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State of the Art on Tannin-Based Micro-/Nano-Carriers as Drug Delivery Systems: A Comprehensive Review

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Abstract

Introduction: Tannins are structurally diverse plant polyphenols increasingly recognized as sustainable building blocks for advanced drug delivery systems. Their capacity for hydrogen bonding, electronic interactions between aromatic moieties ("π-π stacking"), and metal coordination enables the formation of versatile nano- and micro-carriers with intrinsic antioxidant, anti-inflammatory, antimicrobial, and anticancer activities. This review synthesizes current evidence on tannin-based delivery platforms and evaluates their pharmaceutical relevance. **Methods:** A structured narrative review was conducted using major scientific databases, focusing on peer-reviewed studies (2010-2025) reporting clearly identified hydrolysable, condensed, or complex tannins formulated as nano- or micro-carriers. Data were extracted on fabrication strategies, physicochemical properties, drug-loading performance, release behavior, biocompatibility, and *in vitro*/*in vivo* outcomes. The current situation was analyzed qualitatively due to methodological heterogeneity across studies. **Results:** Tannin-based carriers, including metal-phenolic networks, self-assembled nanoparticles, nanogels, microcapsules, and layer-by-layer systems, consistently exhibit high encapsulation efficiencies (60% - 95%) and drug-loading capacities (5% - 30%). Particle sizes typically range from 50 - 400 nm, with negative sur-

face charges ensuring colloidal stability. Many systems demonstrate pH- and redox-responsive release, enhanced muco-adhesion, and synergistic bioactivity. Preclinical studies in cell lines, zebrafish, and rodent models report favorable biocompatibility, low toxicity, and improved therapeutic efficacy in wound healing, infection control, and oncology. **Discussion:** Compared with synthetic polymers, tannin-based carriers offer multifunctionality, biocompatibility, biodegradability, and compatibility with green chemistry principles. However, variability in tannin composition, lack of standardized characterization, and limited pharmacokinetic data constrain reproducibility and translation. **Conclusion:** Tannin-based micro-/nano-carriers represent promising, sustainable drug delivery platforms. Advances in standardization, mechanistic understanding, and GMP-oriented manufacturing are essential to unlock their full clinical and industrial potential.

Keywords

Tannins, Nanocarriers, Drug Delivery Systems, Metal-Phenolic Networks, Biocompatibility

1. Introduction

Tannins constitute a structurally diverse family of high-molecular-weight polyphenols [1]-[3] that play a pivotal role in plant physiology and have gained increasing recognition as renewable multifunctional building blocks in pharmaceutical sciences [4]-[9]. Based on their capacity of undergoing hydrogen bonding, electronic interactions between aromatic systems (so-called "π-π stacking"), hydrophobic interactions, and multidentate coordination with metal ions, tannins exhibit a unique molecular versatility that has positioned them as promising candidates for engineering advanced drug-delivery systems (DDSs) [3] [10]-[14]. Their widespread natural occurrence, low extraction cost, compatibility with green chemistry principles, and broad bioactivity further support their integration into sustainable pharmaceutical platforms.

In addition to serving as structural scaffolds, tannins exhibit intrinsic antioxidant activities and undiscriminating complexing capacities that translate into anti-inflammatory, antimicrobial, antiviral, cardioprotective, and anticancer properties in biological systems, widely documented across multiple biomedical investigations [15]-[17]. These properties are directly linked to their high phenolic density, resulting in redox activity and capacity to modulate key molecular pathways, including NF-κB, MAPK, and Nrf2 signaling. Their dual role as both bioactive co-adjuvants and nanocarrier-forming macromolecules renders them particularly attractive for designing multifunctional therapeutic systems [3] [10] [14] [18].

Recent advances in nanotechnology have enabled the synthesis of a broad range of tannin-based nano- and micro-carriers, including metal-phenolic networks

(MPNs), nanoparticles formed *via* solvent shifting and oxidative cross-linking, polymeric nanogels, nanocapsules, layer-by-layer (LbL) assemblies, microcapsules, emulsions, and organic-inorganic hybrid platforms [3] [8] [9] [12] [13] [18] [19].

The important high drug-loading capacities of tannin-based DDS arise from the dense distribution of phenolic hydroxyl groups and aromatic rings of tannins, which enable polyvalent hydrogen bonding and hydrophobic interactions, and "π-π stacking" with a wide range of therapeutic molecules, including active small-molecules, peptides, and polyphenolic agents [3] [11] [14] [18]. Furthermore, the intrinsic structural rigidity and redox activity of tannins contribute to enhanced stability against enzymatic and oxidative degradation, a property that is particularly valuable for protecting active small molecules and peptide-based therapeutics from premature metabolic breakdown [20]-[22].

Tannin-derived nanoparticles demonstrate pronounced mucoadhesive properties through specific interactions between tannins with mucins as well as epithelial surface proteins, resulting in prolonged residence at oral, gastrointestinal, or other mucosal interfaces, thereby enhancing drug absorption and bioavailability in oral, buccal, or intranasal delivery systems [23]-[26]. In addition, these nanostructures display the synergistic antioxidant and antimicrobial activities derived from both hydrolysable and condensed tannins used for their construction [16] [17]. Preclinical *in vivo* studies in rodent and zebrafish models also demonstrate favorable biocompatibility, minimal systemic toxicity, and efficient biodistribution, supporting the safety of tannin-based nanocarriers and aligning with the long-established use of tannins in food, nutraceutical, and traditional medicinal applications [27]-[32].

Tannin-based nanocarriers are increasingly recognized as versatile drug-delivery platforms due to their high loading capacity, stability, muco-adhesion, bioactivity, and *in vivo* biocompatibility. However, methodological heterogeneity, structural variability, limited solubility, oxidation, and inconsistent bioavailability hinder standardization, prompting exploration of formulation strategies such as nano-encapsulation, PEGylation, polymer blending, and protein-assisted co-assembly [10] [20].

The rapid growth of tannin-based nanotechnologies and the lack of a unified evaluation of their pharmaceutical potential highlight the need for a state-of-the-art review. This work aims to provide a comprehensive and integrative analysis of tannin-based nanocarriers as emerging materials for pharmaceutical applications, synthesizing current knowledge on their structural, physicochemical, and functional properties that enable effective drug delivery systems.

The review also identifies key opportunities for future research and translation, focusing on industrial-scale production, biomedical innovation, and pharmaceutical development. By consolidating mechanistic insights, analytical advances, and functional data across diverse tannin-based nano-delivery platforms, it serves as a valuable reference for researchers and innovators seeking to advance the practical

application of tannin nanotechnology in medicine.

2. Methods

This review was designed as an extensive state-of-the-art synthesis aimed at critically examining the current landscape of tannin-based nano- and micro-carriers. Therefore, a broad and structured literature search was conducted across major scientific databases, including PubMed, Scopus, Web of Science, Google Scholar and ScienceDirect, covering studies published mainly between January 2010 and January 2025. Search strategies combined keyword searches and free-text terms related to tannins, polyphenols, nanocarriers, metal-phenolic networks, biocompatibility, and drug-release behavior. Only peer-reviewed articles reporting explicitly identified tannins (hydrolysable, condensed, or complex) and describing nano- or micro-structured systems with physicochemical characterization and biomedical relevance were retained. Studies lacking identifiable tannin content, insufficient characterization, or non-pharmaceutical context were excluded.

Moreover, eligible studies were examined in full and categorized according to formulation parameters, physicochemical attributes, and biological performance. Extracted information included tannin source and type, fabrication methods (e.g., nanoprecipitation, self-assembly, layer-by-layer assembly, interfacial complexation, metal-phenolic network formation), morphological features, particle size and surface charge, encapsulation efficiency, loading capacity, degradation and stimuli-responsive behaviors, as well as drug-release kinetics and stability in physiological conditions. Biological outcomes such as antioxidant and antimicrobial activity, cytotoxicity, biocompatibility, *in vivo* safety, and therapeutic efficacy in models of wound healing, inflammation, infection, or cancer were systematically documented.

Overall, the data were analyzed mainly qualitatively owing to differences in tannin types, fabrication methods and assessed outcomes. Methodological limitations, contradictions across studies, and variability in tannin characterization were critically evaluated, with attention to translational aspects such as scalability, reproducibility, and alignment with pharmaceutical development pathways. No quantitative meta-analysis was performed, as outcome measures and experimental conditions were not standardized across studies.

3. Results

3.1. Chemical Basis and Structural Determinants of Tannin-Based Micro- and Nano-Carriers

Tannins are broadly classified into hydrolyzable tannins, condensed tannins, and complex tannins, with each category providing distinct molecular features that govern their behavior during the self-assembly of nano- and micro-structured carriers. Hydrolyzable tannins, such as gallotannins and ellagitannins, consist of gallic or ellagic acid residues esterified onto polyols like glucose, a structural configuration that affords a high density of phenolic hydroxyl groups and enables extensive

multidentate hydrogen bonding, rapid metal coordination, and strong affinity for proteins [3] [13] [14] [24] [25] [33]-[38].

In contrast, condensed tannins or proanthocyanidins—oligomeric or polymeric flavan-3-ols—possess rigid aromatic frameworks that promote π-π stacking, hydrophobic interactions, and redox-active behavior, features that support sustained drug loading and slower, more controlled release profiles [20] [34] [38].

Complex tannins, which integrate structural traits from both hydrolyzable and condensed groups, exhibit broadened reactivity and enhanced conformational flexibility, allowing the formation of hybrid carriers with tunable physicochemical characteristics [35] [39] [40].

These fundamental structural distinctions influence the resulting nanocarrier's morphology, size distribution, stability, degradability, and drug-binding affinity, thereby shaping its performance and applicability in drug-delivery systems [3] [10].

3.2. Fabrication Strategies for Tannin-Based Micro-/Nano-Carriers

A wide range of fabrication strategies has been developed for producing tannin-based micro- and nano-carriers, each imparting specific physicochemical, structural, and biopharmaceutical characteristics. Among these, self-assembly-driven approaches such as the formation of metal-phenolic networks (MPNs) represent the most extensively investigated approach. These systems emerge through the rapid coordination of tannins, particularly galloylated structures, with multi-valent metal ions such as Fe^{3+}, Cu^{2+}, Mn^{2+}, Zn^{2+} or Al^{3+}, yielding highly ordered architectures capable of forming hollow capsules or core-shell nanospheres [14] [29] [41]-[50]. Their dynamic metal-ligand interactions confer pH-responsive assembly and disassembly, a property especially beneficial for targeted release in acidic tumor microenvironments or inflamed tissues. MPNs also demonstrate strong affinity for active small-molecules, peptides, and nucleic acids, supporting encapsulation efficiencies often exceeding 70% - 95% and applying the intrinsic chelation and coordination behavior of tannins described in the uploaded review [13] [18] [51].

Another widely used fabrication technique is nanoprecipitation or solvent displacement, in which condensed tannins are transferred from organic or hydroalcoholic media into aqueous phases, resulting in spontaneous particle formation driven by hydrophobic collapse and phenolic interactions. Yet this approach works best for very controlled systems, in which the rather soluble tannins are forced to precipitate not only based on a shift in solvents, but also by means of a co-precipitant that the tannins complex. This method provides fine control over particle size, typically ranging from 80 to 300 nm and enables the preparation of systems with narrow polydispersity indices when mixing conditions are optimized [52] [53]. The preservation of native polyphenolic structures allows these composite nanoparticles to retain strong antioxidant activity, consistent with the reactivity patterns of

condensed tannins highlighted in prior analytical studies.

Oxidative cross-linking constitutes a third fabrication route, relying on the auto-oxidation of phenolic hydroxyl groups into quinones that subsequently undergo covalent cross-linking. This process leads to the formation of nanogels or highly stable nanoparticles with enhanced colloidal stability, slower degradation kinetics, and suitability for controlled-release formulations. Such oxidation-driven polymerization mechanisms parallel the oxidative transformations described in ellagitannin biosynthesis and other tannin-related reactions [54]-[60].

In addition, interfacial complexation between tannins and macromolecules, such as proteins, chitosan, alginate, or lignin, enables the formation of microcapsules at the interface of immiscible phases. These structures exploit the strong protein-precipitating and polysaccharide-binding properties of tannins [30], making them particularly suitable for topical drug delivery, wound-healing formulations, and systems for oral applications requiring gastroprotective shells.

Finally, layer-by-layer (LbL) assembly offers a versatile route for constructing nanostructures with high structural precision. Alternating deposition of tannins with cationic polymers (e.g., poly-l-lysine, chitosan) or proteins yields multilayered films or capsules with tightly tunable shell thickness, enabling the encapsulation of labile biomolecules, such as enzymes, peptides and nucleic acids, and offering adjustable degradation and release profiles [61]-[66]. These assembly behaviors align with the strong intermolecular interactions that tannins undergo, documented in the chemical and structural analyses presented in this review.

3.3. Physicochemical Properties of Tannin-Based Micro-/Nano-Carriers

Tannin-based micro- and nano-formulations demonstrate physicochemical properties that vary according to the tannin class, fabrication method, and material interactions. Reported particle sizes for tannin-derived nanoparticles typically fall within the 50 - 400 nm range, a size window consistent with other polyphenol-based nanomaterials and favorable for cellular uptake and systemic distribution. Microcarrier systems, particularly those produced through interfacial complexation or spray-drying, are generally larger, ranging from 1 to 50 μm, aligning with observations made for plant-derived polyphenolic matrices.

Surface charge profiles also follow a consistent pattern: most tannin-based systems exhibit negative zeta potentials between −15 and −45 mV, reflecting the abundance of deprotonated phenolic groups and conferring satisfactory colloidal stability under physiological conditions [29] [30] [67]-[69]. Morphologically, metal-phenolic networks (MPNs) tend to form smooth and uniform spherical particles due to coordinated metal-ligand self-assembly, whereas tannin-chitosan composites display rougher surfaces resulting from electrostatic interactions and polymer-polyphenol entanglement [3] [10] [11].

Encapsulation performance across studies indicates that tannin-based carriers possess intrinsically high affinities for structurally diverse therapeutic agents. This

includes alkaloids, flavonoids, curcuminoids, antibiotics, anti-inflammatory molecules, and anticancer agents such as doxorubicin, cisplatin and paclitaxel, a property arising from the polyvalent binding capacity of tannins through hydrogen bonding, hydrophobic interactions, π-π stacking, and metal coordination [10] [40] [70]-[77].

Consequently, encapsulation efficiencies (EE%) commonly range between 60% - 95% [7] [8] [14], while drug-loading capacities (DL%) span 5% - 30%, values markedly higher than those observed for many synthetic polymers [78]-[81]. These high efficiencies reflect not only the chemical versatility of tannins but also their ability to form dense supramolecular networks that accommodate both hydrophilic and hydrophobic drug species.

Drug-release behavior in tannin-based delivery systems is dictated by a combination of structural and environmental factors. Many formulations exhibit pH-responsive release, especially MPNs, whose coordination bonds partially dissociate under mildly acidic conditions typical of tumor microenvironments and inflamed tissues [8] [14] [82]-[85]. The susceptibility of tannins to oxidation-induced structural loosening and their controlled micro-/nano-carriers degradation in physiological media further modulate release kinetics [29] [86].

In hydrogel-based systems, swelling behavior plays an additional regulatory role. Release profiles from such gels often conform to well-established kinetic models, including Higuchi diffusion, Korsmeyer-Peppas anomalous transport, and first-order release kinetics for hydrophilic drugs.

Overall, consistently, studies report accelerated release at pH values below 6.5, highlighting the relevance of tannin-based carriers for targeted drug delivery in acidic pathological niches such as tumors, infected tissues, and chronic wounds [82]-[85] [87] [88].

3.4. Biological Activities of Tannin-Based Micro-/Nano-Carriers

Tannins exhibit potent antioxidant and anti-inflammatory activities that arise directly from their polyphenolic structure [15] [89]. Their high density of hydroxyl groups allows for efficient scavenging of reactive oxygen species (ROS), thereby reducing oxidative burden in damaged or inflamed tissues [16] [90].

In parallel, tannins modulate central inflammatory signaling pathways, notably by downregulating NF-κB and MAPK activation and suppressing the expression of pro-inflammatory mediators such as COX-2 [10] [16] [91]. These biochemical effects support fibroblast proliferation, extracellular matrix remodeling, and accelerated tissue regeneration mechanisms that collectively strengthen both wound-healing outcomes and systemic anti-inflammatory responses [70] [89].

In addition to these anti-inflammatory effects, tannins demonstrate broad-spectrum antimicrobial properties attributable to their ability to disrupt bacterial and fungal physiology at multiple levels [76] [90] [92]-[98]. They destabilize microbial membranes, interfere with quorum-sensing pathways, chelate essential metal ions required for microbial metabolism, and compromise fungal cell wall integrity

[17] [23] [26].

Nanostructured formulations such as tannin-lignin and tannin-chitosan capsules amplify these effects through increased surface reactivity and sustained release profiles. As a result, they inhibit clinically relevant pathogens, including *Staphylococcus aureus*, *Pseudomonas aeruginosa*, *Escherichia coli*, and *Candida* species, supporting their application in infection control and wound care [3] [70] [96].

Tannin-based nanocarriers also exhibit promising antitumor synergies through several complementary mechanisms. Their capacity to enhance cellular uptake improves intracellular drug accumulation, while their intrinsic redox activity sensitizes tumor cells to oxidative stress, increasing susceptibility to chemotherapeutic agents [15] [31] [66] [90] [99] [100].

Furthermore, many tannin-derived nanostructures display pH-responsive behavior, enabling targeted drug release within acidic tumor microenvironments and thereby reducing off-target toxicity. MPNs loaded with doxorubicin, in particular, have demonstrated selective release and enhanced cytotoxicity against cancer cells, while maintaining favorable biocompatibility in healthy tissues [23] [26] [51]. In summary, these properties demonstrate the potential of tannin-based systems as effective, multifunctional platforms for oncology.

3.5. *In Vitro* Biocompatibility and Cytotoxicity

Across the literature, tannin-based micro-/nano-carriers consistently demonstrate a favorable biocompatibility profile [27] [29] [31]. Most formulations maintain high cell viability, typically exceeding 80% - 95% in fibroblasts, keratinocytes, and endothelial cell lines, reflecting the well-documented cytocompatibility of both hydrolysable and condensed tannins [3] [16]. Similarly, these systems exhibit low hemolytic activity, generally below 5%, which aligns with the known membrane-stabilizing and antioxidant properties of tannins that mitigate erythrocyte damage [10].

Inflammatory responses also remain minimal, as tannins are recognized for downregulating pro-inflammatory mediators and modulating pathways such as NF-κB and MAPK, further supporting their biological safety in pharmaceutical applications.

At very high concentrations, typically above 200 - 400 μg/mL, certain condensed tannins have been reported to induce moderate reactive oxygen species (ROS) generation. However, these levels remain markedly lower than those observed with several synthetic polymeric carriers, reflecting the inherent redox-buffering capacity of natural polyphenols [15] [99] [101]. Overall, the collective findings indicate that tannin-based nanocarriers combine structural functionality with an advantageous safety profile, making them strong candidates for further translational development.

3.6. *In Vivo* Performance and Toxicology

Preclinical investigations using zebrafish (*Danio rerio*) embryos consistently demon-

strate the high biocompatibility of tannin-based nanomaterials [27]. At standard exposure concentrations, these studies report less than 10% morphological abnormalities, absence of cardiac edema, normal hatching rates, and no significant induction of apoptosis, as confirmed through qRT-PCR analysis of apoptotic and oxidative stress markers [27]. These findings align with the recognized safety profile of natural tannins and their limited embryotoxicity, supporting the use of zebrafish as a sensitive and reliable model for evaluating early-stage toxicity of phenolic-based nanostructures [15] [16].

Complementary rodent studies further reinforce the favorable *in vivo* performance of tannin-derived nanocarriers, including MPNs and self-assembled nanoparticles [102]. These systems exhibit prolonged systemic circulation times, likely attributable to their surface chemistry and capacity to interact with serum proteins, as well as significant reductions in inflammatory markers in wound-healing models, mirroring the documented anti-inflammatory and antioxidant activities of hydrolysable and condensed tannins [10] [17]. Dermatological studies confirm excellent dermal tolerability, with no evidence of irritation or histopathological alteration, consistent with the long-standing topical use of tannin-rich plant extracts in traditional medicine [29] [103]-[105].

Tannin-based micro- and nanocarriers have shown strong antitumor activity and excellent biocompatibility across preclinical models, with studies in zebrafish and xenograft-bearing rodents providing converging evidence of their biomedical potential. In oncology models, tannin-based nanoparticles reduce tumor volume by improving drug delivery to tumor tissues while also leveraging the intrinsic anticancer properties of specific tannin subclasses, such as ellagitannins and proanthocyanins. These effects align with mechanistic insights indicating that tannins can modulate oxidative stress, inhibit proliferative signaling pathways, and enhance therapeutic efficacy when used as co-adjuvants in nano-formulations. Collectively, these findings support the translational promise of tannin-based carriers as safe and effective platforms for diverse therapeutic applications [29] [46] [62] [106]-[108].

3.7. Application Domains

Tannin-based hydrogels, microcapsules, and nanoparticles have demonstrated significant potential in the field of wound healing, owing to the intrinsic astringent, antimicrobial, anti-inflammatory, and antioxidant properties of tannins. These systems promote faster wound closure by accelerating granulation tissue formation, reducing fibrin burden, and modulating the inflammatory response, partly through downregulation of pro-inflammatory mediators and stabilization of extracellular matrices.

Their strong antimicrobial effects further help prevent bacterial colonization and biofilm formation, making tannin-derived biomaterials particularly attractive for the management of diabetic foot ulcers, burns, and chronic non-healing wounds [10] [29] [70] [109].

In oncology, tannin-based nanocarriers leverage several advantageous mechanisms that enhance intra-tumoral drug accumulation and therapeutic efficacy. Their nanoscale size supports enhanced permeability and retention (EPR) effects within tumor vasculature, while the pH-responsive nature of tannin-metal or tannin-polymer assemblies enables selective drug release in acidic tumor microenvironments [16] [23] [26] [90].

Additionally, the inherent redox-modulating activity of tannins contributes to synergistic oxidative stress regulation, which may enhance the activity of chemotherapeutics such as doxorubicin, curcumin, cisplatin, and nucleic acid-based therapies, including siRNA [29] [31] [88] [90] [110].

For oral delivery and gastroprotection, tannins provide functional advantages linked to their stability in acidic environments and their capacity to form mucoadhesive complexes with mucins and epithelial proteins. These interactions protect sensitive therapeutic agents from gastric degradation and enhance mucosal residence time, thereby improving absorption and bioactivity. Tannin-based carriers have shown promise for the oral administration of probiotics, peptides, anti-ulcer phytochemicals, and anti-inflammatory agents, reflecting their long-standing role in modulating gastrointestinal physiology and microbial homeostasis [17] [25].

Emerging evidence also supports the potential of tannin-derived nanomaterials in neurology and neuroprotection. Due to their potent antioxidant properties and ability to interact with cellular membranes, some tannin-based nanoparticles have demonstrated an experimental capacity to cross the blood-brain barrier (BBB), where they reduce oxidative damage and may mitigate neuroinflammatory cascades associated with neurodegenerative disorders [90] [100] [111] [112]. Although still at a preliminary stage, these findings highlight a promising pathway for the development of tannin-enabled neurotherapeutic delivery systems.

4. Discussion

Tannin-based micro- and nanocarriers represent a promising class of bio-derived delivery systems that combine structural versatility, biocompatibility, and inherent therapeutic activity. The findings of this review consolidate evidence from the past decade, highlighting both the strengths and limitations of tannin-centered nanotechnology. While the literature demonstrates converging trends regarding physicochemical performance and biological compatibility, several methodological inconsistencies and translational challenges remain to be addressed before full pharmaceutical exploitation can be achieved.

4.1. Mechanisms of Action and Functional Advantages

The remarkable self-assembly behavior of tannins, arising from their capacity to engage in extensive hydrogen bonding, electronic interactions between aromatic systems ("π-π stacking"), other hydrophobic interactions, and metal-ion coordination [14] [16] [35] [39] [90] enables the formation of highly adaptable supra-

molecular architectures that are difficult to replicate using conventional synthetic polymers. As extensively described in structural and physicochemical studies of hydrolysable and condensed tannins, the density and spatial arrangement of phenolic hydroxyl groups allow tannins to establish multi-valent interactions with a wide range of therapeutic molecules, thereby supporting consistently high encapsulation efficiencies, often ranging between 60% and 95%, across nanoprecipitation, interfacial assembly, metal-phenolic network formation, and layer-by-layer methods [3] [10] [14] [33] [84] [85]. These polyvalent interactions also confer structural stability to nano- and micro-scale assemblies, a property linked to tannins' inherent molecular rigidity and their ability to form extended cross-linked networks [18].

Beyond their structural versatility, tannin-based carriers exhibit pH- and redox-responsive release behavior, a consequence of tannin ionization states, metal-phenolic coordination equilibria, and redox-active catechol or galloyl groups. These features make tannin nanocarriers particularly suitable for site-specific drug delivery in tumor microenvironments, infected tissues, and inflamed regions, where acidic pH and oxidative stress gradients are prominent [83] [86] [113] [114]. The uploaded review highlights that such stimuli-responsive mechanisms derive directly from tannins' intrinsic chemical reactivity and conjugation patterns.

In addition, tannins possess inherent antioxidant, antimicrobial, and anti-inflammatory activities, attributes well documented in phytochemical and biomedical literature and rooted in their redox-active phenolic structures and protein-binding properties [10] [15] [17] [31]. These functionalities provide an important biological advantage over widely used synthetic materials such as PLGA, PEGylated systems, and inert hydrogels, which primarily serve as passive delivery matrices.

By contrast, tannin-based carriers can simultaneously modulate oxidative stress, inhibit pathogen growth, and attenuate inflammatory cascades, thereby contributing directly to therapeutic outcomes. This dual structural-bioactive functionality is especially valuable in wound healing and oncology, where oxidative imbalance, microbial burden, and inflammation play central roles in disease progression and treatment resistance. These properties underscore the potential of tannins to act as multifunctional, responsive, and biologically active nanomaterials, positioning them as a compelling alternative to traditional polymeric carriers in next-generation drug-delivery strategies.

4.2. Comparison with Other Polyphenol- and Polymer-Based Systems

When compared to other naturally occurring polyphenols, such as lignans and lignins, tannins exhibit a distinctively higher capacity for metal chelation, stemming from their dense array of catecholic and gallic polyphenolic groups, which enable multidentate coordination and robust complex formation [14] [41].

Their structural multiplicity also confers a greater propensity for intermolecular and intramolecular cross-linking, facilitating the formation of stable supramo-

lecular assemblies and enhancing their utility in nano-architectured systems [11] [54] [67] [115] [116].

Likewise, tannins demonstrate a remarkably high affinity for biomacromolecules, including proteins, lipids, and polysaccharides, due to polyvalent hydrogen bonding and hydrophobic interactions properties that surpass those documented for simpler phenolics such as catechins and stilbenes [25]. This same chemical versatility underlies their superior colloidal stability in MPNs, a behavior widely exploited in the fabrication of responsive nanocarriers [18] [113].

In contrast with widely used synthetic polymers such as PLGA, PVP, or PEG, tannins offer several intrinsic advantages. They are naturally biodegradable through hydrolysis or microbial enzymatic degradation, aligning them with metabolic pathways common to plant-derived polyphenols [21] [51].

Many tannin-based nano-formulation processes, including metal-phenolic coordination, self-assembly, and nanoprecipitation, can be performed without the need for toxic organic solvents, enhancing their attractiveness for biomedical applications and improving compliance with green chemistry principles [3] [10] [117].

However, the use of tannins also introduces a well-recognized challenge: batch-to-batch variability caused by natural source heterogeneity, differences in plant species, environmental conditions, extraction methods, and degrees of polymerization [38] [51].

These comparisons highlight the unique positioning of tannins as a transitional class of biomaterials that bridge natural polyphenols and engineered nanomaterials. Their chemical richness and ecological sustainability offer distinct advantages; however, realizing their full pharmaceutical potential will depend on further advances in standardization, detailed chemical profiling, and the development of reproducible manufacturing workflows.

4.3. Contradictions and Heterogeneities in the Literature

Despite the expanding body of research on tannin-based nanomaterials, several inconsistencies continue to challenge the comparability and interpretability of published findings. A first source of variability arises from the heterogeneity of tannin origins and compositions. Botanical differences, including plant species, anatomical plant part, geographical conditions, and extraction solvent, substantially influence the molecular weight distribution, phenolic density, degree of galloylation and presence of non-tannin impurities.

In addition, these factors are well documented in foundational analyses of hydrolysable and condensed tannins, which highlight how structural complexity and compositional diversity complicate standardization across studies [31] [36]-[38] [51]. As a result, formulations prepared under nominally similar conditions frequently report divergent particle sizes, zeta potentials, encapsulation efficiencies, and release profiles differences that likely reflect underlying chemical disparities rather than true methodological effects.

A second source of inconsistency relates to the lack of standardized fabrication parameters for tannin-derived nanocarriers. Studies employing MPNs, nanoprecipitation, or self-assembly techniques often differ widely in solvent selection, metal-to-tannin stoichiometry, pH control, mixing speeds, and purification strategies. Variations in these parameters have been shown to markedly influence coordination chemistry, cross-linking density, and supramolecular assembly kinetics, thereby affecting final morphology and drug-loading behavior [18] [51]. The uploaded review similarly underscores that even minor adjustments in extraction or fabrication protocols can produce significant shifts in colloidal stability and functional performance of tannin-based carriers. Such methodological divergence ultimately hampers reproducibility and limits the ability to conduct meaningful cross-study comparisons.

A third persistent challenge arises from inconsistent biological testing protocols used to assess cytotoxicity, biocompatibility, and therapeutic activity. Studies frequently rely on non-comparable cell lines, heterogeneous exposure durations, assay types with differing sensitivity (e.g., MTT) and highly variable concentration ranges. These discrepancies lead to conflicting reports regarding safety thresholds and biological responses to tannin-based nanoparticles. As noted in several toxicological assessments, tannins can exhibit dose-dependent dual behavior, antioxidant at low concentrations and pro-oxidant or cytotoxic at higher doses, which requires standardized testing conditions to accurately interpret [15] [40]. Without harmonized protocols or suitable normalization tools, which could, for example, be based on tannin purity and structural homogeneity, it remains difficult to determine whether observed differences in cytotoxicity arise from intrinsic material properties, assay variability, or experimental design.

4.4. Biocompatibility and Toxicity Considerations

Overall, tannin-based micro-/nano-carriers demonstrate a favorable biocompatibility profile, consistent with the long-recognized safety of hydrolysable and condensed tannins in traditional medicinal, nutritional, and biomedical contexts.

Their inherently low cytotoxicity is largely attributed to the well-defined phenolic architecture and the capacity of tannins to interact reversibly with proteins, lipids, and polysaccharides [3] [10] [11] [23] [38]. Nonetheless, several specific considerations must be acknowledged when evaluating their toxicological behavior. At elevated concentrations, certain condensed tannins have been shown to induce moderate levels of ROS, likely due to their redox-active catechol and pyrogallol motifs, which can undergo autoxidation under physiological conditions [15].

In addition, the incorporation of transition metals during the formation of MPNs may pose risks if the coordination environment is unstable; poorly chelated Fe^{3+} or Cu^{2+} ions can catalyze localized oxidative stress *via* Fenton-like reactions, a phenomenon reported in several MPN-based systems [14] [18] [113]. Another source of variability arises from crude plant extracts, where non-tannin impuri-

ties, such as residual alkaloids, terpenoids, or oxidized phenolics, may influence cellular responses and confound toxicity assessments.

Evidence from *in vivo* studies remains encouraging. Zebrafish embryotoxicity assays consistently show low mortality, absence of major morphological abnormalities, and minimal disruption of developmental gene networks when exposed to well-characterized tannin-based formulations [27] [118]. These findings align with the biocompatible nature of purified gallotannins, ellagitannins, and proanthocyanidins described in the biosynthesis and characterization literature [90].

Similarly, rodent studies demonstrate favorable dermal tolerability, reduced inflammatory responses, and improved healing outcomes in topical or transdermal applications, reinforcing the therapeutic potential and safety margin of these systems [17] [23] [26] [102].

Despite these positive indications, important knowledge gaps remain. Long-term biodistribution, systemic accumulation, and metabolic pathways of tannin-based nanocarriers are still insufficiently characterized, especially under conditions of repeated oral or parenteral administration. The complexity of tannin polymerization, the potential formation of oxidative metabolites and the influence of gut microbiota on tannin degradation further underscore the need for systematic pharmacokinetic and toxicokinetic investigations [10] [16] [119] [120]. Addressing these gaps will be essential to support their safe translation into pharmaceutical products and to refine regulatory frameworks for plant-derived nanomaterials.

4.5. Industrial and Pharmaceutical Translation Challenges

Despite a strong foundational body of evidence demonstrating the chemical versatility, biological activity and technological promise of tannin-based micro-/nano-carriers, relatively few of these systems have advanced toward clinical translation. Several critical barriers continue to impede regulatory progression and industrial deployment.

A major obstacle is the lack of reproducibility and standardization in tannin composition across botanical sources and extraction procedures. As highlighted in this review, tannins exist as complex, heterogeneous mixtures whose structural profiles vary according to species, harvesting conditions, solvent polarity and purification strategies [3] [38] [68] [121].

Such batch-to-batch variability complicates physicochemical characterization and undermines the consistency required for pharmaceutical development. Robust standardization frameworks, encompassing optimized extraction, controlled purification, and validated analytical workflows such as high pressure liquid chromatography (HPLC) MS for qualitative and quantitative analyses [20] [122] [123] matrix-assisted laser-desorption ionization coupled to time-of-flight based mass spectrometry (MALDI-TOF) MS [124]-[126] quantitative ^{31}P nuclear magnetic resonance (NMR) spectroscopy [20] [127] [128] and quantitative or semi-quantitative heteronuclear spin quantum coherence (HSQC) NMR analysis [129]-[131] are essential to ensure reproducibility and regulatory acceptability.

Regulatory acceptance presents a second challenge. Agencies such as the Food and Drug Administration (FDA), European Medicines Agency (EMA), African Medicines Agency (AMA) and West African Economic and Monetary Union (WAEM) GMP authorities require that any natural-origin material intended for human use be supported by rigorous chemical characterization, validated manufacturing processes, and comprehensive toxicological safety packages aligned with the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) guidelines. As noted in prior evaluations of polyphenols and tannins for biomedical use, natural origin does not exempt a material from demonstrating safety, purity and batch consistency [10] [11] [15] [121] [132]. This expectation is particularly relevant to tannins, whose structural heterogeneity and reactivity demand careful control to avoid regulatory ambiguity.

A third barrier concerns scale-up and industrial manufacturing. While MPNs and LbL assemblies exhibit excellent performance at the laboratory scale, their industrial translation remains limited by challenges related to controlled mixing technologies, purification at high throughput, solvent recycling, and maintaining particle size distribution within narrow specifications. Similar constraints have been reported for other natural biomaterial-based nanocarriers, highlighting the need for scalable, eco-friendly, and GMP-compatible production platforms [18] [23] [26] [29] [114].

A final limitation is the scarcity of *in vivo* pharmacokinetic and biodistribution studies. Although many publications provide extensive *in vitro* characterization of tannin-based nanoparticles, including drug-loading efficiency, release kinetics and cytocompatibility, comparatively fewer studies investigate absorption pathways, systemic biodistribution, metabolic fate, clearance mechanisms, or long-term safety in animal models.

Without detailed pharmacokinetic profiling, translational progress from bench to bedside remains slow, mirroring challenges encountered in the broader field of polyphenol-based therapeutics. Therefore, these barriers illustrate that the future success of tannin-based drug-delivery systems relies not only on their inherent bio-functionality but also on advancements in standardization, regulatory science, scalable engineering and systematic *in vivo* evaluation.

4.6. Opportunities for Future Research

Over the past decade, tannin-based nanotechnology has emerged as a highly dynamic and fertile domain for pharmaceutical innovation, driven by the structural versatility, bioactivity, and sustainability of tannin-derived materials. Building on the advances outlined in this review, several strategic research directions are essential to accelerate scientific progress and translational adoption.

A first priority is the development of standardized extraction and characterization frameworks, as current methodologies remain heterogeneous across studies. Robust analytical fingerprints, based on HPLC, liquid chromatography coupled

to mass spectrometry (LC-MS), quantitative NMR spectroscopy, and MALDI-TOF spectrometry, are needed to ensure reliable identification of tannin subclasses, degree of polymerization, and phenolic subunit composition. Such standardization would allow for an eventual refining of tannins, such as to arrive at more homogeneous compounds, and thus address long-standing challenges associated with the intrinsic complexity of hydrolysable and condensed tannins and would align tannin analytics with contemporary pharmaceutical quality requirements.

Future progress also depends on deeper mechanistic investigations into the molecular basis of drug-tannin interactions. Advanced computational and experimental tools, including molecular dynamics simulations, ligand docking, synchrotron-based scattering methods, and microfluidic-assisted nano-assembly, offer powerful avenues to elucidate binding thermodynamics, supramolecular self-assembly, and nanoscale structural evolution. These approaches have already proven invaluable in related polyphenol and MPN systems [14] [18] [32] [113] and are poised to reveal fundamental principles governing the behavior of tannin nanostructures.

From a translational standpoint, there is an urgent need to establish GMP-oriented manufacturing pathways capable of supporting production on industrial scales. The intrinsic advantages of tannins, their natural abundance, biodegradability and compatibility with green chemistry principles, make them ideal candidates for sustainable, energy-efficient, and environmentally sustainable fabrication strategies. Developing scalable production lines will be essential for regulatory acceptance, commercialization, and integration into pharmaceutical supply chains [3] [11] [23] [35] [45] [90] [121].

The application space for tannin-based nanocarriers is constantly expanding, and several high-potential biomedical innovations warrant targeted exploration. These include mucosal vaccine platforms leveraging the mucoadhesive and immunomodulatory properties of tannins, theranostic nanoplatforms combining imaging and therapeutic functions, neuroprotective delivery systems for polyphenol-sensitive neurological pathways, and topical formulations for infectious or inflammatory skin disorders where the antimicrobial and anti-inflammatory effects of tannins may provide synergistic therapeutic benefit. In addition, tannin-based systems show promise for gut microbiota-targeted therapies, consistent with their established interactions with intestinal microbes and mucosal surfaces [3] [16] [17] [23] [120].

Finally, tannin-based nanotechnologies hold significant promise for clinical translation in low- and middle-income countries, particularly in Africa, where their low cost, local availability, and compatibility with plant-based industrial infrastructures offer unique advantages. By enabling locally manufacturable and scalable drug-delivery platforms, tannin-derived carriers may support regional pharmaceutical sovereignty, align with traditional medicinal practices, and offer cost-effective alternatives for priority health challenges in resource-limited settings. These future directions underscore the transformative potential of tannin-based nano-

materials and highlight the multidisciplinary collaborations required to translate this promising class of bio-derived nanocarriers into clinically and industrially impactful technologies.

5. Conclusions

Tannin-based micro-/nano-carriers have emerged as a highly promising class of sustainable, multifunctional, and biocompatible delivery systems within modern pharmaceutical sciences. Their unique molecular architecture, defined by polyphenolic versatility, multidentate coordination capacity, and strong intermolecular interaction potential, enables the formation of structurally robust nanoscale assemblies capable of transporting a wide variety of therapeutic agents. The intrinsic biological properties of tannins, including antioxidant, anti-inflammatory, antimicrobial, and antitumor effects, further enhance their appeal by offering built-in pharmacological synergies absent in most synthetic excipients.

Across the literature, tannin-derived carriers consistently demonstrate high encapsulation efficiencies, favorable release profiles, excellent stability, and strong performance in both *in vitro* and *in vivo* models. These findings support their potential use across several therapeutic domains, particularly wound healing, oncology, gastrointestinal delivery, infection control, and oxidative-stress-related pathologies. Studies employing zebrafish and rodent models reinforce their safety and biodegradability, while metal-phenolic networks and self-assembled nanoparticles illustrate impressive adaptability for both hydrophilic and hydrophobic drugs, as well as peptides and nucleic acids.

However, despite abundant proof-of-concept work, several critical gaps impede pharmaceutical translation. Variability in tannin composition, lack of standardized analytical characterization, heterogeneous fabrication methods, and insufficient pharmacokinetic data all pose major obstacles to industrial scalability and regulatory approval. Likewise, long-term biodistribution and metabolic fate remain underexplored, especially for chronic administration or high-dose regimens. Addressing these challenges requires harmonized quality-control procedures, GMP-aligned production strategies, mechanistic elucidation using advanced analytical and computational tools, and more comprehensive preclinical evaluations.

Looking forward, tannin-based nano- and micro-technologies stand at the forefront of green nanomedicine, offering cost-effective, eco-friendly, and clinically relevant alternatives to synthetic polymeric carriers. Their accessibility and low production costs make them particularly attractive for pharmaceutical development in low- and middle-income countries, where local manufacturing capacity and affordable therapeutics are urgently needed. By integrating advances in nanotechnology, biopharmaceutics, analytical chemistry, and industrial pharmacy, tannin-based systems hold the potential to evolve from laboratory innovation to clinically validated, globally accessible drug-delivery platforms.

In summary, tannins represent one of the most versatile natural biomaterials available for nanomedicine. With continued interdisciplinary research and careful

standardization, tannin-based nano- and micro-carriers could play a transformative role in the future of drug delivery, personalized medicine, and sustainable pharmaceutical development.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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