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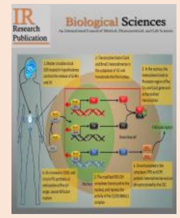

A review on nanogel/emulgel formulations of traditional medicines

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ABSTRACT

Nanotechnology is being ventured into as an emerging trend eliciting improvements in nearly all technological fields, and the pharmaceutical sector is no exception to this. It has been used for many years for synthetic drugs. But nowadays, the focus is on traditional medicines. This work is focused on the nanogel and nanoemulgel formulations of traditional medication and holds strong relevance in the surging era of nanomedicine. Herbal medicines are making a resurgence in the twenty-first century, as the dangers and limitations of modern medicine become increasingly evident, and herbal remedies are considered a balanced and reasonable approach to treatment. Advances in analysis and clinical research demonstrate the efficacy of herbal drugs in disease prevention and treatment. The main issue with herbal remedies is their inability to dissolve and stabilize. New technical breakthroughs have the potential to eliminate the problems connected with herbal therapy. Nanoformulations reflect the interface between new technology and herboceuticals. Thus, nanosized novel drug delivery system of herbal drugs has an inevitable potential due to their high drug encapsulation capacity, homogeneity, low toxicity, and improved stability.

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Introduction

There is a worldwide shift away from synthetic drugs and toward herbal or natural treatments, with people returning to herbal therapies. The active chemical found in herbs or plant species has a synergistic impact, enhancing the therapeutic effects and effectiveness of the product. The therapeutic effectiveness of such treatments commits to standardized herbal products of consonant quality and unambiguous constituents. The phytochemical

elements in any herbal product must be pharmacologically effective [1]. Herbal medications have become more popular due to their capacity to treat various ailments with minimal side effects. Since ancient times, herbal medicines have been enormously used worldwide for their admirable therapeutic values, and minimal adverse effects are analyzed to modern medicines. Due to a lack of scientific explanation and processing obstacles, herbal medications were not scrutinized for producing fresh formulations for a long time [2].
There are thousands of different kinds of plants like these accessible worldwide. *Withania somnifera, Aloe vera, Azadirachtaindica, MurrayaKoenigii, Carica papaya, Allium sativum,* and others are such plants. Through the extraction, distillation, fermentation, fractionation, and purification of fragmented pieces of plant part and procure the herbal preparations. These involve processed exudates, tinctures, extracts, expressed juices, essential oils, and comminuted or powdered herbal compounds [2]. The global's earliest polyherbal mouth dissolving tablet was launched by Asoka Life Science Limited [3].

About 85% of the global population who are afflicted with hypersensitivity reactions, diabetes, fungal and viral infection, and skin diseases get cured with herbal treatment or remedies. Herbal medications are gaining popularity due to their ability to treat almost all diseases. Herbal drugs, on the other hand, are restricted in their use due to several concerns (low oral absorption, poor solubility, instability, poor bioavailability, and unpredictable toxicity) [3]. To surmount such issues, "Nanotechnology" has developed rectifier therapies for the pharmaceutical that will encounter the exude associated with herbal medicines. Herbal drugs are being incorporated into nanocarriers which enrich the effectual and valuable effect of drugs [4]. Additionally, accumulating pharmaceuticals in non-targeted locations reduces drug degradation, premeditated metabolism, and significant adverse effects. It increases the ease of administration in geriatric and pediatric patients.

In 1974, the late Norio Taniguchi invented the term "nanotechnology," inspired by a 1959 suggestion by a nuclear physicist. Nanotechnology is accompanied at nanoscale magnitudes; it is the molecular dominance to construct gigantic structures through the new molecular arrangement. The command to manage and use a system's physical, biological, and chemical assets come from the interconnectivity of nanotechnology's building blocks and inter-atomic forces. Safe materials, such as artificial perishable polymers, lipids, and polysaccharides, are used to make the nanocarriers. These innovative carriers should ideally meet certain requirements.

- First and foremost, direct proportionality between the amount of drug and the cure requirement and duration.
- Herbal medicine should also reach the proper target [5].

Advantages of nanotechnology

Controlling drug distribution in new drug delivery technology is accomplished by putting the drug into a carrier system or modifying the drug's structure at the molecular level. The following are some of the benefits of novel drug delivery systems-

- An increase in solubility.
- The bioavailability of the drug has improved.
- Pharmacological activity has increased.
- The level of stability has improved.
- Better tissue macrophage dispersion.
- Reliable delivery [6].
- Protect from physical and chemical (Due to some limitations of herbal extracts/plant actives like instability in highly acidic pH, liver metabolism, etc., leads to drug levels below therapeutic concentration in the blood resulting in less or no therapeutic effect) degradation [7,8].

Disadvantages of nanotechnology

- Sometimes, particles of surfactant can cause toxicity.
- It requires expensive techniques [9].
- The change in the physicochemical and structural properties of nanosized materials due to size decrease could result in several material interactions that may lead to toxicological effects [10].

Nanoformulation incorporating herbal medicines

Isolated phytochemical compounds from plants and employed in formulation with the help of nanotechnology for therapeutic effectiveness. Several nanoformulations incorporating herbal medicines were prepared like nanoparticles, nanoemulsions, nanosuspension, nano gel/ emulgel, etc. This review focuses on the herbal medicines formulated as nanogel or nanoemulgel and the effect of nanoformulation on their stability and pharmacological activity. Different methods are used to make nanoparticles by using herbal extracts. These include the following:

- High-pressure homogenization method.
- Complex coacervation method.
- Coprecipitation method.
- Salting-out method.
- Solvent displacement method.
- Supercritical fluid method [11].

Nanogels are a type of nanoformulation that can be used to deliver hydrophobic therapeutic agents. Nanogels are nanosystems made up of hydrophilic, hydrophobic, or amphiphilic polymers that have been physically or chemically crosslinked. Polysaccharides and proteins may also be included in the nanogel-forming components chosen for their biodegradability and low immunogenicity. Nanogels are a promising and innovative drug delivery method that has the potential to help overcome the challenges related to the selected drugs. The therapeutic index of the loaded drug can be improved by formulating nanogels that shelter the encapsulated drugs from degradation and offer controlled release over prolonged periods. Nanogels made of biodegradable polymers are good options for medication delivery. In terms of bio-degradability, biological origin, abundance in nature, and non-toxicity, biopolymer-based nanogels outperform synthetic ones. Another advantage is that many functional groups are available for subsequent conjugation with biomolecules [12].

Nanotechnology tries to modulate the release of poorly water-soluble herbal medications to boost their bioavailability. Because of their natural tendency to swell owing to chemical change, nanogels are used for local and systemic medication action. This allows the drug to be released in the dosage form needed. Dermal patches, biosensors, and ionic drug delivery can be made with nanogels. The composition of the lipids and polymer in these nanostructures can be used to distinguish them. Using lectin functionalization, drug delivery from carbohydrate-based nanogels can be improved. Nanogels can be different from other nanoformulation, i.e. nanogels are crosslinked polymer networks that are nanoscale in size and capable of absorbing enormous amounts of water. Nanoemulgel has emerged as a novel drug delivery system and shows the most promising candidates for sustaining and controlling drug release systems. Nanoemulgel is composed of nanoemulsion and gel. In this, both of them were separately prepared, i.e. nanoemulsion and gel. Nanoemulsion can be o/w or w/o type emulsion. Lastly, the nanoemulsion is dispersed in the gel phase and found in the nanoemulgel formulation of any herbal medicine. Therefore, this composition formulation shows a dual release control system and influences better skin penetration [13].

Nanoemulgel consists of particle sizes ranging from 10-100nm, through which the drug can penetrate or deliver easily and quickly. Gelling phase enhances the viscosity of nanoemulgel and stabilizes the formulation by reducing the surface and interfacial tension of the emulsion and transport properties. The preparation procedure is schematically represented in **Figure 1**.

Step 1: The oil and aqueous phase is prepared separately.

Step 2: The oily and aqueous phases are heated individually at 70-80□C for 20 min.

Step 3: Then Oily phase is added to the aqueous phase by stirring on a magnetic stirrer and allowed to cool.

Step 4: Next, the homogenization process gets nanoemulsion.

Step 5: Gelling agent is dispersed in purified water and stirred continuously at a gentle speed with a magnetic stirrer to establish the gel phase in the formulations.

Step 6: The nanoemulsion is combined with the gel bases by gently swirling.

Step 7: Gellified nanoemulsion obtained.

Step 8: Finally prepared nanoemulgel.

Curcumin nanogel/emulgel

Turmeric is a rhizomatous herbaceous perennial plant (Curcuma longa) of the ginger family [14]. A wide range of chemical constituents is obtained from the plant portion of rhizomes which consist of different volatile oil molecules just like mono and sesquiterpenoids. These also contain bioactive non-volatile curcuminoids (curcumin, dimethoxy-, and bisdemethoxycurcumin). Different pharmacological properties are given by Curcuma species that is antiproliferative, antiviral, anticancer, antihepatotoxic, carminative, anti-inflammatory, antimicrobial, insecticidal, hypotensive, larvicidal anti-thrombotic, antidiarrheal, anti-diabetic, hypocholesterolemic, diuretic, antirheumatic, antioxidant, antivenomous, and, among others [15]. C. longa includes a variety of curcuminoids, with curcumin being the most active, having been isolated in 1815, and Polish scientists Milobedzka and Lampeidentified the curcumin structure in 1910 [16]. Sarika et al. employed an inverse microemulsion technique for preparing encapsulated curcumin alginate aldehyde–gelatin

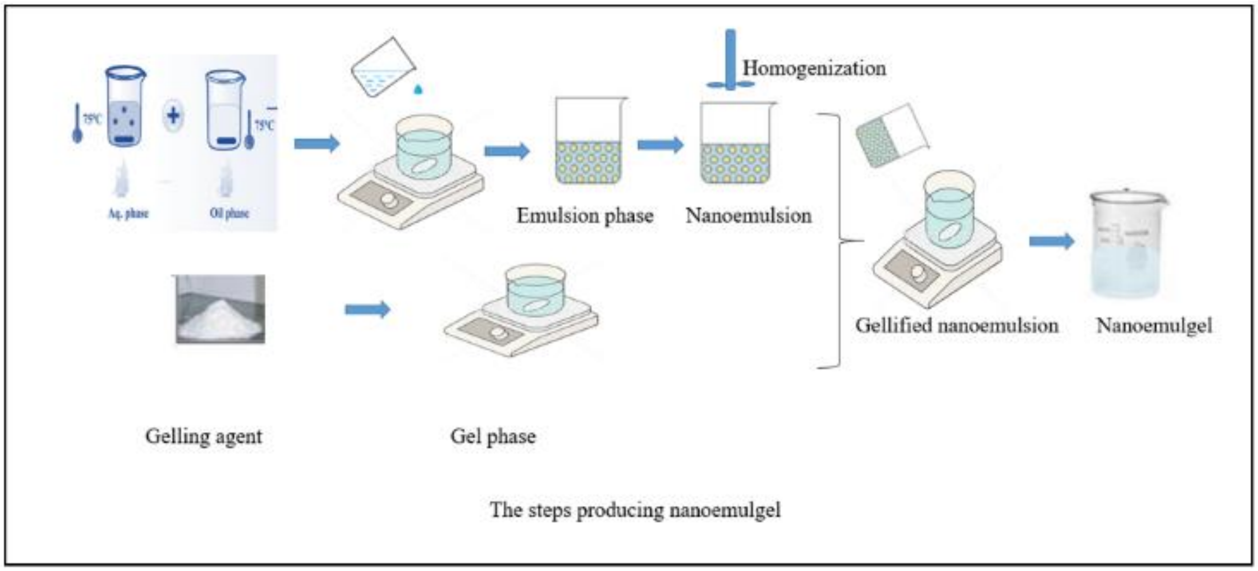

Figure 1. Schematic representation of the preparation of nanoemulgel.

(AlgAld-Gel) nanogels, increasing bioavailability and therapeutic efficacy. Bioavailability and water solubility of curcumin get enhanced with Nanogels. At acidic pH, nanogels release more curcumin and cause cytotoxicity in MCF-7 cells. Confocal laser scanning microscopy demonstrated the in vitro cellular absorption of curcumin-laden nanogels. As a result, curcumin-loaded AlgAld-Gel nanogel should be a potential drug delivery technology for breast cancer treatment [17]. In another study, a curcumin-loaded nanogel system was developed and tested in Wistar rats to see if it improves the therapeutic efficacy of curcumin for wound healing. The curcumin was encased in a nanoemulsion system using a high-energy ultrasonic emulsification technology with the least amount of Labrafac PG surfactant used in the curcumin-loaded oil system for nanoemulsify. The percutaneous drug flux of curcumin through the curcumin-nanoemulgel (NEG) (13.74±1.08) was almost six times higher than the drug flux of curcumin through the curcumin gel (2.19 ± 0.010). When comparing curcumin-nanoemulgel preparation (5.49±0.67) to the curcumin gel (0.876±0.01), the permeability coefficient (K103) of curcumin increased almost six-fold [18, 19].

Green tea nanogel/emulgel

Around 4000 bioactive components are present in green tea extract (GTE). Some of the most frequent catechins are obtained from Green tea like Epicatechin-3-gallates, Epigallocatechin (EGC), epigallocatechin-3-gallate (EGCG), epicatechin (EC). Green tea extract is prepared from *Camellia sinensis,* which belongs to the family of Theaceae. GTE-loaded nanogel was prepared by dispersing the GTE chitosan nanoparticle into Carbopol 934 gel base [20]. In one study, to control the antioxidant the activity of GTE, the GTE was encapsulated in chitosan citrate nanogel. The amount of loaded GTE impacts the primary features of chitosan nanoparticles- green tea (CS-NP-GT) effectively, comparing PDI, zeta potential, particle size, and EE associated with unrelated CS: GT ratios. The DPPH technique of measuring antioxidant activity revealed the scavenging activity of CS-NP-GT is higher than that of free GT [21]. In another study, epigallocatechin-3-gallate is one such GTE molecule that has chemotherapeutic activities and can lower cholesterol levels in the blood. Because topical medication administration is complex, nanogels, with their smaller particle size and structural features, have much potential for producing green tea extract-loaded chitosan nanogel. In vitro diffusion, viscosity, and pH were investigated for independent variables such as carbopol and triethanolamine (TEA) concentrations on nanogel. To prepare nanogel, all formulations were created using the Box-Behnken design and the nanoprecipitation technique. The encapsulation efficiency of the produced chitosan nanoparticle designated F5 was 94.11 percent, with a practical yield of 94.41 percent. The nanogel formulation NG15 also revealed optimal drug content of 99.87 percent following GTE loading. The GTE-loaded nanogel appears to be durable and has the potential to be employed for topical medication delivery [22, 23].

Ginger nanogel/emulgel

For nearly 2000 years, ginger (*Zingiber officinale* (L.) Rosc) has been preoccupied as a spice. Ginger has antinausea, respiratory protective, antioxidant, neuroprotective, anti-inflammatory, antiemetic, antibacterial, antiobesity, anticancer, cardiovascular protective, and antidiabetic properties, among producing light of various hues. Heavy metal-based others. The active ingredients of the ginger extract are paradol, gingerdione, 6-gingerols, shogaol gingerdiol, which can be found in the roots and extracts [24]. The ginger extract was converted into nanoemulgel for curative rheumatoid arthritis through a topical route, enhancing ginger extract's bioavailability and reducing the dose of ginger extract. Namoemulgel was formulated by the freeze-thaw cycle technique between the temperature of 00C and 250C [25]. Another study used the spontaneous emulsification approach to create nanoemulsions containing lemon, ginger, turmeric, and coconut oil. Nanoemulgels showed PDI ranging from 0.21 to 0.75, with maximum stability at 25 ±2 oC. From days 7 to 28, anti-arthritic tests revealed that lemon and ginger nanoemulgels had more robust and identical percent inhibition sequences, but only ginger nanoemulgel achieved basal paw levels on day 28. As a result, ginger nanoemulgel was proposed as the most effective treatment for rheumatoid arthritis [26].

Nigella sativa nanogel/emulgel

Nigella sativa L., a part of the Ranunculaceae family, is grown in many places, but particularly in the East Mediterranean. Its seeds are used as a condiment in regions of Germany, France, and Asia. Due to their aromatic flavor, the seeds are used as a spice in cooking, particularly in Italy and Southern France. Oriental folks also utilize them as carminative and diuretic [27]. Diuretics, analgesics, antifungals, antihypertensives, antidiarrheal, liver tonics, and antibacterial agents are all found in Nigella sativa (NSO) L. seeds and oil. The primary medicinal constituent of Nigella sativa oil (NSO) is Thymoquinone (TQ) which is the bioactive component. Moreover, TQ (30–48%), 4-terpineol (2–7%), thymol, carvacrol (6-12%), thymohydroquinone, cymene (7–15%), dithymoquinon, t-anethol (1–4%), and -pinene are all attending at appropriate amounts (NSO). NSO in a nanoemulgel formulation for periodontal disease therapy. The oil's low toxicity means that at therapeutic levels of NSO, there is a large margin of safety. A GC–MS approach was used to characterize NSO acquired from a local market. Here the Nanoemulsion of NSO was prepared, and this dispersed into a methylcellulose gel base. Statistical design (quadratic model) of Box-Behnken was applied to investigate the best formulation. In 17 runs, independent variables including polymer concentration, oil, and water on two dependent responses: viscosity and pH. Another study aims to increase the biopharmaceutical properties of thymoquinone to improve its topical effectiveness in wound healing. Using a high-energy emulsification technique, a nanoemulsion-based hydrogel system was created and characterized as a nanotechnology-mediated drug delivery access to ameliorate the therapeutic effectiveness of thymoquinone. In comparison to the ordinary hydrogel of thymoquinone, the evolved nanoemulgel system of thymoquinone manifested pseudoplastic behavior with thixotropic properties. It exhibited faster and earlier healing in wounded Wistar rats while revealing approximate healing effectiveness to marketed silver sulfadiazine (1%) cream. In addition, histopathological investigation of animals treated with a newly designed formulation system revealed the creation of a thick epidermal layer, papillary dermis, and vast and structured collagen fibers in freshly repaired tissues.

Thymol nanogel/emulgel

Thymol (2-isopropyl-5-methyl phenol) is a chemical substance found in North American wildflowers, thyme (Thymus vulgaris) essential oil, and oregano essential oil (Origanum vulgare). Thymol possesses antifungal, anti-inflammatory, and antibacterial properties. Thymol was used in one trial to treat oral candidiasis, a painful infection that arises under the cheek and mouth cavity. The antifungal efficacy of a UV crosslinked Polyacrylamide loaded thymol nanogel in treating oral candidiasis was investigated. Thymol-nanogel was investigated as a potential replacement for traditional creams. By UV-induced crosslinking, polyacrylamide nanogel was made from acrylamide monomer utilizing N, N'-methylene bisacrylamide (cross-linker), and Irgacure (initiator). The optimization was done by varying reaction parameters such as light intensity, cross-linker, exposure period, and initiator. In vitro drug release, ex vivo permeability, FTIR Spectroscopy, FESEM, and antifungal activity were all used to assess nanogel properties. By utilizing the low-energy emulsification approach, the thymol-loaded nanoemulgel-based formulation design is expected to encourage patient compliance and adequacy as topical employment for acne treatment in another investigation. With PDI 0.197 ±0.008, the optimal thymol-loaded nanoemulsion existed to be 13.60 ±0.117 nm. Nanoemulsions will have a large surface area, allowing therapeutic substances to penetrate deeper into the pilosebaceous region, resulting in increased effectiveness [28].

Naringin nanogel/emulgel

Naringin, a flavanone glycoside, exists naturally in Chinese herbal medicine and citrus fruits [29]. The skin of pummelo contained a higher amount of naringin (3910 µg/g fresh weight) than the juice (220·0 µg/g fresh weight), whereas the amounts of naringin obtained from the skin, juice, and seed of rough lime were 517·2 µg/g, 98·4 µg/g and 29·2 µg/g fresh weight, respectively [30]. Numerous biological and pharmacological features of naringin have been discovered through research. Naringin has been demonstrated to have promising therapeutic promise in treating neurodegenerative diseases. Several approaches could be used to increase naringin administration, including structural modification, complexation, and liposomal and nanoparticle formulations [31]. A self-emulsifying nanosystem of naringin was designed with a smart, biopolymeric, ion-triggered hydrogel as the mucoadhesive carrier for increased delivery to the brain via an intranasal route. The produced nanoemulsion had a tiny droplet size, long-term naringin delivery, and improved diffusivity [32]. In the new study, a tocotrienol-rich naringenin nanoemulgel was formulated for topical treatment in chronic wounds associated with diabetes. The spontaneous emulsification method was used to create the nanoemulsions. Carbopols were added to the optimized nanoemulsions to create equivalent nanoemulgels. The mucoadhesive property, globule size, surface charge, PDI, in vitro release, viscosity, spreadability, and release mechanism of thermodynamically stable optimized nanoemulgels were examined. The optimized nanoemulgel (NG1) exhibited a release profile up to a maximum of 74.62 ± 4.54% of in vitro release of naringenin in phosphate buffer saline under the timeframe of 24 h. and viscosity of 297,600cP with good spreadability, uniform dispersion (PDI, 0.452 ±0.03) of the nanometric globules (145.58 ±12.5) in the dispersed phase as well as a negative surface charge (-21.1±3.32 mV) [33].

Mangosteen nanogel/emulgel

Mangosteen is a term used to describe the compounds taken from plants, including Garcinia mangostana L. Mangosteen is a tropical fruit native to Southeast Asia, Southwest India, and additional tropical locations such as Puerto Rico and Florida. Antibacterial, Antioxidant, anti-allergy, anti-tumoral, antiviral, anti-inflammatory, and antifungal properties are found in the secondary metabolites associated with xanthones in mangosteen fruit and leaves. Mangosteens cannot be directly formed into a gel due to their hydrophobic nature. The high-speed homogenization technique produced Nanoemulsion of Oil-in-water type containing virgin coconut oil (VCO), Tween 80, and Span 80. A uniform milky white gel was generated by combining the nanoemulsion with an aqueous xanthan gum solution and adding phenoxyethanol as a preservative. The nanoemulgel was stable for at least one year after being subjected to vigorous centrifugation and freeze-thaw cycles [34]. Mangosteen (Garcinia mangostana Linn.) rind is recognized to have anti-inflammatory properties. Topical administration of dosage forms can be used to treat local tissue inflammation. The activity of gel and nanoemulgel formulations comprising fractions of mangosteen rind extract is investigated in this study (n-hexane: ethyl acetate). Nanoemulgels containing 0.0625 percent and 0.125 percent mangosteen rind fraction concentrations produced better percent inhibition ($p < 0.05$) in the 90th minute of a carrageenan-induced laboratory mouse inflammatory test than gels containing 0.1%, 0.5%, and 1% mangosteen rind fraction concentrations. However, from the 120th minute to the end of the test, the difference was insignificant [35].

The mangosteen fruit rind fraction was shown to contain flavonoids and polyphenols, which can act as antioxidants and anti-inflammatory agents in the third investigation. To support percutaneous penetration, the use of mangosteen rind fraction in topical medicines necessitates a reliable delivery strategy, one of which is nanoemulsion. Because the nanoemulsion has a low viscosity, it must be formed into nanoemulgel preparations to maximize the active compound's penetration. To generate a nanoemulgel that meets the physical and chemical parameters of the gel preparation, the optimal concentration of gelling agents is required. As a result, glyceryl polyacrylate was tweaked to produce a nanoemulgel with good properties. The nanoemulgel showed optimum adhesion (1 ± 0.02s), viscosity (8340 ± 555), spreadability (6.87 ± 0.39 cm2), and pH (6.39 ± 0.01) and resulting that glyceryl polyacrylate with a concentration of 1% could produce good nanoemulgel [36, 37].

Conclusion

The real benefit of novel drug delivery (NDDS) such as nanoparticles is targeted drug administration, which reduces dosing frequency while improving solubility, absorption, and elimination [49, 50]. Drug delivery methods using nanoparticles have become very popular in recent years. Among these, controlled and targeted therapy using nanoparticulate systems made of biodegradable and biocompatible polymers is an intriguing possibility [51]. This nanoemulgel has been the attention of many scientists to develop numerous drugs that treat various skin disorders. In recent decades, the growth of nanotechnology has played a significant role in developing nanocarriers in which a drug is incorporated. So, a new drug carrier system practically evolved for herbal Nanogel products. At low drug concentration, the synergistic effect and minimal side effects of herbal Nanogel formulation are expected by the pharmaceutical industry. For lipophilic drugs, solubilization takes place in the emulsion's oily phase and is further converted into nanoemulsion and then later added into the gel matrix; withdrawal of hydrogel limitations and expected for better stability and promote drug release. There are new opportunities for scientists to develop and expand nanogel's

Table 1. Nanogel/emulgel of herbal medicine

Sr. No.	Name of Plant	Polymer	Biological activity	Reference
1.	Ocimum Sanctum	Carbopol 974P (0.5%)	Wound healing	Sood R [38]
2.	Tea tree oil	Carbopol 940	Antimicrobial	Sinha P [39]
3.	Coriandrum sativum	Carbopol 940	Antimicrobial and Anticancer effects	Eid AM [40]
4.	Mustard oil (Brassica juncea)	Carbopol 934	Rheumatoid arthritis	Suryawanshi JS [41]
5.	Aegle oil	1% Carbopol 934	Antimicrobial activity	Bakr RO [42]
6.	Safrole oil	Carbopol® 940	Antimicrobial activity	Eid AM [43]
7.	Piper betle oils	Carbopol 940	Antimicrobial; antioxidant	Ting TC [44]
8.	Swietenia macrophylla oil	Carbopol grades 934 and 940	Anti-inflammatory	Eid AM [45]
9.	Babchi oil	Carbopol gel	Psoriasis	Kumar S [46]
10.	Cymbopogoncitratus	Carbopol®	Anti-herpetic activity	Almeida KB [47]
11.	Pongamiapinnata. L root	paraffin wax	Anti-inflammatory	Paul S [48]

fascinating properties like its drug loading capacity, swelling properties of gels, permeability with particle size, biocompatibility, degradability and colloidal stability. There has been a surge in interest in developing natural and environmentally friendly products with various beneficial bioactivities. Researchers may find that combining nanoemulgel and plant-based oils is an excellent way to optimize application formulation and meet market demands.

Contribution of authors

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Conflict of interest

The authors declare that there is no conflict of interest regarding the publication of this review article.

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