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Nanotechnology-Based Formulations of *Curcuma xanthorrhiza* for Modern Herbal Therapy: A Narrative Literature Review

(*Formulasi Berbasis Nanoteknologi Curcuma xanthorrhiza Roxb. sebagai Terapi Herbal Modern: Tinjauan Literatur Naratif*)

Hanif Luthfiansyah Azhar[1], Hannie Fitriani[2*], Yandi Syukri[1], Arba Pramundita Ramadani[1]

[1]*Program Studi Magister Farmasi, Fakultas Matematika dan Ilmu Pengetahuan Alam, Universitas Islam Indonesia, Yogyakarta, Indonesia.*
[2]*Program Studi Farmasi, Fakultas Matematika dan Ilmu Pengetahuan Alam, Universitas Islam Indonesia, Yogyakarta, Indonesia.*
[*]*E-mail: hanniefitriani@uii.ac.id*

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Corresponding Author:
Hannie Fitriani
Jurusan Farmasi
Fakultas MIPA
Universitas Islam Indonesia
Yogyakarta
55584
Indonesia
email: hanniefitriani@uii.ac.id

ABSTRACT

Background: *Curcuma xanthorrhiza* Roxb. (*temulawak*) is an Indonesian medicinal plant with documented antibacterial, anti-inflammatory, antioxidant, hepatoprotective, and anticancer activities, yet its major active compounds, curcuminoids and xanthorrhizol, suffer from poor aqueous solubility, low stability, and very limited oral bioavailability. **Objectives:** This study aims to review nanotechnology-based formulation strategies developed to overcome the biopharmaceutical limitations of *C. xanthorrhiza* and to optimise its potential as a modern herbal therapy. **Methods:** A narrative literature review was conducted using national and international articles published mainly between 2015 and 2025 that were retrieved from PubMed, ScienceDirect, and Google Scholar with keywords related to *Curcuma xanthorrhiza*, nanoformulation, and drug delivery systems; data were qualitatively summarised according to type of nanoformulation, physicochemical characteristics, and in vitro or in vivo biological activities. **Results:** Various nanotechnology-based delivery systems were identified, including nanosuspensions, nanoemulsions, Solid Lipid Nanoparticles (SLN), Self-Nanoemulsifying Drug Delivery Systems (SNEDDS), Solid-SNEDDS, nanogels, polymeric nanoparticles, and green-synthesised metallic nanoparticles; these formulations consistently reduced particle size to the nanometre range, improved solubility and chemical stability, increased entrapment efficiency, and enhanced pharmacological effects such as anti-inflammatory, antioxidant, antimicrobial, and anticancer activities compared with conventional extracts. **Conclusions:** Nanotechnology-based formulations of *Curcuma xanthorrhiza* represent a promising strategy to improve the efficacy, safety, and practicality of *temulawak* as a modern herbal medicine, and further well-designed preclinical and clinical studies are required to confirm their therapeutic advantages.

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INTRODUCTION

Curcuma xanthorrhiza (*C. xanthorrhiza*), commonly known as *temulawak*, is an Indonesian medicinal plant widely used in traditional and contemporary herbal products. Preclinical investigations have reported diverse pharmacological activities, including antioxidant, anti-inflammatory, antibacterial, hepatoprotective, and anticancer effects (E. Rahmat et al., 2021). These activities are associated with a characteristic phytochemical profile comprising curcuminoids and a prominent sesquiterpenoid marker, xanthorrhizol, which is more specifically linked to *C. xanthorrhiza*-based preparations than to other *Curcuma* species. Importantly, although *C. xanthorrhiza* is closely related to *Curcuma longa* (*C. longa*), the two species should not be treated as interchangeable in the context of nanoformulation research and translational development. The nanoformulation literature is abundant for curcumin (largely from *C. longa*), whereas *temulawak*-based development often involves xanthorrhizol-enriched extracts and a compositionally distinct extract matrix; therefore, reviews that generalize temulawak as merely "another curcumin source" risk under-emphasizing *C. xanthorrhiza* specific challenges and opportunities.

Curcumin demonstrates oral bioavailability of only ~1% due to first-pass metabolism and rapid degradation under light, heat, and neutral–alkaline pH conditions (Anand et al., 2007; Jeliński et al., 2019). Similar instability is observed in *temulawak* extracts exposed to elevated temperatures (Oon et al., 2015). Such physicochemical limitations significantly reduce therapeutic efficacy and hinder their application in modern pharmacotherapy. Nanotechnology-based delivery systems including nanosuspensions, nanoemulsions, Solid Lipid Nanoparticles (SLN), SNEDDS, Solid-SNEDDS, polymeric nanoparticles, and green-synthesized metallic nanoparticles have emerged as promising approaches to overcome these barriers. These systems enhance solubility, stability, permeability, and controlled release, leading to improved biological activity across anti-inflammatory, antioxidant, antimicrobial, and anticancer models (Ezani et al. 2024; Fitriani et al. 2021; Syukri et al. 2025).

Several studies have reported that nanoformulated temulawak derived compounds produce stronger pharmacodynamic outcomes compared with conventional extract or suspension forms at comparable dose ranges**.** Nanocurcuminoid formulations administered at 175–250 mg/kg body weight produced up to 37.10% inhibition of edema formation in a rat paw edema model, while nanoemulsion-based systems significantly reduced malondialdehyde (MDA) levels, indicating improved antioxidant and anti-inflammatory effects in vivo (Novita et al., 2015; Nurcholis et al., 2019). Similarly, SLN formulations of temulawak extracts have been reported to enhance antioxidant enzyme activity and reduce oxidative stress markers in CCl_4-induced oxidative stress models, suggesting improved pharmacological performance through enhanced delivery and stability of bioactive compounds (Ambarsari et al., 2019).

The novelty and research gap addressed by this review is not the general proposition that "curcumin nanoformulations are beneficial" a topic already extensively covered, but rather the lack of an integrated, temulawak centered synthesis that consolidates nanoformulation strategies specifically developed for *C. xanthorrhiza* extracts and/or *temulawak* derived marker compounds (including xanthorrhizol), and critically links formulation attributes to in vivo relevant outcomes and translational readiness. Therefore, this review aims to summarize recent advances in temulawak nanoformulations across major delivery platforms, critically evaluate their advantages and limitations with emphasis on formulation-performance relationships and in vivo evidence where available, and outline practical considerations for future development, including extract standardization (marker based), scalability, stability, and safety. By providing this temulawak specific critical perspective, this work is intended to guide researchers in selecting appropriate nano-delivery strategies for *C. xanthorrhiza*-based drug candidates and to support the development of more effective and clinically relevant herbal therapeutics.

MATERIAL AND METHODS

This review was conducted using a narrative approach with structured search and screening procedures to improve methodological transparency and reduce potential selection bias, with the overall workflow for study identification, screening, eligibility assessment, and final inclusion summarized in Figure 1. A comprehensive literature search was performed in PubMed, ScienceDirect, and Google Scholar using combinations of Medical Subject Headings (MeSH) and free-text keywords, including "*Curcuma xanthorrhiza*", "*temulawa*k", "*temulawak* nanoparticles", "*temulawak* nanoformulation", "nanoemulsion", "nanosuspension", "SLN", "SNEDDS", "solid-SNEDDS", "polymeric nanoparticles", and "bioavailability enhancement", with Boolean operators ("AND", "OR") applied to refine the search results. The search was restricted to publications from 2015–2025 to capture recent advances in nanotechnology-enabled drug delivery systems, particularly modern lipid-based and polymeric carriers, and to provide a contemporary perspective on formulation strategies, characterization standards, and translational considerations.

Studies were included if they were peer reviewed original research articles investigating nanoformulations derived from *C. xanthorrhiza* extracts or *temulawak* derived bioactive compounds (e.g., xanthorrhizol or curcuminoid fractions) and reported at least one aspect of nanoformulation development such as formulation design, physicochemical characterization, stability, bioavailability enhancement, or biological activity evaluation in vitro or in vivo models. studies were excluded if the investigated material was not derived from *C. xanthorrhiza*, such as studies focusing solely on *curcuma longa* or general curcumin without clear indication of temulawak origin. articles were also excluded if they did not involve a nanotechnology-based delivery system, if they were published before 2015 without providing essential foundational information, or if they were non-research publications such as editorials, letters, conference abstracts, or review articles. Studies lacking sufficient methodological details, full-text availability, or outcomes relevant to formulation performance or biological activity were also excluded from the final analysis.

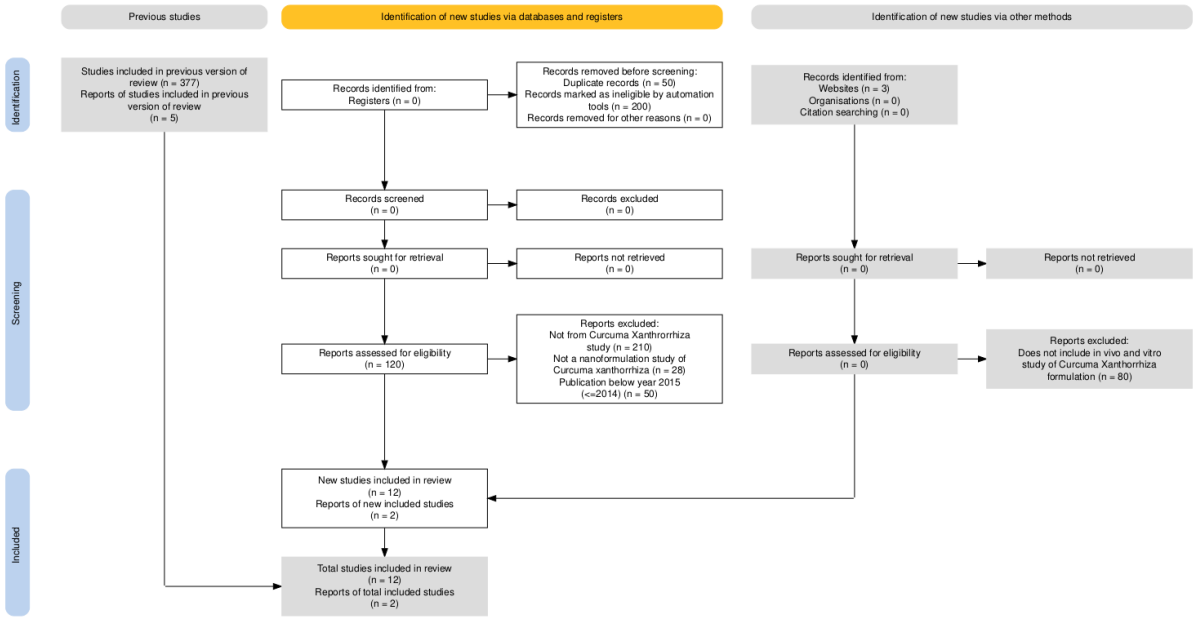

Figure 1. PRISMA Diagram

As shown in **Figure 1**, records were identified primarily through database searching (n = 280). After duplicate removal (n = 50), the remaining records were retained for screening. Full-text articles were assessed for eligibility (n = 120), and studies were excluded when they did not meet the *temulawak*-specific scope (not from *C. xanthorrhiza*), did not involve a nanoformulation, or fell outside the defined publication window. Ultimately, 12 new studies met the inclusion criteria, and 2 additional reports were included through complementary identification routes as summarized in the flow chart. In addition, the diagram notes previously included studies (n = 377) and reports from previous review version (n = 5) to contextualize continuity with prior screening stages. Although this is a narrative review, methodological credibility was strengthened through a structured appraisal of included studies. Each eligible study was

assessed using a simplified quality checklist covering clarity of temulawak source identification (species verification and extract/compound description), adequacy of nanoformulation characterization (size distribution and key parameters relevant to the system), appropriateness of controls/comparators (non-nano extract/solution), transparency of experimental methods and reproducibility, and relevance of outcomes (in vitro and/or in vivo endpoints). Quality considerations were used to guide interpretation and to highlight limitations rather than to exclude studies post-hoc.

RESULTS AND DISCUSSION

THERAPEUTIC POTENTIAL OF *C. xanthorrhiza* EXTRACT

Recent research suggests that *Curcuma xanthorrhiza* (*temulawak*), a traditional Indonesian medicinal plant, has strong potential as a source of natural therapeutics. Studies report a wide range of biological effects, including antioxidant, anti-inflammatory, antibacterial, anticancer, hepatoprotective, and antidiabetic activities. These benefits are mainly linked to its key bioactive compounds especially xanthorrhizol and curcuminoids such as curcumin, demethoxycurcumin, and bisdemethoxycurcumin (E. Rahmat et al., 2021). Xanthorrhizol, the major sesquiterpene found in temulawak rhizomes, is frequently highlighted for its notable anti-inflammatory and anticancer effects. Interestingly, Ultrasonic-Assisted Extraction (UAE) has been reported as one of the most effective methods to obtain xanthorrhizol-rich extracts, producing yields with stronger overall bioactivity (Rahmadansah et al., 2023). Another sesquiterpene, germacrone, has also shown promising antibacterial activity. One study reported an MIC of 15.6 µg/mL against *Pseudomonas aeruginosa*, suggesting that germacrone could be developed as a natural antimicrobial agent (Diastuti et al., 2016). *Temulawak* has also been explored for its anti-tuberculosis potential. An ethanolic extract demonstrated activity against *Mycobacterium tuberculosis* H37Rv, with an MIC of 1600 µg/mL supporting its possible role as an adjunct option in tuberculosis management (Ngadino et al., 2018). In addition, the essential oil of *temulawak* has been reported to inhibit the proliferation of P38 leukemia cells, indicating potential anticancer relevance (Nurcholis et al. 2019). Its antibacterial effects against common pathogens are also well documented. For example, a 3.125% temulawak extract was reported to inhibit *Lactobacillus acidophilus*, although its effect was still weaker than 0.2% *chlorhexidine*. Similarly, *temulawak* extract at 500 ppm was shown to inhibit *Escherichia coli* and *Staphylococcus aureus*, producing clear inhibition zones (Purnamaningsih & Kalor, 2017). Beyond antibacterial activity, a broader review also noted additional antifungal, anti-insecticidal, and anti-aging potential (Mukti & Hermady, 2020). Applied studies have even examined temulawak's traditional use as an appetite stimulant. In mice, a 30% *temulawak* emulsion significantly increased body weight, suggesting potential use in nutritional supplementation (Permana et al., 2023). Finally, *temulawak's* hepatoprotective effect largely attributed to curcumin is thought to occur through

its ability to neutralize superoxide ions and reduce lipid peroxidation, helping protect liver cells from oxidative stress (Syafitri, 2019).

PHARMACEUTICAL AND BIOPHARMACEUTICAL LIMITATIONS OF *C. xanthorrhiza*

Despite the highly promising pharmacological potential of *C. xanthorrhiza*, its clinical development still faces several challenges, particularly in pharmaceutical and biopharmaceutical aspects. The most critical limitation is the poor solubility and low bioavailability of its active constituents, especially curcumin and xanthorrhizol, which are lipophilic compounds with very low aqueous solubility (Anand et al., 2007; E. Rahmat et al., 2021). Curcumin exhibits an oral bioavailability of only about 1% due to its rapid degradation by hepatic and intestinal metabolic enzymes, as well as extensive biliary excretion. These factors result in insufficient systemic concentrations to achieve optimal therapeutic effects. The solubility of curcumin in water is only approximately 0.0006 mg/g, greatly limiting its oral absorption. Curcumin is also prone to degradation when exposed to light and high temperatures, even in its powdered form (Jeliński et al., 2019). The bioavailability of curcumin present in *temulawak* is also considered very low because it undergoes rapid metabolism in the liver and intestines and is quickly excreted, preventing it from reaching adequate therapeutic concentrations in systemic circulation (Ghoran et al., 2022). Characterisation of *temulawak* ethanol extract by Oon et al. (2015) revealed that although the extract contains a complex profile of active compounds, it is unstable when exposed to heat, with curcumin content decreasing significantly at 40 °C over a six-week period. Curcumin is also unstable under neutral and alkaline pH conditions, further reducing its bioavailability in the gastrointestinal tract.

NANOPARTICLE DELIVERY SYSTEMS FOR *C. xanthorrhiza*

C. xanthorrhiza has several limitations in its therapeutic application, particularly its poor absorption, low solubility, and limited bioavailability. To overcome these challenges, nanoparticle-based delivery systems have been increasingly developed. Nanoparticle delivery systems aim to enhance the stability, solubility, and absorption of *temulawak*'s active compounds, thereby improving their pharmacological effects. This classification includes studies that investigate various nanoparticle formulation strategies, such as SLN and encapsulation using supercritical solvents, as approaches to optimize the delivery of *temulawak*'s bioactive constituents. **Figure 2** represents the limitations of *C. xanthorrhiza* as pharmaceutical preparation and nanoformulation as its alternative solution.

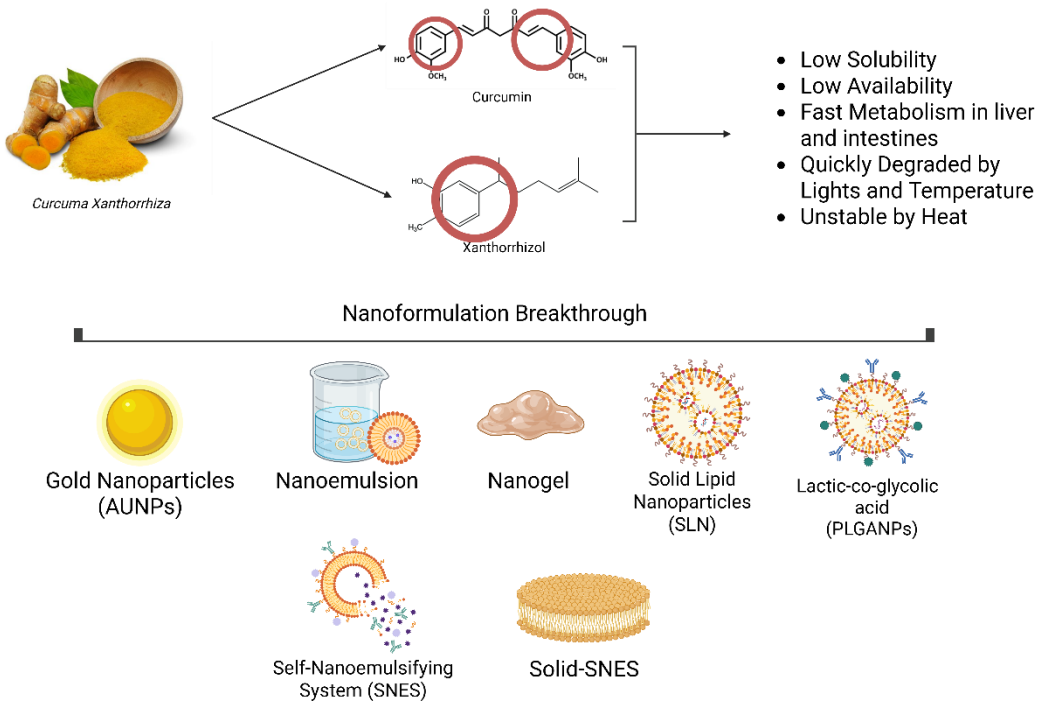

Figure 2. Pharmaceutical and Biopharmaceutical Limitations of *C. xanthorrhiza* Active Compounds and Nanotechnology Approaches as Formulation Solutions

The application of various nanoparticle-based formulations of *C. xanthorrhiza* has demonstrated significant progress in overcoming the pharmacokinetic limitations of its major active compounds. Innovations in nanoformulation offer clear advantages in enhancing therapeutic efficacy, bioavailability, and the stability of active constituents. Green synthesis of nanoparticles using *C. xanthorrhiza* extract has successfully produced materials with promising antibacterial and antioxidant activities, while also serving as an environmentally friendly approach for therapeutic and natural cosmetic applications (Noah & Ndangili, 2021). This method further reinforces the potential of *temulawak* as a natural reducing agent in plant-based nanomedicine technology. **Table 1** summarizes research related to the development of different nanoparticle delivery systems designed to address the biopharmaceutical barriers of *temulawak*'s active compounds, including low solubility and poor chemical stability.

Table 1 Nanoformulation-Based Delivery Systems of *C. xanthorrhiza*

No.	Delivery System	Results	References
1	Phytochemical Nanoparticles	Enhancing the solubility, stability, and bioavailability of curcumin through its very small particle size, which enables better penetration across cell membranes.	(Noah & Ndangili, 2021)
2	SLN (Solid Lipid Nanoparticles)	Nanoparticles enter the cell through endocytosis or passive bilayer penetration, then release curcumin more efficiently to the cancer cell targets.	(Masitoh & Sopyan, 2019)
3	Nanoemulsion	The nanoscale size increases surface contact, accelerates diffusion, and enables curcumin to penetrate cell membranes more easily. Nanoemulsion also protects curcumin from degradation and results in higher antioxidant activity.	(Jusnita et al., 2019)
4	Nanogel	Nanoscale size increases the surface contact area, allowing the active compounds to penetrate the skin more effectively and enhancing both antioxidant activity and SPF value.	(Wilapangga et al., 2023)
5	S-SNEDDS (Solid Self-Nanoemulsifying Drug Delivery System)	Protects the extract from degradation, improves physical stability, and facilitates conversion into a solid form without compromising its biological activity. Mannitol as a carrier contributes to producing a crystalline/semi-crystalline structure with good flow properties, further enhancing nano-delivery performance.	(Syukri et al. 2025)
6	Lactic-co-glycolic acid Nanoparticles (PLGANPs)	PLGA facilitates cellular uptake through endocytosis, and enables gradual drug release, thereby improving its cytotoxic effect against cancer cells.	(Ezani et al., 2024)
7	Gold Nanoparticles (AUNPs)	Bioactive compounds act as reducing and stabilizing agents to form small-sized AuNPs, which subsequently enhance reactivity and allow more efficient biological interactions.	(Lubis et al., 2020)
8	SNEDDS	The active compounds become more soluble, stable, and readily absorbed. The small droplet size increases the interfacial surface area and enables lymphatic absorption, thereby bypassing first-pass metabolism.	(Fitriani et al. 2021)

A study by Lubis et al. (2020) showed that *C. xanthorrhiza* can be utilized in the biogenic synthesis of gold nanoparticles. The resulting nanoparticles exhibited high catalytic activity and (Ezani et al., 2024)biocompatibility, offering promising potential in antimicrobial therapy and noble-metal delivery

systems. The use of *temulawak* in gold nanoparticle synthesis also demonstrates its role as a natural reducing agent, strengthening the ecological and sustainable value of traditional medicinal materials. Meanwhile, Fitriani et al. (2021) formulated *temulawak* into a Self-Nanoemulsifying System (SNES), which significantly improved extract solubility and demonstrated formulation stability under thermodynamic and accelerated testing. These findings indicate that SNES can enhance pharmacological effects at lower doses, supporting long-term safety and user convenience.

Encapsulated *temulawak*-derived curcumin within a PLGA polymer matrix successfully increased cytotoxicity against MCF-7 breast cancer cells but also extended the biological half-life of curcumin by up to 60-fold, indicating markedly improved bioavailability and tissue distribution compared to free curcumin (Ezani et al., 2024). The application of nanoparticle-based delivery systems in the form of a S-SNEDDS for *C. xanthorrhiza* extract has demonstrated a significant impact on improving its pharmaceutical performance. Through this approach, common limitations such as poor aqueous solubility, limited bioavailability, and low formulation stability were effectively addressed (Syukri et al., 2025). The nanoparticle gel formulation of *C. xanthorrhiza* extract showed strong potential as an effective and stable herbal sunscreen product. This success was reflected in the significant increase in Sun Protection Factor (SPF), where the nanoparticle gel achieved an SPF of 19.88, considerably higher than the conventional extract gel (16.77) (Wilapangga et al., 2023).

The nanoemulsion formulation of *C. xanthorrhiza* also significantly improved the solubility, stability, and active curcumin content compared with the conventional extract. The curcumin content in the nanoemulsion stored at room temperature reached 227.57 mg/L and 215 mg/L at 10°C, compared to only 28.16 mg/g in the conventional extract, making it more effective for pharmaceutical and cosmetic applications (Jusnita et al., 2019). Overall, these findings reinforce the urgency of developing nanoparticle-based formulation technologies to enhance the stability, solubility, and therapeutic effectiveness of *temulawak* in clinical applications. Through advanced nano-delivery systems, *C. xanthorrhiza* is expected to achieve its full pharmacological potential with lower doses and more consistent therapeutic outcomes.

CHARACTERISTICS OF C. *xanthorrhiza*-BASED NANOFORMULATIONS

Each nanoformulation system of *C. xanthorrhiza* developed to date exhibits distinct physicochemical characteristics, such as particle size, polydispersity index, and zeta potential, which directly influence the stability and effectiveness of drug delivery. **Table 2** presents a summary of the variations in characteristics among the different *temulawak* nanoformulations that have been investigated, serving as a scientific basis for selecting and developing the most optimal delivery system.

Table 2 Characteristics of *C. xanthorrhiza* nanoformulation

Nanoformulation Type	Characterization	References
Nanosuspension	• Particle size: 470.6 nm • PDI: 0.395 • Zeta Potential: +48.3	(Budiati et al., 2021)
	• Particle size: 300.4-538.8 nm • PDI: 0.292-0.619 • Zeta Potential: +47.7	(Arifin *et al*., 2022)
S-SNEDDS	• Particle size: 97.16 nm • PDI: 97.16 • Zeta Potential: -35.0	(Syukri et al., 2025)
SNEDDS	• Particle size: 13.0 nm • PDI: 0.3 • Zeta Potential: -42.4	(Fitriani et al. 2021)
AUNPs	• Particle size: 16.0 nm • Color and visual stability: purple coloration, stable up to 72 hours after synthesis, indicating good initial suspension stability • Morphology: spherical	(Lubis et al., 2020)
SLN	• Particle size: 684.4 nm • PDI: 0.219 • Entrapment efficiency: 29.8% • Color: yellow • Solubility: water-soluble	(Riki et al., 2017)
PLGANPs	• Particle size: 444.7 nm • PDI: 0.372 • Zeta Potensial: -28.7 mV ± 6.19 mV. • Entrapment efficiency: 50% • Mophology: spherical	(Ezani et al., 2024)

Numerous studies have demonstrated that nanoformulations of *C. xanthorrhiza* produce physicochemical characteristics that strongly support the biological effectiveness of its active compounds, such as curcumin and xanthorrhizol. Particle size is one of the key factors, with the ideal range being 10-200 nm, as this enables efficient cellular penetration while avoiding rapid elimination by the immune system (Gautham U. et al., 2023). However, for certain applications such as transdermal or oral delivery, sizes up to 500 nm are still acceptable. The polydispersity index (PDI) reflects particle size distribution, with values of 0.2–0.7 considered indicative of a monodisperse and stable system. Zeta potential, representing particle surface charge, is considered optimal at ≥±30 mV because it provides sufficient electrostatic stability against aggregation (Betala et al., 2018). Particle morphology also plays an important role; spherical particles with smooth surfaces and no aggregation indicate high-quality formulations and predictable biological distribution (Syukri et al. 2025). Additionally, a minimum

acceptable entrapment efficiency (EE%) is typically 50%, with values above 70% being more desirable since they reflect high drug-loading capacity within the nanoparticles (Gautham U. et al., 2023).

The data presented in **Table 2** show the variability of characteristics across different *C. xanthorrhiza* nanoformulations. Nanosuspension formulations exhibit particle sizes ranging from 300 to 470 nm with PDI values between 0.292 and 0.395, indicating a relatively homogeneous size distribution. The high zeta potential values (≥ +47 mV) reflect strong electrostatic stability within the dispersion system, ensuring resistance to aggregation during storage (Arifin et al., 2022; Budiati et al., 2021). The use of SNEDDS and S-SNEDDS results in much smaller particle sizes, between 13.0 and 97.16 nm, accompanied by strongly negative zeta potentials (up to -42.4 mV), suggesting system stability through repulsion between negatively charged particles (Fitriani et al. 2021; Syukri et al. 2025). Meanwhile, gold nanoparticles (AuNPs) synthesized via green methods using *C. xanthorrhiza* extract yielded 16.0 nm spherical particles with visual stability lasting up to 72 hours post-synthesis, as indicated by their characteristic purple color (Lubis et al., 2020). This demonstrates successful metal ion reduction by phenolic compounds in *temulawak* and adequate short-term colloidal stability.

In the SLN system, the particles were larger (684.4 nm) but still exhibited a low PDI (0.219) and an entrapment efficiency of 29.8%. This solid-lipid formulation also showed good water solubility and retained the characteristic yellow color of curcuminoids (Riki et al., 2017). Overall, these characteristics confirm that nanotechnology-based formulations allow the development of *temulawak* herbal preparations that are more stable, effective, and compatible with biological systems. Research by Ezani et al. (2024) revealed, through Scanning Electron Microscope (SEM) analysis, that PLGA-loaded curcumin formulations possess spherical morphology. This spherical shape reflects well-formed particles that physically traverse biological membranes more easily than other shapes. In drug delivery systems, spherical morphology is considered optimal because it promotes more efficient diffusion, enhances cellular uptake, and reduces the risk of aggregation, which could otherwise impair therapeutic effectiveness. The average particle size based on SEM images was 498.9 ± 597.4 nm, while Zetasizer measurements showed a Z-average of 444.7 nm. The PDI value of 0.372 indicates considerable variation in size distribution. In terms of entrapment efficiency, the formulation was able to encapsulate 50% of curcumin into the PLGA matrix. The diversity of these nanoformulation characteristics provides valuable flexibility in tailoring drug delivery routes, therapeutic targets, and release profiles of *C. xanthorrhiza* active compounds factors that are crucial in advancing natural product–based drug development.

IN VIVO AND IN VITRO STUDIES OF *C. xanthorrhiza*

The evaluation of the efficacy and safety of a natural product-based drug formulation requires a systematic scientific approach, including both in vitro and in vivo testing. Nanoformulations of *Curcuma xanthorrhiza* Roxb., developed to enhance the bioavailability and stability of active compounds such as curcumin and xanthorrhizol, have been assessed across various biological systems to validate their therapeutic potential. In vitro studies play a crucial role in identifying initial pharmacological activities, such as antibacterial, antioxidant, and cytotoxic effects against cancer cells. Meanwhile, in vivo studies provide a comprehensive understanding of pharmacokinetic profiles, systemic toxicity, and therapeutic responses within whole organisms. These two approaches complement one another in ensuring that the developed nanoformulations are not only superior in physicochemical characteristics but also effective and safe for clinical application. Therefore, **Table 3** presents a classification of literature specifically evaluating the biological tests of *temulawak* nanoformulations, both in vitro and in vivo, serving as a scientific foundation to support the development of nano-based phytopharmaceutical products.

Table 3 In Vitro and In Vivo Studies of *C. xanthorrhiza* Nanoformulations

Nanoformulation Type	Test Model	Test Method	Findings	References
Nanoemulsion	Anticancer	Brine shrimp lethality & MTT assay	LC_{50} of *temulawak* extract: 213.24 ppm; nanoemulsion: 328.78 ppm. Although less toxic, the nanoparticle system demonstrated better therapeutic potential and is considered a promising anticancer agent.	(Riki et al., 2017)
	Anti-inflammation	Rat paw edema test	Nanocurcuminoid at 175, 200, and 250 mg/kg BW demonstrated better anti-inflammatory activity than the positive control (diclofenac sodium) and curcuminoid extract, achieving 37.10% inhibition.	(Novita et al., 2015)
	Anti-inflammation & Antioxidant	Rat paw edema test & Thiobarbituric Acid (TBA) Assay	Nanocurcuminoid significantly reduced MDA levels (oxidative stress indicator), especially at 400 mg/kg BW, comparable to diclofenac.	(Nurcholis et al., 2019)
Ionic-gelation nanoformulation	Anti-inflammation	Protein denaturation inhibition	*C. xanthorrhiza* rhizome nanoparticle extract showed anti-inflammatory activity with an IC_{50} value of 398.02 ± 1.78 µg/mL, more effective than 96% ethanol extract.	(Farida et al., 2018)
Chitosan-TPP polymeric nanoparticles	Antibacterial (antiacne)	Disk diffusion	Gel containing *temulawak* nanoparticles showed greater antibacterial activity than the conventional extract gel. The	(D. Rahmat & Wirawan, 2020)

			inhibition zone of nanoparticle gel reached 26.34 ± 0.49 mm, compared with 22.89 ± 0.13 mm for extract gel and 16.5 ± 0.17 mm for blank gel. The improved activity is attributed to better penetration of nanoparticles into bacterial cells.	
SLN	Antioxidant	Oxidative stress induced by CCl_4	Increased antioxidant enzyme activity and decreased malondialdehyde (MDA) levels.	(Ambarsari et al., 2019)
PLGANPs	Cytotoxicity	MTT assay on MCF-7 cells	30% reduction in cancer cell viability in PLGA-curcumin nanoparticles compared with free curcumin extract, indicating improved cytotoxicity.	(Ezani et al., 2024)

Table 3 presents a summary of various in vivo and in vitro test models conducted on different types of *C. xanthorrhiza* nanoformulations, including anti-inflammatory, anticancer, antioxidant, and antimicrobial activities. One notable study is the use of a nanosuspension of *temulawak* rhizome extract for anti-inflammatory activity, evaluated using the protein denaturation inhibition method. The results showed an IC_{50} value of 398.02 ± 1.78 µg/mL, which was significantly more effective than the non-nano extract. The nanoparticle extracts inhibited heat-induced protein denaturation by stabilizing protein structures through active compounds. The lower IC_{50} value demonstrates that the nanoparticle formulation enhances bioactivity compared with the free extract (Farida et al., 2018).

In terms of anticancer activity, a nanoemulsion of *temulawak* extract exhibited high toxicity against *Artemia salina*, with an LC_{50} of 313.24 ppm and an IC_{50} of 828.78 ppm against cancer cells in the MTT assay. Curcuminoid nanoparticles performed more effectively than the conventional extract because they improved intracellular delivery of curcuminoids and triggered apoptosis, telomerase inhibition, and disruption of HeLa cell proliferation through molecular pathways such as NF-κB, Akt, and telomerase (Riki et al., 2017). In vivo studies using SLN also showed significant outcomes in antioxidant activity. Administration of *temulawak* SLN in a CCl_4-induced oxidative stress model resulted in increased antioxidant enzyme activity and reduced malondialdehyde (MDA) levels, an indicator of oxidative stress. This effect is attributed to the nanoformulation's ability to enhance stability, penetration, and interaction of the active compounds with biological targets (Ambarsari et al., 2019).

Furthermore, a *temulawak* nanoemulsion in the rat paw edema inflammation model demonstrated significant anti-inflammatory activity compared with sodium diclofenac and the non-nano extract. Doses of 175, 200, and 250 mg/kg BW produced edema inhibition of 37.10% (Novita et al., 2015). This finding is supported by another study reporting that nanoemulsions significantly reduced MDA levels

at a dose of 400 mg/kg BW, indicating their role as both anti-inflammatory and antioxidant agents (Nurcholis et al., 2019).

Palmitic acid-coated nanocurcuminoids significantly enhanced the anti-inflammatory effectiveness of curcuminoids by optimizing particle size, entrapment efficiency, and formulation stability. The activity was mediated through inhibition of prostaglandin pathways via COX-2 and NF-κB, as well as protection of proteins from inflammation, evidenced by significant reduction in rat paw edema volume. Doses of 175–250 mg/kg BW produced the highest anti-inflammatory effect (37.10%), surpassing the positive control, sodium diclofenac (14.52%) (Novita et al., 2015; Nurcholis et al., 2019).

Regarding antimicrobial testing, the nanoparticle-based gel demonstrated superior antibacterial activity compared with the conventional extract gel. The inhibition zone of the nanoparticle gel reached 26.34 ± 0.49 mm, whereas the extract gel showed 22.89 ± 0.13 mm, and the blank gel exhibited the lowest inhibition zone (16.5 ± 0.17 mm). These findings indicate that nanoparticle incorporation enhances the antimicrobial efficacy of temulawak extract against acne-causing bacteria. The improved antibacterial activity may be attributed to the smaller particle size and higher surface area of the nanoparticles, which facilitate better penetration into bacterial cell membranes and allow more efficient delivery of bioactive compounds. Furthermore, the chitosan matrix itself may contribute to antibacterial effects due to its inherent antimicrobial properties and its ability to interact with negatively charged bacterial cell walls (D. Rahmat & Wirawan, 2020).

In the study conducted by Ezani et al. (2024), cytotoxicity testing using the MTT method on MCF-7 breast cancer cells showed that PLGA–curcumin nanoparticles exhibited stronger cytotoxic effects compared with free curcumin extract. Cell viability decreased by 30% in the nanoparticle-treated group compared with the extract group. A statistically significant difference ($p < 0.05$) was also observed between the nanoparticle group and both the untreated control (negative control) and the tamoxifen-treated group (positive control). This indicates that encapsulating curcumin within the PLGA matrix enhances its ability to inhibit cancer cell growth. This improvement may be attributed to the higher bioavailability and superior cellular penetration of the nanoformulated curcumin compared with the highly hydrophobic extract form.

Despite these encouraging results, several limitations of the available studies should be acknowledged. Many experiments are conducted using relatively small sample sizes typical of preclinical studies, and methodological differences between studies including variations in animal models, dose ranges, formulation composition, and analytical methods make direct comparison challenging. Furthermore, most studies focus on short-term biological endpoints and lack long-term safety evaluations or standardized pharmacokinetic analyses. As a result, while the reviewed data collectively suggest that

nanoformulation significantly enhances the pharmacological performance of *C. xanthorrhiza*, further well-designed and adequately powered preclinical and clinical studies are required to confirm the robustness and translational relevance of these findings.

CONCLUSION

The application of nanotechnology to *C. xanthorrhiza* (*temulawak*) extract has been shown to enhance its pharmacological effectiveness, particularly in antibacterial, anti-inflammatory, antioxidant, and anticancer activities. Through nanoformulations such as SNEDDS, S-SNEDDS, nanosuspensions, nanoemulsions, and SLNs. Limitations of the plant's active compounds, such as low solubility, poor stability, and limited bioavailability can be effectively overcome. Moreover, the physicochemical characteristics of each nanoformulation system support both formulation stability and therapeutic performance. Therefore, *temulawak* nanoformulations hold strong potential for further development as modern herbal medicines that are safe, effective, and practical, and they merit continued investigation through more advanced clinical testing.

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CONFLICT OF INTEREST

The author declares that there is no conflict of interest regarding the publication of this review article. The research, analysis, and manuscript preparation were conducted independently without any financial, commercial, or institutional influence that could affect the objectivity of the work.

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