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Nanoparticle Technology for Development of Immunostimulant Drugs Using Natural Product: Narrative Review

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Abstract
The field of nanotechnology focuses on nanometer-scale systems. Nanotechnology is widely used in the medical field for the development of medicines. One application of nanotechnology is nanoparticles. Nanoparticles have a size range of nanometers with a scale of 1 to 100 nm. Nanoparticles can be designed to stimulate the immune system. Based on the search for various literature studies, it is proven that natural product preparations can increase immunostimulants in vitro by testing lymphocyte proliferation, phagocytosis and cytokine production and in vivo testing of infection models, bioavalability, determination of body weight index, kidney and liver. Testing of natural products is also carried out using various instruments, namely FTIR (Fourier Transform Infrared) has phenol and aldehyde groups and is expressed by spectrum peaks, SEM (Scanning Electron Microscopy) is characterized by sizes < 33 nm and is spherical and round, XRD (X-ray Diffraction) is generally crystalline and forms peaks. The particle size of some preparations such as ZNPs is 169.37 nm and CoFe2O4 is 11 and 5 nm. Until now, it has been proven that natural products can change the response of the immune system and there have been many developments in herbal medicinal preparations that utilize nanotechnology but it is still rare to test immunostimulant activity.

Keywords: Immunostimulants; nanoparticles; particle size; zeta potential.

Teknologi Nanopartikel untuk Pengembangan Obat Immunostimulan menggunakan Produk Alami : Ulasan Narasi

Abstrak
Bidang nanoteknologi berfokus pada sistem dengan skala nanometer. Nanoteknologi banyak digunakan dalam bidang medis untuk pengembangan obat-obatan. Salah satu penerapan nanoteknologi adalah nanopartikel. Nanopartikel memiliki ukuran rentang nanometer dengan skala 1 hingga 100 nm. Nanopartikel dapat dirancang untuk merangsang sistem kekebalan tubuh. Studi literatur menggunakan riset artikel dari jurnal nasional dan internasional dengan aplikasi *Publish or Perish 8*. Berdasarkan penelusuran berbagai studi literatur, terbukti bahwa sediaan produk alami dapat meningkatkan imunostimulan secara *in vitro* dengan pengujian proliferasi limfosit, fagositosis dan produksi sitokin serta *in vivo* pengujian model infeksi, bioavalabilitas, penentuan indeks bobot badan, ginjal dan hati. Pengujian produk alami juga dilakukan menggunakan berbagai instrument yaitu FTIR (*Fourier Transform Infrared*) memiliki gugus fenol dan aldehida serta dinyatakan dengan puncak spektrum, SEM (*Scanning Electron Microscopy*) dikarakterisasikan dengan ukuran < 33 nm serta berbentuk bola dan bulat, XRD (*X-ray Diffraction*) umumnya berbentuk kristal dan membentuk puncak. Ukuran partikel pada beberapa sediaan seperti ZNPs sebesar 169.37 nm serta CoFe2O4 berukuran 11 dan 5 nm. Hingga saat ini telah terbukti produk alami dapat mengubah respons sistem imun dan telah banyak pengembangan sediaan obat herbal yang memanfaatkan nanoteknologi tetapi masih jarang dilakukan pengujian aktivitas imunostimulan.

Kata Kunci: Imunostimulan; nanopartikel; nanoteknologi; produk alami.

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1. Introduction

Immunostimulants are signaling molecules that play an essential rolethe in activating the immune system by triggering the innate immune response and leading to its activation and maturation of antigen-presenting cells (APC). Immunostimulants act as pathogen-associated molecular patterns (PUMP) and danger-associated molecular patterns (DAMP) that interact with pattern recognition receptors (PRR) in APCs, trigger an innate immune response, and prepare cells to respond to specific antigens.[1] Stimulation of PAMPs and signaling pathways such as receptors toll-like receptors (TLR), caspase-1, and destabilization of Syk/Card lysosomes 9 have a role in the recruitment and activation of effector cells, including T and B cells as well-antigen-presenting cells (APC). APC activation triggers antigen-specific T-cell responses effectively. The antigen-specific T cell phenotype is influenced by the nature of the activation of innate immune signals, such that the secretion of interleukin-18 (IL-18) by stimulated subcapsular macrophages can promote the development of interferon-gamma (IFN-y)-secreting CD4+ T cells. [2]

Immunomodulators are defined as substances capable of interacting with the immune system, resulting in up- or down-regulation of certain parts of the immune response. Immunomodulators represent a wide range of synthetic, natural, and recombinant molecules, some of which have been approved for human treatment. Natural molecules including curcumin, thyme, bay leaves, resveratrol, ellagic acid, ginseng, Echinacea, Aloe vera, Astragalus, Goldenseal, flavonoids, and essential oils have been widely used due to their demonstrated biological effects.[3] Traditional herbal medicine is used throughout the world, including Chinese herbal medicine, Kampo in Japan, Ayurveda, and Unani in India, Central Asia, and North African countries. Herbal medicines are generally made from boiled water extracts, and many of the active components are in the form of secondary metabolites. The development of drugs from natural sources such as plants and fungi has become an area of research in search of alternatives to synthetic drugs.[4]

A drug delivery system (Drug Delivery System) is a formulation that facilitates the introduction of therapeutic substances into the human body and increases their effectiveness and safety by regulating the rate, time, and location of drug release in the body. One of the drug delivery systems transports the correct dose of the drug to the site of action and maintains the desired concentration of the drug in the body's tissues, thereby creating a pharmacological effect without causing side effects. Widely used pharmaceutical technologies include Nano-Emulsifying Drug Delivery Systems (SNEDDS), microparticles, inclusion complexes, solid dispersions, pH modification, and nanoparticles.[5,6] Nanoparticles are atoms or molecules with sizes ranging from 1-100 nm, which are classified into various categories depending on their size and shape. The size and surface shape of nanoparticles influence nanotoxicity. The smaller size and larger surface area can easily penetrate biological membranes, causing toxicity to organs and tissues. Differences in surface charge between nanoparticles and cell walls can also cause toxicity.[7] Nanoparticles have become the focus of research, especially the structural, colloidal, adsorption, and magnetic properties of nanoparticles. Nanoparticles have great potential in various technological applications.[8] This review aims to evaluate the use of nanotechnology for the development of immunostimulant drugs and examine progress in the application of nanoparticles to stimulate the immune system. The focus is on presenting effective and efficient synthesis methods, analyzing nanoparticles interacting with immune system cells, and potential clinical applications of nanoparticle-based immunostimulant drugs, including disease treatment, safety, and toxicity.

2. Methods

The search approach taken for this article involved searching several trusted sources, such as Google Scholar, PubMed, and ScienceDirect, using the application Publish or Perish 8. There were 20,858 articles obtained from the search that used specific keywords such as "Immunostimulants, Nanotechnology, Nanoparticle, Gold Nanoparticle, and Silver

Nanoparticle." Inclusion criteria limited original articles published during the last 10 years (2014–2024), ensuring that the literature accessed was related to nanoparticle technology for immunostimulant drug development. In the selection stage with criteria text, 65 articles were obtained, which were used as research references. Literature studies can be seen in Figure 1.

3. Results and Disscusion

The immune system functions as a defense against foreign antigens and external stimuli, including viruses. Dysfunction in the immune system can lead to autoimmune and inflammatory diseases. Two types of immune responses, namely innate and adaptive immunity, work to monitor immune defenses throughout the human body.[9] However, medications that suppress immunity can cause significant side effects and an

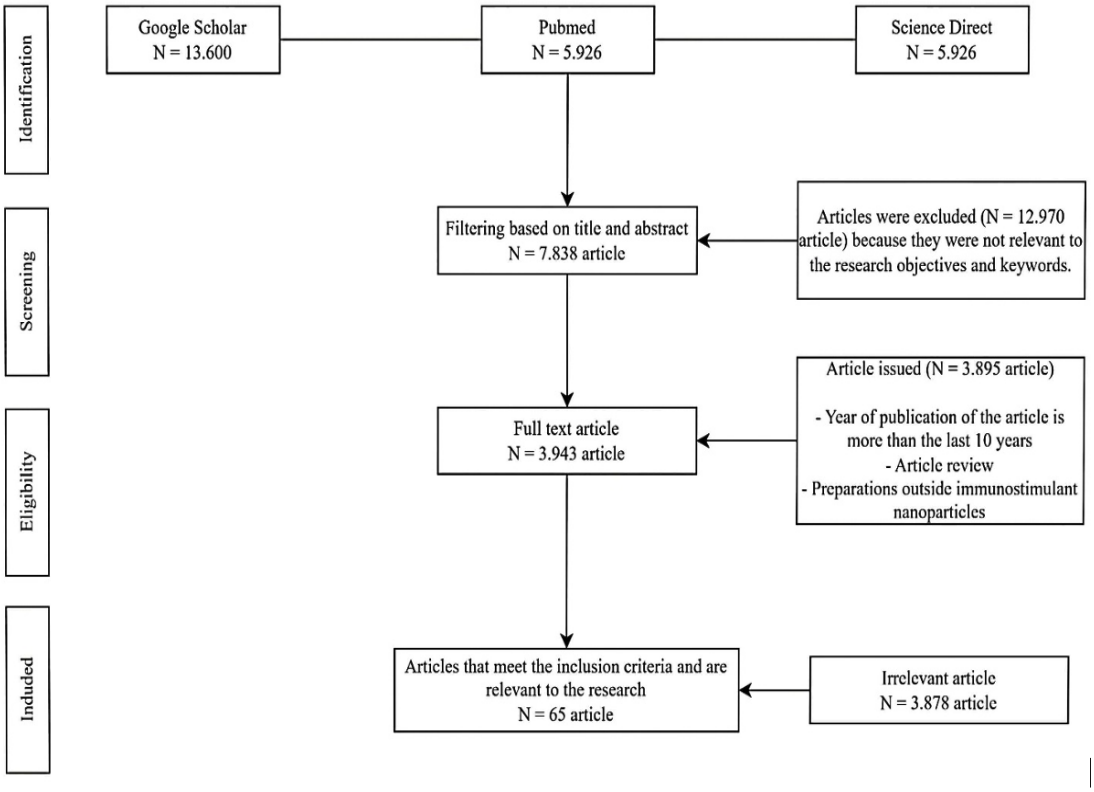

Figure 1. Article review writing scheme

uncontrolled dosage, resulting in an overload of the immune system. The application of nanotechnology has become known in the 21st century and has become an innovation applied globally to increase body resistance data. The use of nanomaterials, especially metal nanoparticles, has been widely used in the last few decades because of their electronic and chemical properties. The application of nanomaterials involves many fields, such as nanomedicine with antimicrobial activity and use in imaging, therapy, and monotherapy. The development of nanomaterials is closely related to new synthesis methods, including environmentally friendly and cost-effective methods.[10,11]

3.1. Immunostimulant Effect

Complement has a significant role in mobilizing rapid and efficient immune protection against pathogenic organisms and damaged host cells. The role of complement in the modulation of immune responses suggests a link between innate and adaptive immunity.[12] The immune system has a role in fighting foreign substances and infections. Most disorders involve the immune system, such as autoimmune diseases, immunodeficiency disorders, and hypersensitivity. Immunomodulators are a class of drugs or substances that function to regulate the activity of the immune system—divided into 3 groups, namely immunoadjuvants, immunostimulants, and immunosuppressants. Long-term use of immunosuppressants and immunostimulant drugs can cause unwanted side effects. The development of drugs from natural sources, predominantly plants, can contain active compounds that have the potential to influence the immune system without causing side effects. Some plants, such as Echinacea, ginseng, and curcumin from turmeric, are known to have immunomodulatory properties.[13] Herbal preparations play an essential role in disease control by exhibiting antioxidant and antimicrobial activities. Herbal extracts can stimulate the body's immunity, are low in concentration, are biodegradable, and can be made using simple techniques. Herbal products are cheaper and more accurate therapeutic agents than chemotherapy agents.[14]

Disorders of the immune system components can cause various health problems. Immune disorders become susceptible to infections that can occur when microorganisms enter the host tissue. The immune system does not function properly; it is very susceptible to infectious diseases. Figure 2. illustrates the critical role of the immune system in protecting the body from infection. The body's defense against infections and other immunological disorders is provided by its defense capacity, which is known as immunity. Immunity is divided into innate and adaptive immunity. Innate immunity is broad and is a nonspecific immune

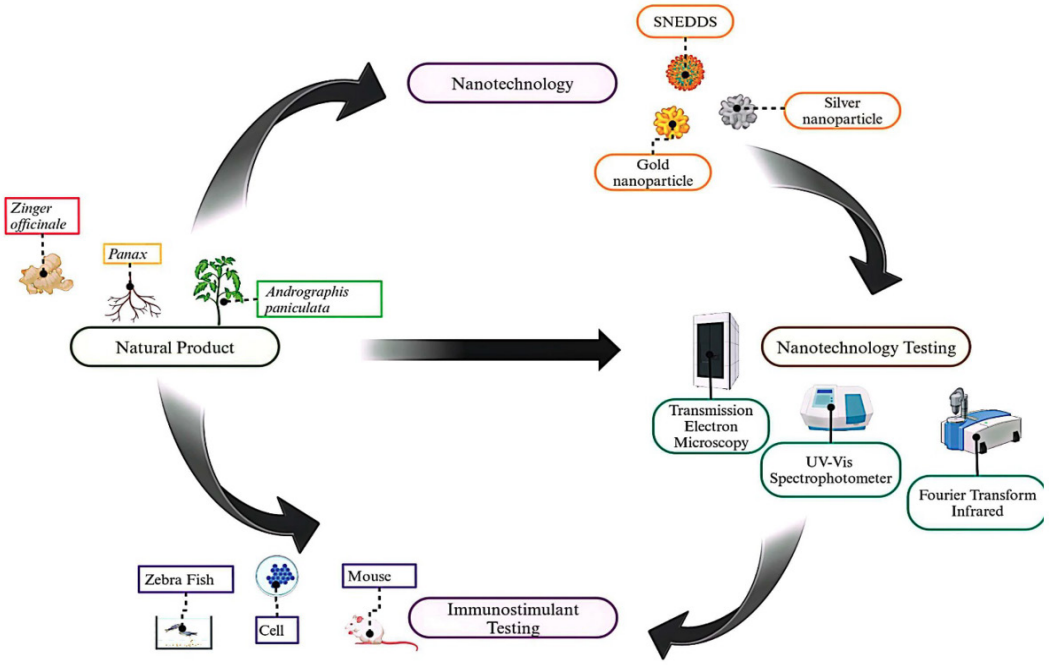

Figure 2. Immunostimulany Process

response to any antigen that is genetically developed. Meanwhile, adaptive immunity is a specific immune response involving a complex of cells, genes, proteins, and cytokines against previously encountered antigens. Adaptive immunity can be expressed in humoral form involving antibodies derived from B lymphocytes and cell-mediated immunity involving T lymphocytes.[15]

3.2. Immunostimulant Activity In Vitro

Nanoliposome technology for broad-spectrum antibacterial and antiviral protection has been widely developed. Nanoliposomes are designed to contain bacterial lipopolysaccharides and poly, which are synthetic analogs of viral dsRNA. Nanoliposomes have been shown to be taken up in vitro by macrophages and regulate the expression of immunologically relevant genes. This most likely occurs by triggering a signaling pathway.[16] The use of herbal plants such as garlic, pomegranate, Bermuda grass, Indian ginseng, ginger, American ginseng, carob, Fernleaf lavender leaves, and fenugreek seeds has shown potential as an effective biological chemical. Evaluation was carried out on the viability and immune activity of leukocytes from European sea bass head kidneys, including phagocytic and respiratory activities and peroxidase content. Okra fruit, leaves, and seeds have potential as immunostimulants. Activity can support the fish's immune system. Okra showed cytotoxic and bactericidal activities that depended on the dose and plant organ. This suggests the possible use of okra in treating disease and as a cytotoxic agent.[17] Table 1 demonstrates in vitro activity with various types of nanoparticle technology.

Nanotechnology has developed rapidly and spread in various fields, such as medicine, biotechnology, agriculture, food production, and aquaculture. Nanoparticles range in size from 1 to 100 nm and are widely used [23,24]. Nanotechnology in vitro testing enables advanced developments to detect, modify, and manipulate at the nanometer scale. The role of nanotechnology creates new opportunities for innovation in the fields of health, drug development, and medical diagnostics. Nanotechnology can improve precision, sensitivity, and efficiency in in vitro testing.

3.3. Immunostimulant Activity In Vivo

The use of immunomodulatory agents in disease management focuses on comparisons between conventional and natural immunomodulators. The use of immunomodulatory agents has become popular in the management of diseases such as cancer, AIDS, and autoimmune or inflammatory diseases. Immunostimulants such as levamisole and tetramisole, as well as immunosuppressants such as cyclophosphamide, cyclosporine, and azathioprine, have limitations, and side effects include agranulocytosis, bone marrow suppression, and skin, kidney, and liver toxicity. Available natural immunomodulatory products offer more significant benefits due to possible variations in active constituents when using mental extracts. This may reduce the overall therapeutic properties. The limitations of

Table 1. Immunomodulatory activity in vitro using natural product

No.	Natural Product	Immunomodulatory Agent	Immunomodulatory Method	Immunomodulatory Method	References
1.	*Weissella koreensis* and *Pediococcus pentosaceus*	mRNA (IL-1β, IL-6, TNF-α, iNOS) and the anti-inflammatory cytokine IL-10	Cell viability assays of RAW 264.7	Cell viability assays of RAW 264.7	18
2.	Extract silver nanoparticlesLoad papaya (CPL-AgNPs)	TNF- α and IL-1β	Minimum inhibition concentration (MIC) and minimum bactericidal concentration (MBC).	Minimum inhibition concentration (MIC) and minimum bactericidal concentration (MBC).	19
3.	Guava leaf (*Psidium guajava* L.)	Cell lymphocyte proliferation	Lymphocyte proliferation test through assay.	Lymphocyte proliferation test through assay.	20
4.	Nanoparticles Fe3O4	IL-6, TNF-α and TGF-β	Bacillus coagulans, Staphylococcus aureus, Escherichia coli, and Klebsiella pneumoniae.	Bacillus coagulans, Staphylococcus aureus, Escherichia coli, and Klebsiella pneumoniae.	21
5.	*Andrographis paniculata* (Burm.f.)	Cell line A459, proliferasion of lymphocyte cells	3-(4,5-dimenthylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.	3-(4,5-dimenthylthiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay.	22

natural immunomodulatory products can be reduced by the use of nanotechnology.[25] Table 2 demonstrates in vivo activity with various types of nanoparticle technology.

Extracellular vesicles are a nano-sized communication system and have the potential to be an efficient tool for exchanging complex information in multicellular organisms and working simultaneously to transfer several biomolecules, thereby creating an efficient way to synchronize various processes in the body. Treatment of diseases in research and development using artificial nanoparticles or microparticles in nanotechnology has been widely used. The use of artificial nanoparticles or microparticles to deliver immunomodulatory molecules to dendritic cells with the aim of modulating nonspecific antigen immune function. Experiments carried out in vivo are presented in Table 1. This test has a vital role in the development of science and clinical applications and is used together in research and drug development.[31]

3.4. Characterization of Nanotechnology

Nanomedicine is an application of nanotechnology in the medical field that has proven to be an effective solution for delivering drugs to targets that have been difficult to reach over the last few years. Advances are occurring in polymer chemistry and colloid physicochemistry, enabling the production of polymer nanoparticles for broad clinical applications. Polymer nanoparticles have the ability to increase the bioavailability of drugs that are difficult to dissolve in water and provide targeted release.[32] The development of the field of nanotechnology is based on its ability to overcome the limitations of conventional treatments, such as high doses, low bioavailability, first-pass effects, intolerance, instability, plasma

Table 2. Immunomodulatory activity in vivo and using natural product

No.	Natural Product	Activity	Reference
1.	Self-Nano-Emulsifying Curcumin (SNEC30)	Improves the adverse effects of arsenic and immune suppression on the mouse body	26
2.	Nanoconjugates	Hinder accumulation of malodialhehid (MDA) and improve superoxide dismutase enzymatic activity (SOD) and glutathione peroxidase (GPx). Reduce interleukin (IL)-6 expression and tumor necrosis factor (TNF)-alfa.	27
3.	Self-Nano Emulsifying Drug Delivery System (SNEDDS)	Using Wistar male rats and has the effect of increasing dissolution, absorption and surface area thereby increasing the bioavailability of SNEDDS preparations.	28
4.	Self Nano Emulsifying Drug Delivery System (SNEDDS) propolis	The result showed that the animals did not show symptoms of ketoxity, and their body weight increased, with an LD50 > 2000 mg/kgBB. Organ histopathology showed no anomalies in the kidney or liver. This indicates the ability of propolis SNEDDS to boost the immune system.	29
5.	Okra Raw Polysaccharide Extract (ORPE)	Result showed that ORPE inhibited the accumulation of regulatory T cells, stopped macrophage activation, and restored the balance of effector T cell numbers. All the doses, ORPE drugs increased CD8+ T cell activation and interleukin-2 levels. ORPE has properties that can boost the immune system.	30

concentration fluctuations, and adverse reactions. Nanoparticle systems are designed for the treatment of various diseases, such as neurological disorders, diabetes, cancer, infectious diseases, allergies, and the administration of vaccines.[33] Radadi's research in 2024 stated innovation in synthesizing gold nanoparticles (AuNPs) using aqueous sweet granadilla (Passiflora ligularisJuss). The characterization of gold nanoparticles is carried out through various techniques, including X-ray diffraction, zeta potential, EDX, UV-visible absorption, and TEM.[34] The use of sophisticated and diverse laboratory instruments in research is everyday, and the information provided indicates that a variety of analytical techniques are used to characterize a material or structure. Physical, chemical, and thermal characterization tools for nanoparticles provide extensive information about the properties and structure of materials.[35] The use of various analytical techniques to characterize nanoparticles with UV spectroscopy has a visible absorption peak at 349 nm in the range of 200–600 nm. Interpretation of the 349 nm absorption peak at a specific wavelength in the UV-vis spectrum is often associated with electronic transitions that occur in certain compounds or particles.[36]

Nanoapplications and developments that can be used in various aspects of science and technology are presented in Table 3. Biosynthesis techniques have been used for nanoparticles involving biological microbes such as fungi, bacteria, and plant extracts. Metal-based nanoparticles such as gold, selenium, silver, zinc sulfide, and zinc oxide have become a focus due to their unique properties. Silver nanoparticles (AgNPs) are easy to synthesize, chemically stable, and effective as antibacterial, antiviral, and antifungal agents. AgNP preparations have been widely used in various applications, such as treating wounds, burn infections, and chronic ulcers.[42] Other nanotechnologies, such as gold nanoparticles, have distinctive performance that differentiates them from other nanoparticles. Sakore Researcher et al. (2024) explained that AuNP preparations have advantages such as high surface area, plasmonic properties, and

Table 3. Nanotechnology uses testing instruments

No.	Types of Nanoparticles	Natural Product	Testing Instruments	Results	References
1.	Silver nanoparticles (AgNP)	Extract *Sargassum algae* spp.	TEM-SAED (Transmission Electron Microscopy—Selected Area Electron Diffraction), XRD (X-ray Diffraction), FT-IR (Fourier Transform Infrared) and XPS (X-ray Photoelectron Spectroscopy)	Zeta Potential: 22.6 mV, DLS: negative value, PDI: 0.246, TEM: 11.99 nm, FTIR: can reduce and stabilize nanoparticles, XPS: spectrum resolution of no reduced Ag; XRD: crystalline, cubic, and surface-centered (11.24 nm).	(18)
2.	Iron oxide nanoparticles	Aloe vera extract	Scanning Electron Microscopy, EDX (Energy Dispersive X-ray Spectroscopy), XRD (X-ray Diffraction), BET surface area (Brunauer-Emmett-Teller), FTIR (Fourier Transform Infrared) and Spectroscopy UV-visible	XRD: crystals, crystal size, and strain. EDX contains Fe and O elements, and the FTIR phenolic group reduces and is stable towards Fe. SEM: Nanoparticles are spherical and synthesized at temperatures between 25 and 900 °C.	(19)
3.	Titanium dioxide (TiO2) nanoparticles	Extract: *Annona muricata* L.	UV-Vis Spectrophotometer, FTIR (Fourier Transform Infrared), XRD (X-ray Diffraction), FE-SEM (Field Emission Scanning Electron Microscopy), EDX (Energy Dispersive X-ray), HE HAS (Transmission Electron Microscopy), XRF (X-ray fluorescence), and Confocal Microscopy.	UV-Vis Spectrophotometer: 306 and 320 nm; FTIR: I.R. absorption vibration intensity spectrum: 474.32 cm1; and corresponds to TiO2. XRD: forms crystals (12.45 nm), FE-SEM: good distribution and uniformity, so low polydispersity (average 12.31 nm), EDX: 74.8% TiO compound2 with a concentration of 748,000 ppm. TEM: average 13.41+ 1,0 nm.	(20)
4.	Nanoparticles (ZNPs)	Chestnut shell (*Castanea sativa* Mill.), cedar (Cedar of Lebanon), and sweetgum bark (Eastern liquidambar)	Particle size, polydispersity index, transmittance, zeta potential, and TEM (Transmission Electron Microscopy).	Particle size: 169.37. PDI: 0.03% cedar bark extract. Zeta potential: -25 mV cedar and sweetgum extract. Transmittance: 38.55, 79.50, 0.60, 79.25, 1.25, and 76.80 sweetgum tree bark extract.	(21)
5.	Composite nanoparticles (CoFe2O4)	Moringa leaf extract (*Moringa oleifera*)	Spectroscopy Particle size, SEM (Transmission Electron Microscopy), FTIR Spectroscopy, UV-Vis spectroscopy, and EDX (X-ray spectroscopy).	TEM: 12 and 17 nm; particle size: 11 and 5 nm. EDX: ZnS and S elements increase the synthesis of composites CoFe2O4/ZnS. FTIR shows the incorporation of ZnS on the surface of CoFe nanoparticles (2O4).	(22)

simple functionalization, which make them promising tools. Therapy that utilizes nanotechnology promises better results, including more efficient drug delivery and minimal tissue injury.[43]

4. Conclusion

Natural product preparations have activity as immunostimulants, which can affect the immune system response. Several previous studies have evaluated the immunomodulatory activity of natural preparations in vitro and in vivo using different types of natural products using several nanotechnologies. Nanotechnology preparations have advantages such as better drug delivery and bringing drugs to specific targets to multifunctional applications. Many nanotechnology preparations are tested such as X-Ray diffraction, Fourier Transform Infrared and Spectroscopy particle size with good results but there are still very few immunostimulant tests carried out. So that it has the potential to cause toxicity and environmental pollution if not managed properly to biocompatibility with living organisms.

Conflict of Interest

The authors declare no conflict of interest.

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