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Nano-hydrogel systems in herbal medicine: A systematic review

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ABSTRACT

Introduction: The growing popularity of herbal medications among the general public can be attributed to the belief that they are safer and have lower adverse drug reactions compared to synthetic treatments. In vitro studies showing the efficacy of herbal treatments may not always be directly applicable in vivo. Furthermore, the drug's efficiency in the body is limited by its low solubility in water, necessitating bigger doses and longer dosing intervals for maximum effectiveness. As a result, it is critical to improve the efficiency and effectiveness of nanotechnology in the delivery of herbal medication. This study aims to investigate and collect scientific reports on the characteristics, increased activity and solubility, drug loading, drug release, and nanotoxicity of nano-hydrogel-containing herbal medicines.

Methods: This review used a literature search of the Google Scholar, PubMed, and ScienceDirect databases from January 2024 to July 2024 using the keywords "nano-hydrogel" and "herbal" and "enhance solubility" and "enhance the antibacterial, antioxidant, wound healing activity".

Results: The literature findings showed that nano-hydrogel was highly effective for the internal and external delivery of medications. The decreased surface-to-volume ratio of nano-hydrogels resulted in a higher efficacy in transporting herbal active compounds across human cell membranes.

Conclusion: Nano-hydrogel is an effective formulation when mixed with herbal active ingredients and might be used for drug production.

Implication for health policy/practice/research/medical education:
Nano-hydrogel is an effective formulation when mixed with herbal active ingredients. It can improve the activity and solubility of herbal active ingredients and might be used for drug production in the future.

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Introduction

The increasing popularity of herbal remedies among the public is due to the perception that they are safer and exhibit fewer side effects than synthetic treatments (1). However, herbal medicine is susceptible to some limits, including the possibility of overdose due to the lack of specific dosage recommendations, the dangers of toxicity and poisoning caused by faulty plant identification, inferior plant material, and several other problems (2). Additional difficulties develop as a result of insufficient and irregular absorption of active phytochemical compounds obtained from plants. In vitro studies showing the efficacy of herbal treatments may not always be directly applicable in vivo. The drug's efficiency in the body is limited by its low solubility in water, low absorption, low distribution, and low target specificity, which results in low bioavailability (3). In addition, bigger doses and shorter dosing intervals are required for maximum effectiveness and activity (4).

Turmeric, scientifically known as *Curcuma longa* L., is a rhizome plant belonging to the *Zingiberaceae* family. It is predominantly found in Asia, particularly Southeast Asia (5). Curcumin is a compound found in turmeric that demonstrates pharmacological activities, including chemoprotective, antihyperlipidemic, and neuroprotective effects (6,7). Although curcumin has advantageous pharmacological properties, it suffers

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from the drawback of limited bioavailability (8). One approach to enhance the bioavailability and solubility of curcumin is by developing a nanosuspension formulation. Nanosuspension formulation is recognized for its capacity to enhance the bioavailability and solubility of curcumin, allowing it to dissolve in pH 7, such as in bodily fluids. Compared to conventional curcumin suspension, curcumin nanosuspension exhibits enhanced antioxidant and antimicrobial properties. The nanosuspension demonstrates notable antibacterial activities against *Escherichia coli* and *Aspergillus niger*, with an IC_{50} value of 123.8 µg/mL, surpassing even that of ascorbic acid (9). The nano-emulsion gel formulation of pineapple extract (*Ananas comosus* L. Merr) has been found to enhance the antioxidant activity of pineapple extract, with an IC_{50} value of 0.1 µg/mL, placing it in the highly potent category. It exhibits a robust anti-acne effect against *Staphylococcus aureus* bacteria, as evidenced by an inhibition zone size of 10.5 mm ± 0.1 (10).

Nano-hydrogels are polymeric networks with a three-dimensional architecture capable of retaining substantial amounts of water. Hydrogels are dermal applications utilized on the skin; they remain insoluble in water due to the critical cross-linking present in their structure. Nano-hydrogels exhibit potential because of their flexibility, versatility, and excellent biocompatibility (11). These features are highly significant for several applications in biomedical engineering, such as medication delivery, tissue engineering, and enhancing the bioavailability of active compounds in herbal plants (12).

Nano-hydrogels differ from other nanocarrier systems, such as liposome, dendrimer, and micelle. Nano-hydrogels can hold and swell in water and maintain a large volume of water to prolong the drug's contact duration with the skin (13). They are considerably more stable than liposomes, which have less stability, and short life. The main disadvantage of liposomes is the ABC phenomenon (Accelerated Blood Clearance), an unexpected pharmacokinetic change from the second dose of injected liposome (14). Dendrimers also present disadvantages, namely their cytotoxicity and the inability to control drug release. They also require high manufacturing costs and specialized techniques (15). Nanomedicine holds great potential for enhancing the bioavailability of several bioactive and herbal components (16). In particular, nano-hydrogels possess the capacity to enhance stability, facilitate efficient drug loading, maintain biological consistency, and exhibit robust skin penetration (17). This review aims to present the development of nano-hydrogel delivery methods enhancing the bioavailability and efficacy of herbal active ingredients, as well as drug release mechanisms and the potential toxicities associated with nano-hydrogel formulations.

Methods

A literature search was conducted utilizing the Google Scholar, PubMed, and ScienceDirect databases. The search query included the terms "nano-hydrogel" and "herbal" and "enhance solubility" and "enhance the antibacterial, antioxidant, wound healing activity". This study was conducted to July 2024. This literature review aimed to find nano-hydrogel formulations containing active herbal ingredients that enhance the solubility and efficacy of antibacterial, antioxidant, and wound healing activities. The criteria for inclusion encompassed publications written in either Indonesian or English, articles published within the past five years, studies including the use of active herbal plant ingredients, and freely accessible full articles. The exclusion criteria consisted of review papers and studies that did not utilize herbal active ingredients. According to the database search, a total of 1072 articles were acquired, as depicted in Figure 1. After conducting a screening process to exclude duplicate articles using the article title and abstract, the total number of articles was reduced to 386. A comprehensive analysis of the complete texts of the other publications, which were deemed possibly relevant, was conducted. Thirteen articles that satisfied the predetermined criteria were ultimately included.

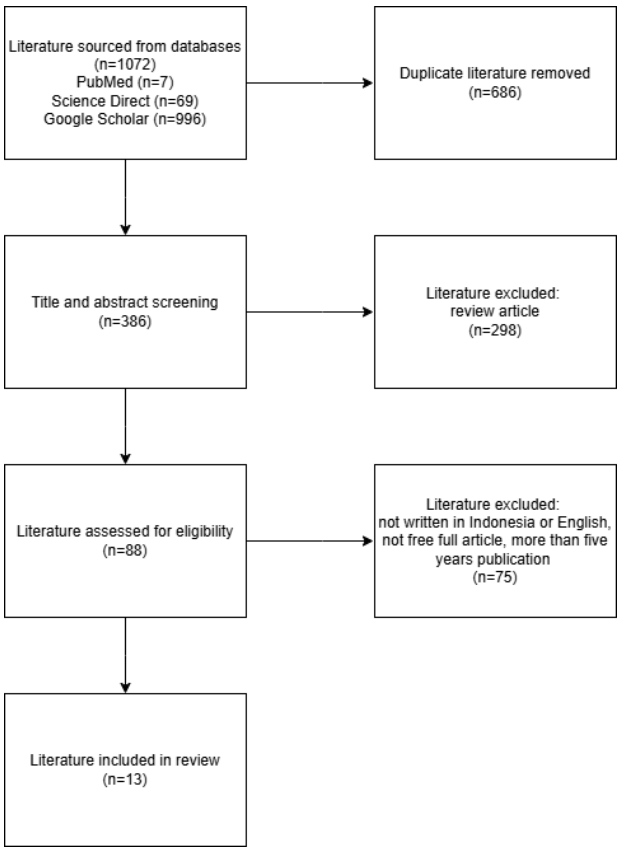

Figure 1. Flowchart of study selection.

Results

Nano-hydrogel increases the activity and solubility of active compounds

Nano-hydrogel is a delivery method that can improve the

solubility and bioavailability of herbal active compounds. Nano-hydrogel is highly appropriate for use in topical medications, particularly when integrating herbal active components, due to their capacity to be tailored to accomplish specific effects, penetrate deeper into tissues, and give widespread systemic effects (2). The advantage of nano-hydrogel over any other nanocarrier system is that it is hydrophilic and flexible, which can enhance water absorption (11). Table 1 is a list of nano-hydrogels formulated with several bioactive compounds.

Nepeta cataria's essential oil, comprising of nepetalactone and caryophyllene, exhibits antiparasitic properties. The results of in vivo testing demonstrated that the NCEO-CsNPs (chitosan nanoparticles and essential oil of *N. cataria*) at a concentration of 200 µL effectively prolonged the lifespan of test animals infected with *Toxoplasma gondii* by up to 8 days. Additionally, it exhibited superior antiparasitic activity compared to Spiramycin used alone (18).

Mucin, a protein extracted from snails (*Achatina fulica*), is known for its antibacterial, anti-inflammatory, and wound-healing activity (19). However, it has some disadvantages, namely poor solubility and bioavailability. The nano-hydrogel formulation of ZnO+Mucin increased the healing effect in albino rats within 8 days, while the mucin formulation and positive control (gentamicin) took 12 days for maximum effects. Based on the result, ZnO nanoparticles can act as an antioxidant, while the snail mucin in nano-hydrogel formulation increases the wound healing activity (20).

Curcumin, extracted from *Curcuma longa*, exhibits numerous health advantages, including its efficacy in treating psoriasis while causing minimal adverse reactions (21). The nano-hydrogel, which was synthesized using CALIX micelles (choline-calix[4]arene) and curcumin, exhibited negligible toxicity and effectively reduced pro-inflammatory processes, hence demonstrating its anti-psoriatic benefits in the IMQ-induced psoriasis model. The results indicate that curcumin retains anti-inflammatory properties when encapsulated in a hydrogel based on calixarene. This further supports the effects of the nano-hydrogel since it is able to dissolve and protect curcumin from rapid deterioration (22). Thymoquin, extracted from *Nigella sativa*, exhibits significant antifungal properties. Ethanol and methanol extracts of black cumin demonstrated a significant suppression of *Aspergillus flavus*, *Aspergillus fumigatus*, *Cryptococcus laurentii*, and *Candida albicans* (23).

Essential oils primarily serve as hydrophobic agents, enabling them to penetrate bacterial membranes, damage cellular structure, induce ion ejection, and ultimately lead to cell death (24). The integration of nano-hydrogel with black cumin essential oil, derived from the mucilage of Kwinsi seed extract, demonstrated enhanced antifungal efficacy against *C. albicans* and *Malassezia furfur*, achieving a minimum inhibitory concentration (MIC) of 3.125 mg/mL (25).

Lemons are recognized for their ability to contain various compounds that can inhibit the growth of both gram-positive and gram-negative bacteria (26). Sulfur nanoparticles (SNPs) combined with lemon extract enhance antibacterial and antifungal activity, effectively penetrating cell walls and interacting with DNA and protein components, leading to the destruction of these elements (27). The integration of SNPs with lemon extract demonstrates a synergistic effect on wound healing (28). The formulation demonstrated notable wound-closing activity, accelerating the wound-healing process in rats (29).

Qiai essential oil, derived from a Chinese herbal plant and primarily composed of the compound thujone, exhibits promising antibacterial properties (30). However, essential oils present various challenges, including limited solubility in water and their inherently volatile nature. The development of Qiai essential oil nano-hydrogels has been shown to enhance solubility and antibacterial properties. The analysis of particle size through the dynamic light scattering (DLS) method indicated that the blank particles exhibited a spherical size ranging from 100 to 160 nm, whereas the QEO micelles displayed a spherical size within the range of 80 to 100 nm. This indicates that micelles containing Qiai essential oil exhibit a significant encapsulation value and can sustain a continuous release (31,32).

Azadirachta indica essential oil is recognized for its mosquito-repellent, anti-diabetic, and anti-inflammatory properties (33-35). Meanwhile, the antibacterial efficacy is attributed to the propyl disulfide component. Nevertheless, this molecule is highly vulnerable and readily degrades through oxidation, diminishing its bioactivity (36,37).

The nano-hydrogel formulation utilizing an oil-in-water nano-emulsion demonstrated enhanced solubility and efficacy of *A. indica* essential oil, as evidenced by chromatographic analysis revealing the presence of polyphenolic and other stable components within the nano-hydrogel formulation. Anti-inflammatory testing indicated that the nano-hydrogel had an activity ranging from 50.23% to 82.57%, in comparison to the standard sodium diclofenac, which showed an activity between 59.47% and 92.32%. Antibacterial testing demonstrated that the nano-hydrogel formulation effectively inhibited the development of both gram-negative and gram-positive bacteria, surpassing the efficacy of streptomycin and the nanoparticle base alone (38).

In a pilot study, the formulation of nano-hydrogel embedded with quercetin, a flavonoid that is able to increase the wound healing process (39), and oleic acid, known for modulating the immune response and restoring inflammatory phase in wound healing, showed a significantly shorter time healing within 10 days while the hyaluronic acid alone group took 25 days to heal in every 28 patients, depending on wound size and common

Table 1. Nano-hydrogel formulations containing plant extracts

Utilized herbal extracts	Purpose of study	Supplementary components	Results of formulation	Increased activity and solubility	Reference
Nepeta cataria essential oil	To assess the efficacy of a nano-hydrogel formulation containing *N. cataria* essential oil in combating toxoplasmosis.	Chitosan and TPP	The *N. cataria*-chitosan essential oil nano-hydrogel formulation possessed a more reliable layer compared to the chitosan nano-hydrogel formulation. It also increased the particle size and larger zeta potential value compared to the chitosan nano-hydrogel formulation alone.	The *N. cataria*-chitosan essential oil nano-hydrogel effectively extended the lifespan of toxoplasmosis-infected animals. Animals treated with it experienced a reduced occurrence of tachyzoites.	(18)
Calendula officinalis flower extract	Observing the wound healing activity of carbopol nano-hydrogel formulations, Okra mucilage nano-hydrogel, and gum arabic-*C. officinalis* nano-hydrogel	Carbopol-940, Okra fruit mucilage, gum Arabic powder	The gum arabic-Cal formulation exhibited a polydispersity index of 0.389, suggesting that the particles in the preparation had a consistent size but were distributed across a wide range.	Nano-hydrogel with gum arabic-Cal formulation accelerated wound healing activity within 10 days in male white rats, surpassing the healing time of both the gum Arabic alone and the untreated groups which took 15 days to heal.	(41)
Solanum torvum L. leaf extract	Examining the effects of a nano-hydrogel formulation including *S. torvum* L. leaf extract, mucin, and zinc oxide on the healing of diabetic wounds in albino mice.	Zinc oxide powder, a mucin extracted from large African snails	The nano-hydrogel formulation had a size within the range of 13-42 nm. The TEM investigation revealed the production of spherical particles.	The nano-hydrogel formulation increased wound healing activity in Albino rats within 8 days, while the positive control (gentamicin) and blank nano-hydrogel took 12 days to heal.	(20)
Curcumin (CUR; *Curcuma longa*)	Evaluating the therapeutic properties of turmeric extract in treating psoriasis, with the use of Choline-calix[4]arene	Turmeric extract (curcumin), choline-calixarene powder, PBS	The nano-hydrogel was slowly dissolved in PBS medium, releasing curcumin-loaded micellar nano aggregates (90 nm mean hydrodynamic diameter, 23 mV surface zeta potential) as Curcumin delivery systems.	CALIX-curcumin nano-hydrogel effectively decreased the expression of TNF-α and IL-1β, indicating the ability to inhibit the production of pro-inflammatory cytokines. Encapsulating curcumin within micellar nano aggregates was advantageous for preserving its solubility and stability.	(22)
Soursop extract (*Annona muricata*)	Determining the optimal formulation for soursop extract nano-hydrogel preparation that added zinc to improve the therapeutic effect	Carbopol-940, chitosan powder, sodium TPP) and zinc oxide	The prepared nano-hydrogel exhibited a greenish hue, uniformity in texture, soft consistency, and stability during storage. The pH value fell within a tolerable range for the skin without irritation.	The solubility of *A. muricata* extract was enhanced by manufacturing a nano-hydrogel utilizing the ionic gelation method with chitosan and sodium tripolyphosphate. This formulation was suitable for drug delivery and many biological applications.	(42)
Essential oils of black cumin (*Nigella sativa*), cinnamon bark (*Cinnamomum verum*), and orange peel (*Citrus sinensis*)	To determine the antifungal properties of a nano-hydrogel formulation, including quince seed mucilage, in combination with essential oils derived from *N. sativa*, *C. verum*, and *C. sinensis*, against *Malassezia furfur* and *C. albicans*	Kwinsi seed mucilage, *N. sativa*, *C. verum*, and *C. sinensis*	The size of the nanothreads decreased from 361 nm to 31 nm after undergoing a 5-minute ultrasonic treatment. Following a 15-minute ultrasound treatment, the nano threads underwent a transformation into nanoparticles.	The nano-hydrogel formulation showed greater antifungal activity than essential oil alone, with a minimum inhibitory concentration of 3.125 mg/mL.	(25)
Lemon leaf extract (*Citrus limon*)	Creating SNPs from the lemon extract and embedding them in nano-hydrogel preparations, analyzing and describing the properties of the nanoparticles, and testing their effectiveness in vivo and in vitro.	Sodium thiosulfate, hydrochloric acid, carbopol, triethanolamine, lemon leaf extract	The SNPs produced from lemon leaf extract had a diameter of 40 nm, and mostly had a spherical morphology, while a few displayed an elliptical form.	The nano-hydrogel formulation exhibited independent antibacterial and antifungal properties, synergistic effects when combined with traditional antibacterial and antifungal medications, and significant wound closure, indicating its effectiveness in accelerating the healing process.	(29)

Table 1. Continued

Utilized herbal extracts	Purpose of study	Supplementary components	Results of formulation	Increased activity and solubility	Reference
Qiai essential oil (*Artemisia argyi*)	Assessing the production of Qiai essential oil nano-hydrogel preparations and examining the effectiveness of the formulation against bacteria	Qiai essential oil and pluronic F108	Micelles incorporating Qiai essential oil exhibited a reduced ball size and shrinkage ranging from 80 to 100 nm, in contrast to empty micelles.	The antibacterial efficacy of Qiai essential oil nano-hydrogel against *Staphylococcus aureus* and *Escherichia coli* was shown to be much higher compared to Qiai essential oil alone.	(31)
Millettia pinnata seed oil extract and *Nardostachys jatamansi* root extract	Characterization of herbal nano-hydrogel formulations bound to carboxymethyl cellulose and evaluating antibacterial, biofilm, and anti-inflammatory activities.	Lecithin, carboxymethyl cellulose, pectin, and guar gum	The nano-hydrogel formulation exhibited a bright yellow hue and a gel-like structure that was uniform and stable. It was soft with a uniform dispersion of extracts and a higher density of cross-links.	The nano-hydrogel formulation showed efficacy in suppressing bacteria and biofilm growth, the greatest inhibition was observed against gram-positive bacteria. It also demonstrated a moderate level of anti-inflammatory activity.	(43)
Neem plant oil (*Azadirachta indica*)	Characterization of nano-hydrogel formulations and their abilities to combat microbial infections and inflammation.	Tween-40, guar gum, glicerol	SEM analysis of the nano-hydrogel preparations revealed well-defined networks and a uniform, compact surface morphology.	The nano-hydrogel formulation exhibited anti-inflammatory and antibacterial efficacy against *S. aureus, E. coli*, and *C. albicans*. It had higher efficacy against Gram-negative bacteria.	(38)
Mangiferin (*Mangifera indica*)	Enhancing the administration and absorption of mangiferin through the use of a nano-hydrogel formulation, including phospholipids for topical application.	Hydrochloric acid, chloroform, IPP	The preparations were in the shape of globules or spherical granules, with no signs of aggregation and a size smaller than 150 nm. The drug capture rate was found to be greater than 75%, with a drug loading of approximately 25%.	The formulation enhanced in-vitro anti-cancer activity by a factor of four, with a threefold increase in cell uptake reported in MCF-7 cells. *Ex vivo* dermato-kinetic tests showed a significant amount of a substance available for absorption via the skin when applied topically, and it remained on the skin for a lengthy time.	(44)
Plantago ovata Forssk seed extract.	To develop and analyze magnetized nanospheres as carriers in a drug delivery system, utilizing a hydrogel made from *P. ovata* Forssk seed extract, in conjunction with mefenamic acid	TEOS, MAA, EGDMA, TMVS, CTAB, AIBN	The iron oxide nanoparticles had a spherical shape and uniform shape, excellent dispersion, and homogeneity. The diameter varied from 20 to 30 nm.	The formulations had the potential to act as anti-inflammatory medicines with the highest level of inhibitory activity against swelling at a pH of 7.4.	(45)
Teucrium polium extract	Developing a chitosan nano-hydrogel infused with *T. polium* extract and evaluating its effectiveness in promoting wound healing in diabetic mice.	Chitosan and sodium tripolyphosphate	The *T. polium* extract nano-hydrogel preparation was characterized by a hydrodynamic diameter of 203 nm, a polydispersity index value of 0.50, and a zeta potential value of 21 mV.	The TP-NPs preparation expedited wound healing and significantly higher healing activity in comparison to the group that received TP extract therapy alone.	(46)

TME, Transmission electron microscopy; TPP, tripolyphosphate; PBS, Phosphate buffered saline; IPP, isopropyl palmitate; TEOS, Tetraethyl orthosilicate; MAA, methacrylic acid; EGDMA, ethylene glycol dimethacrylate; TMVS, trimethoxyvinylsilane; CTAB, cetyltrimethylammonium bromide; AIBN, A,A›- azobisisobutyronitrile; TP-NPs, Teucrium polium nanoparticles; SEM, Scanning electron microscopy; SNPs, Sulfur nanoparticles.

patient condition. Based on the results, a group of patients treated with hyaluronic acid had emerging local infection and required antimicrobial treatment, while patients treated with nano-hydrogel formulation had no side effects, suggesting it can be safely used in diabetic foot ulcer patients (40).

Mangiferin, a bioactive compound extracted from *Mangifera indica*, is known for its potential to manage breast cancer. However, mangiferin is associated with several problems, such as lipophilicity, poor solubility in biological fluids, and poor bioavailability, which is reported to be under 2% (47,48). The cancer cell viability against MF-7 cells showed that the nano-hydrogel-incorporated mangiferin obtained IC_{50} values of about 6.25 µg/mL, which was higher than plain gel and conventional gel formulations. The dermato-kinetic studies revealed that drug concentration from the nano-hydrogel formulation in the skin was higher than the plain gel and conventional gel formulations. This result showed that nano-hydrogel could improve the anti-cancer activity of mangiferin two-fold and also improve the bioavailability of mangiferin (44).

The extract of *Teucrium polium* is known to possess anti-inflammatory activity, antioxidant, and wound-healing activity (49). The nano-hydrogel of *T. polium* formulation showed significantly increased wound healing activity in diabetic rats than *T. polium* extract and positive control after 21 days. Based on the result, nano-hydrogel formulation also increased the activity of *T. polium* via its antioxidant, anti-inflammatory, and wound-healing properties (46).

Drug-loading and drug release in nano-hydrogel

According to nanomedicine, drug loading refers to the drug mass ratio to the formulation. The drug loading indicates the efficacy of drug utilization throughout the formulation preparation procedure. The drug loading is influenced by the carrier's structure, physical and chemical properties, drug loading process, drug mass, and additional parameters (50). The loading of drugs onto nano-hydrogels is crucial due to their design for regulated and targeted drug delivery, facilitated by their adjustable scalability and capacity to swell in response to stimuli (51). Drug incorporation into nanogels is accomplished by physical trapping and both covalent and noncovalent interactions, as in Figure 2 (52,53).

Phthalic anhydride, an antiviral agent, and hexamethylenetetramine, an antibacterial agent, are heterocyclic organic compounds extensively utilized in the pharmaceutical industry. The application of these two compounds is restricted due to their solubility under acidic conditions and their hydrophobic nature, which result in constrained drug loading and release capabilities (54). The synthesis of chitosan nano-hydrogel and its derivatives is recognized for enhancing the interface of functional groups with drug solutions and cell surfaces, hence increasing drug loading to 75.49% and enabling controlled release up to 85.56% (54,55).

Curcumin is a bioactive substance present in *Curcuma longa*. Curcumin has been extensively utilized as a culinary spice and for the treatment of psoriasis (56,57). The nano-hydrogel formulation, including chitosan and TPP, included with gold and curcumin nanoparticles, achieved a drug capture and loading efficiency of 11±3.55% and an encapsulation efficacy of 78.66 ± 3.05% (58,59).

Essential oils derived from Fennel can be used in nano-hydrogels to enhance drug loading and improve the efficacy of drug release. This work employed the oil-in-water nano-emulsion technique, using poly (lactide-co-glycolide) (PLGA) in the formulation. The FEO-PLGA formulation exhibited a substantial drug loading capacity of 66.4 ± 3.127%. The drug release rate indicated that the FEO-PLGA gel formulation achieved 88.55%, whilst the FEO-PLGANPs formulation reached 86.63% (60).

Mentha piperita essential oil exhibits an inhibitory effect against bacterial biofilms, particularly on dental surfaces. The nano-gel formulation of *M. piperita* essential oil exhibited a drug release of approximately 50% throughout a testing duration of 480 minutes.

The release of a component in the formulation is affected by factors, including the nanogel's loading capacity, the porosity of the polymer structure, and the interaction between the essential oil and the polymer during synthesis. The efficiency of medication release is also determined by the particle size inside a formulation (61).

Mangiferin extracted from *M. indica* is known for its anti-

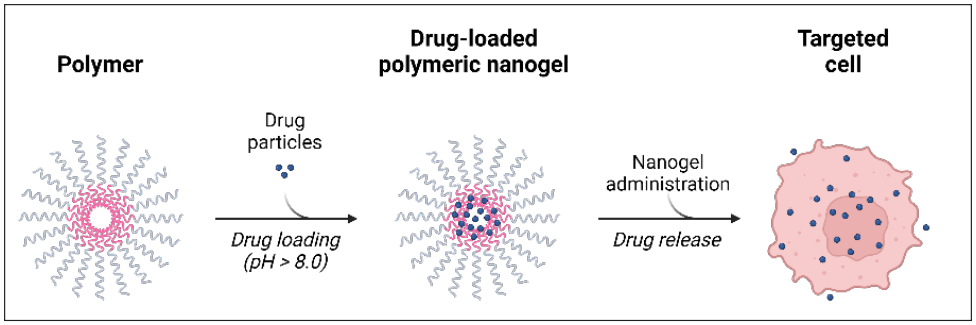

Figure 2. Drug incorporation into nano-hydrogel.

cancer activity. The various nano-hydrogel-incorporated mangiferin formulation using the microemulsion method has entrapment efficiency of more than 75%, invariably for every oil ratio. The drug release study showed that plain gel and conventional gel formulations were completely released in 3 hours, while the nano-hydrogel could retain the drug release for 8 hours (44).

The formulation of nano-hydrogel using *Plantago ovata* Forssk combined with mefenamic acid showed that the drug entrapment efficiency was 64.35%. The maximum drug release was 57.3 ± 0.6% for 72 hours. Based on the results, it is known that the existence of various functional groups and structures represents drug encapsulation and loading efficiencies (45).

Nanotoxicity

Nanotoxicology is the evaluation of the toxicity of nanoparticles, aiming to ascertain their potential risks and the magnitude of these risks to environmental and human health. Their physical and chemical properties render nanoparticles applicable in numerous domains, although they also pose potential toxicity risks (62). Factors influencing nanotoxicity include exposure duration, dosage, concentration, particle dimensions, particle morphology, and surface area (63).

Nanomaterials with smaller particle sizes have a larger surface area, which attracts more molecules and enhances their harmful effect (64). A study demonstrated that silver nanoparticles (AgNPs) ranging from 10 to 160 nm exhibited the largest amounts accumulated in the gills and liver of the test subjects (65). Gold nanoparticles (AuNPs) ranging in size from 15 to 50 nm can rapidly migrate throughout body organs such as the blood, liver, lungs, and kidneys in test mice, and they can cross the blood-brain barrier (66).

The green synthesis of Se-ZnO-NAB utilizing *Curcuma longa* extract exhibited a potent inhibitory effect on the growth of MRSA (methicillin-resistant *S. aureus*) bacteria. Additionally, the study indicated that high doses might result in moderate alterations in liver function tests (LFT) and renal function tests (RFT) in both normal and pregnant rat subjects, requiring caution in their administration and application (50).

The forms of nanomaterials, including spheres, rods, cubes, triangles, and wires, affect nanoparticle dynamics and transport in the environment (62). Surface charge also plays an important role in controlling particle dispersion and influencing ion and biomolecule adsorption (51). A study found that providing SiO2, ZrO2, and Al2O3 nanoparticle powder at concentrations more than 1 mg/mL caused erythrocytes to lose their typical biconcave shape. Additionally, electrostatic interactions of SiO2 with cells promote cell adhesion and swelling of erythrocytes in test animals (52).

Inhalation is the predominant and most recognized pathway for nanomaterial exposure. Furthermore, they can infiltrate the human body via the skin, gastrointestinal tract, or injection (63). Particles smaller than 0.1 μm can access distal airways within respiratory units. The inhaled nanoparticles reach the respiratory epithelium and traverse the pores in the alveolar-capillary membrane, initially entering the interstitium and subsequently entering systemic circulation via blood and lymphatic pathways. Experimental studies on mice have proven that nanoparticles introduced into the trachea enter systemic circulation through this mechanism (53).

The dimensions of the nanoparticles, their gravitational resistance, and their dispersion pattern, dictate the region of deposition within the respiratory system. Nanoparticles inhaled into the body via the respiratory tract are cleared in respiratory system by the mucociliary layer and macrophages, or they aggregate in the lungs and disseminate throughout the body via the bloodstream (67).

Conclusion

This research showed the capacity of nano-hydrogels to improve the effectiveness, durability, and accessibility of herbal ingredients. Using nano-hydrogels to encapsulate phytochemical compound enables precise and regulated release of herbal medicines, leading to optimal therapeutic effects and minimal adverse reactions. Nano-hydrogels possess a wide range of physical and chemical properties that may be adjusted, making them highly adaptable for creating delivery systems that are specifically designed for certain herbal ingredients and therapeutic requirements. Few studies have been performed on the drug load and drug release of nano-hydrogel. Therefore, it is recommended that researchers investigate the specific nanotoxicity and specific drug release of herbal nano-hydrogel.

Authors' contribution

Conceptualization: Muhammad Rifqi Fadillah Muslim, Lutfi Chabib, Hasyrul Hamzah.
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Conflict of interests

The authors declare there are no conflicts of interests.

Ethical considerations

Ethical considerations, including plagiarism, misconduct, falsification, double publication, and submission, were completely observed by the authors.

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