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Review

Medicinal Plant Enriched Metal Nanoparticles and Nanoemulsion for Inflammation Treatment: A Narrative Review on Current Status and Future Perspective

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Abstract: Inflammation is considered a natural reaction of the immune system that can be caused by several factors such as pathogens, chemical substances, and damaged cells. Since the classical era, therapeutic substances have been made from medicinal plants. According to recent studies, nanotechnology provides a fresh approach to maintaining the standard quality, distribution, and bioactivity of therapeutic compounds. This review emphasizes the anti-inflammatory effects of green, synthetic, plant-based nanoparticles and nanoemulsions. A reduction of the dosage of anti-inflammatory medications and an improved therapeutic impact is highly desirable with an efficient drug delivery method. Along with the discussion of nanotechnology of medicinal plant-based anti-inflammatory effects, this review also offers a perspective view of the use of nanoparticles and nanoemulsions in inflammatory diseases in the future.

Keywords: nanoemulsions; inflammation; nanoparticles; medicinal plant; anti-inflammatory effects

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1. Introduction

Nanotechnology is focused on the synthesis of materials and small-scale (1–100 nm) manipulation of plant-based, chemical, and microbial materials and diverse nanoparticle types have shown novel features that may open up new therapeutic possibilities [1]. Due to their small size and favorable interactions with the cellular membrane, receptors, organic molecules, and amino acids, nanoparticles are widely used in biomedicine [2]. Therapeutic plants enriched with active metabolites are shown to be an affordable approach to eco-friendly metal nanoparticle manufacturing and can decrease the metal ion to Cu^{3+} and Pt^{2+}, as poor solubility and less absorption in the human body can be resolved by encapsulating the active form of the medicinal plant as a nanocapsule by a different method for various biomedical applications such as inflammation [3].

Among various disorders, the inflammatory reaction is a key pathogenic component. While defending the host from inflammatory processes, the innate immune reaction also activates the innate inflammatory response system. Inflammatory and immunological responses can be regulated with the aid of anti-inflammatory medications [4]. The use of nanoparticles and nanoemulsions to target inflammation through the identification of molecules highly expressed on the surface of inflammatory cytokines or endothelial cells through increased vasculature permeability, or even through biomimicry, offers a promising treatment for inflammatory diseases [5]. This review offers a comprehensive insight into medicinal plant-based nanotechnology and outlines the various formation (Figure 1) and sizes of nanoparticles with their anti-inflammatory capabilities.

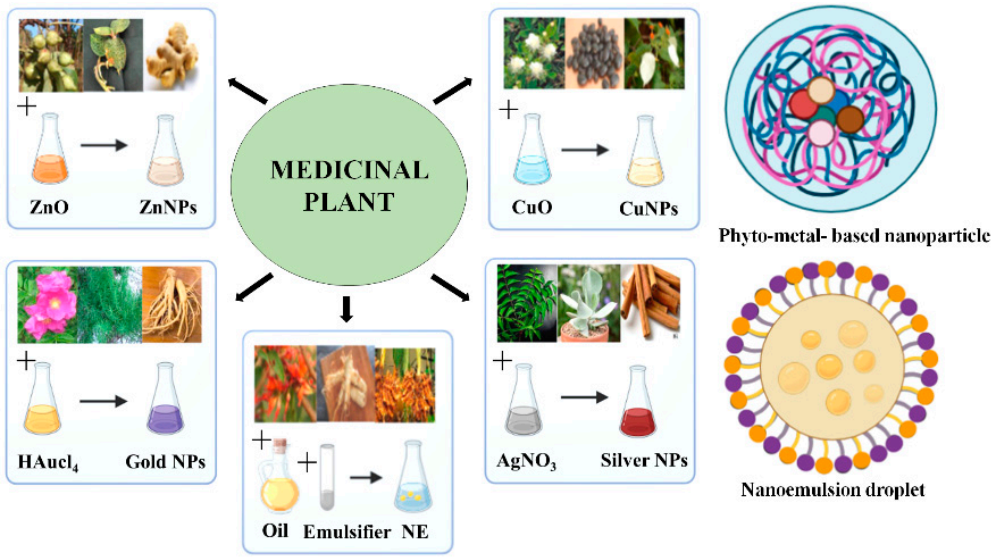

Figure 1. Bio formation and structure of phyto-metal nanoparticles and nanoemulsion.

2. Synthesis of Medicinal Plant-Based Metal Nanoparticles and Nanoemulsion

The need for metal nanoparticle synthesis grows along with the number of applications, which are expanding daily. A different way of creating biocompatible NPs known as "green synthesis" has emerged in response to the difficulties in the traditional chemical synthesis process [6]. Utilizing plant extracts is a relatively straightforward approach to making nanoparticles, and it is one of the accessible green methods of synthesis for metal/metal oxide nanoparticles. Water is consistently regarded as the best and most appropriate solvent solution for synthesis operations to dissolve plant extracts [7]. Plant extracts are regarded as a superior and safe source for the creation of metal nanoparticles. Various phytochemicals present in medicinal plants are responsible for the reduction of metal ions present in metal nanoparticles. Metal ions change into metal atoms and change color and form nanoparticles characterized by several techniques (TEM, SEM, FTIR, and UV-Vis spectroscopy) [8].

Nanoemulsions are incredibly flexible systems when it comes to encapsulating components that dissolve in the disperse phase. Most typically, hydrophobic molecules from herbal plant extracts are necessary to keep the tiny drops of a dispersed phase from floating around in a continuous phase. In three different types of nanoemulsion, the o/w type nanoemulsion consists of the water phase and oil phase. Then, surfactants are used for both hydrophilic and hydrophobic parts which stabilize the droplet emulsion and prevent phase separation [9,10]. Due to the low energy requirements, easy processing, low cost, and small droplets, the ultrasonic homogenizers method is commonly used for the synthesis of nanoemulsion. Other methods include high-pressure homogenization, micro fluidization, and the inversion technique [11].

3. Anti-Inflammatory Properties of Metal Nanoparticles and Nanoemulsion

Throughout the past few decades, nanomedicine has become recognized as a promising anti-inflammatory agent. One of the most popular methods for creating nanoparticles is plant-mediated "green" synthesis, which typically requires a neutral pH and occurs at room temperature [12]. Macrophages ingest the debris from cells and tissue during inflammation through a process known as phagocytosis and support inflammation by producing activation signals such as LPS, interferon, interleukin, etc., that activate macrophages. When there is inflammation, neutrophils migrate to the area and produce pro-inflammatory mediators that draw macrophages to the area [13]. Nanomedicine has a stronger ability to penetrate epithelial cells and inflammatory cells, which improves the treatment's efficiency and endurance [14]. In this review, we will only focus on medicinal plant-based metal nanoparticles and nanoemulsion mechanisms (Figure 2) and a brief discussion about that.

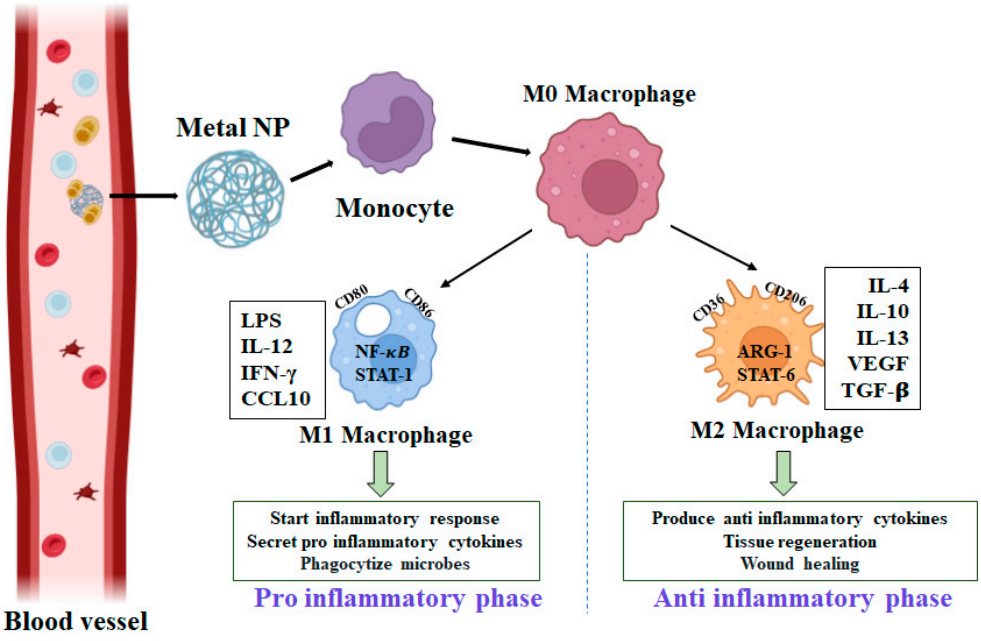

Figure 2. Inflammatory mechanism of the metal nanoparticle.

Reactive oxygen species (ROS) are by-products of the electron transport chain (ETC) and are created by NADPH oxidases found in phagocytes. Cellular lipids and proteins are oxidized by ROS, which damages DNA, encouraging endothelial dysfunction. Gold nanoparticles reduce ROS production and are an anti-inflammatory substance [15]. AuNPs decrease the release of IL17 and TNF-α which is stimulated by LPS from splenocytes. The MAPK pathway activates toll-like receptors from monocytes and some kinase which alter gene expression. The PI3K pathway inhibits LPS-induced TNF-α and activates NF-κB. Here, AuNPs downregulate cytokine production by modulating the MAPK and PI3K signaling pathways [16,17]. Silver nanoparticles inhibit vascular endothelial growth factor which stimulates T helper cell-induced inflammation and secretes pro-inflammatory cytokines. AgNPs also inhibit the production of COX2 gene expression by decreasing the secretion of IL-12 and TNF-α [18,19].

Similar to a silver nanoparticle, Zn nanoparticles inhibit both NF-κB and the caspase-1 enzyme in stimulated mast cells [20]. ZnNPs reduce the cytosolic degradation of IκBα, a cellular protein that suppresses NF-κB transcription, as well as NF-κB nuclear translocation which is triggered by LPS. In other ways, ZnNPs prevent mast cell proliferation and decrease LPS-induced COX-2 activation along with suppressing NO generation by IFN-γ in LPS-activated macrophages [21,22]. Copper nanoparticles prevent inflammation by efficiently assisting in membrane stability by limiting the release of RBC lysosomal enzymes to specific amounts in most of the studies [23].

Nanoemulsions (NE) are a promising method for improving the oral bioavailability of drugs with poor solubility. [24]. Enhanced oral bioavailability is responsible for increasing the solubility of plant-extract-based NE into the gut and a reduction of the droplet size in the formulation. Nanoemulsions also prevents inflammation by blocking NF-κB and MCP-1 to prevent macrophage migration. Likewise, the study revealed that a nanoemulsion is also capable of downregulating the MAPK and NF-κB signaling cascade depending on the dosage at a molecular level [25,26] (Figure 3).

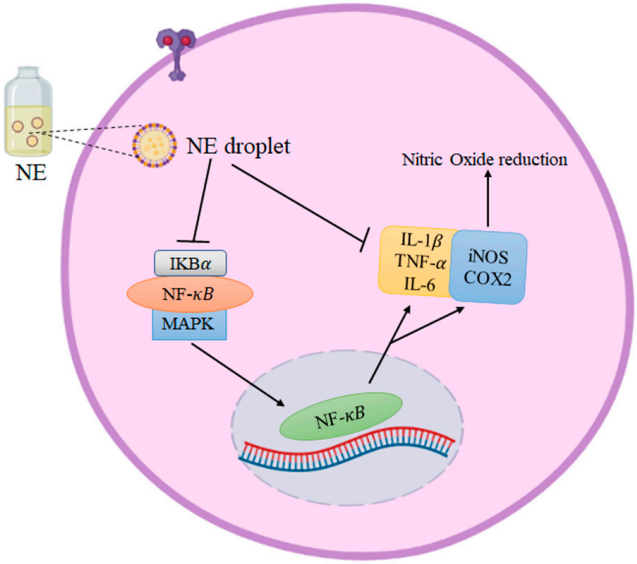

Figure 3. Inflammatory mechanism of medicinal plant-based nanoemulsion.

4. Medicinal Plant-Based Metal Nanoparticle

Currently, there has been a considerable increase in the production of NPs from therapeutic plants, which are crucial for the synthesis of nano drugs. Moreover, medicinal plants are considered a dependable and essential source of natural bioactive chemicals. The use of NPs has significantly improved nanoparticles and nanoemulsion, particularly in terms of lowering the dose frequency, enhancing drug solubility, and lengthening the half-life of some medications, leading to significant advances in targeted drug delivery [27]. Medicinal plants are extracts rich in proteins, carbohydrates, terpenoids, bioactive alkaloids, and phenolic acids that can reduce the metallic ions and stabilize them [28,29].

4.1. Therapeutic Gold and Ag Nanoparticles in Inflammation

Gold nanoparticles (AuNPs) have been utilized effectively for drug delivery and have well-established bioactivities. Gold nanoparticles (GNPs or AuNPs) appear to be the most efficient nanoparticles studied in experimental research, with the least systemic toxicity. AuNPs reduce NO generation and iNOS expression in RAW264.7 cells activated with LPS by preventing NF-kB and STAT1 activation [30]. Numerous research studies have revealed that *Panax ginseng Meyer* may have minimal to no negative side effects and have potentially helpful impacts on a range of illnesses and human health. Natural materials used in biologically generated AuNPs exhibit a variety of benefits that present different phytochemicals found in plants [31,32]. Synthesized Panax ginseng leaf extract-mediated gold nanoparticles (10–20 nm) inhibit the expression of NF-kB in LPS-induced RAW 264 [33] cells through the blocking of the MAPK pathway. Another medicinal plant named Suaeda japonica is a halophytic herb originating from Korea and Japan, and has been used to synthesize gold nanoparticles which are 20–30 nm and spherical. S. japonica successfully revealed its anti-inflammatory potential by reducing the release of pro-inflammatory cytokines and suppressing the expression of the genes iNOS, COX-2, and TNF-a [34,35].

As a first line of defense, the skin plays a crucial role in the immune system against different environmental stimuli and acts as tissue homeostasis. Moreover, an aberrant skin immune response potentially leads to inflammatory skin diseases [36,37]. Medicinal plant *Rosa Rogusa*-mediated gold nanoparticles exhibit significant anti-inflammatory effects in keratinocytes. The study revealed a novel approach to synthesizing RRAuNPs which were only 38.2 mm in size and significantly downregulated the gene expression of RANTES, TARC, CTACK, IL-6, and IL-8 of TNF-α/IFN-γ-induced HaCaT cells [38].

Natural killer cells possess the ability to both stimulate and limit adaptive immune systems that could otherwise result in excessive inflammation or even autoimmunity [39]. Innate and adaptive immune cell recruitment in chronic inflammation produces the synthesis of significant amounts of pro-inflammatory modulators. Elbagory et al. demonstrated that gold nanoparticles based on the medicinal plant *Hypoxis Hemerocallidea* suppressed pro-inflammatory cytokines production in THP1 cells and prevented chronic inflammation involving NK cells [40,41].

Nearly every component of an organism's immunological reaction involves macrophages. Localized macrophages control inflammation by serving as sentinels and reacting to internal and external physiological changes [42]. As autophagy is considered an important component of innate immunity, inflammatory and viral disorders can be made more likely by autophagy dysfunction [43,44]. Damaged mitochondria accumulated as a result of an impaired autophagic flux could produce too much ROS and lead to cell death [45]. Recent research reported medicinal plant *Hibiscus Syriacus L*-mediated gold nanoparticles acted as an inducer of autophagy for LPS-induced macrophage inflammation. HCE-NPs reduced the overproduction of pro-inflammatory mediators in RAW264.7 cells after LPS-induced inflammation via an autophagy-dependent approach. By decreasing ROS generation and restoring the levels of ATP, NPs prevent accelerated inflammation [46]. We have summarized some of the interesting research works on the anti-inflammatory effects of current gold and silver nanoparticles in Table 1.

Table 1. Anti-inflammatory effects of current gold and silver nanoparticles.

Nanoparticle	Medicinal Plants	Observation	Characteristics Size/Shape	Anti-Inflammatory Action	Ref
Gold	Panax gin-seng Meyer leaf	In vitro	10–20 nm	Reduction of the expression of the inflammatory mediators in the NF-κB signaling pathway	[33]
Gold	Suaeda japonica Leaf	In vitro	8.75 nm Crystalline	Suppress the generation of nitric oxide (NO) and repress the expression of the pro-inflammatory gene	[35]
Gold	Rosa ru-gosa(beach rosea)	In vitro	38.2 ± 3.7 nm Polygonal	Treat skin inflammation by reducing oxidative stress via the MAPK and NF-κB sig-naling pathways	[38]
Gold	Hypoxis hemerocallidea	In vitro	26 ± 2 nm Spherical	Reduce the amounts of pro-inflammatory cytokines in macrophage cells	[41]
Gold	Hibiscus syriacus L	In vitro	3–20 nm Spherical	Suppress pro-inflammatory cytokines and decrease the expressions of PINK1 and Parkin in autophagy-dependent mechanism	[46]
Silver	Azadirachta indica kernel	In vitro	19.27–22.15 nm Spherical	Control protein degradation to fight inflammation	[47]
Silver	Cotyledon orbiculata	In vitro	20 to 40 nm	Suppress the secretion of the pro-inflammatory marker in LPS-treated macrophage	[48]
Silver	Cin-namomum zeylanicum bark	In vitro	60–80 nm Spherical	Decrease TNF-α, IL-6, and IL-18 inflammatory markers of PCOS	[49]
Silver	Syzygium cumini fruit	In vitro	~47 nm Spherical	Protein denaturation in higher concentration	[50]
Silver	Selaginella myosurus	In vitro	33.7, 44.2	Inhibition of thermally induced denaturation of albumin	[51]

A growing number of sectors, including those in medicine, food, health care, consumer goods, and industrial uses, are using silver nanoparticles (AgNPs) based on distinctive

physical and chemical characteristics [52]. AgNPs are produced using multiple strategies, such as chemical and physical ones; however, they all involve the employment of dangerous substances and high temperatures [53,54]. Researchers' curiosity has been piqued by the special properties of plant-based silver nanoparticles, such as non-toxic efficiency [55,56]. Research has shown that silver nanoparticles synthesized from *Azadirachta indica* kernel aqueous extract have a significant anti-inflammatory effect in vitro. A variety of biological activities make *Azadirachta indica* one of the most useful therapeutic herbs. Spherical-shaped 19–22 nm sized green synthesized AgNPs control protein degradation dose-dependently which prevents arthritic inflammation [47]. Another traditional plant named *Cotyledon orbiculate* from South Africa is very notable to treat skin inflammation. Synthesized stable silver nanoparticles from *Cotyledon orbiculate* exert immunomodulatory effects in the THP-1 macrophage by a reduction of pro-inflammatory cytokines such as TNF-α, IL-6, and IL-1β [48].

Asparagus racemosus has been employed in conventional treatments for several immune-related illnesses [57]. The study discovered that medicinal *A. racemosus* biosynthesized mixed Ag–Au bimetallic alloy nanoparticles had significant effects on NK92 cells than only synthesized gold or silver nanoparticle aqueous extract, considered as an anti-inflammatory response. In that study, IFN-y release was dramatically decreased, and the cytokine response was impacted by the Ag–Au bimetallic alloy nanoparticles in NK92 compared to individual nanoparticles or extract [58].

Stein Leventhal syndrome, also referred to as PCOS (polycystic ovary syndrome), is an inflammatory condition that causes metabolic imbalance, ovarian dysfunction, and infertility in women. Specific mediators of inflammation (IL-6, IL-18, and TNF-α) are elevated in PCOS women, which points to a change in their immune system [59]. A *Cinnamomum zeylanicum*-synthesized silver nanoparticle study revealed a reduction of an inflammatory biomarker in PCOS in female rats [49].

4.2. Medicinal Plant-Based Zinc and Copper Nanoparticles and Their Impact on Inflammation

ZnO NPs have been produced using a range of plants, microbes, algae, fungi, and other biological materials such as starch and eggs. The plant technique provides many benefits over the microbe strategy since it does not require isolation, culture development, or maintenance [60]. The primary mechanism of action involves a phytochemical present in natural extracts oxidizing and reducing zinc ions. The strategy of green synthesis also demonstrates an increased catalytic process and minimizes exposition to the use of dangerous and pricey chemicals, which can aid in reducing their toxicity to the environment [61].

Recent work investigated the anti-inflammatory effects of the medicinal plant *Terminalia ferdinandiana* (Kakadu plum). (ZnO) nanoparticles (NPs) were flower shaped with an average size of 21.99 nm. Nitric oxide (NO), a main mediator during inflammatory reactions, is produced by macrophages. It is created from the amino acid arginine by the enzyme inducible nitric oxide synthase (iNOS). ZnO nanoparticles formed from the Kakadu plum successfully suppressed the release of nitric oxide in LPS-triggered raw 264.7 cells [62,63]. According to Vijaykumar et al., *Anoectochilus elatus* leaf extracts were used to develop zinc nanoparticles and investigate their anti-inflammatory properties. An in vitro assay by ZnNPs revealed the inhibition of protein (albumin) denaturation and protease activity compared to the standard drug aspirin in the microbiome [64]. Another popular medicinal plant, *Zingiber officinale*, was used to develop ZnO nanoparticles. This bioinspired nanoparticle is used to check inflammatory activity through an enzyme assay. Usually, prostaglandins cause swelling, discomfort, fever, and redness at the injection site when there is inflammation. Ginger-capped ZnNPs inhibit COX1 and COX2 enzymes which are responsible for PG production and act as a potential anti-inflammatory response [65,66]. Dhivyadharshin et al. reported another zinc oxide nanoparticle formation from the Unani plant *Adhatoda vasica*, which showed significant anti-inflammatory efficacy by protein degradation [67]. We have illustrated some of the research activities on the current copper and zinc nanoparticles in Table 2.

Table 2. Anti-inflammatory effects of current copper and zinc nanoparticles.

Nanoparticle	Medicinal Plants	Observation	Characteristics Size/Shape	Anti-Inflammatory Action	Ref
Zn	Terminalia ferdinandiana (Kakadu plum)	In vitro	21.89 nm Crystalline	Inhibition of pro-inflammatory nitric oxide production	[63]
Zn	Zingiber officinale	In vitro	30 nm Spherical	Inhibition of COX1 and COX2	[66]
Zn	Polygala tenuifolia root)	In vitro	9.22 nm Spherical	Downregulation of both mRNA and protein ex-pressions of inflammatory mediators	[68]
Zn	Kalanchoe pinnata	In vitro	24 nm	Suppress pro-inflammatory mediators such as interleukin 6 (IL-6), interleukin 1 (IL-1), tumor necrosis factor (TNF-α), and cyclooxy-genase-2 (COX-2)	[69]
Copper	Myrtus Communis leaves	In vitro	53.55 nm Crystalline	Inhibition of protein oxidation	[70]
Copper	Mucuna pruriens seed	In vitro	NA	Suppress the inflammatory mediators	[71]
Copper	Abies spectabilis	In vitro	NA	Suppress the inflammatory cytokines IL-1β, IL-6, and TNF-α	[72]

Besides zinc, copper is commonly used to synthesize nanoparticles due to its distinct physical and molecular characteristics such as a large surface area, strength, flexibility, and rigidity [73]. Many studies have reported the anti-inflammatory efficacy of copper nanoparticles. Among them, traditional herbal plant-based copper nanoparticles such as *Myrtus Communis* leaves extract-formed CuNPs attained maximum level albumin inhibition compared to the standard drug aspirin [70]. Similarly, *Mucuna pruriens* seed extract-mediated CuNPs can inhibit protein denaturation dose-dependently and act as a potential drug for inflammation [71]. Some research with CuNPs focused on the anti-inflammatory activity via the membrane stabilization method. Copper nanoparticles using Cissus quadrangularis and *Mussaenda frondosa L* were used on red blood cells where these nanoparticles efficiently assisted in membrane stability by limiting the release of RBC lysosomal enzymes to specific amounts [74,75].

5. Plant-Based Nanoemulsion for Inflammation

Nanoemulsions are now appealing nanocarriers among other nanoparticles due to their capacity to increase drug delivery via bio-membranes, lengthen the half-life (t1/2) in the body, and encapsulate drugs with a high lipophilic capability. Several studies support the oil in water (O/W) type of nanoemulsion as an effective carrier to solubilize the hydrophobic chemical in their oily cores among the three varieties of nanoemulsions (o/w, w/o, and w/o/w) [76]. Recently, nanoemulsions have become widely used to safeguard plant active ingredients from harsh environments, improve medicine solubility and stability, and heighten drug efficacy [77]. When compared to traditional preparation, the encapsulation of herbal plant components is an effective method for delivering NE and can include a greater amount of medicines [78]. The study revealed that *Panax ginseng*, which is known as the king of medicinal plants, successfully formed NE with sea buckwheat fruit oil. That study also demonstrated the inhibition of pro-inflammatory mediators in vitro compared to *Panax ginseng* alone [79,80]. Previously, an in vivo study in a mouse ear model with curcumin NE (formed with MCT) from the *Curcuma longa* medicinal plant focused on the inhibition effects of edema as an anti-inflammatory potential [81]. Table 3 has summarized the recent work on medicinal plant-based nanoemulsions and their anti-inflammatory activities.

Table 3. Medicinal plant-based nanoemulsions (O/W) and their anti-inflammatory activities.

Medicinal Plants	Phases	Types	Observation	Mechanism/Pathway/Action	Ref
Panax ginseng leaf extract	Leaf extract + Water + Sea buckthorn oil	O/W	In vitro	Suppression of pro-inflammatory mediators for (Cox 2, IL-6, IL-1β, and TNF-α, NF-κB, Ikkα, and iNOS) gene expression	[80]
Curcumin	Curcumin + Water + MCT	O/W	In vitro	Inhibition of TPA-induced edema of mouse ear	[81]
Rosmarinus officinalis L	Leaf extract + Essential oil	O/W	In vitro	Inhibiting the production of the pro-inflammatory mediator nitric oxide	[82]
Mountain gin-seng	Ginseng ex-tract + Gin-seng seed oil	O/W	In vitro	Inhibition of pro-inflammatory genes and proteins, including IL-1β, IL-6, and TNF-α via NF-κB and MAPK signaling pathways	[83]
Woodfordia fruticosa flower extract	Flower extract + Sunflower seed oil	O/W	Bacterial cell membrane	Inhibit the release of inflammatory mediators and stabilize cell membrane	[84]
Malva parviflora leaf extract	Leaf extract + Yoghurt b	O/W	In vitro	Diminish the production of superoxide by inhibiting NADPH oxidase	[85]
Punica granatum peel	Fruit Peel extract + Cremophor RH40	O/W	In vitro	Stabilize the lysosomal membrane as anti-inflammatory efficacy.	[86]

By exhibiting the immunomodulatory activity and preventing the generation of nitric oxide, a pro-inflammatory agent, NE has additionally shown the ability to enhance the anti-inflammatory effects of medicinal plant-based essential oils. A *Rosmarinus officinalis L*-derived essential oil was used to make an O/W NE and anti-inflammatory activity was demonstrated in zebrafish [82]. Moreover, an advanced approach has been made in recent research where a nanoemulsion was made with nanoparticles and exhibited an anti-inflammatory capacity. A mountain ginseng-based gold nanoparticle was used to prepare NE with another medicinal plant constituting silydianin and investigated potent anti-inflammatory activity in Raw 264.7 cells through MAPK downregulation and NF-κB signaling pathways [83]. The phytocompound of the flower extract of the herbal plant *Woodfordia fruticose K* synthesized a nanoemulsion and revealed protein denaturation which assured further tissue inflammation and cell stabilization potential in a human red blood cell membrane [84].

6. Current Status, Limitation, and Future Perspective of Metal-Based Nanoparticles and Nanoemulsion for Inflammation

In the past two decades, considerable study has been conducted on the biosynthesis of metal nanoparticles utilizing plant derivatives. Plant metabolites encourage the environmentally beneficial creation of metallic nanoparticles. The current study provides a noteworthy and succinct report on the anti-inflammatory strategies used by different medicinal plant-based nanoparticles, including silver, gold, zinc oxide, and nanoemulsion. It is unnecessary to use hazardous chemicals as reducing and capping agents when synthesizing nanoparticles from plant sources. This process is also more economical and beneficial to the environment. Nanomedicine has already been proven to have a stronger ability to penetrate epithelial cells and inflammatory cells, which improves the treatment's efficiency and endurance by choosing the probable target site. Moreover, green-synthesized nanoparticles had a more potent impact on inflammation than conventionally synthesized nanoparticles. Different interactions between nanomedicines and inflammatory efficacy in

cells, common mechanisms involved in the anti-inflammatory activity, and the synthesis of herbal nanoparticles and nanoemulsions has been briefly discussed in this research.

Although used for various biomedical applications, especially for cancer, inflammation, and radiotherapy, metal nanoparticles' immunotoxicity has been inconsistent and even contradictory. Immune toxicity is defined as the harmful effect on the immune system as the chronic inflammation of immunosuppression and autoimmune diseases [87,88]. Despite the potential biomedical application of metal NPs, biohazards and toxicities remain unclear.

Among the metal Nps, ZnO Nps are used in biomedical applications but due to their unique physicochemical properties, they could easily access several immune tissues and cells by inhalation and skin uptake. Further, oral administration could cause severe damage to several organs such as the kidney, heart, and liver. Size and charge are crucial factors for enhancing toxicity. The negative charge is less toxic in vitro Raw264.7 cells than positive ZnO NPs [89–92]. The different sized and charged ZnO and CuO NPs would cause in vitro and in vivo immunotoxicity, of which their nature is immunosuppression. To solve the issue further, there is a need to find the surface properties that greatly affect the toxicity and interaction of the organ and cell before evaluating the toxicity (geno toxicity/cytotoxicity/immunotoxicity) of the nanomaterial parameters such as morphology, size, chemical composition, surface properties (chemistry, charge) mechanism, or pathways that are involved in toxicity. On the other hand, nanoemulsions also have toxicity during oral administration due to their ability to change the biological fate of bioactive components within the gastrointestinal tract. Some of these lipophilic components are typically digested within the human gastrointestinal (GI) tract (e.g., triacylglycerols), some normally pass through the GI tract without being absorbed (e.g., mineral oils and fat substitutes), while some are absorbed without being digested [93].

As per the future strategy, more research is needed to find feasible molecules to synthesize metal (gold, silver, zinc, and copper) for commercialization. In addition, relevant research should be conducted in vivo on green metal nanoparticles and used as a safe medication in inflammatory disorders and progressive chronic inflammation.

Nanoemulsions have drawn great interest over the past few decades for a variety of applications. Many herbal plant compounds have been used to develop emulsions in nano size and improve bioavailability with anti-inflammatory potential. Mostly, nanoemulsions have been developed to encapsulate the hydrophobic green components of plants and deliver them to the target site efficiently. This study briefly demonstrated medicinal plant-based nanoemulsions, their mechanism, and their efficacy in inflammation. This study also noticed some research on nanoparticle-encapsulated nanoemulsion formation preventing inflammatory disorder.

In the preparation of nanoemulsions using some organic solvents, such as acetone, hexane, or ethyl acetate, those solvents used are removed by evaporation during the preparation of the nanoemulsion, but some residual solvents may remain in the final product [94]. It is therefore important to be aware of the potential toxic effects associated with any residual organic solvents if nanoemulsions are produced using this approach.

In the future world, nanoemulsions could be used as a vaccine delivery as well as immunotherapy for a genetic disorder. So, further research is needed to evaluate the inflammatory efficacy of potential hydrophobic medicinal plant parts with bio formation by nanoemulsions in an animal and clinical trial. It is urgently necessary to make progress in this area since it will be necessary to build sustainable nanotechnology for vaccines and other biological applications. Above all, it is urgently crucial to make progress in this area since it will be necessary to build sustainable nanotechnology not only to treat inflammation but also for developing a vaccine, immune-enhancing drug, and chemotherapy.

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