPs showed over double the efficacy in degrading methyl orange (MO) compared to pristine TiO_2. Hydroxyl radical generation was confirmed, and cyclic stability was demonstrated. In the reduction of 4-nitrophenol (4-NP) to 4-aminophenol (4-AP), the catalyst exhibited about 16 times higher activity than UV-irradiation-prepared counterparts, suggesting potential for water treatment applications [92].

Feng Cai *et al.* explored the application of ZnO nanoparticles to enhance the stability of oregano essential oil Pickering emulsion to produce functional cellulose nanofibrils (CNFs) packaging films. The antimicrobial properties of the CNF film were significantly enhanced through the synergic effects of oregano essential oil and ZnO nanoparticles [93]. Furthermore, the resulting environmentally friendly and biodegradable packaging film exhibited favorable mechanical and barrier properties. This film holds potential for use in food packaging, including products such as hams, fats, and juices, offering the prospect of enhancing food quality and extending durability. The utilization of Pickering emulsion technology represents a sustainable and effective approach to creating green and biodegradable active packaging films [94].

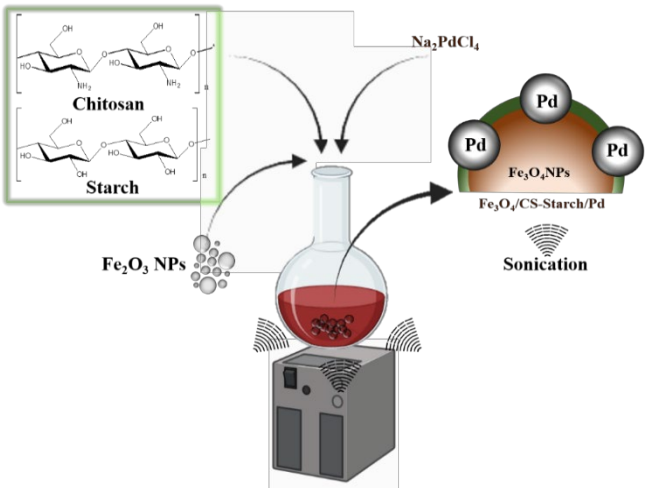

Figure 4. Schematic illustration of the synthesis of Pd@Chitosan/Cellulose composite.

Jorge A. R. Navarro *et al.* utilized sonochemical modification to enhance the UV protection and antibacterial features of cotton fabrics. Pre-treating with oxidation increased active sites for subsequent PABA (UV-blocking agent) treatment [95]. Sonochemically synthesizing nano ZnO on PABA-oxidized fabric improved UV-protection efficiency, aided by PABA in nanoparticle formation. PABA cross-linking fortified ZnO nanoparticle stability, ensuring life-period of UV protection and antibacterial properties [96]. Oxidized fabric exhibited denser and more uniform nanoparticle distribution. After washing and polishing, modified fabric retained properties due to substantial nano ZnO presence, unlike unmodified fabric. Organic-agent-facilitated sonochemical synthesis proved effective for durable antibacterial and UV-protection properties on cotton fabric [97].

In conclusion, the recent advances in utilizing cellulose as a natural stabilizer for various metal nanoparticles underscore the remarkable potential of this biopolymer in nanotechnology. The tabulated summary provides a comprehensive overview of the mode of action and diverse applications of cellulose in stabilizing metal nanoparticles [98]. Through exploiting the unique structural and chemical attributes of cellulose, researchers have achieved significant progress in creating eco-friendly and sustainable alternatives for nanoparticle stabilization. The versatile applications span across catalysis, sensing, biomedical devices, and environmental remediation, showcasing the adaptability of cellulose-based nanomaterials [88]. As the field continues to evolve, the use of cellulose as a natural stabilizer is assure to play a vital role in shaping the future of nanomaterial applications, emphasizing sustainability and biocompatibility in the pursuit of innovative solutions [99].

5.1.2 Chitosan: molecular structure, properties, and bio-applications

Chitosan (CS), resulting from the deacetylation (DDA) of chitin, represents a lined polysaccharide composed of N-acetylglucosamine and glucosamine units. Acknowledged for its odorless, biocompatible, non-toxic, and biodegradable nature, CS stands out as a sustainable, renewable, and cost-effective biopolymer [100]. The structure of CS reveals reactive functional groups, including amino and hydroxyl groups,

both principal and secondary [101]. The configuration of CS, influenced by inter-molecular and intra-molecular hydrogen bonds facilitated by the amino group, imparts distinct physicochemical properties. The molecular weight (MW) and degree of DDA emerge as vital parameters governing CS's characteristics [102]. The polymeric MW significantly affects its physical factors. DDA, on the other hand, impacts the solubility of CS in acidic solutions and the flexibility of CS molecules [103]. High DDA results in a more flexible CS chain, forming intramolecular hydrogen bonds, to make the chain less intertangled and exhibiting a more elliptical shape.

Conversely, lower DDA leads to a more expanded CS chain with stronger intermolecular interactions, enhancing intertwining. Additionally, DDA plays a key role in cell proliferation and adhesion, with lower DDA favoring cell growth and adhesion [101]. With temperature while increasing with DDA and concentration decreases the viscosity of CS. Solubility, influenced by pKa and solvent acidity, renders CS soluble in weakly acidic solutions but insoluble at pH values exceeding 7. CS, constituting the other most abundant natural polymer, stands out as the exclusive natural polycationic alkaline polysaccharide, boasting a glucosamine content exceeding 90% [104]. Its extraction from natural sources is straightforward, and it comes at a comparatively low cost compared to certain other polymers like fucoidan or hyaluronic acid. CS's glucosamine-rich backbone, characterized by a high density of amino groups, endows it with significant bioactivity. imposing these exceptional attributes, CS emerges as a polymer of choice in the eco-friendly synthesis of metal nanoparticles, particularly for applications in biomedicine [105].

Numerous studies have highlighted the dual role of chitosan (CS) as both a reducing and stabilizing agent in the eco-friendly synthesis of various metal nanoparticles such as silver (AgNPs), copper (CuNPs), and gold (AuNPs). Carapeto *et al.* conducted a detailed investigation into the mechanism of Ag ion reduction by CS, employing UV-Vis absorption and X-ray photoelectron spectra analyses. Their findings indicated a rapid reduction of Ag ions in CS solutions, particularly at higher temperatures. The oxidation of OH-groups in CS provided electrons for the reduction of Ag^{+}, forming carbonyl groups. Analysis using UV-Vis spectra and X-ray photoelectron spectroscopy confirmed the presence of carbonyl groups as the main products, and the cationic CS coating resulted in positively charged nanoparticles with enhanced stability against aggregation [106].

Zaheer Khan *et al.* synthesized chitosan-capped Au@Pd@Ag nanoparticles as shown in Figure 5, for efficient textile dye removal. UV-visible spectroscopy highlighted silver's influence on optical properties. Chitosan acted as a capping agent, forming electrostatic interactions with nanoparticle surfaces, confirmed through ninhydrin testing. Adsorption formed a Langmuir monolayer of acid orange, displaying high efficiency ($q0\ max = 71.42\ mg{\cdot}g^{-1}$, $R2 = 0.995$) and pseudo-second-order kinetics. The nanoparticles exhibited robust durability and stability. These findings underscore chitosan's potential as a capping agent for durable absorbents, offering enduring applications in wastewater treatment [107].

In another report, a novel approach for the fabrication of chitosan aerogels, incorporating amino acids, Au-NPs (gold nanoparticles), and microwave radiation was studied. The resulting biomaterials exhibit a highly porous morphology and improved mechanical stability. The scaffolds demonstrate exceptional swelling capability when exposed to various aqueous solutions. Importantly, the aerogels prove to be biodegradable while retaining the antibacterial activity inherent in raw chitosan. Furthermore, the degree of deacetylation in the initial chitosan significantly influences the properties of the finalized scaffolds. Comprehensive studies confirm the biocompatibility of the proposed aerogels and their positive impact on fibroblast proliferation. The findings suggest that these biomaterials have potential applications in tissue engineering for skin regeneration, as they can facilitate the remedial process and reduce the hazard of infection in treated wounds [108].

Shahid Ali Khan *et al.* investigated MnO_2, MnO_2/AC1, and MnO_2/AC2 nanocomposites synthesized via the sol-gel method impact on chitosan polymer (CS). Incorporating these nanocomposites and activated carbon (AC) as fillers in CS films, Co NPs were formed through treatment with $NaBH_4$. CS-AC@Co NPs exhibited effective antibacterial activity against P. aeruginosa but not E. coli. CS-MnO_2/AC1@Co and CS-AC@Co NPs showed higher rate constants for 4NP hydrogenation. CS-AC@Co, CS-MnO_2/AC1@Co, and CS-MnO_2/AC1 @Co NPs effectively degraded MO and CR dyes. CS-AC@Co NPs displayed notable recyclability for 4NP hydrogenation with minimal loss of activity in subsequent cycles [109].

Xiaoying Wang *et al.* research, a novel and environmentally friendly approach was devised for the synthesis of copper sulfide nanoparticles (CuS-NPs) as revealed in Figure 6. Within this system, QCS molecules served both as a stabilizing agent and growth template. The resulting CuS@QCS-NPs, exhibiting an average diameter of 5.6 nm, demonstrated a notably high photothermal conversion efficacy. Consequently, these nanoparticles displayed effective antitumor activity both in vitro and in vivo, without inducing lethal toxicity. This innovative method holds promise as an alternative for the clinical application of CuS-based photothermal therapy [110].

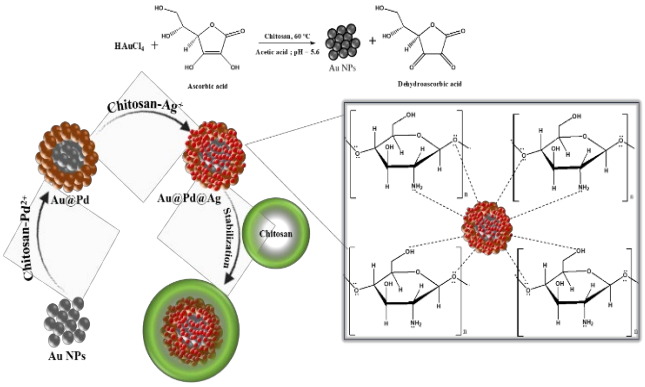

Figure 5. Synthesis of Au@Pd@Ag@Chitosan as a natural stabilizer.

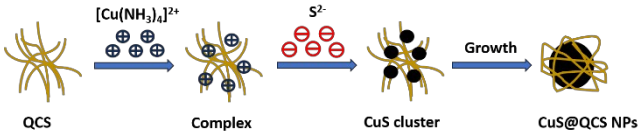

Figure 6. Synthesis of CuS@QCS nanoparticles.

Yadollah Omidi *et al.* developed a chitosan-based copolymer to synthesize CGH NPs, modulating size, and surface Plasmon resonance by adjusting CS copolymer and $HAuCl_4$ concentrations. These NPs, with positive surface charge and a lower critical solution temperature of around 36°C, efficiently loaded hydrophobic anticancer drug ETB molecules, achieving 30% efficacy. ETB release exhibited thermo-responsive behavior, notably enhanced above the LCST. Cellular uptake of CGH NPs was confirmed, and cytotoxicity evaluation affirmed their cytocompatibility, suggesting their potential as effective anticancer drug carriers for passive and active tumor targeting [111].

CH-LDH composite microspheres were created and templated with Cu, Ag, and Cu-Ag NPs. The maximum distribution coefficient (Kd) for Cu(II) ions was 3.35×102 mL·g^{-1}, indicating superior selectivity. These composites, containing NiAl layered double hydroxide (LDH), served as templates for metal ion impregnation. ICP-OES analysis confirmed the highest Kd for Cu(II) ions, highlighting selectivity over Ag(I). Adsorbed metal ions were transformed into zero-valent metal NPs (ZVM). Catalytic properties were evaluated for dye and nitrophenol degradation, with CH-LDH@Cu exhibiting the highest rate constants (kapp) against Congo red (CR) and 4-nitrophenol (4-NP). Turnover frequency (TOF) was highest for CR degradation. CH44 LDH@Cu NPs were effective for simultaneous dye and nitrophenol removal [112].

The diverse applications of chitosan (CS) and its composites, as highlighted in the reports, underscore its versatility and potential across various fields. Studies highlight its role as a reducing and stabilizing agent in metal nanoparticle synthesis, demonstrating its effectiveness in producing silver, gold, and copper nanoparticles with distinct properties and applications [113]. From eco-friendly synthesis of metal nanoparticles to fabricating aerogels for tissue engineering and developing smart drug delivery systems, CS demonstrates remarkable efficacy and biocompatibility. Its role as a stabilizing and reducing agent in nanoparticle synthesis, coupled with its ability to enhance mechanical stability and antibacterial properties in biomaterials, showcases its multifaceted utility[114]. Moreover, the synthesis of CuS-NPs within quaternate chitosan opens avenues for innovative cancer therapy, while CS-based nanocomposites exhibit promising catalytic activities, offering sustainable solutions for pollutant degradation. Overall, these findings emphasize CS's significance in advancing eco-friendly materials and biomedical applications [115].

5.1.3 Hyaleuronic acid: Molecular structure, properties, and bio-applications

Hyaluronic acid (HA) is a biopolymer composed of units of D-glucuronic acid and N-acetyl-D-glucosamine [116]. Due to its hydrophilic nature, HA contains hydroxyl groups that can form hydrogen bonds with H_2O molecules. Moreover, the –COOH, –OH, and acetamido functional groups on HA offer prospects for chemical variations [117]. This biodegradable and biocompatible biopolymer finds extensive use in cancer therapy. Under physical conditions, the carboxyl groups of HA undergo deprotonation, given their 3-4 pKa value. The hydrophilic properties of HA enable it to create sticky and elastic gels over hydration, supporting the water molecules' binding.

In current years, there has remained a growing focus on polymers of natural polysaccharides due to their diverse health benefits, including enhanced pharmacological activity, antioxidant, anticoagulant, and anticancer properties [118]. HA stands out as a promising natural polysaccharide polymer for cancer therapy, given its reactive sites like carboxylic, hydroxyl, and –$NHCOCH_3$ groups that allow for covalent modifications [100]. Notably, for chemical changes like amination, esterification, or coupling with M-NPs and other compounds, carboxylic groups are useful [119,120]. The strong binding attraction of HA to CD44 molecules expressed on cancer cells positions it as an important tool for treating cancer, with widespread applications for this purpose. CD44, a cell surface glycoprotein, plays multifunctional characters in processes like angiogenesis, proliferation, and migration. The capacity of HA to bind to CD44 makes it easier to internalize into cells, making it a promising candidate for suppressing cancer progression [121].

A versatile theragnostic nanoplatform, polylactic acid, incorporating laponite, polyethylene glycol, polyethylenimine, gold, and a hyaluronic acid (HA) system overloaded with the DOX drug (LAP-PLA-PEG-PEI-Au-HA/DOX), enables CT imaging of tumors and targeted chemotherapy. These hybrids exhibit a high DOX loading efficacy of $91.0 \pm 1.8\%$ and demonstrate pH-sensitive continued release. In vitro experimentations reveal that the designed hybrids selectively deliver to cancer cells overexpressing CD44, leading to the inhibition of cancer cell proliferation and enhanced CT imaging. In vivo experiments demonstrate the ability of the hybrids to serve the customized contrast agents for CT imaging, effectively inhibiting tumor growth while minimizing unwanted effects. Figure 3 illustrates the overall process for obtaining the LAP-PLA-PEG-PEI-Au-HA/DOX multifunctional theragnostic nano platforms [122].

Zhou *et al.* developed a comprehensive nano platform named Au-NRs-mSiO_2-HA-RGD, combining gold nanorods (Au NRs), mesoporous silica, HA, and arginyl glycyl aspartic acid (RGD) for dual-targeted chemo-photothermal therapy. Utilizing DOX as a model drug, the researchers assessed drug loading, in vitro release profiles, and cellular effects. The nano platform exhibited significant photothermal capabilities and achieved a high drug loading capacity of approximately 20.16%. Cellular uptake studies revealed dual-targeted delivery to ovarian cancer cells through endocytosis mediated by CD44 and integrin receptors [123].

A pentameric nano complex (PNC) for TNBC and CSCs contained Au-NPs, DOX coupled to thiolated HA and PEG, and a DNA CD44 aptamer [124]. The PNC exhibited tenfold increased potency over DOX alone, with enhanced drug release at pH 4.7 in the presence of glutathione. Another platform, Au-NRs-HA-FA, combining Au-NRs, HA, and folate, efficiently delivered DOX to MCF-7 cells, showcasing complete tumor elimination in vivo [125].

In an additional method, The strong cytotoxic agent, SN38, was conjugated to HA and deposited on Au-NPs, exhibiting selective toxicity to MUC1 positive HT29 and SW480 colon cancer cells over MUC1 negative CHO cells [126]. Additionally, a strategy involving hollow silica nanoparticles (HSNs) incorporating Au nanocomposites (Au-HSNs) without surfactants demonstrated better photothermal characteristics. The Au-HSN/DA-HA exhibited exceptional endocytosis in cancer cells under near-infrared irradiation without inducing cytotoxicity [127].

Zhang *et al.* described the development of nanocomposites with Au-NPs, Poly(glycidyl methacrylate) (PGMA) microspheres with HA for accurate photothermal applications. PGMA microspheres were synthesized through emulsifier-free emulsion polymerization followed

by amination, with Au seeds adsorbed via chelation to form Au-PGMA. To achieve specific targeting of cancer cells and minimize Side effects on normal cells, HA was conjugated to the surface of Au-PGMA. The resulting Au-PGMA-HA exhibited remarkable selectivity in targeting cancer cells and demonstrated outstanding photothermal effects, displaying three times greater therapeutic effectiveness of cancer cells in contrast to normal cells [128].

Polyethyleneimine (PEI)-assisted HA tagged with Ceria (PEI-HA-Ce) demonstrates significant anticancer effects in triple-negative breast cancer (TNBC). PEI-HA-Ce induces reactive oxygen species (ROS) in MDA-MB-231 cells, leading to mitochondrial membrane potential loss and cytochrome c release, activating caspases-3 and -9 and reducing Bcl-2 levels. Treatment results in irreversible nuclear chromatin condensation, offering promise as a therapeutic agent for TNBC [129].

A dual-targeted drug distribution structure for solid tumours was created, comprising a pH-sensitive polymer and an inorganic enzyme. Indocyanine green (ICG) was adsorbed onto the core of polyethyleneimine (PEI) polymer. At the tumor site, cerium oxide nanoparticles (CeO_2 NPs) catalysed hydrogen peroxide conversion into oxygen, enhancing photothermal therapy (PTT) and photodynamic therapy (PDT). This approach improved ICG uptake, induced apoptosis, and increased in vivo ICG bioavailability, promisingly addressing the hypoxic tumor microenvironment [130].

Superparamagnetic iron oxide nanoparticles (SPIONPs or Fe_3O_4) were utilized for targeted delivery, incorporating CeO_2 on the surface to induce reactive oxygen species (ROS) in the tumor environment, selectively eliminating cancer cells. HA coating facilitated targeted delivery to CD44-overexpressing tumor cells, while natural zirconium (natZr) chelation allowed for radioisotope 89Zr labelling. The nanoparticles effectively generated ROS and demonstrated targeted delivery, promising for cancer therapy [131].

To enhance PDT efficacy in cancer treatment, a novel approach involves modifying HA on CeO_2 surfaces (Figure 7), Decorated with metal-organic frameworks (MOFs), forming HA-CeO_2-MOF. CeO_2 catalyses hydrogen peroxide (H_2O_2) into oxygen (O_2), addressing hypoxia, while HA targets CD44 receptors on tumor cell membranes. Upon incubation and laser irradiation, HA-CeO_2-MOF effectively controls tumor cell growth (4T1 and MCF-7) with minimal impact on normal cells (LO_2). Notably, HA-CeO_2-MOF accumulates in tumor areas and significantly prevent the tumor growth, demonstrating promise for PDT enhancement [100].

Ulcerative colitis (UC), a stimulating and rapidly progressing chronic nonspecific inflammatory bowel bug, is categorized by elevated myeloperoxidase (MPO) expression in colonic ulcers, leading to A high percentage of phagocytosis and ROS [132]. In response, Gao *et al.* developed a solution in the form of electrostatically assembled MPO-targeting hyaluronic acid/serotonin/(5-HT) ceria nanoenzyme (HA-5-HT-CeO_2). Through the utilization of 5-HT, CeO_2 NPs, and HA, dual targeting effects on MPO and macrophage CD44+ receptors were achieved [133]. The resulting HA-5-HT-CeO_2 could effectively locate the inflammatory site and neutralize O_2, H_2O_2, and ROS. This approach positively restored the gut epithelial barrier by targeting certain inflammatory factors. Both in vitro, Pharmacodynamic studies and animal models of acute colitis showed that HA-5-HT-CeO_2 was more effective than standard medications at reducing inflammation and treating ulcerative colitis [134].

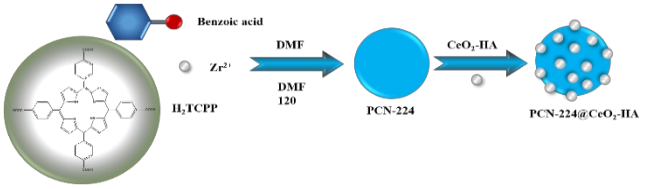

Figure 7. Schematic representation of PCN-224@CeO_2-MOF for PDT therapy.

To improve therapeutic efficacy, a novel system was developed utilizing PEG-modified oxidized mesoporous carbon nanospheres (OMCNPs) loaded with the drug DOX. HA modification was employed on OMCNPs to specifically target lung cancer cells. Additionally, zinc oxide quantum dots (ZnO QDs) were introduced to cap the OMCNP and chelate with DOX, achieving a loading content of 52%. Upon cellular absorption, the pH-sensitive ZnO lids disintegrated in tumor cells, releasing Zn^{2+} and causing the dissociation of the Zn^{2+}-DOX complex, thereby facilitating the controlled release of DOX. The OMCNP-based system, when exposed to near-infrared (NIR) irradiation, induced hyperthermia and enhanced the release of DOX. The combination of targeted chemo-PTT demonstrated superior outcomes compared to either single chemotherapy or photothermal therapy alone [135].

In a different study, a bio-reducible carrier designed for siRNA transport was developed by conjugating Zn (II)-dipicolylamine onto HA, resulting in HA-DPA(Zn). This allowed for the coordination with siRNAs, creating a formulation that remains stable in the presence of zinc ions. The siRNA synthesized using this carrier demonstrated efficient uptake by U87MG cells and released the incorporated siRNAs in response to reduction signals. In vitro studies indicated that siRNA formulated with HA-DPA(Zn) effectively silenced genes with minimal toxicity. Furthermore, It displayed longer circulation in the bloodstream, enhanced accumulation at the tumor site, and significant anticancer activity in a U87MG tumor-bearing mice model, all without causing organ damage [136].

In a different research study, ZnO was conjugated with HA Using a co-precipitation technique, resulting in (HA-ZnO). Subsequently, the conjugated system was further modified using ginsenoside Rh2, yielding Rh2-HA-ZnO. The designed Rh2-HA-ZnO demonstrated anti-cancer effects on three distinct cancer cell lines—A549 lung cancer, HT29 colon cancer, and MCF7 breast cancer cells. Furthermore, Intracellular ROS were detected in all three cancer cell lines [137].

Wang et al. synthesized block copolymer micelles of PEG and polycaprolactone (PCL), forming PEG-PCL, and incorporated HA, manganese, and zinc ferrite magnetic nanoparticles (MZF) to enhance radiotherapy (RT) effects on non-small-cell lung cancer (NSCLC). Micelles with HA surface modification (MZF-HA) targeted CD44-expressing tumor cells like A549. In xenograft models, MRI confirmed increased MZF-HA accumulation in tumors, and immunohistochemistry showed enhanced tumor oxygenation post-hyperthermia. MZF-HA led to a 49.6% tumor volume reduction, contrasting with a 58.8% increase in the untreated group, promising targeted cancer therapy [138].

Using targeted PTT in cancer treatment can improve therapeutic outcomes while reducing adverse effects. However, incorporating more functionality frequently results in higher synthetic stages, potential toxicity problems, and complex in vivo behavior. To overcome these challenges, a one-pot method is employed to create tumour-targeted systems comprising HA and platinum (Pt). In vitro, experiments

confirmed more efficient internalization of CD44-overexpressing cancer cells by these systems compared to non-targeted alginate acid-Pt nanoparticles. Similarly, in-vivo investigations showed that HA/Pt accumulated higher in CD44-overexpressing tumors than AA/Pt, showing superior efficacy in suppressing tumor growth via PTT [139].

Developing a nano platform that effectively targets PDT for hypoxic tumors is crucial in contemporary cancer research. In this context, a ROS generator named HA-modified Pt NPs/carbon dots-loaded mesoporous silica (HA-PCD) was developed. Pt NPs and carbon-dot-loaded dendritic mesoporous silica nanoparticles (DMSNs) were further modified with HA, and HA-PCD produced singlet oxygen ($1O_2$) upon exposure to 635 nm laser irradiation. Pt NPs enhance photo-dynamic therapy under hypoxic conditions by catalyzing oxygen production via catalase-mimicking activity. Additionally, it produces hydroxyl radicals (OH.) and superoxide ions (O_2^-) for catalytic therapy through peroxidase and oxidase-mimicking actions [140].

A multifunctional drug delivery system, Pd-Pt-GO/HA as shown in Figure 8, incorporating Pt, Pd, glucose oxidase (GO), and HA, was developed to address inefficiencies and potential side effects of GO-mediated starvation therapy. Targeting CD44-overexpressing cancer cells, It has hyaluronidase-responsive GO, catalase and peroxidase (POD)-like activities, and glutathione oxidation capacity, which improves therapeutic efficacy and biosafety. Selective uptake induces ROS-mediated apoptosis in cancer cells. In vivo tests indicated significant therapeutic success in the 4T1 and H22 tumor-bearing animal models, highlighting its potential for cancer therapy [141].

Zhang *et al.* devised a nanosystem designed for both PTT and antioxidant therapy, creating Pd-Se-HA nanosystems. Selenium (Se) nanoparticles and palladium (Pd) nanoparticles were incorporated into the core-shell structure, with Pd NPs exhibiting photothermal effects. The surface of the nanosystem was bonded with HA to confer targeting functionality, resulting in the formation of Pd-Se-HA nanosystems. In vitro studies established a strong hydroxyl radical (–OH) scavenging ability, ROS production, effective inhibition of macrophage infiltration, photothermal effect, and cytokine-mediated inflammation. Moreover, afterward 15 days of treatment, Pd-Se-HA nearly completely stopped the inflammatory response in the joints of mice with an induced rheumatoid arthritis (RA) model, preventing joint deterioration [142].

In 2018, a novel combination of HA and AgNPs was introduced, exploiting electrostatic interaction and ultrasonication-induced assembly. HA-Ag-NPs demonstrated potent Anti-leukemic action by promoting ROS overproduction, surpassing AgNPs alone. They significantly inhibited leukemia cell viability by inducing apoptosis via specific binding to CD44 receptors. This strategy offers a targeted approach for leukemia treatment, to hold the changed redox conditions in cancer cells while decreasing systemic toxicity, providing new insights into leukemia-specific chemotherapeutic improvement [143].

Another study employed HA as a gel-forming agent, using Amanita muscaria extract as the capping agent during the production of silver and ultra-small iron oxide to create Fe-Ag-NPs with synergistic anti-cancer activities. Cytotoxicity investigations were performed on both 2D and 3D HeLa cell cultures demonstrated the potential of the HA/Fe-Ag gel for localized cancer treatment. The gel formulation, employing HA as a gelling agent, improved the transfer of active components within HeLa spheroids, increasing their efficacy. These data indicate that HA/Fe-Ag NPs might be a useful method for cancer therapy [144].

To overwhelmed the boundaries of "single-strategy" treatment in the internal environments of the body, Liu et al. developed HA-modified Ag-S-nitrosothiol core-shell NPs using (EGDMA, TEOS) for synergistic therapy, combining PTT and nitric oxide (NO)-based chemotherapy. Under NIR irradiation, the Ag core generated cytotoxic heat, inducing cancer cell apoptosis. Additionally, In response to NIR and heat, S-nitrosothiol polymeric shells released significant amounts of free NO, leading to NO-based chemotherapy. The effectiveness of this photothermal and NO-based chemical synergistic treatment in targeting tumors was proven by both in vitro cytotoxicity testing and in vivo trials done on mice with tumors [145].

In a study targeting hepatocellular carcinoma, a twofold system combining HA and doxorubicin (DOX) was synthesized and then conjugated with amine-modified Fe-NPs. The resultant hybrid system has excellent water dispersibility, superparamagnetic characteristics, and strong magnetic reflexivity. Notably, the hybrid system demonstrated significant cellular uptake, and the buildup of HA in HepG2 cells, a kind of human liver cancer cell, is thought to be aided by its unique function. In vitro studies indicated that the release of DOX from the hybrid system was notably accelerated under mild acidic conditions (pH 5.0 to pH 6.0), ideal for effective chemotherapy. Moreover, in vivo experiments in mice confirmed the substantial therapeutic potential of these hybrid systems, demonstrating significant antitumor efficacy [146].

Another noteworthy investigation introduced a novel magnetic nano vehicle using HA-conjugated iron oxide nanoparticles (IONPs) for the targeted delivery of chemotherapy drugs to tumor areas guided by an external magnetic field. The IONPs could carry the model drug homocamptothecin (HCPT), with 75% of HCPT encapsulated in the HA-IONPs. In vitro and in vivo experiments demonstrated remarkable magnetic tumor targeting and effective tumor cell depletion. Importantly, no systemic toxicity was observed, highlighting the potential clinical translatability of the designed nano vehicle as a magnetic field-responsive platform for targeted delivery applications [147].

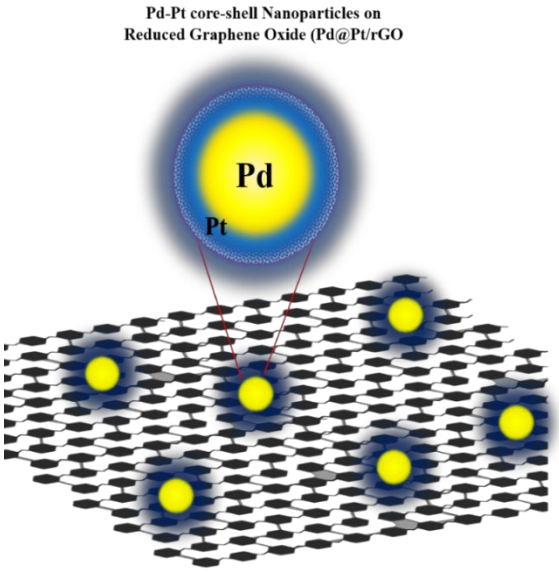

Figure 8. Graphical illustration of the synthesis of Pd-Pt-GO/HA nanocomposite.

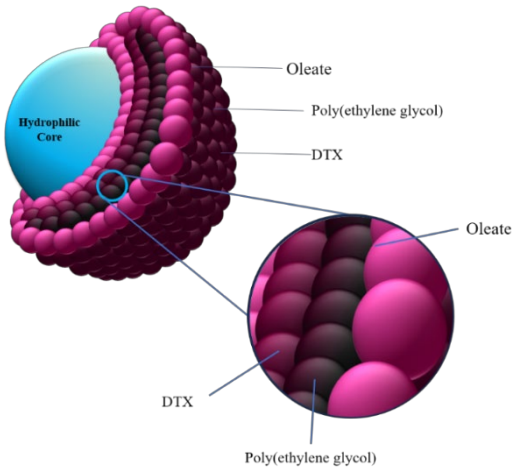

Figure 9. Systematic scheme of DTX drug loaded by micelle.

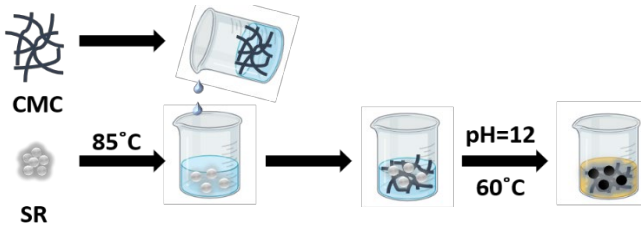

Figure 10. Systematic illustration for preparation of Ag@CMC@SR composite films.

Zheng *et al.* developed nanoplatforms consisting of HA-SPION micelles loaded with the docetaxel (DTX) drug (Figure 9), achieving a loading efficiency of 10.9%. Cellular uptake studies revealed that MDA-MB-231 cells were internalized via CD44 receptor-mediated endocytosis, facilitated by the presence of a magnetic field, and exhibited promising MRI potential. Additionally, the micelles demonstrated superior localized photothermal depletion in MDA-MB-231 cells, showcasing their potential as effective photo-absorbers in photothermal therapy. The overall scheme to obtain micelle-loaded DTX drug and the dual tumor-targeted therapies is depicted in Figure 10 [148].

In summary, the extensive research on HA in conjunction with various nanoparticles underscores its significant potential in cancer therapy. From targeted drug delivery systems to multifunctional theranostic nanoplatforms, HA plays a crucial role in enhancing treatment efficacy while minimizing side effects. The utilization of diverse nanoparticles, including gold, silver, iron oxide, and selenium, combined with HA, demonstrates remarkable outcomes in targeting cancer cells, inducing apoptosis, and inhibiting tumor growth through photothermal therapy, chemotherapy, and ROS-mediated mechanisms. These findings collectively highlight the promising future of HA-based nanomedicine in combating cancer with improved precision and efficacy.

5.1.4 Starch: molecular structure, properties, and bio-applications

Starch is primarily found in plants, and plays a central role in both the natural world and various industrial applications, owing to its unique molecular structure, diverse properties, and wide-ranging bio-applications. With its abundant hydroxyl groups, starch exhibits excellent hydrophilicity, enabling it to form hydrogen bonds with water molecules [149]. Additionally, the numerous hydroxyl groups provide enough opportunities for chemical modifications, enhancing its functionality as a stabilizer. At its core, starch is a complex carbohydrate composed of glucose units linked by α-glycosidic bonds. Its molecular structure exhibits a hierarchical organization, comprising two main components: amylose and amylopectin. Amylose consists of linear chains of glucose units connected by α(1→4) linkages, while amylopectin features a branched structure with additional α(1→6) linkages at branching points [150].

This intricate arrangement contributes to the distinctive properties of starch, including its solubility, viscosity, and gelatinization behavior. It is a vital carbohydrate with a complex molecular structure, that showcases properties like viscosity, gelatinization, solubility, and texture modification. Its film-forming ability, adhesive properties, and biodegradability make it versatile in industries spanning from food to packaging, offering thermal stability and ongoing potential for sustainable advancements [151].

Changqing Fang *et al.* fabricated antibacterial films of carboxy methyl cellulose (CMC) (Figure 10) using an in-situ reduction method, enhancing mechanical properties with AgNPs incorporation. Optimal tensile strength (9.8 MPa) and elongation at break (63%) were achieved at 4 g AgNPs content, while increased AgNPs reduced film crystallization. All films exhibited excellent antibacterial activity against *S. aureus* and *E. coli*, with inhibition increasing with higher $AgNO_3$ concentrations. These findings highlight the potential of the developed antibacterial CMC films for antimicrobial packaging applications [152].

M. Chakraborty *et al.* synthesized stable colloidal dispersion of starch-stabilized AgNPs via a chemical reduction method, ideal for nano device applications. Characterization confirmed narrow particle size distribution, predominantly below 10 nm at 100 mg starch concentration. Colloidal AgNPs showed potent antibacterial effects at low silver concentrations (<1.39 $mg \cdot mL^{-1}$) and inhibited fungal growth at 5.5 $mg \cdot mL^{-1}$. This work demonstrates promising potential for biologically relevant nanodevice applications [153].

S. Tajammul Hussain *et al.* synthesized AuNPs through $AuCl_4^-$ reduction with hydrazine in an aqueous solution containing starch and ethylene glycol at room temperature. Characterization revealed 3.5 nm spherical AuNPs composed of pure metallic gold. Varying concentrations of reactants impacted particle size. Starch played a vital role in nanoparticle stabilization, confirmed by FT-IR and TGA analysis. UV-vis spectrum displayed a blue shift, indicating AuNP formation, with stability maintained over three months. This study highlights efficient AuNP synthesis and stabilization mechanisms [154].

Haoran Dong *et al.* assessed Fe/Ni nanoparticles (NPs) and starch-stabilized Fe/Ni (S-Fe/Ni) NPs toxicity in *E. coli.* Fe/Ni NPs showed concentration and time-dependent toxicity, with greater toxicity than bare Fe0 NPs. The addition of Ni increased toxicity, yet no consistent correlation with Ni content was observed. Starch coating diminishes the Fe/Ni NPs toxicity, dependent on starch concentration. TEM showed membrane disruption and NP uptake. FTIR suggested NP-cell surface interactions. S-Fe/Ni NPs exhibited reduced toxicity due to starch coating hindering NP-cell contact. ROS scavenger reduced toxicity, indicating ROS-induced oxidative stress. Aging experiments showed decreased toxicity over time, implying reduced long-term environmental impact [155].

Mario Gauthier *et al.* investigated starch-stabilized iron oxide nanoparticles for the photocatalytic Fenton process, addressing challenges of acidity. The catalysts, stable near neutral pH, efficiently degraded methylene blue, partially mineralizing it at pH levels up to 4. Catalysts demonstrated reusability and potential for degrading various pollutants, highlighting their environmental friendliness and cost-effectiveness. This study underscores starch's efficacy in stabilizing iron nanoparticles for aqueous applications, offering a promising solution for water treatment[156].

In this investigation, Sanoe Chairam *et al.* successfully synthesized Au NPs stabilized by a starch polymer as shown in Figure 11. The catalytic performance of the starch-stabilized Au NPs was evaluated for the homocoupling reaction of phenylboronic acid in water, utilizing oxygen from air as the oxidant at room temperature. Different parameters including catalyst loading, base equivalent, base type, and reaction duration were systematically examined. This study presents a straightforward, cost-effective, and eco-friendly method for stabilizing colloidal gold catalysts by utilizing the hydroxyl-rich structure of starch polymer, offering promising applications in related fields [157].

Vishakha *et al.* investigated factors affecting CMS preparation and characterized its structure using various techniques. Rheological analysis showed increased intrinsic viscosity with higher degrees of substitution (DS). CMS with DS ranging from 0.05 to 0.45 effectively stabilized selenium nanoparticles (Se-NPs), yielding spherical Se-NPs (~50 nm). Stability of NP size and shape was confirmed via DLS, SEM, and TEM [158].

Mohan Rao K *et al.* zinc sulfide (ZnS) nanoparticles were synthesized through the chemical co-precipitation method, with starch serving as the capping agent. Microwave irradiation was employed for heating. X-ray diffraction analysis revealed that the obtained nanopowders were polycrystalline and exhibited a simple cubic structure characteristic of ZnS. Transmission electron microscopy observations indicated that starch played a role in preventing the clumps through steric stabilization. Fourier transform infrared spectroscopy and Raman scattering studies confirmed the interaction between ZnS and starch. Optical absorption studies revealed quantum size effects, while photoluminescence spectra indicated an enhancement in the quenching of defect states on nanoparticles with increased starch addition [159].

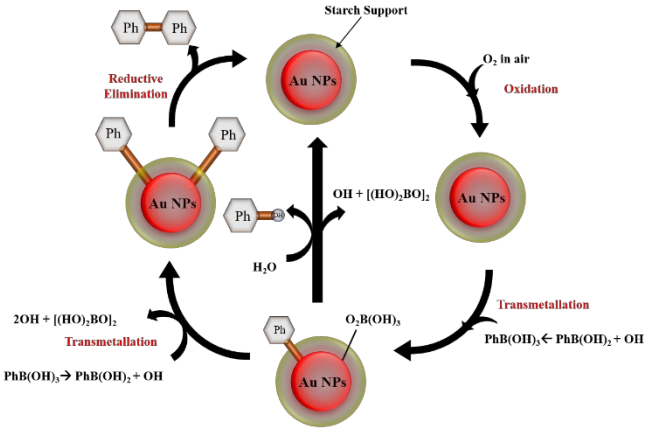

Figure 11. The possible mechanism for homocoupling of phenylboronic acid over starch-stabilized Au-NPs to form biphenyl and phenol.

In conclusion, the reports highlight the versatile applications and advancements achieved through the utilization of starch-based materials in nanoparticle synthesis and modification [156]. From the successful stabilization of gold nanoparticles (Au NPs) using starch polymers to the efficient preparation of carboxymethyl starch (CMS) for stabilizing selenium nanoparticles (Se-NPs), starch emerges as a promising and eco-friendly candidate for nanoparticle stabilization and functionalization. Additionally, the investigation into the green synthesis of zinc sulfide (ZnS) nanoparticles with starch as a capping agent demonstrates the potential of starch in diminishing the clumps and enhancing nanoparticle stability [160].

Through comprehensive characterization techniques including X-ray diffraction, transmission electron microscopy, Fourier transform infrared spectroscopy, and optical absorption studies, the chemical interactions and structural properties of these starch-stabilized nanoparticles were elucidated [153]. Notably, the observed quantum size effects and improved quenching of defect states in photoluminescence spectra underscore the significance of starch modify the optical and electronic properties of nanoparticles. Overall, these findings underscore the promising role of starch as a versatile and sustainable material for nanoparticle synthesis and modification, paving the way for innovative applications in various fields including medicine, biosensors, and environmental remediation [161].

5.1.5 Alginate: molecular structure, properties, and bio-applications

Alginate, a naturally occurring polysaccharide derived from brown seaweeds, is renowned for its remarkable stabilizing properties across a spectrum of industries [162]. Composed primarily of mannuronic and guluronic acid units, alginate boasts a distinctive structure conducive to stabilizing aqueous systems through its abundant hydroxyl groups [163]. These hydroxyl groups promotes the strong interactions with water molecules, facilitating hydration and the formation of vigorous gels with exceptional viscoelastic properties [164,165]. In recent years, there has been a surge in interest surrounding natural polysaccharide stabilizers, driven by their eco-friendly nature and diverse functional benefits [166,167]. Alginate emerges as a standout candidate in this field, owing to its biocompatibility, biodegradability, and versatility. Its unique chemical structure offers numerous sites for chemical modifications, including cross-linking, esterification, and conjugation with various substances, enhancing its stabilizing capabilities [168].

The hydrophilic nature of alginate enables it to stabilize emulsions, suspensions, and foams effectively, thereby improving product texture, shelf life, and overall quality [169]. Furthermore, alginate's ability to form strong gels in the presence of divalent cations, such as calcium ions, makes it a valuable tool in pharmaceutical formulations, wound dressings, and tissue engineering applications [170]. Moreover, the role of alginate extends beyond stabilization, encompassing functionalities such as drug delivery, tissue regeneration, and biotechnological applications. Its interactions with biological molecules and cells make it a versatile tool in biomedical research and therapeutic interventions [171].

Yaqin Hu *et al*. synthesized AgNPs using sodium alginate (Na-Alg) as the stabilizing agent and ascorbic acid (Vc) as the reducing agent (Figure 12). The study delved into the possible mechanism underlying nanoparticle reduction and stabilization. Various reaction conditions such as pH, $AgNO_3$ and Vc addition, and ultrasonication

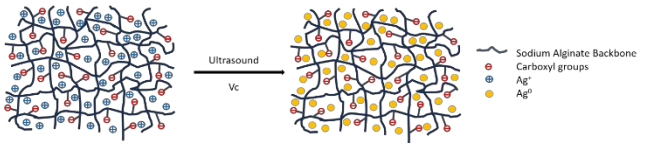

Figure 12. Graphical illustration of the synthesis of AgNPs using Na-Alg as the stabilizing agent and Vc as the reducing agent.

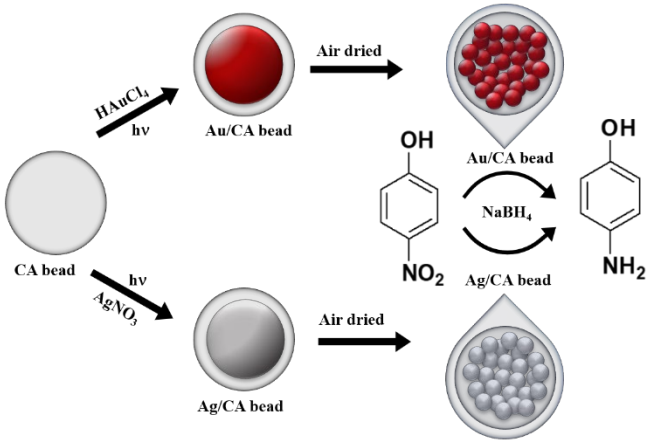

Figure 13. Schematic overview for catalytic reduction of 4-NP through $NaBH_4$ in the presence of dried Ag/CA and Au/CA beads.

treatments were explored for their impact on AgNP synthesis. Notably, the synthesized AgNPs exhibited potent antibacterial activity against Staphylococcus aureus and *E. coli*, attributed to their ability to increase membrane permeability and disrupt bacterial wall integrity. This suggests the potential application of Na-Alg-AgNPs in food packaging materials. [172]

Yanzhi Xia *et al.* utilized a sustainable and environmentally friendly method to synthesize AgNPs using Na-Alg as a stabilizer and glucose as a reducing agent in water. These AgNPs were then incorporated into alginate fibers to create composite materials and stability within the composite fibers, exhibiting strong antibacterial properties against both *E. coli* and *S. aureus.* The mechanical properties of the alginate fibers were evaluated before and after nanoparticle incorporation. This approach holds promise for developing various alginate-based composite materials, offering potential applications in functional textiles and biomedical materials, particularly in wound healing and dressing applications, due to their sustainability, biodegradability, and ease of preparation [173].

Tarasankar Pal *et al.* reported the utilization of a green photochemical method, where biopolymer calcium alginate gel beads were employed as templates for the growth of AgNPs and AuNPs, where alginate functioned as both a reducing agent and a stabilizer (Figure 13). Sorption experiments indicated a higher loading of gold compared to silver on alginate. Evaluation of the alginate-stabilized silver and gold nanoparticles as catalysts for 4-nitrophenol reduction revealed that the reaction proceeded faster with silver compared to gold. Both catalysts exhibited high efficiency and followed zero-order kinetics, with silver demonstrating superior efficiency and recyclability [174].

Nguyen Quoc Hien *et al.* presented a study of a successful gamma irradiation method for synthesizing AuNPs using sodium alginate as a stabilizing agent. The size of the Au-NPs was influenced by the concentrations of Au^{3+} and alginate. By increasing the ratio of Au^{3+} to Au (0 to 6), larger and more uniformly sized AuNPs (40 nm) were achieved through the enlargement of seed particles (20 nm). These alginate-stabilized AuNPs, ranging in size from 5 nm to 40 nm, hold promise for various biological applications due to the biocompatibility of sodium alginate [175].

AuNPs can be synthesized by Yoki Yulizar *et al.* using a green, straightforward, and rapid technique that does not require a chemical reducing agent, with alginate serving both as a reducing agent and stabilizer. This synthesis method, assisted by microwave irradiation instead of conventional heating, offers improved efficiency. Alginate effectively acts as a capping agent for the resulting AuNPs, enhancing their stability. The concentration ratio of alginate to metal precursor and the pH of the reaction solution significantly impact the size, shape, and uniformity of the produced AuNPs [176].

Yasir Anwar *et al.* synthesized Alginate/Foam Particles (Alg/FP), Alginate-CoNi1/Foam Particles (Alg-CoNi1/FP), and Alginate/$CoNi_2$/Foam Particles (Alg/$CoNi_2$/FP) to stabilize zero-valent Cobalt (Co) nanoparticles (NPs). Among these, Alg-$CoNi_2$/FP@Co NPs showed the most significant inhibition of Bacillus subtilis growth. These catalysts were effective in degrading CR and methyl orange (MO) dyes, and reducing 4NP, with increased CoNi nanocomposite quantities enhancing performance. Alg-$CoNi_2$/FP@Co NPs exhibited the highest activity, particularly against MO dye degradation, with a rate constant of 4.68×10^{-1} min^{-1}. Superior performance was observed in both chemical and biological activities, highlighting the crucial role of the CoNi nanocomposite within the polymer network [177].

In conclusion, the versatility and efficacy of sodium alginate (Na-Alg) as a stabilizing agent and reducing agent in the synthesis of metal nanoparticles, particularly silver (AgNPs) and gold nanoparticles (Au-NPs), have been extensively explored across various studies [178]. These nanoparticles, incorporated into alginate-based materials or existing as standalone entities, exhibit remarkable properties ranging from antibacterial activity to catalytic prowess in diverse applications [56]. The eco-friendly nature of alginate, coupled with its biocompatibility and biodegradability, underscores its suitability for biomedical and environmental applications. Furthermore, the facile synthesis methods, including green and sustainable approaches, highlight the potential for scalable production of alginate-based nanocomposites for commercial utilization [161]. The promising results showcased in these studies not only validate the efficacy of alginate in nanoparticle synthesis but also pave the way for further exploration and innovation in the development of advanced materials with enhanced functionalities and applications in fields spanning from healthcare to environmental remediation [179].

6. Role of natural stabilizers in sustainable synthesis and biomedical applications

Recent advances have highlighted the potential of natural stabilizers in creating sustainable and functional nanomaterials, particularly metal nanoparticles [28]. Natural polymers like cellulose, starch, alginate, and chitosan have been widely explored due to their non-toxic, biodegradable, and eco-friendly properties, reducing dependence on harmful synthetic stabilizers. These materials act as reducing and capping agents, facilitating nanoparticle synthesis with improved stability and functionality [111].

For instance, plant-derived compounds, such as polyphenols and flavonoids, have been used in green synthesis to produce nanoparticles with intrinsic antimicrobial and antioxidant properties [92]. Such approaches enhance biocompatibility and biosafety, essential for biomedical applications like drug delivery, wound healing, and tissue regeneration. Recent studies also show that natural stabilizers contribute to stimuli-responsive drug delivery systems, making them valuable in cancer therapy and precision medicine [175].

Furthermore, innovations in using biopolymers derived from renewable resources (e.g., vegetable oils) have enabled applications in 3D printing, regenerative medicine, and biodegradable scaffolds. These scaffolds support cell growth and proliferation while maintaining mechanical strength and durability, vital for tissue engineering applications [51]. Functionalized nanomaterials synthesized using these stabilizers are being explored for theragnostic, combining therapy and diagnostics in a single platform. These advancements demonstrate the dual benefit of natural stabilizers: enabling eco-friendly nanoparticle synthesis and expanding the scope of biocompatible applications in the medical field. This reflects a promising shift towards sustainable nanotechnology with significant biomedical potential [161].

7. Miscellaneous natural stabilizers for the synthesis of metal nanoparticles

MNPs have garnered significant attention due to their unique properties and applications in various fields. Beyond conventional stabilizers, natural sources such as microorganisms, plant extracts, proteins, peptides, and other biomolecules offer eco-friendly and multifunctional alternatives. These natural stabilizers not only prevent agglomeration but also enhance the bioactivity of MNPs, broadening their application scope [6].

7.1 Microbial sources

Microorganisms like bacteria, fungi, and algae serve as effective stabilizing agents in MNP synthesis. These microbes secrete bioactive metabolites, including enzymes, proteins, and polysaccharides, which act as both reducing and stabilizing agents. For instance, Bacillus and Pseudomonas species are commonly used to synthesize silver and gold nanoparticles, while fungi such as Aspergillus and Penicillium produce extracellular enzymes that stabilize nanoparticles during their formation. Marine algae release polysaccharides and proteins that are particularly effective in stabilizing nanoparticles like ZnO and TiO_2, contributing to enhanced environmental applications [180].

7.2 Plant extracts

Plant-derived compounds such as polyphenols, flavonoids, alkaloids, and tannins are widely used as natural stabilizers. These biomolecules act as capping agents, providing stability and preventing nanoparticle agglomeration. For example, catechins from green tea act as efficient stabilizers for silver and gold nanoparticles, while flavonoids such as quercetin and rutin are effective for zinc oxide nanoparticle stabilization. Additionally, plant-based alkaloids impart not only stability but also bioactivity, making the resulting nanoparticles suitable for applications in antimicrobial and antioxidant fields [181].

7.3 Proteins and peptides

Proteins like gelatin, casein, and whey are excellent bio-friendly stabilizers, thanks to their ability to bind to the surface of nanoparticles through functional groups such as –SH, $–NH_2$, and –COOH. This binding enhances nanoparticle stability, biocompatibility, and biofunctionality. Similarly, peptides derived from biological systems stabilize MNPs through electrostatic interactions, making them suitable for drug delivery and targeted biomedical applications [182].

7.4 Other biomolecules

In addition to microorganisms and plant extracts, other bioactive molecules like vitamins, amino acids, and alkaloids play a significant role in nanoparticle stabilization. For instance, vitamin C (ascorbic acid) acts as both a reducing and stabilizing agent, while amino acids such as glutamic acid and lysine enhance nanoparticle dispersion and prevent agglomeration. Bioactive compounds like terpenoids and alkaloids add multifunctionality to MNPs by combining stabilization with antimicrobial or catalytic properties [183].

The nanoparticles synthesized using these natural stabilizers have numerous bioapplications. In the biomedical field, they serve as potent antimicrobial agents, effectively combating drug-resistant pathogens. For example, silver nanoparticles stabilized with plant polyphenols show enhanced bactericidal properties. Protein-stabilized nanoparticles are also used in drug delivery systems due to their biocompatibility and targeting ability, while gold nanoparticles stabilized with vitamins or alkaloids exhibit promising potential in anticancer photothermal therapy.

In environmental applications, biosynthesized nanoparticles have shown remarkable efficacy. Stabilizers derived from algal polysaccharides enhance the sensitivity and selectivity of MNPs for detecting heavy metals like lead (Pb^{2+}) and mercury (Hg^{2+}). Additionally, amino acid-stabilized zinc oxide nanoparticles catalyze the photo-degradation of toxic dyes in wastewater, addressing industrial pollution. In catalysis, MNPs stabilized with microbial enzymes or plant-based biomolecules demonstrate high efficiency in organic transformations such as oxidation and reduction reactions, offering greener solutions for industrial processes [184].

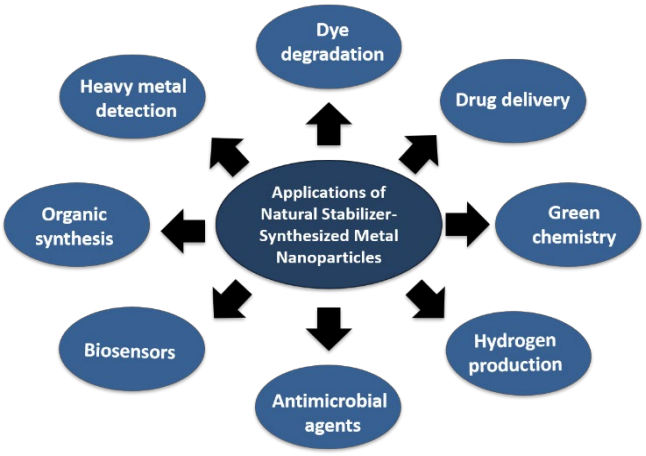

Figure 14. General applications of natural stabilizer-synthesized metal nanoparticles.

Nanoparticles synthesized using natural stabilizers, like plant extracts or biopolymers, have eco-friendly and sustainable applications. They are employed in environmental clean-up, including heavy metal ion detection and dye degradation, leveraging their biocompatibility and functional groups. In catalysis, they facilitate organic transformations under mild conditions, minimizing toxic waste. Their potential in biomedical applications, such as antimicrobial activity and targeted drug delivery, underscores their green and multifunctional nature, as depicted in Figure 14.

8. Comparison of characterization techniques and properties

NPs are extensively studied for their unique properties, including high surface area, optical activity, and catalytic potential. These properties are heavily influenced by the choice of stabilizing agents used during their synthesis. Stabilizers play a dual role: they prevent agglomeration and dictate the nanoparticles' morphology, size, stability, and overall functionality.

While synthetic stabilizers such as surfactants, polymers, and chemical reducing agents have been widely employed, natural stabilizers derived from biological sources—like microorganisms, plant extracts, proteins, and bioactive molecules—have emerged as eco-friendly and sustainable alternatives. The green synthesis approach, leveraging natural stabilizers, has gained prominence due to its non-toxic, cost-effective, and renewable nature [117].

Characterization techniques are pivotal in evaluating the differences between nanoparticles synthesized using natural and synthetic stabilizers, as discussed in Table 1. These techniques provide insights into crucial parameters such as particle size, morphology, stability, crystallinity, surface interactions, and thermal behavior. They also help to compare the effects of stabilizers on the colloidal and structural properties of nanoparticles. This comparison highlights the influence of natural stabilizers in producing nanoparticles with enhanced uniformity, smaller size, higher stability, and improved biocompatibility. The use of green stabilizers also aligns with the growing demand for sustainable nanotechnology applications in medicine, catalysis, and environmental remediation. Thus, understanding the distinctions revealed through characterization techniques is vital for advancing nanoparticle synthesis methodologies [108].

Table 1. Comparison of characterization techniques and properties for nanoparticle synthesis.

Characterization technique	Aspect studied	Natural stabilizers	Synthetic stabilizers	Influence of natural stabilizers	Reference
UV-Visible Spectroscopy	Surface Plasmon Resonance (SPR) Peaks	Narrow and sharper SPR peaks indicate smaller and uniform NPs.	Broader SPR peaks due to possible polydispersity.	Natural stabilizers enhance uniformity and reduce polydispersity.	[89]
Fourier Transform Infrared (FTIR) Spectroscopy	Functional group interaction	Peaks corresponding to biomolecules like phenols, and proteins.	Peaks represent synthetic stabilizers like polymers or surfactants.	Biomolecules bind through specific interactions, ensuring stability.	[115]
Dynamic Light Scattering (DLS)	Hydrodynamic size and polydispersity index (PDI)	Smaller hydrodynamic size with lower PDI values.	Larger hydrodynamic size and higher PDI values.	Biomolecules prevent agglomeration, ensuring uniform particle distribution.	[21]
Transmission Electron Microscopy (TEM)	Morphology and size distribution	Mostly spherical or polyhedral shapes, highly uniform sizes.	Irregular shapes and varied sizes due to uneven stabilization.	Natural stabilizers control morphology through biomolecular interactions.	[77]
X-Ray Diffraction (XRD)	Crystallinity and phase analysis	Peaks with sharper intensities due to reduced particle size.	Broader peaks indicating larger and less crystalline particles.	Smaller NPs with improved crystallinity are produced by natural stabilizers.	[108]
Zeta Potential Analysis	Surface charge and colloidal stability	Higher zeta potential values ensuring better stability.	Moderate to low zeta potential values leading to lower stability.	Natural stabilizers enhance stability by forming a robust bio-capping layer.	[99]
Thermogravimetric Analysis (TGA)	Thermal stability and organic content	Indicates the presence of organic biomolecules as stabilizers.	Minimal organic content; stability depends on synthetic agents.	Natural stabilizers contribute to thermal stability through strong capping.	[112]
Scanning Electron Microscopy (SEM)	Surface morphology	Smooth and well-defined surfaces.	Rough surfaces due to inconsistent stabilization.	Natural stabilizers improve surface quality via uniform binding.	[132]
Energy Dispersive X-Ray Analysis (EDX)	Elemental composition	Peaks for metals and biomolecules like carbon and oxygen.	Peaks only for metals and synthetic stabilizer components.	Natural stabilizers add bio-components that enhance functionality.	[140]
Stability Studies	Long-term stability in solution	Higher stability over extended periods.	Moderate stability, with potential aggregation over time.	Bio-capping prevents aggregation, increasing shelf life.	[103]

9. Comparison between natural and synthetic stabilizers for nanoparticle synthesis

Natural and synthetic stabilizers play pivotal roles in nanoparticle synthesis, with each offering distinct advantages depending on the application. Natural stabilizers, derived from renewable and biodegradable resources, are favored for their environmental benefits and biocompatibility, particularly in biomedical and eco-friendly applications. On the other hand, synthetic stabilizers provide superior control over nanoparticle size, shape, and stability, which makes them indispensable in specialized applications such as electronics and high-performance catalysts. The following table presents a detailed comparison between natural and synthetic stabilizers, highlighting key factors like cost, environmental impact, and versatility, helping researchers choose the most suitable stabilizer for specific needs, as discussed in Table 2.

10. Challenges and future directions

Despite significant advancements in the use of natural stabilizers for nanoparticle synthesis, several challenges remain that need to be addressed to fully harness their potential. One key challenge is the limited control over the size, shape, and dispersion of nanoparticles when using natural stabilizers, which may not always meet the precise requirements of specific applications. Additionally, the scalability of green synthesis methods remains a concern, particularly when translating laboratory-scale results to industrial production, where consistency and reproducibility are crucial.

Table 2. Comparison between natural and synthetic stabilizers for nanoparticle synthesis

Property	Natural stabilizers	Synthetic stabilizers	Best use cases	Reference
Source	Derived from renewable, biodegradable materials (e.g., cellulose, starch, chitosan)	Chemically synthesized, often petroleum-based or engineered polymers	Natural stabilizers are ideal when sustainability and eco-friendliness are prioritized, while synthetic stabilizers may be preferred for precise, controlled synthesis.	[36]
Biocompatibility	High biocompatibility, especially in biomedical applications	Can be biocompatible, but some synthetic stabilizers may have toxicity concerns	Natural stabilizers are often better suited for medical applications (drug delivery, tissue engineering), while synthetic stabilizers may be necessary in specialized industrial applications.	[44]
Environmental Impact	Low environmental impact, biodegradable and eco-friendly	Can have higher environmental costs, depending on synthesis process	Natural stabilizers are favorable for green chemistry, while synthetic stabilizers can be more suitable for high-performance applications, but may require careful disposal considerations.	[50]
Size	Smaller nanoparticles (typically < 50 nm). Narrow size distribution.	Larger nanoparticles with size > 50 nm. Broad size distribution.	Natural stabilizers provide controlled nucleation and growth due to biomolecular interactions, resulting in smaller and uniform nanoparticles.	[177]
Morphology	Uniform shapes, predominantly spherical, polyhedral, or rod-like. Smooth and well-defined surfaces.	Irregular or mixed morphologies. Surfaces may appear rough due to inconsistent stabilization.	Biomolecules selectively bind to specific crystal faces, directing uniform shape and smooth surface formation.	[77]
Stability	Highly stable colloids with zeta potential > ±30 mV. Resistant to agglomeration over long periods.	Moderate stability with zeta potential < ±20 mV. Prone to agglomeration and sedimentation over time.	Natural stabilizers form a robust bio-capping layer through hydrogen bonding, electrostatic, or van der waals interactions, enhancing long-term stability.	[112]
Cost	Generally cost-effective (if sourced locally)	Often more expensive, depending on the material and synthesis method	Natural stabilizers are more cost-effective in large-scale applications, while synthetic stabilizers may be justified for specialized or high-performance needs.	[36]
Recyclability	High recyclability due to biodegradability	Depends on the material; some synthetic stabilizers are non-recyclable	Natural stabilizers are better suited for applications with an emphasis on sustainability and recycling, while synthetic stabilizers may be necessary for reusable systems or when stability is paramount.	[50]
Versatility	Versatile for a range of applications (environmental remediation)	Highly versatile but limited by chemical composition and regulatory approval	Synthetic stabilizers can offer specialized functionality for a narrow set of applications, while natural stabilizers excel in diverse, eco-friendly scenarios.	[44]

Furthermore, the interaction of natural stabilizers with metal nanoparticles can sometimes lead to instability under extreme conditions, such as high temperatures or varying pH levels. Addressing the stability and durability of natural-stabilized nanoparticles is essential for applications in harsh environments, such as in catalytic processes and industrial settings.

In terms of future directions, there is a growing need for the development of hybrid stabilizers that combine the benefits of natural and synthetic materials. This could offer enhanced control over nanoparticle properties while maintaining the eco-friendly nature of natural stabilizers. Additionally, incorporating advanced techniques like machine learning and artificial intelligence into nanoparticle design could aid in predicting and optimizing the properties of stabilized nanoparticles, allowing for more efficient and targeted synthesis methods.

The use of natural stabilizers in biomedical applications, such as drug delivery and tissue engineering, holds great promise, but more research is required to understand their long-term biocompatibility, potential toxicity, and behavior in vivo. Exploring the integration of natural stabilizers with other biomaterials and nanostructures could lead to novel therapeutic and diagnostic solutions. Moreover, life-cycle assessments and sustainability evaluations will become increasingly important to ensure that the benefits of green synthesis methods outweigh their environmental and economic costs. Overall, continued research into natural stabilizers and their applications, coupled with interdisciplinary approaches, will likely pave the way for more sustainable, efficient, and impactful nanotechnology solutions in the future.

11. Conclusion

In conclusion, natural polymers such as cellulose, starch, alginate, hyaluronic acid (HA), and chitosan (CS) demonstrate remarkable potential in nanoparticle synthesis and functionalization due to their eco-friendly nature, biocompatibility, and versatility. Recent advancements, such as cellulose's role in green nanotechnology, have enabled sustainable alternatives for applications in catalysis, sensing, and biomedical devices, while starch, alginate, HA, and CS enhance nanoparticle stabilization for diverse uses like drug delivery and tissue engineering. However, future research should focus on tailoring natural stabilizers to achieve precise nanoparticle control, optimizing scalable production processes for industrial applications, and leveraging technologies like artificial intelligence for predictive modeling and design. Additionally, comprehensive lifecycle assessments to evaluate environmental impacts and the development of innovative biomedical applications, such as combating antimicrobial resistance and advancing regenerative medicine, will further establish these polymers as pivotal in shaping sustainable nanotechnology. By addressing these directions, the field will continue to evolve, aligning innovation with sustainability to tackle global challenges in healthcare and environmental remediation.

Acknowledgements

All authors are also thankful to Chandigarh University, Gharuan, Mohali, India, for their support and all other essential facilities to conduct this research.

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