Therapeutic potential of biosynthesized nanoparticles using *Echinacea* species in biological applications

Potencial terapéutico de nanopartículas biosintetizadas a partir de especies de *Echinacea* en aplicaciones biológicas

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Highlights

- *Echinacea* species exhibits significantly enhanced therapeutic efficacy when integrated with nanoparticles, showing potent antimicrobial, anticancer, and immunomodulatory effects.
- Nanoparticle formulations improve bioavailability, targeted delivery, and pathogen inhibition, positioning *Echinacea*-based nanosystems as a superior alternative to conventional extracts.
- Systematic characterization demonstrates that nanoparticle-assisted *Echinacea* preparations consistently outperform traditional formulations in biomedicine.

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SYSTEMATIC REVIEW

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ABSTRACT

Introduction. *Echinacea* species, particularly *Echinacea purpurea*, possess bioactive compounds with antimicrobial, antioxidant, and immunomodulatory properties. When formulated into nanoparticles, these compounds may overcome limitations of solubility, stability, and bioavailability, thereby enhancing therapeutic potential against conditions such as antimicrobial resistance, oxidative stress, immune dysregulation, and cancer. **Objective.** The aim was to synthesize available evidence on the physicochemical properties and biomedical applications of *Echinacea*-based nanostructures. **Methods.** A systematic literature search was conducted in PubMed, Google Scholar, and ScienceDirect following PRISMA guidelines. Peer-reviewed studies in English describing *Echinacea*-derived nanoparticles with reported biomedical or therapeutic effects were included. Non-peer-reviewed and non-English works were excluded. Screening was performed in two stages, and data on nanoparticle properties, analytical methods, and biological outcomes were narratively synthesized. From 2,862 records, 22 studies met inclusion criteria. **Results.** Evidence consistently demonstrated that *Echinacea*-derived nanoparticles possess multifunctional biological activities. Inorganic systems showed strong antimicrobial, antioxidant, and anticancer effects, with performance influenced by particle size, crystallinity, and surface chemistry. Polymeric and lipid-based carriers improved stability, enhanced bioactive retention, and promoted higher cell viability, while hybrid systems such as electrospun nanofibers integrated antimicrobial action with wound-healing capacity. Immunomodulatory and anti-inflammatory outcomes were frequently reported, confirming broad therapeutic relevance. **Conclusions.** Nanoparticle-enhanced formulations of *Echinacea* exhibit strong potential for innovative biomedical applications, including antimicrobial coatings, wound healing, immunotherapy, targeted drug delivery, and chronic disease management. To advance clinical translation, future work must focus on standardizing synthesis protocols, ensuring long-term safety, and clarifying underlying molecular mechanisms.

RESUMEN

Introducción. Las especies de *Echinacea*, especialmente *Echinacea purpurea*, contienen compuestos bioactivos con propiedades antimicrobianas, antioxidantes e inmunomoduladoras. Al formularse en nanopartículas, pueden superar limitaciones de solubilidad, estabilidad y biodisponibilidad, potenciando su valor terapéutico frente a la resistencia antimicrobiana, el estrés oxidativo, la desregulación inmunitaria y el cáncer. **Objetivo.** Sintetizar la evidencia disponible sobre las propiedades fisicoquímicas y las aplicaciones biomédicas de nanostructuras derivadas de *Echinacea*. **Métodos.** Se realizó una búsqueda sistemática en PubMed, Google Scholar y ScienceDirect siguiendo PRISMA. Se incluyeron estudios revisados por pares en inglés que describieran nanopartículas basadas en *Echinacea* con efectos biomédicos reportados. Se excluyeron trabajos no revisados por pares o en otros idiomas. El cribado se hizo en dos etapas y los datos sobre propiedades, métodos analíticos y resultados biológicos se sintetizaron de forma narrativa. De 2.862 registros, 22 cumplieron los criterios. **Resultados.** Las nanopartículas derivadas de *Echinacea* muestran actividades biológicas multifuncionales. Los sistemas inorgánicos presentaron efectos antimicrobianos, antioxidantes y anticancerígenos, influenciados por parámetros como tamaño, cristalinidad y química superficial. Los sistemas poliméricos y lipídicos mejoraron estabilidad, retención de bioactivos y viabilidad celular. Los sistemas híbridos, como nanofibras electrohiladas, combinaron actividad antimicrobiana y capacidad de cicatrización. Se observaron también efectos inmunomoduladores y antiinflamatorios. **Conclusiones.** Las formulaciones de *Echinacea* basadas en nanopartículas ofrecen potencial para aplicaciones biomédicas innovadoras, como recubrimientos antimicrobianos, cicatrización de heridas, inmunoterapia, liberación dirigida de fármacos y manejo de enfermedades crónicas. Su avance clínico requiere estandarizar la síntesis, evaluar la seguridad a largo plazo y aclarar mecanismos moleculares.

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INTRODUCTION

For millennia, nature has served as a source of therapeutic compounds, with medicinal plants and herbs forming the foundation of both traditional and modern medicine [1]. These plants are reservoirs of bioactive phytochemicals with diverse biological and pharmacological properties, making them indispensable in the development of natural remedies and pharmaceutical agents [2]. Among these, the *Echinacea* genus—commonly known as purple coneflower—has gained prominence due to its widespread use in traditional medicine. Native to North America, *Echinacea* comprises nine distinct species, of which *Echinacea purpurea*, *Echinacea pallida*, and *Echinacea angustifolia* are the most extensively studied for their medicinal properties [3-4].

The therapeutic efficacy of *Echinacea* is attributed to its diverse bioactive profile, including polysaccharides, alkylamides, glycoproteins, flavonoids, and phenolic acids such as chicoric, caffeic, and chlorogenic acids [5-6]. In *Echinacea purpurea* specifically, major constituents include caffeic-acid derivatives (e.g., chicoric, caftaric, and chlorogenic acids), alkylamides (isobutylamides), high-molecular-weight polysaccharides and glycoproteins, and flavonoids (e.g., quercetin and kaempferol) [7-8]. These compounds collectively underpin antimicrobial, antioxidant, anti-inflammatory, anticancer, and immunomodulatory activities [9-10]. Nevertheless, clinical translation of *Echinacea*-derived compounds is constrained by low bioavailability, poor solubility, and instability under physiological conditions [11].

Nanotechnology offers strategies to mitigate these limitations. Conventional nanoparticle synthesis typically relies on chemical reduction (e.g., borohydrides), sol–gel processing, hydro/solvothermal routes, thermal decomposition, microemulsions, or physical techniques such as sputtering and laser ablation—approaches that often involve toxic reagents, high energy input, and hazardous by-products [12-13]. By contrast, green (biogenic) synthesis leverages plant extracts in which endogenous phytochemicals (polyphenols, sugars, proteins, alkylamides) serve as reducing and capping/stabilizing agents to produce nanomaterials, offering advantages in cost, environmental compatibility, energy efficiency, and biocompatibility [14-15]. The objective of this review is not to compare conventional versus green methods; the methods overview is provided to justify the focus on *Echinacea*-mediated, green synthesis routes relevant to biomedical use.

E. purpurea is particularly notable for its immune-modulating constituents, especially alkylamides, which enhance the phagocytic activity of polymorphonuclear leukocytes and increase natural killer cell cytotoxicity [16]. These immune-enhancing mechanisms contribute to its broader antimicrobial profile. Indeed, several *in vitro* and *in vivo* studies have documented inhibitory effects of *Echinacea* extracts against bacterial pathogens, such as *Staphylococcus aureus* and *Escherichia coli*, as well as antiviral activity against influenza and herpes viruses [10]. Such findings underscore the relevance of *Echinacea* as a dual-function agent: providing direct antimicrobial activity while also boosting host defense pathways.

Beyond its direct biological activity, *Echinacea* extracts have been employed in the green synthesis of diverse nanoparticles, including gold, silver, nickel, iron, zinc, copper, and polymeric systems [17-18]. In these processes, secondary metabolites act as natural reducing and capping agents, enabling the rapid and eco-friendly production of stable nanostructures without the need for harsh chemicals. The physicochemical properties of the resulting nanoparticles—such as size, morphology, and surface charge—have been shown to influence their biomedical performance. For instance, silver nanoparticles synthesized with *Echinacea* extracts have demonstrated potent antibacterial effects, while gold nanoparticles exhibit promise in targeted drug delivery and cancer therapeutics [19-20]. The ability of *Echinacea* to mediate the synthesis of multiple nanoparticle classes highlights its versatility as a biological platform for nanomedicine.

Despite growing momentum, no consolidated synthesis currently integrates *Echinacea* phytochemistry, green nanoparticle synthesis, and downstream biomedical applications. This gap impedes systematic evaluation of translational potential. Accordingly, this review addresses the research question: What is the current evidence on the development, pharmacological activities, and therapeutic applications of nanoparticles synthesized from *Echinacea* extracts?

METHODS

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. The objective was to identify and synthesize peer-reviewed studies examining the medicinal and therapeutic properties of nanoparticles synthesized from *Echinacea* extracts. A structured approach was applied across all stages of the process, including literature search, study selection, data extraction, and synthesis.

Search Strategy

A comprehensive literature search was performed across three major databases: Google Scholar, PubMed, and ScienceDirect. For PubMed, the full search equation used was: PubMed search equation: ("Echinacea" [Title/Abstract] and ("nanoparticle" or "nanoformulation" or "nanotechnology") [Title/Abstract] and ("medicinal" or "therapeutic" or "biological activity") [Title/Abstract]). *Filters:* English language; *Article type*: Journal Article. *Search period*: Database inception to 15 December 2024. *Time of last search*: 09:00–11:30 UTC. Google Scholar and ScienceDirect searches used the keyword combinations "Echinacea" and "medicinal properties" and "nanoparticles", with no temporal restrictions to maximize coverage. Reference lists of included studies were manually screened to identify additional relevant publications. Only peer-reviewed articles published in English were included. Non-English studies were excluded due to resource limitations that prevented reliable translation and critical appraisal.

Inclusion and Exclusion Criteria

Inclusion criteria. (i) studies explicitly evaluating nanoparticles synthesized from *Echinacea* extracts; (ii) investigation of medicinal, or therapeutic activities of such nanoparticles; (iii) peer-reviewed journal articles written in English. *Exclusion criteria.* (i) articles with unavailable full texts, unpublished data, theses, or final-year university projects; (ii) non-English publications; (iii) editorial comments, newspaper articles, preprints, or other non-peer-reviewed sources.

Article Screening and Selection

To minimize bias and ensure reproducibility, study selection was conducted in two stages. First, titles and abstracts were screened against the predefined inclusion criteria: direct assessment of *Echinacea*-mediated nanoparticle synthesis and investigation of associated medicinal, or therapeutic properties. Studies outside this scope—for example, those focusing solely on *Echinacea* cultivation, general phytochemistry, or unrelated nanomaterials—were classified as *irrelevant content* and excluded. Second, full-text evaluation of shortlisted studies was conducted to confirm eligibility. Studies were excluded if they failed to meet inclusion criteria, contained incomplete or inconsistent data, or were duplicates.

Data Extraction

For all eligible studies, key details—including title, year of publication, country of origin, study type, nanoparticle characteristics, analytical techniques, and principal findings—were systematically recorded in an Excel database. This standardized documentation ensured transparency, facilitated cross-study comparison, and provided a reliable foundation for synthesis.

Quality Assessment

No formal critical appraisal instrument—such as the Joanna Briggs Institute (JBI) appraisal tools, Critical Appraisal Skills Programme (CASP) checklists, or Cochrane Risk of Bias (RoB) instruments—was applied to the included studies. This represents a methodological limitation, as the absence of a structured quality assessment may affect the reliability and comparability of findings. Instead, methodological rigor was assessed descriptively by examining clarity of synthesis protocols, adequacy of nanoparticle characterization, completeness of biological or pharmacological assays, and transparency of reported outcomes. Although this approach allowed for basic evaluation, future reviews would benefit from standardized appraisal frameworks.

Consistency With the Research Question

To maintain alignment between the research question and methodology, biological and pharmacological activities were identified and classified according to predefined therapeutic categories central to the review's objective. These categories included antimicrobial, antioxidant, anti-inflammatory, anticancer, immunomodulatory, and wound-healing activities. Classification was based strictly on measurable experimental evidence—such as inhibition zone diameters, radical scavenging IC_{50} values, cytokine modulation, cell

viability outcomes, ROS assays, or histological markers of tissue repair. Only studies reporting at least one quantifiable pharmacological or biological endpoint were included, ensuring that all extracted data directly informed the evaluation of therapeutic potential in *Echinacea*-based nanoparticles.

Data Synthesis

The initial database search yielded 2,862 records. During the initial screening, 2,618 records were excluded, including 2 duplicates, 18 non-English studies, and 2,596 records that did not meet the eligibility criteria. This left 244 studies for full-text assessment. Among these, 15 studies were excluded due to unavailable full texts, and 211 studies were excluded after detailed evaluation for reasons such as methodological ineligibility or lack of relevance to the research objectives. Consequently, 20 studies met the inclusion criteria. Additionally, 2 studies were identified through manual reference checking, resulting in a total of 22 studies included in the final synthesis **(Figure 1)**.

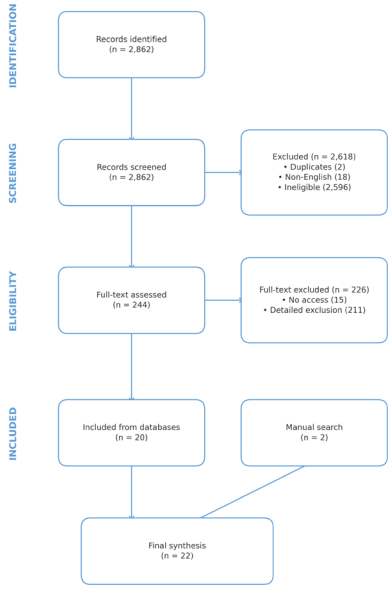

Figure 1: PRISMA flow diagram illustrating the systematic search, screening, eligibility assessment, and inclusion process used in this review.

This systematic review integrates the findings from these 22 studies, with emphasis on the medicinal and therapeutic efficacy of nanoparticles synthesized from *Echinacea* extracts. The synthesized evidence provides critical insights into their potential biomedical and pharmaceutical applications, supporting further translational research and clinical exploration.

RESULTS

A total of twenty-two studies met the inclusion criteria. Publication frequency increased in recent years: three studies were published in 2018, one in 2019, two in 2020, two in 2021, seven in 2022, six in 2023, and one in 2024. The median publication year was 2022, indicating a concentration of recent research output. Geographically, Asia contributed the majority of studies (17/22; 77.3%), led by Iran (11 studies), followed by India (2), Taiwan (2), China (1), and Saudi Arabia (1). Europe accounted for four studies (18.2%), predominantly from Turkey (3) and Romania (1), while Africa was represented by a single study from Egypt (1/22; 4.5%). This distribution reflects regional clustering in countries with active research programs in medicinal plants and nanotechnology.

Types of Nanoparticles Reported

Across the surveyed literature, a wide spectrum of nanoparticle systems has been reported, reflecting the diversity of approaches to exploiting both inorganic and organic nanostructures **(Table 1)**. Inorganic nanoparticles represented the largest share (approximately half of the studies), including silver, gold, zinc oxide, copper, nickel, iron oxide, and selenium nanoparticles. Organic carriers such as liposomes, niosomes, and phytosomes accounted for roughly one-fifth of the formulations, while polymeric systems (e.g., chitosan, alginate, Eudragit) comprised a similar proportion. A smaller subset of studies investigated hybrid or composite nanoparticles (~7%), combining organic polymers with inorganic cores to achieve multifunctionality. This distribution highlights a dual emphasis: harnessing the intrinsic reactivity of crystalline, metal-based nanoparticles and engineering biocompatible carriers for drug delivery and bioactive stabilization.

Physicochemical and Morphological Characterization

Characterization data consistently demonstrated the importance of using complementary analytical techniques. Reported particle sizes ranged from ultra-small ZnO nanoparticles (14–45 nm) to much larger systems, including polyphenol–Zn complexes (~300 nm) and phytosome lipid particles (135–380 nm). Inorganic nanoparticles most frequently fell in the 10–100 nm domain, although certain formulations (e.g., ZnO 90–170 nm; AgNPs up to ~347 nm) extended beyond this range. Polymeric and lipid-based systems generally exhibited broader distributions (200–400 nm), reflecting the influence of encapsulation, matrix density, and vesicle swelling on particle growth.

Optical properties provided robust indicators of nanoscale features. Ultraviolet–visible spectroscopy revealed size-dependent band shifts: ZnO nanoparticles absorbed at ~375 nm compared to ~385 nm for ZnO microparticles, corresponding to a band gap increase from 3.22 eV to 3.31 eV. Metallic nanoparticles displayed well-defined surface plasmon resonance peaks—AgNPs at 468–481 nm and AuNPs at ~560 nm—validating their successful formation and demonstrating sensitivity to particle size and polydispersity. Fourier-transform infrared spectroscopy consistently identified functional groups involved in nanoparticle reduction and stabilization. Common signatures included O–H/N–H stretches at 3200–3500 cm^{-1}, C=O

vibrations around 1580–1630 cm^{-1}, and metal–oxygen bands between 518–636 cm^{-1}, confirming both organic capping and inorganic core structures. Polymeric formulations exhibited additional peaks, such as C–N stretching near 1059–1098 cm^{-1} in chitosan/alginate systems and ester vibrations at 1743 cm^{-1} in electrospun nanofibers, indicative of matrix-specific interactions. Morphological studies (SEM, TEM, AFM) predominantly described spherical to quasi-spherical nanoparticles, though composite and encapsulated systems displayed greater heterogeneity. Crystallographic analyses via XRD confirmed expected phases, including wurtzite ZnO and face-centered cubic Ag and Au, with crystallite sizes frequently reported in the 30–70 nm range.

Encapsulation and Phytochemical Loading

A consistent trend across encapsulation studies was an increase in nanoparticle size following incorporation of bioactive compounds. For instance, alginate/chitosan nanoparticles expanded from 245 ± 1.6 nm (unloaded) to 335 ± 1.4 nm when loaded with *E. angustifolia*. Phytosome lipid particles exhibited a broad 135–380 nm size range, while niosomes varied from 119 to 395 nm depending on extract composition and vesicle swelling.

These shifts reflect encapsulation efficiency and heterogeneity in phytochemical loading. Quantitative phytochemical analyses further highlighted the impact of nanoformulation. High-performance liquid chromatography studies demonstrated altered retention of bioactives, such as a ~76% reduction in isobutylamides in nano-*E. purpurea* extract (0.21 mg/g) compared to crude extract (0.88 mg/g), suggesting controlled release kinetics.

Conversely, catechin content was enhanced in AgNP systems (55.0 mg/g vs. 51.0 mg/g in ethanolic extract), likely due to nanoparticle-mediated stabilization. Calibration curves for key phytochemicals (e.g., cichoric acid with $R^2 = 0.9998$ in electrospun nanofibers) further supported the reproducibility of these assays. Additionally, GC–MS analysis of Eudragit RS100 nanoparticles revealed dominant phytochemical constituents, including melezitose (24.95%) and palmitic acid (14.44%), highlighting the dual role of sugars and fatty acids as both structural stabilizers and bioactive payloads. Gas chromatography–mass spectrometry provided mechanistic insights into the role of phytochemicals in green synthesis. Compounds such as phytol (17.7%) and germacrene D (17.7%) were repeatedly identified in Ni- and Fe-based nanostructures, confirming their dual function as natural reducing and stabilizing agents.

Therapeutic Activities of *Echinacea*-Based Nanoparticles

The reviewed studies demonstrated a broad spectrum of biomedical activities for *Echinacea*-mediated nanoparticles, encompassing antimicrobial, antioxidant, anticancer, anti-inflammatory, immunomodulatory, antidiabetic, and wound-healing functions **(Table 2)**. Antimicrobial activity was most consistently reported. ZnO nanoparticles inhibited both Gram-positive and Gram-negative bacteria, with inhibition zones ranging from 10–16 mm against *Staphylococcus aureus*, 9–12 mm against *Streptococcus mutans*, and 14–18 mm against

Enterococcus faecalis [8]. Fungal inhibition was also evident, with zones of 9–14 mm against *Candida albicans*. Comparative studies showed that AuNPs produced stronger antibacterial effects (19.5 mm for *S. aureus*, 15.6 mm for E. coli) than ZnO nanoparticles (11.5 and 10.2 mm, respectively) [10]. Ni-doped FeOOH nanowires exhibited superior antibacterial activity against *S. aureus* compared to undoped FeOOH, while combined NiS + FeOOH systems demonstrated synergistic DNA cleavage activity, highlighting the enhanced performance of doped or composite nanostructures [29].

Nanoparticles	Size	Techniques	Key Findings	Ref.
ZnO NPs / ZnO MPs	NPs: 14–45 nmMPs: 25–70 nm	DLS, SEM, UV-Vis, XRD, FTIR, HPLC	UV-Vis: ZnO NPs absorb ~375 nm, MPs ~385 nm.Band gap: 3.31 eV (NPs), 3.22 eV (MPs).FTIR: 3429 cm^{-1} (O–H), 536 cm^{-1} (ZnO), 1631 cm^{-1} (C=O), 1061 cm^{-1} (S=O).	**(21)**
ZnO NPs / Au NPs	ZnONPs: 90–170 nmAuNPs: 80–120 nm	UV-Vis, FTIR	UV-Vis: 368 nm (ZnO), 560 nm (Au).FTIR: 3482 cm^{-1} (–OH), 1226 cm^{-1} (O–H).	**(22)**
Silver NPs (Ep-AgNPs)	XRD: 77.8 nmSEM: 30–95 nm	UV-Vis, FTIR, XRD, SEM	UV-Vis peak: 468 nm.FTIR: 3175 cm^{-1} (O–H), 518 cm^{-1} (Ag–O).	**(17)**
Chitosan/Pectin NPs (E. pallida/CS/PN)	CS/PN: 122.3 nmE. pallida: 113.5 nm	FTIR, XRD, SEM	FTIR: 1059 cm^{-1} (C–N), 3334 cm^{-1} (N–H, O–H).	**(23)**
ALG/CS NPs – E. angustifolia	Free: 245.1 ± 1.57 nmLoaded: 335.3 ± 1.43 nm	FTIR, SEM, DLS	FTIR: 3435 cm^{-1} (N–H/O–H), 1098 cm^{-1} (C–N).	**(19)**
Polyphenol-Zn NPs	~300 nm	IR, Cryo-TEM	IR: 1542 cm^{-1} (amide II), 3436 cm^{-1} (–OH).	**(24)**
EP-Eudragit RS100 NPs	—	Electrospinning, GC-MS, SEM	GC-MS: Melezitose (24.95%), Palmitic acid (14.44%).	**(25)**
***E. angustifolia*-loaded Niosomes**	119.1–395.4 nm	SEM, TEM, FTIR	FTIR: 1020 cm^{-1} (C–O); reduced intensity in niosomes.	**(26)**
ZnO NPs / MPs	NPs: ~40 nmMPs: >1 µm	XRD, AFM, TEM, SEM, FTIR	FTIR: 3429 cm^{-1} (O–H), 536 cm^{-1} (ZnO).	**(27)**
EPLPs	135.6–380 nm	DLS, SEM, TEM, XRD, UV-Vis, HPLC	FTIR: 2924.82 cm^{-1}.HPLC peaks: CGA (1.56 min), CA (8.36 min).	**(28)**
AgNPs	68.24 nm	XRD, EDX, SEM, UV-Vis, FTIR	UV-Vis: 481 nm.FTIR: 3203 cm^{-1} (O–H), 1585 cm^{-1} (C=O).	**(14)**
NiS-NPs / Ni-doped FeO(OH) NWs	—	GC-MS	Phytol (17.7%), Germacrene D (17.7%).	**(29)**
FeOOH NPs	30–60 nm	XRD, FTIR, SEM, TEM, MTT	FTIR: 3451 cm^{-1} (O–H), 623 cm^{-1} (C–H), 559–636 cm^{-1} (Fe–O).	**(30)**
Nano-encapsulated *E. purpurea*	218 ± 42 nm	SEM, DLS, HPLC	HPLC isobutylamides: 0.21 mg/g (nano-EE) vs. 0.88 mg/g (EE).	**(31)**
AgNPs	62–347.5 nm	XRD, DLS, HPLC, UV-Vis	HPLC: Catechin 55.004 mg/g (Emw) vs. 51.008 mg/g (Ee).	**(32)**
Nanoparticle Ethanolic Extract	145 ± 11 nm	HPLC, SEM, DLS	Cichoric acid curve $R^2 = 0.9998$.	**(33)**
Electrospun Nanofibers	128.78 nm	FESEM, FTIR	FTIR: 2936 cm^{-1} (C–H), 1743 cm^{-1} (PCL ester).	**(34)**

Table 1. Characterization Techniques and Key Properties of Nanoparticles

NPs: Nanoparticles; **MPs**: Microparticles; **DLS:** Dynamic Light Scattering; **SEM:** Scanning Electron Microscopy; **UV-Vis:** Ultraviolet-Visible Spectroscopy; **XRD:** X-Ray Diffraction; **FTIR:** Fourier Transform Infrared Spectroscopy; **HPLC:** High-Performance Liquid Chromatography; **SPR:** Surface Plasmon Resonance; **TEM:** Transmission Electron Microscopy; **AFM:** Atomic Force Microscopy; **EDX:** Energy Dispersive **X-Ray** Spectroscopy; **GC-MS:** Gas Chromatography-Mass Spectrometry; **FESEM:** Field Emission Scanning Electron Microscopy; **MTT** Assay: 3-(4,5-Dimethylthiazol-2-yl)-2,5-Diphenyltetrazolium Bromide Assay; **PCL:** Polycaprolactone; **CL**: Caprolactone.

Electrospun PVA nanofibers and PCL/PVA/CL/EP hybrid fibers extended antimicrobial activity to wound healing contexts, where they reduced inflammatory cell infiltration, accelerated wound closure, and supported tissue regeneration [23, 36].

Antioxidant activity was robustly validated through radical scavenging assays. Ep-AgNPs exhibited potent antioxidant effects, with IC_{50} values of 6.34 μg/mL (DPPH) and 3.46 μg/mL (ABTS), alongside a reducing power of 3.45 μmol/mg [11]. In comparison, *E. purpurea*–AgNP formulations displayed higher IC_{50} values (21.9 mg/mL for DPPH; 8.0 mg/mL for ABTS), indicating moderate activity but improved reducing power relative to ethanolic extracts [27]. Simple AgNPs and polymer-encapsulated systems demonstrated comparable antioxidant responses, with differences largely attributable to particle size, surface capping, and phytochemical content [37]. Nano-EE and Nano-EE5X systems further combined antioxidant action with antidiabetic or cartilage-protective effects, reducing oxidative stress and inflammatory markers while improving glucose tolerance and joint health [30, 34].

Anticancer and cytotoxic activities varied depending on nanoparticle type and target cell line. ZnO nanoparticles and *E. purpurea*–ZnO composites exhibited selective cytotoxicity against MCF-7 breast cancer cells, while concurrently enhancing PBMC proliferation without impairing $CD4^+$ T cell viability [25]. Goethite (FeOOH) nanoparticles reduced survival of A549 lung cancer cells in a dose-dependent manner, while PPZn nanoparticles exerted antiglycation effects, downregulated apoptosis, and promoted extracellular matrix maintenance through COL1A2 upregulation [22, 29].

In contrast, alginate/chitosan nanoparticles encapsulating *E. angustifolia* extract increased cell viability to 90.5%, compared with 57.5% for the free extract, confirming their cytoprotective role and reduced off-target toxicity [7]. Chitosan/pectin nanoparticles further demonstrated combined antimicrobial and cytoprotective properties.

These systems effectively inhibited bacterial growth and biofilm formation, while exhibiting low cytotoxicity in cell-based assays, underscoring their potential as safe and multifunctional carriers for *Echinacea* extracts [21].

Immunomodulatory effects were demonstrated across multiple nanoparticle systems. Eudragit RS100 nanoparticles loaded with *E. purpurea* increased WBC counts, lymphocytes, TNF-α, and IL-1β compared to plain extract, indicating strong immune stimulation [31]. Liposomal nanoparticles similarly enhanced immune responses, elevating IgA and IgG levels in vaccinated broilers and improving resistance against H9N2 and *Mycoplasma gallisepticum* [32]. Cerium oxide nanoparticles further synergized with *Echinacea* extracts, enhancing hematological parameters (RBCs, hemoglobin, leukocytes) and antioxidant levels, with the mixture performing better than either component alone [35].

Anti-inflammatory properties were evident in ZnO nanoparticles, which achieved 77% inhibition in albumin denaturation assays, comparable to diclofenac sodium [33]. Nano-EE5X formulations significantly reduced inflammatory mediators, improved cartilage integrity, and alleviated pain in osteoarthritis models,

demonstrating targeted therapeutic applications [34]. Collectively, these findings establish that *Echinacea*-based nanoparticles provide not only pathogen inhibition and antioxidant protection but also immune enhancement, cytoprotection, and tissue regeneration, supporting their translational promise across multiple therapeutic domains.

Table 2: Summary of Nanoparticle Types, Methods, and Their Associated Biological Activities.

S#	Nanoparticles	Methods/ Techniques	Activities	Key Findings	Ref.
1	**ZnO Nanoparticles**	Disk Diffusion	Anticarcinogenic	S. aureus (10–16 mm); S. mutans (9–12 mm); E. faecalis (14–18 mm); C. albicans (9–14 mm).	**(20)**
2	**ZnO & Gold Nanoparticles**	Well Diffusion	Antibacterial	ZnONPs: S. aureus (11.5), E. coli (10.2). AuNPs: S. aureus (19.5), E. coli (15.6).	**(22)**
3	**Silver NPs (Ep-AgNPs)**	DPPH, ABTS, Reducing Power	Antioxidant	DPPH IC50 = 6.34 µg/mL; ABTS IC50 = 3.46 µg/mL; reducing power 3.45 µmol/mg.	**(17)**
4	**Chitosan/Pectin NPs**	Well Diffusion, MTT	Antimicrobial, Anti-biofilm, Cytotoxicity	Effective antibacterial, biofilm inhibition, low cytotoxicity.	**(23)**
5	**Alginate/Chitosan NPs**	MTT	Cytotoxicity	Viability: free extract 57.5%, NPs 85.5%, EA-loaded NPs 90.5%.	**(19)**
6	**PPZn Nanoparticles**	Western Blot, TUNEL, Cell Cycle	Anti-glycation, Apoptosis inhibition	Reduced AGEs; ↑COL1A2; improved cell cycle; apoptosis inhibition.	**(24)**
7	**EP-Eudragit RS100 NPs**	Cytokines, CBC, ELISA	Immunomodulatory	↑WBC, lymphocytes, TNF-α, IL-1β vs. extract alone.	**(32)**
8	**Electrospun PVA Nanofibers**	IHC, Histology, MIC, MBC	Antibacterial, Wound healing	↓ inflammation; ↑ hair growth; ↓ wound size.	**(25)**
9	**E. purpurea + ZnO NPs/ MPs**	Cytotoxicity, PBMC proliferation	Anticancer	↑ cytotoxicity in MCF-7; ↑ PBMC proliferation; no effect on CD4+.	**(27)**
10	**Liposomal Nanoparticles**	ELISA	Immune enhancement	↑IgA, ↑IgG in broilers; improved protection vs H9N2 & MG.	**(33)**
11	**E. purpurea + AgNPs**	DPPH, Reducing Power	Antioxidant, Antimicrobial	DPPH IC50 21.9 mg/mL; ABTS IC50 8.0 mg/mL; ↑ reducing power.	**(14)**
12	**Zinc Oxide NPs**	Albumin Denaturation Assay	Anti-inflammatory	77% inhibition at 50 µL (similar to diclofenac).	**(34)**
13	**Ni:FeO(OH) Nanowires & NiS NPs**	Disc Diffusion, MIC, MBC, DNA cleavage	Antibacterial, Antifungal	Best activity: Ni-doped FeO(OH); strong DNA cleavage.	**(30)**
14	**Goethite (FeOOH) NPs**	MTT	Cytotoxicity	Reduced A549 cell viability (dose-dependent).	**(30)**
15	**Nano-EE**	MTT, Murine model	Antioxidant, Antidiabetic	Sustained release; ↓ oxidative stress; ↑ glucose tolerance; ↑ insulin sensitivity.	**(31)**
16	**Nano-EE FiveX**	ELISA, Histology, Pain test	Anti-inflammatory, Cartilage protection	↓ inflammatory markers; improved cartilage; ↓ pain (OA rats).	**(35)**
17	**Cerium Oxide NPs (CeONPs)**	ELISA, Histology, Hematology	Immune & antioxidant enhancement	Improved RBC, Hb, leukocyte profile; best effect with CeONPs + E. purpurea.	**(36)**
18	**PCL/PVA/CL/EP Nanofibers**	MIC, DPPH, Cytotoxicity	Antibacterial, Antioxidant, Wound healing	High antibacterial & antioxidant activity; accelerated wound closure.	**(37)**
19	**Silver Nanoparticles**	DPPH inhibition	Antioxidant, Antimicrobial	Strong antioxidant activity; effective microbial inhibition.	**(38)**

ZnO NPs: Zinc Oxide Nanoparticles; **AuNPs**: Gold Nanoparticles; **AgNPs:** Silver Nanoparticles; **Ep:** *Echinacea purpurea*; **DPPH:** 2,2-diphenyl-1-picrylhydrazyl; **ABTS:** 2,2'-azino-bis(3-ethylbenzothiazoline-6-sulfonic acid); **PPZn:** Polyphosphate Zinc; **MTT:** 3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide; **CBC:** Complete Blood Count; **WBC:** White Blood Cells; **TNF-α**: Tumor Necrosis Factor-Alpha; **IL-1β:** Interleukin-1 Beta; **MIC:** Minimum Inhibitory Concentration; **MBC**: Minimum Bactericidal Concentration; **PBMC:** Peripheral Blood Mononuclear Cells; **FeOOH:** Iron Oxyhydroxide; **CeO:** Cerium Oxide; **PVA:** Polyvinyl Alcohol; **PCL:** Polycaprolactone; **CL:** Collagen; **EA**: Ethyl Acetate; **AGEs**: Advanced Glycation End-products.

DISCUSSION

Structure–Property–Function Relationships

The body of evidence reviewed underscores that nanoparticle functionality is governed not only by particle size but also by crystallinity, morphology, and surface chemistry, each of which contributes uniquely to stability and performance. Inorganic nanoparticles, particularly ZnO, Ag, and Au, consistently displayed size- and structure-dependent optical phenomena **(Table 1)**. For instance, ZnO nanoparticles (14–45 nm) exhibited blue-shifted UV–Vis absorption at ~375 nm and a widened band gap of 3.31 eV compared to microparticles (385 nm, 3.22 eV), a pattern attributed to quantum confinement [20]. Metallic systems followed similar principles: AuNPs in the 80–120 nm range showed a sharp SPR peak at 560 nm, whereas AgNPs, with broader size distributions (30–95 nm), exhibited red-shifted absorbance at 468–481 nm, reflecting both polydispersity and interparticle coupling [22,17,14]. These findings are consistent with theoretical predictions that smaller, monodisperse particles generate sharper plasmonic signals, while larger or heterogeneous populations yield broadened spectra.

In contrast, polymeric and lipid-based nanoparticles demonstrated property shifts largely driven by encapsulation dynamics rather than crystallinity. Alginate/chitosan carriers expanded from 245 ± 1.6 nm (unloaded) to 335 ± 1.4 nm upon incorporation of *E. angustifolia*, confirming encapsulation-induced swelling rather than aggregation [19]. FTIR peaks at 3435 cm^{-1} (O–H/N–H) and 1098 cm^{-1} (C–N) substantiated polymer–bioactive interactions, highlighting the functional role of hydrogen bonding in stabilization. Similar patterns were observed in phytosome lipid particles (135–380 nm) and niosomes (119–395 nm), where broad size ranges reflected heterogeneous bioactive incorporation [23,24,26]. Eudragit RS100 nanoparticles further exemplified this trend: GC–MS analysis identified melezitose (~25%) and palmitic acid (~14%) as dominant phytochemical constituents, underscoring the stabilizing contribution of saccharides and fatty acids within polymeric carriers [23]. Unlike inorganic systems, which achieve stability through crystalline order, these carriers rely on matrix density and polymer–phytochemical affinity to modulate performance **(Table 1)**.

Phytochemical quantification studies provided further insight into nanoparticle–bioactive interplay. High-performance liquid chromatography revealed a marked decrease in isobutylamides in nano-*E. purpurea* (0.21 mg/g) compared to crude extract (0.88 mg/g), consistent with controlled release mechanisms [31]. Conversely, catechin content was enhanced in AgNP formulations (55.0 mg/g) relative to ethanolic extracts (51.0 mg/g), suggesting nanoparticle-mediated stabilization of phenolic compounds [32]. Robust analytical validation, exemplified by the high linearity of cichoric acid standard curves ($R^2 = 0.9998$), reinforced the reliability of these measurements [33].

Green synthesis approaches highlighted the pivotal role of natural metabolites as dual-function agents—acting simultaneously as reducing agents and stabilizers. GC–MS studies of Ni- and Fe-based nanostructures identified phytol and germacrene D (~17.7% each) as dominant constituents, a finding corroborated by FTIR bands corresponding to hydroxyl and carbonyl groups [28,30]. Together with the Eudragit RS100 data,

these findings emphasize that phytochemicals spanning multiple classes—terpenoids, saccharides, fatty acids, and phenolics—cooperate to stabilize nanostructures while contributing to bioactive payload delivery [23,28,30]. This duality underscores the capacity of plant-derived compounds to replace conventional surfactants, yielding nanoparticles that are both crystalline and biocompatible.

Crystallographic and imaging techniques added another layer of comparative validation. XRD confirmed phase-specific crystallinity, including wurtzite ZnO [20,27], FCC Ag and Au [22,17,14], and orthorhombic FeOOH [30], with crystallite sizes typically ranging between 30–70 nm. SEM and TEM consistently revealed spherical to quasi-spherical morphologies, though electrospun nanofibers (~129 nm) demonstrated the adaptability of nanofabrication toward anisotropic architectures better suited for scaffold applications [34].

Taken together, the evidence delineates two complementary paradigms. Inorganic nanoparticles derive functionality primarily from quantum-size effects and crystalline structure, translating into tunable optical and electronic properties. In contrast, polymeric and lipid-based carriers emphasize encapsulation efficiency, polymer–bioactive interactions, and controlled release, often at the expense of monodispersity. The use of phytochemicals as green stabilizers bridges these paradigms, offering both sustainability and improved biocompatibility.

Overall, these findings establish a structure–property–function framework **(Table 2)**, in which quantitative measures (size, band gap, phytochemical content) and qualitative signatures (functional groups, crystallinity, morphology) converge to explain nanoparticle behavior. Such integrative understanding is crucial for translating nanomaterials into biomedical applications, where optimization depends on balancing optical/electronic performance with biocompatibility and delivery efficiency.

Therapeutic Activities and Clinical Potential

The body of evidence highlights that *Echinacea*-based nanoparticles display multifunctional therapeutic potential, leveraging both inherent nanoparticle properties and bioactive-mediated enhancements. Antimicrobial activity was consistently observed across inorganic and hybrid systems. ZnO nanoparticles inhibited a broad spectrum of pathogens, while AuNPs displayed stronger antibacterial activity than ZnO in direct comparisons [22]. Ni-doped FeOOH nanowires showed superior antibacterial and DNA-cleaving effects relative to undoped FeOOH [30], underscoring the role of doping in enhancing antimicrobial potency. Electrospun nanofibers, particularly PVA and PCL/PVA/CL/EP composites, demonstrated synergistic antibacterial and wound-healing properties [23,37], integrating local infection control with tissue repair.

Antioxidant activity was particularly pronounced for Ep-AgNPs, with IC_{50} values (DPPH: 6.34 μg/mL, ABTS: 3.46 μg/mL) significantly lower than those of other formulations [17], validating their radical-scavenging efficiency. By contrast, higher IC_{50} values in *E. purpurea*–AgNPs suggested weaker activity, although their enhanced reducing power highlights variability introduced by extract composition and nanoparticle surface chemistry [14]. Beyond these formulations, simple AgNPs and polymer-stabilized silver systems consistently

displayed both antimicrobial and antioxidant activity, with notable differences in inhibition zone diameters and free radical neutralization efficiencies [38]. These variations are largely attributable to particle size and capping agents, which govern reactivity and stability. Polymeric formulations such as Nano-EE and Nano-EE5X extended antioxidant action to disease-specific contexts, reducing oxidative stress and inflammatory markers in diabetes and osteoarthritis, respectively [31,35]. These findings emphasize the therapeutic advantage of tailoring nanoformulations to specific pathological conditions.

Anticancer outcomes revealed differential selectivity among nanoparticle systems. ZnO nanoparticles demonstrated cytotoxicity against MCF-7 breast cancer cells while supporting PBMC proliferation, suggesting immune compatibility [27]. FeOOH nanoparticles reduced survival of A549 lung cancer cells [30], whereas PPZn formulations exerted antiglycation and anti-apoptotic effects through molecular regulation of COL1A2 expression [24]. However, cytotoxic selectivity remains a concern for metallic nanoparticles, as silver-based systems have previously demonstrated disproportionate effects on cancer versus normal cells. In contrast, alginate/chitosan and chitosan/pectin formulations promoted higher cell viability compared with free extracts, supporting their use as safer carriers [19,23]. In particular, chitosan/pectin nanoparticles not only maintained cell viability but also enhanced anti-biofilm and antimicrobial performance [23], highlighting the dual advantage of safety and functional efficacy when combining natural polymers with phytochemical payloads.

Immunomodulatory properties are a recurring theme. Eudragit RS100 nanoparticles significantly elevated WBC, lymphocyte counts, TNF-α, and IL-1β [32], aligning with their potential as immune-supporting therapeutics. Liposomal carriers enhanced vaccine efficacy by boosting IgA and IgG responses in poultry [33], while cerium oxide nanoparticles synergized with *E. purpurea* to improve hematological and antioxidant parameters [36]. These results collectively indicate that nanocarriers not only preserve phytochemical integrity but also amplify immune function *in vivo*.

Anti-inflammatory activities spanned both inorganic and organic carriers. ZnO nanoparticles exhibited inhibition comparable to standard anti-inflammatory drugs [34], while Nano-EE5X demonstrated superior protection against osteoarthritic inflammation and cartilage degradation [35]. Such findings underscore the dual applicability of these systems in both acute inflammation control and chronic disease management.

Taken together, the reviewed evidence suggests that *Echinacea*-based nanostructures operate within a multi-domain therapeutic framework **(Table 2)**. Inorganic nanoparticles such as ZnO, Au, Ag, FeOOH, and CeONPs primarily contribute antimicrobial, anticancer, and antioxidant properties, largely attributed to their size-dependent reactivity, crystalline structure, and radical-scavenging activity [14,17,20,22,30,34,36,38]. In contrast, polymeric and lipid-based systems, including alginate/chitosan, Eudragit, liposomes, and Nano-EE5X, demonstrate enhanced safety, bioactive retention, and immunomodulatory potential, often achieved through encapsulation-driven stability that improves cell viability and amplifies immune responses [19,23,31-33,35]. Hybrid nanofibers and composites, such as PVA- and PCL/EP-based systems, offer multifunctionality by integrating antimicrobial, anti-inflammatory, and regenerative effects, thereby extending therapeutic applications to wound healing and tissue repair [23,37].

Safety and Biocompatibility

Despite promising activity, safety remains a defining concern. Metallic nanoparticles, particularly AgNPs, have been associated with disproportionate cytotoxicity, raising questions about therapeutic index and off-target damage [14,17]. In contrast, polymeric formulations consistently enhanced safety, with alginate/chitosan and chitosan/pectin carriers showing significantly higher cell viability compared to free extracts [19,23]. This divergence indicates that while inorganic systems may require careful dose optimization or surface modification, polymer-based nanocarriers may be more readily adaptable for clinical translation due to their favorable cytocompatibility.

Synergy with Conventional Therapies

An important insight across the literature is the potential for synergy between *Echinacea*-based nanoparticles and existing therapies. Immunomodulatory systems, including liposomal carriers and CeONPs, demonstrated adjuvant potential by amplifying antibody and hematological responses [33,36]. Polymeric formulations such as Nano-EE and Nano-EE5X offered complementary antioxidant and anti-inflammatory effects, supporting their use in chronic conditions like diabetes and osteoarthritis [31,35]. These synergies not only enhance efficacy but also suggest a pathway to reduce reliance on high-dose conventional drugs, potentially mitigating resistance and side effects.

Current Limitations and Research Gaps

As with other domains of nanomedicine, reporting heterogeneity remains a limitation. Standardized parameters such as zeta potential, release kinetics, and in vivo safety data were frequently underreported. Furthermore, while antibacterial and antioxidant assays were common, fewer studies conducted detailed pharmacokinetic or mechanistic evaluations, limiting translational insights.

Pharmacological Considerations and Translational Limitations

A broader consideration involves the pharmacological limitations that emerge when translating these nano-enabled biological activities into clinically meaningful outcomes. Although many formulations demonstrate potent antimicrobial, antioxidant, and anti-inflammatory properties *in vitro*, their pharmacological performance in vivo is constrained by short circulation times, limited tissue penetration, potential dose-dependent toxicity, and incomplete understanding of biodistribution. These limitations underscore that biological activity alone does not predict therapeutic success. Instead, it is the pharmacological behavior, including absorption, stability in biological fluids, release kinetics, and interaction with immune and detoxification pathways, that determines whether the observed mechanistic effects can be sustained at physiologically relevant concentrations. For instance, the strong radical-scavenging and antimicrobial activity of metallic nanoparticles may be offset by rapid clearance or cytotoxicity at therapeutic doses, while polymeric carriers, despite excellent biocompatibility, may suffer from slower release or insufficient potency without optimization of loading efficiency. Thus, the biological activities reported across nanoparticle classes must be interpreted through a pharmacological lens, integrating efficacy, safety, and kinetic behavior to ensure that mechanistic promise translates into realistic therapeutic potential.

CONCLUSIONS

The studies reviewed demonstrate that *Echinacea*-based nanoparticles possess multifunctional therapeutic potential, with outcomes that consistently surpass those of crude extracts. Inorganic systems such as ZnO, Ag, Au, and FeOOH showed broad-spectrum antimicrobial, antioxidant, and anticancer effects, largely governed by particle size, crystallinity, and surface chemistry. Polymeric and lipid-based carriers, including alginate/chitosan, chitosan/pectin, Eudragit, liposomes, and Nano-EE formulations, complemented these benefits by improving stability, enhancing bioactive retention, and supporting higher cell viability, thereby reducing toxicity concerns. Hybrid systems, such as electrospun nanofibers, further extended applications by integrating antimicrobial action with wound-healing and tissue regeneration properties. Across these diverse formulations, antioxidant and anti-inflammatory effects were repeatedly validated, while immunomodulatory outcomes—including enhanced lymphocyte counts and elevated antibody levels—highlighted their potential in immune support and vaccine adjuvancy. Taken together, these findings confirm that *Echinacea*-based nanostructures provide a versatile platform that combines enhanced efficacy with improved safety and multifunctionality. At the same time, progress toward clinical application will require standardized extraction and synthesis protocols, rigorous long-term safety assessment, and mechanistic insight into bioactive–nanoparticle interactions. With these advances, *Echinacea* nanomedicine holds strong promise as a sustainable and biocompatible approach to addressing contemporary biomedical challenges. Ultimately, by uniting improved therapeutic potency with enhanced safety and targeted delivery, *Echinacea*-based nanoparticles represent a promising translational pathway toward clinically deployable, plant-derived nanomedicines capable of supporting infection control, immune modulation, wound repair, and chronic disease management.

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DECLARATION OF COMPETING INTEREST

The authors declare no conflict of interest

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