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Trends and Prospects of Nano-delivered Phytopharmaceuticals for disease of Public health importance: A Review

[1]Ajala, T. O., [1*]Omoteso, O. A., and [2]Ghazali, Y. O.

[1]Department of Pharmaceutics and Industrial Pharmacy, University of Ibadan, Ibadan, Nigeria.
[2]Department of Pharmaceutics and Industrial Pharmacy, University of Ilorin, Ilorin, Nigeria.

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Abstract

A significant amount of effective medicine can be found in phytochemicals that are found in natural products or herb extracts. These natural drugs can be used in the treatment of public health diseases such as diabetes, cardiovascular disease, malaria, HIV, COVID-19, gastrointestinal disorders, neurodegenerative diseases, and cancer. There are significant therapeutic limitations when phytomedicines are administered in conventional pharmaceutical dosage forms like powders, tablets, solutions, brews, and balms. These include low aqueous solubility, poor permeability, degradation, and instability. As a result, there is low production yield, poor absorption and bioavailability, poor potency and efficacy, and toxicity in the body. As a result, phytomedicines are not as effective as they could be. Polymeric nanoparticles, lipid nanoparticles, liposomes, sterosomes, and metallic nanoparticles are novel drug delivery systems that circumvent the problems of conventional drug delivery systems. These nanocarriers can enhance phytomedicine's solubility, stability, and control, prolong the release of herbal medicine, and target specific sites within the body. As a result, herbal medicine can achieve maximum potency and efficacy with significantly fewer adverse effects. The use of phytopharmaceuticals as treatments for diseases that affect public health is extensively covered in this paper, as is the topic of nano-derived phytopharmaceuticals.

1. Introduction

The use of plant-derived elements as therapeutic agents is as old as man [1]. In their crude forms, extracts obtained from various plant parts are traditionally used for the management of many diseases and infections. While this trend of traditional application of herbal substances for treatment has produced significant therapeutic benefits in many communities, the associated risks of inadequate dosing, compromised stability, and avoidable toxicities (due to indiscriminate use) cannot be neglected [2]. Owing to this, a lot of research efforts are being channeled to address these limitations and ensure the safety and efficacy of herbs when used in therapy. One of such is the presentation of these herbal extracts as conventional dosage forms, ranging from solids (powders, granules, and capsules) to liquids (suspensions, emulsions, and solutions) [3]. Through these interventions, herbal drugs are now gaining more acceptance as usable alternatives to synthetic molecules in the management of many health deficiencies [4]. To consolidate on these advancements in phytotherapy and ensure that phytopharmaceuticals have improved stability and drug delivery properties,

Corresponding author: omotesoomobolanle@gmail.com

this review discusses the application of nanotechnologies to improve the utilization of plant-based drugs. Since the priority in drug development is to ensure that medicines are presented in formulations that are safe, stable, and efficacious, leading to the achievement of desired outcomes in ailing patients, assessing the trends and potentials of fusing nanoparticles with phytomedicines for improved action is worthy of exploration. Given the prevalence and evolution of many diseases and infections in our world today, the focus of these appraisals of nanomedicine-driven enhancements to herbal medicines will be centered on disease of public health importance (Figure 1), especially those that afflict developing and underdeveloped communities of the world.

2.1 HIV and COVID-19

Starting with infections, many antibiotics are becoming less effective owing to antibiotic resistance [5]. Bacteria and viruses are evolving and adapting by the day, thereby fostering the progression of different disease conditions. Of these trends of infections, HIV (Human Immunodeficiency Virus) and COVID-19 (Coronavirus Disease 2019) have deadly implications; they are major threats to our well-being and public health. HIV is a retrovirus that primarily targets the immune system's CD4+ T cells, which play a crucial role in defending the body against infections [6]. Once inside the body, HIV gradually weakens the immune system, making it difficult for the body to fight off other infections and diseases. If left untreated, HIV can progress to acquired immunodeficiency syndrome (AIDS), which is the advanced stage of the infection. So far, there has been no cure for HIV, but antiretroviral therapy (ART) has been highly effective in controlling the virus [7]. ART can suppress viral replication, restore immune function, and prevent the progression of AIDS. As we continue to explore different sources in search of the cure for HIV, phytopharmaceuticals and their subsequent enhancement with nanotechnology must be adequately considered in this search.

In 2019, the world was hit by COVID-19, and even till date, the residual impact of this disease condition still affects our public health systems significantly. COVID-19 is caused by the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), a novel coronavirus that recently emerged [8]. It affects the respiratory system and can range from mild to severe illness, leading to fatalities in some cases, especially among vulnerable populations. COVID-19 primarily spreads through respiratory droplets when an infected person coughs, sneezes, talks, or breathes [9]. It can also spread by touching surfaces contaminated with the virus and then touching the face, especially the mouth, nose, or eyes. Most people with COVID-19 experience mild to moderate symptoms and can recover at home with supportive care, such as rest, hydration, and over-the-counter medications to relieve symptoms [10]. Severe cases may require hospitalization and supportive therapies, including supplemental oxygen and mechanical ventilation. In 2021, several vaccines became available, helping reduce the severity of the disease and control its spread. To ensure that our war against COVID is truly won, there still exists a need to turn to phytochemicals as potential drug sources for the management of this viral infection, in addition to the waves made with vaccination. These phytochemicals can be delivered in inert nano-carriers and utilized as a well-delivered course of therapy to treat COVID in instances where vaccination has failed to disallow the occurrence of the disease, especially in vulnerable populations. This is the approach this review seeks to consider. Leaf extract from *Vitis vinifera* is virucidal to RNA viruses like SARS-CoV-2 and enveloped DNA viruses like HSV-1 [11]. It has been reported that pterostilbene and resveratrol, with IC50 values of 19 and 66 μM, respectively, prevent the formation of SARS-CoV-2 progeny in Vero cells. These two compounds were also documented to possess prolonged antiviral properties against SARS-CoV-2 [12].

2.2 Cancer and the problem with chemotherapeutic agents

Cancer is a complex and diverse disease. It is characterized by the uncontrolled growth and division of abnormal cells that can invade and destroy normal body tissues. Chemotherapy is one of the primary treatment options for cancer, along with surgery, radiation therapy, and targeted therapies [13]. Chemotherapy involves using drugs to destroy or slow the growth of cancer cells. While chemotherapy has been effective in treating many types of cancer and has saved countless lives, it is not without its challenges and side effects. A prominent challenge is that of selectivity in action. Chemotherapy drugs are not specific to cancer cells; they can affect both cancerous and healthy cells [14]. Healthy cells with a high rate of division, such as hair follicle cells and cells lining the gastrointestinal tract, are also affected. This leads to side effects like hair loss, nausea, vomiting, and damage to the digestive system.

Furthermore, cancer cells can develop resistance to chemotherapy over time, making the treatment less effective. This resistance can be intrinsic (pre-existing in some cancer cells) or acquired (developed during treatment) [15]. As a result, chemotherapy may need to be changed or combined with other treatments to overcome resistance. Some chemotherapeutic agents can also be toxic to organs and tissues, especially if administered at high doses or for an extended period [16]. These drugs can cause damage to the heart, lungs, kidneys, or nervous system. The bone marrow is responsible for producing blood cells. Chemotherapy can suppress bone marrow function, leading to low levels of red blood cells (anemia), white blood cells (neutropenia), and platelets (thrombocytopenia) [17]. This can weaken the immune system and increase the risk of infection and bleeding. Additionally, some chemotherapy side effects can persist long after treatment has ended. These may include cognitive issues ("chemo brain"), neuropathy (nerve damage), and secondary cancers caused by the treatment itself [18].

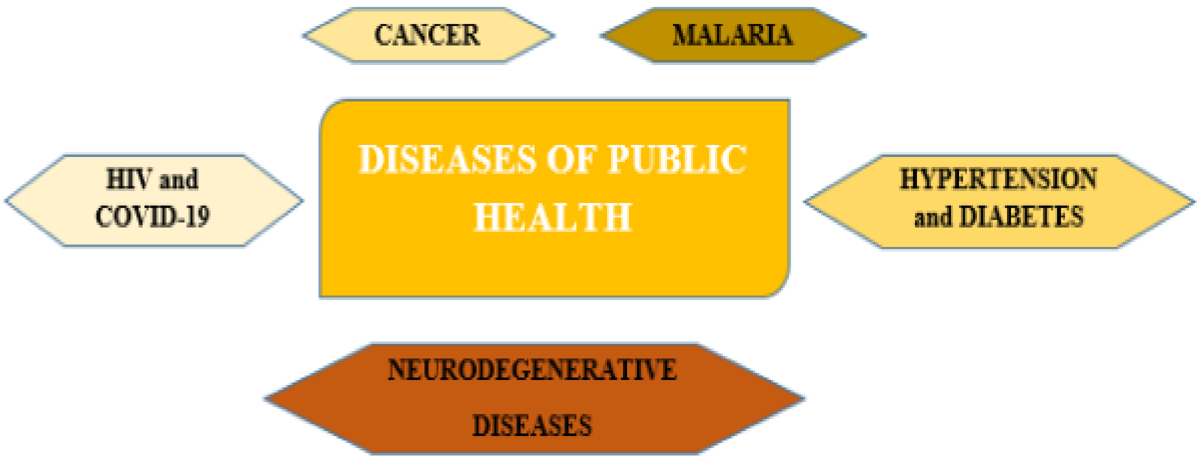

Fig. 1: Schematic illustration of some diseases of Public health importance .

Researchers and healthcare providers are continuously working to improve chemotherapy and develop targeted therapies that specifically attack cancer cells while minimizing damage to healthy cells. Targeted therapies involving the use of phytomedicines are examples of such advancement; designed to be more precise and selective in their actions.

2.3 The Public health concerns with hypertension and diabetes

Hypertension (high blood pressure) and diabetes are two non-communicable common chronic health conditions that pose significant public health concerns due to their prevalence, associated complications, and the burden they place on healthcare systems. Hypertension is a widespread condition globally, affecting millions of people. It is often called the "silent killer" because it usually has no symptoms but can lead to serious health problems if left untreated. Untreated or uncontrolled hypertension can lead to severe health consequences, including heart disease, stroke, kidney damage, vision loss, and vascular disorders [19]. It contributes to a significant proportion of cardiovascular diseases and related deaths worldwide. Public health initiatives should aim to promote hypertension management through lifestyle modifications and, when necessary, antihypertensive medication. Access to affordable and effective medications is essential for optimal control of blood pressure [20]. This is where phytomedicines come in.

Similarly, diabetes, particularly type 2 diabetes, has reached epidemic proportions globally [21]. Unhealthy dietary habits, sedentary lifestyles, and obesity are contributing factors to the increasing prevalence of diabetes. Diabetes can lead to numerous complications, such as cardiovascular disease, kidney failure, neuropathy (nerve damage), retinopathy (eye damage), and an increased risk of infections [22]. It also increases the risk of other chronic conditions, including hypertension and certain cancers. The management of diabetes can be resource-intensive for healthcare systems due to the need for regular monitoring, medications, and potential complications [23]. It is therefore crucial to aim at reducing the burden by preventing new cases and improving the quality of care for those with diabetes. To achieve this, natural derived molecules, optimized with nano-carries should be considered for better clinical outcomes in diabetes. A berberine-loaded lecithin-chitosan nanoparticulate system (BER-LC-CTS-NPs) has been developed by Panda et al. [24] and may be incorporated into a topically applied formulation for the treatment of type 2 diabetes wounds. The experimental results indicate that the use of lecithin-chitosan nanoparticles containing berberine shows promise as a technique to speed up the wound healing process in diabetes patients [24]. In an in vitro investigation, Golfakhrabadi *et al*. conducted research demonstrating the effective protective properties of berberine and berberine nanoparticles against insulin secretion and oxidative stress caused by carbon nanotubes. Utilising berberine and berberine nanoparticles as antioxidants has shown the ability to protect the pancreatic β-islets and halt the advancement of diabetes [25].

2.4 Malaria in Africa

Malaria is a significant public health concern in Africa, as the continent bears the highest burden of the disease worldwide. It is a life-threatening mosquito-borne infectious disease caused by the *Plasmodium* parasite. The most severe form of malaria is caused by *Plasmodium falciparum*, which is prevalent in many African countries. According to the World Health Organization (WHO) World Malaria Report 2020, the African region accounted for approximately 94% of all malaria cases and deaths in 2019 [26]. Malaria disproportionately affects vulnerable populations in Africa, particularly young children, and pregnant women [27]. Children under the age of five are at the highest risk of severe illness and death from malaria, and pregnant women have an increased risk of problems for both themselves and their unborn new-borns [28].

Various strategies have been implemented to combat malaria in Africa. These include the distribution of insecticide-treated bed nets, indoor residual spraying to kill mosquitoes, and the administration of antimalarial drugs for prevention and treatment. While the use of artemisinin-based combination therapies (ACT) can be described to be effective in the treatment of malaria, there are newly emerging concerns about the sustainability of these drugs as a few *Plasmodium* species are beginning to show resistance to prominent ACT combinations [29]. To stay ahead of this challenge, it is quite imperative that like artemisinins, new drug candidates are explored from plant sources and delivered utilizing advanced techniques like nanotechnologies to ensure that minimum doses of these drugs generate the desired therapeutic results, making it more difficult of resistance to set in.

2.5 Neurodegenerative diseases

Age-dependent illnesses known as neurodegenerative diseases (NDs), which include epilepsy, Parkinson's disease (PD), and Alzheimer's disease (AD), are linked to severe health problems and financial strains on global health care systems. NDs are not curable and can only be prevented and managed. The treatments currently available, which consist of synthetic drugs, are only able to manage symptoms or slow down the progression of the disease. The incidence of these neurodegenerative disorders, which affect memory, cognition, and motor function, is on the rise due to the aging of the global population [30, 31, 32, 33]. Certain neurodegenerative disorders arise from genetic mutations, whereas others are associated with adverse living environments. Nevertheless, the specific causes of the phenomenon remain unidentified [31].

According to the World Health Organization (WHO), it is projected that in two decades, NDs that mainly impact motor functions will surpass cancer and become the second leading cause of death, following cardiovascular diseases [30]. Consequently, pursuing novel pharmaceuticals and therapeutic approaches has gained significance as a research subject. Natural products, specifically those obtained from Traditional Chinese Medicines (TCMs), are the primary reservoirs of pharmaceuticals and have captivated researchers in their potential for treating ND [32]. Natural products have been shown to improve blood flow to the brain, stop neurodegeneration, make it easier for cerebral hematomas to dissolve, heal damaged nerve tissue, help memory recovery, and make nerve function better [33, 34,35].

3. Challenges in the management of some diseases of public health importance.

3.1 Scarcity of new drug molecules for disease management

The scarcity of new drug molecules for disease management is a significant concern in the field of pharmaceutical research and development [36]. Several factors contribute to this challenge, making it difficult to bring new and innovative drugs to the market for various diseases. Developing a new drug is a lengthy and costly process that involves extensive research, preclinical studies, clinical trials, and regulatory approvals [37]. The high expenses associated with drug development can discourage pharmaceutical companies from investing in research for diseases that may not have a guaranteed market or a significant return on investment. In addition, many diseases, especially chronic and complex conditions, involve intricate biological processes that are not fully understood [38]. Identifying appropriate drug targets and developing molecules that can safely and effectively modulate these processes is a challenging task. To worsen this, infections and diseases can develop resistance to existing drugs over time, reducing their effectiveness [39]. Developing new drugs that can overcome resistance can therefore be a difficult task. For diseases with a smaller patient population or in low-income countries, pharmaceutical companies may perceive limited market potential, making it less attractive to invest in drug development for these conditions [40], even when these diseases constitute a significant public health burden. By addressing these challenges with the aid of phytomedicines and additional technologies, it is possible to improve the availability of new and effective drugs for disease management and ultimately benefit global public health.

3.2 Problems associated with the formulation of currently existing drugs

The formulation of currently existing drugs can face several problems and challenges, impacting their effectiveness, safety, and patient compliance. These issues can arise due to various factors in the drug development process, manufacturing, and administration. Some drugs have low bioavailability due to poor solubility, stability, or absorption, leading to suboptimal therapeutic outcomes [41, 42]. Some drugs are chemically unstable or prone to degradation, especially under certain storage conditions, such as temperature and humidity [43]. This can lead to reduced potency and effectiveness over time. Certain drugs are difficult to formulate into suitable dosage forms (e.g., tablets, capsules, injections) due to their physicochemical properties [44]. Formulation challenges can affect drug delivery and patient compliance.

The speed at which a drug exerts its therapeutic effect can be critical for some conditions. Inconsistent or slow onset of action can impact patient satisfaction and treatment outcomes. Similarly, some drugs may interact with other medications, food, or substances, affecting their absorption, metabolism, or efficacy [45]. Formulation scientists may need to consider these potential interactions to minimize adverse effects. For oral medications, taste and palatability can be significant factors affecting patient compliance, especially in pediatric and geriatric populations [46]. In some cases, patients may develop allergies to certain excipients (inactive ingredients) used in drug formulations, leading to adverse reactions [47]. For drugs requiring sustained or controlled release over time, formulation challenges may arise in designing dosage forms that maintain the desired release profile.

To address these formulation issues, pharmaceutical companies and researchers engage in continuous improvement and innovation. Advancements in drug delivery technologies, such as nanotechnology, liposomal formulations, and controlled-release systems, aim to overcome some of these challenges and improve drug efficacy, safety, and patient compliance. By applying these nanomedicine-driven advancements to phytomedicines, the delivery challenges associated with drug formulation has the potential for sustainable rectification.

4. Phytopharmaceuticals as a solution to mitigating public health diseases.

Phytopharmaceuticals, also known as herbal medicines or botanical drugs, are medicinal products derived from plants that have therapeutic properties [48]. They have been used for centuries in traditional medicine sys-

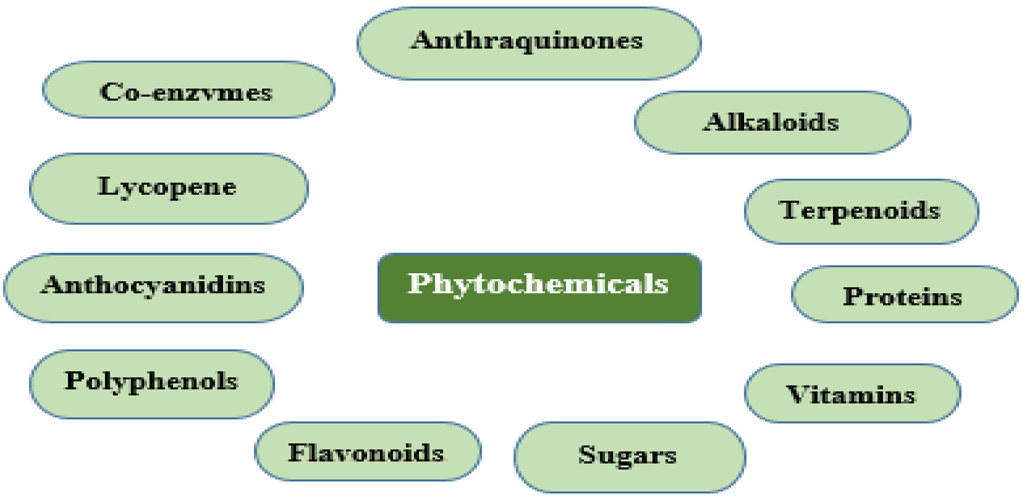

Fig. 2: Few examples of phytochemicals or bioactive compounds present in natural products or herbal medicines [42, 50] .

tems worldwide and are increasingly gaining attention as potential solutions to various public health diseases. Phytopharmaceuticals are derived from plants, making them a natural source of therapeutic compounds. Many traditional herbal remedies have been used for generations and have a long history of safe use [49]. Medicinal plants are abundant in nature and can be found in various regions around the world. This accessibility can be particularly beneficial in areas with limited access to modern healthcare facilities.

Phytopharmaceuticals contain a wide range of bioactive compounds (**Figure 2**) with potential health benefits. These compounds can have various pharmacological effects, such as anti-inflammatory, antioxidant, antimicrobial, analgesic, and immunomodulatory properties [50]. They have shown promise in managing chronic diseases, such as diabetes, gastrointestinal disorders, cardiovascular disorders, and certain cancers thereby improving disease outcomes and quality of life for patients. Compared to some synthetic pharmaceutical drugs, phytopharmaceuticals may have a lower incidence of adverse effects when used appropriately [51, 52]. However, it is essential to note that herbal medicines can still interact with other medications, and their safety and efficacy should be carefully evaluated [53]. In many regions, herbal medicines are more affordable than conventional pharmaceuticals, making them a cost-effective option for public health management [54]. In addition to these, the use of phytopharmaceuticals have the secondary advantage of being able to promote the conservation of medicinal plant species and biodiversity, as well as support sustainable practices in their cultivation and harvest [55].

Traditional herbal remedies are often rooted in indigenous knowledge, passed down through generations [56]. Incorporating this knowledge into modern healthcare systems can enrich medical practices and promote cultural preservation. It is essential to approach the integration of phytopharmaceuticals into public health systems with caution and scientific rigor. This can be achieved through careful augmentation with suitable techniques such as nanotechnology for more efficient delivery of these natural products.

5. Nanotechnology in drug delivery and nano-derived phytopharmaceuticals.

5.1 What is Nanotechnology?

Nanotechnology is a field of science and technology that deals with the manipulation and control of matter at the nanoscale [42, 57]. It involves studying and engineering of materials and devices at the nanometer level, which is typically in the range of 1 to 100 nanometers (1 nanometer = 1 billionth of a meter) [58]. At this tiny scale, the properties of materials can differ significantly from their bulk counterparts, leading to unique and novel characteristics. Nanotechnology allows scientists and engineers to work with atoms and molecules to create new materials, structures, and devices with enhanced properties and functionalities. Nanomaterials are a key aspect of nanotechnology. These are materials with nanoscale dimensions, exhibiting unique properties due to their high surface area-to-volume ratio and quantum effects [59]. Nanomaterials can be classified as nanoparticles, nanotubes, nanoshells, nanowires, and more [42, 60, 61]. Typically, nanotechnology involves both "bottom-up" and "top-down" approaches [42, 62]. Bottom-up approaches involve building structures and materials by assembling individual atoms or molecules. Top-down approaches involve scaling down larger structures or materials to the nanoscale. Nanotechnology is highly interdisciplinary, drawing knowledge and techniques from various fields such as physics, chemistry, biology, materials science, and engineering.

Applications of nanotechnology are widespread and have the potential to revolutionize numerous industries, prominent of which are the healthcare and pharmaceutical industries. Nanomedicine aims to develop targeted drug delivery systems, diagnostic tools, and imaging agents at the nanoscale to improve treatments and diagnosis of diseases [63]. Additionally, nanotechnology can lead to the creation of stronger, lighter, and more durable materials with unique properties, transforming various industries such as aerospace, automotive, and construction [64]. In this review, nanotechnology will be explored as a means of improving the delivery of phytomedicines, to the ultimate benefit of vulnerable and ailing patients.

5.2 Formulating phytopharmaceuticals as nanomedicine.

Formulating natural medicines as nanomedicines involves incorporating natural compounds or extracts into nanoscale carriers to enhance their therapeutic efficacy, improve targeted delivery, and overcome challenges associated with their use in traditional formulations. This approach leverages the benefits of nanotechnology to optimize the delivery of natural medicines, which are derived from plant, animal, or microbial sources. Natural compounds can be encapsulated within nanoparticles, such as liposomes, polymeric nanoparticles, or solid lipid nanoparticles [52, 65]. This protects the compounds from degradation, improves their solubility, and enables controlled release [66]. While micelles and nanoemulsions can solubilize hydrophobic natural compounds [67], making them more bioavailable and improving their absorption, nanocrystals or nanoparticles can improve the dissolution rate of poorly water-soluble natural compounds, enhancing their bioavailability [68]. Metallic (silver, gold, copper) nanoparticles can be synthesized by the green method, using extracts from plants as capping or reducing agents to form the nanoparticles for such metals [52].

Nanostructured Lipid Carriers (NLCs) are another way of applying nanotechnology in drug formulation. NLCs are lipid-based nanoparticles that can incorporate both hydrophilic and lipophilic components [69], making them suitable for delivering a wide range of natural medicines. Like NLC, dendrimers are highly branched nanoscale polymers that can carry natural medicines within their branches and offer unique properties for drug delivery of phytomedicines [70]. Nevertheless, natural compounds can be entrapped within nanogels, which are cross-linked hydrogel nanoparticles [71]. These gels can improve stability and control the release of the drugs. Nanomedicine platforms can be functionalized by targeting ligands that recognize specific receptors on diseased cells [72]. This allows for enhanced accumulation of natural medicines at the target site, reducing off-target effects. Additionally, nanomedicines can deliver multiple natural medicines simultaneously, allowing for combination therapies that target different aspects of diseases, such as cancers [73].

A novel non-phospholipid liposomal nanocarrier called "Phyto-Sterosomes" was synthesized using sitosterol, extracted from *Senecio fulgens*, as a "heart-friendly" substitute for cholesterol. While the sitosterol-sterosomes loaded with rutin had a notable therapeutic effect, the unmedicated sitosterol-sterosomes also demonstrated a significant anti-carcinogenic effect. When treating hepatocellular carcinoma, phytosterosomes increased the solubility and biological efficacy of the poorly soluble phytophenolic compound "rutin." [74].

5.3 Common techniques deployed in converting phytomedicine to nanomedicine.

Converting phytomedicines into nanomedicines involves the use of various techniques (Table 1) to encapsulate or incorporate the bioactive compounds from medicinal plants into nanoscale carriers. These nanocarriers protect the bioactive compounds, improve their stability, solubility, and bioavailability, and enable targeted delivery.

Nanoprecipitation is one of the techniques deployed in converting phytomedicines into nanomedicines. It is a simple and widely used technique. It involves the rapid precipitation of a drug or natural compound from a solu-

Table 1: Methods used in the preparation of nano-delivered phytomedicines, examples of phytomedicine nanoformulations and their applications

Method	Examples of phytomedicine nanoformulations	Applications	References
Nanoprecipitation or solvent displacement	trans-resveratrol-loaded polymeric nanoparticles, chrysin-loaded polymeric nanoparticles	Antioxidant, anti-inflammatory	[75, 76, 77]
Emulsification-solvent evaporation	Bavachinin-loaded polymeric nanoparticles	Anti-inflammatory	[78, 79]
Coacervation	Baicalein-loaded polymeric nanoparticles	Anti-inflammatory	[80, 81]
Supercritical fluids method	α-Tocopherol nanosuspensions, *Curcuma longa* nanoparticles	Antioxidant, anti-cancer	[82, 83, 84]
Film hydration method	Rutin-loaded phyto-sterosomes	Anti-cancer	[85]
High-pressure homogenization or bead milling	Zerumbone-loaded nanosuspension	Anti-cancer	[86, 87, 88]
Self-assembly technique	Ergosterol nanoparticles	Anti-cancer	[90, 91]
Green method	Silver nanoparticles	Antibacterial	[52, 92]

tion using a non-solvent or by changing the solvent composition [75]. This leads to the formation of nanoparticles with the natural compound encapsulated within them. Another technique utilized is the 'emulsification-solvent' evaporation [78]. In this method, the phytomedicine or natural compound is dissolved or dispersed in an organic solvent and emulsified in an aqueous phase. The solvent is then evaporated, leading to the formation of nanoparticles.

Phytomedicines can also be formulated into nanomedicines through coacervation. Coacervation is a phase separation technique where natural compounds are encapsulated within polymer-based coacervates, leading to the formation of nano-sized particles [80]. With supercritical fluid technology, supercritical fluids (e.g., supercritical carbon dioxide) can be used to solubilize and encapsulate natural compounds, which are then precipitated as nanoparticles upon depressurization [82]. The use of lipid-based nanoparticles is another common way of enhancing natural medicines with nano-sized carriers. Liposomes, solid lipid nanoparticles (SLNs), and nanostructured lipid carriers (NLCs) are typically used as lipid-based nanocarriers to encapsulate lipophilic phytomedicines [85]. AbouSamra *et al*. [74] developed rutin loaded -phytosterosomes using the commonly known film hydration method. In addition to this, phytomedicines can be formulated as nanosuspension [86]. Nanosuspensions involve reducing the particle size of natural compounds to the nanometer range using techniques like high-pressure homogenization or bead milling [87]. The resulting nanosuspensions can improve drug dissolution and bioavailability. Natural compounds can also be incorporated into polymeric nanoparticles, such as poly (lactic-co-glycolic acid) (PLGA) or chitosan nanoparticles, using techniques like nanoprecipitation or emulsification [89].

Although not as prominently used as the afore-discussed techniques, the self-assembly technique involves the spontaneous organization of natural compounds into nanostructures, such as micelles or nanoemulsions, through their hydrophobic and hydrophilic interactions [90]. Green silver nanoparticles (AgNPs) synthesis are usually prepared from natural reducing agents (plant extracts) and silver nitrate. Traditional NPs production methods such as chemical method are costly, dangerous, and environmentally unfriendly. Thus, experts have adopted green NPs synthesis methods to avoid these issues. Extracts from plant leaves, fruits, roots, seeds, and stems contain biomolecules that benefit the environment and are medicinal. These biomolecules include enzymes, alkaloids, polysaccharides, tannins, terpenoids, phenols, and vitamins. All hazardous substances, such as sodium borohydride ($NaBH_4$) and trisodium citrate used in chemical method, are replaced with plant extracts. Plant extract aids in this process because leaf extract's flavonoid and terpenoid components stabilize AgNPs, which aid in NPs synthesis, and its polyol and water-soluble heterocyclic components reduce silver ions [52, 92].

These techniques offer diverse approaches for converting phytomedicines into nanomedicines, tailoring their properties to suit specific applications. Each method may have advantages and limitations depending on the physicochemical properties of the natural compounds and the desired characteristics of the nanomedicine. Proper characterization and evaluation of the nanomedicines' physicochemical properties, stability, biocompatibility, and drug release kinetics are essential to ensure their efficacy and safety for therapeutic use.

6. Applications of nanotechnologies in the development of phytopharmaceuticals.

Nanotechnology has made significant advancements in the field of medicine and healthcare, leading to the emergence of nanomedicine. Nanotechnology-based approaches offer unique opportunities for targeted drug delivery, improved diagnostics, and personalized treatments [93]. Nanoparticles can be engineered to deliver drugs directly to specific tissues or cells in the body. This targeted drug delivery approach reduces side effects and enhances the therapeutic efficacy of medications. Nanocarriers, such as liposomes, sterosomes, micelles, and polymeric nanoparticles, can encapsulate drugs and release them at the desired site of action. Nanoparticles are extensively used in cancer therapy [74, 94]. They can passively accumulate in tumor tissues through the enhanced permeability and retention (EPR) effect, which occurs due to the leaky blood vessels in tumors. Additionally, active targeting strategies can be employed to guide nanoparticles specifically to cancer cells [95], increasing treatment effectiveness while minimizing damage to healthy tissues.

Nanotechnology allows for the design and production of personalized nanomedicine tailored to an individual's specific needs. By incorporating patient-specific characteristics, such as genetic profiles, into the design of nanomedicines, treatments can be optimized for maximum effectiveness [96]. With regards to the unique applications of nanoparticles in different drug delivery models and disease conditions, nanoparticles, such as silver nanoparticles, have antimicrobial properties and can be used to combat bacterial infections, including drug-resistant bacteria [52, 97]. Furthermore, nanoparticles can enhance vaccine efficacy by improving antigen delivery and stimulating robust immune responses [98]. Nanoparticles also have the potential to bypass the BBB and deliver therapeutic agents to the central nervous system, opening new possibilities for treating neurological disorders [99].

A synergy between these nanotechnology applications and already existing plant-derived drugs (with different therapeutic potentials) holds great prospects for additive benefits in the clinical management of different diseases; it is therefore worthy of continuous exploration. The field of nanomedicine continues to evolve rapidly, and ongoing research and development aim to address challenges, such as biocompatibility, toxicity, and manufacturing scalability. Therefore, nanotechnology-based medical innovations hold great promise in improving patient outcomes, in situations where phytomedicines are to be deployed.

6.1 Solving the challenges of insolubility and instability in phytomedicines using nanomedicines.

Nanomedicines offer promising solutions to the challenges of drug insolubility and instability, which are common issues in the pharmaceutical development of phytomedicines. By utilizing nanotechnology, these challenges can be addressed effectively, improving the solubility and stability of drugs. Nanoparticle-based drug delivery systems, such as nanosuspensions, liposomes, sterosomes and micelles, can significantly improve the solubility of poorly water-soluble extracts of plant parts [74, 100]. With nanoparticles, hydrophobic drugs can be encapsulated within their core or on their surface, creating a hydrophilic shell that enhances their dispersibility in water or biological fluids [101]. Nanoparticles have a high surface area-to-volume ratio, exposing more naturally derived molecules to the surrounding medium. This increased surface area enhances dissolution rates and bioavailability, overcoming the limitations of poorly soluble drugs [102]. Nanocarriers, such as liposomes and polymeric nanoparticles, can also protect herbal derivatives from enzymatic degradation or chemical degradation in the body [102]. The encapsulation of drugs within nanoparticles shields them from interactions with degrading enzymes and pH changes, leading to improved stability. In addition to this, these nanocarriers can co-deliver stabilizing agents or excipients along with drug principles. These stabilizers can prevent degradation and maintain drug integrity during storage and administration. Furthermore, nanotechnologies can be deployed to protect labile phytochemicals from denaturation by encapsulating them in a stable environment [103]. Since nanoparticles themselves have some inherent stability, protecting the phytomedicine from external factors that may cause degradation, such as light, temperature, and humidity [104]. By addressing drug insolubility and instability constraints in phytomedicines through nanomedicines, pharmaceutical researchers can unlock the potential of many natural medicines that were previously limited by their poor solubility or susceptibility to degradation. These advancements can lead to the development of more effective and patient-friendly medications, contributing to improved therapeutic outcomes and better healthcare overall.

6.2 Using nanotechnologies to improve the yield of herbal extracts.

Nanotechnologies offer promising approaches to improve the yield and stability of herbal extracts, enhancing their therapeutic potential and commercial viability [105]. With nanoemulsions (stable colloidal systems composed of oil, water, and surfactants, with droplet sizes in the nanometer range), the solubility of hydrophobic bioactive compounds present in herbal extracts can be improved [106], leading to increased yield during the extraction process. Nanoemulsions can also enhance the stability of the extract by protecting it from degradation and aggregation. Similarly, nanosuspensions which involve reducing the particle size of herbal extracts to the nanometer range, resulting in increased surface area and improved dissolution rate, can enhance the release of active compounds, leading to higher yield and improved bioavailability of herbal extracts [107]. By employing nanotechnologies to improve the yield and stability of herbal extracts, it becomes possible to harness the full potential of these bioactive compounds for medicinal and nutraceutical applications. These advancements can also contribute to the development of more efficient and sustainable processes for herbal extract production, benefiting both the pharmaceutical and herbal industries.

6.3 Using nanotechnologies to improve the potency and efficacy of natural products.

Nanotechnologies offer a range of strategies to enhance the potency and efficacy of natural products, optimizing their therapeutic potential and expanding their applications in various fields. Many natural products have limited bioavailability due to poor solubility or rapid metabolism [74, 108]. Nanotechnology can improve the solubility of hydrophobic natural compounds, enabling better absorption and increased bioavailability [74, 109]. This enhancement ensures a higher proportion of the administered dose reaches the systemic circulation, leading to more significant therapeutic effects. Nanoparticles can also be engineered to target specific tissues, cells, or organs in the body, allowing for site-specific drug delivery. This targeted approach concentrates the natural product at the desired site, increasing therapeutic efficacy while minimizing off-target effects [100]. As stated earlier, nanomedicine platforms enable the controlled and sustained release of natural products over time. This controlled release ensures a steady and prolonged supply of active compounds from natural medicines, leading to sustained therapeutic effects and reduced dosing frequency [110].

Nanotechnologies can overcome biological barriers, such as the blood-brain barrier, by utilizing carriers with the capability to transport natural products across these barriers [111]. This opens new possibilities for treating diseases affecting the central nervous system and other challenging targets with phytomedicines. Nanoparticles can also facilitate enhanced intracellular delivery of natural products, allowing them to reach their targets inside cells [74, 112]. This is particularly valuable for conditions where the therapeutic target is located within cells. These advancements can lead to the development of more efficient and sustainable processes for producing and delivering natural products.

6.4 Sustained release of natural drug compounds using nanotechnology.

Nanotechnology offers effective strategies for achieving sustained release of natural drug compounds, ensuring a controlled and prolonged delivery of the active substances [113]. By utilizing nanoscale drug delivery systems and formulations, the sustained release of natural drug compounds can be implemented. To achieve this, natural drug compounds can be encapsulated within polymeric nanoparticles, such as chitosan nanoparticles [114]. These nanoparticles can provide sustained release of the natural drugs due to their matrix-like structure, which allows for controlled diffusion of the drug over time. Furthermore, by modulating the lipid composition and bilayer structure, liposomes can be designed to release phytomedicines in a controlled and sustained manner [115] enabling prolonged therapeutic effects.

Hydrogel-based nanocarriers can entrap natural drug compounds within a three-dimensional network [116]. The hydrogel matrix provides a controlled release mechanism, allowing the drug to diffuse slowly out of the gel over an extended period [117]. In addition to this, micro and nanofibers composed of biodegradable polymers can be loaded with natural drug compounds [118]. These fibers can be engineered to have a high surface area-to-volume ratio, enabling sustained release as the drug slowly diffuses out of the fibrous structure. Biodegradable implants, such as nanocomposites or nanofibrous scaffolds, can also be loaded with natural drug compounds [119]. The implants gradually degrade over time, releasing the drug and providing sustained therapeutic effects.

In trying to achieve the programmed release of phytochemicals, nanotechnologies enable the development of stimulus-responsive drug delivery systems [120]. These systems can be designed to respond to specific triggers, such as pH, temperature, enzymes, or external stimuli, releasing the natural drug compounds in a controlled and sustained manner. Hybrid nanosystems that combine different types of nanocarriers or materials can be designed to achieve sustained release [121]. For example, a combination of liposomes and hydrogels can provide a dual-controlled release mechanism for natural drug compounds [122]. These nanotechnology-based approaches allow for tailored and sustained release of natural drug compounds, ensuring a prolonged therapeutic effect, reduced dosing frequency, and improved patient compliance. However, it is crucial to conduct thorough characterization, optimization, and safety evaluations to ensure the efficacy and safety of these sustained release nano systems for natural drug compounds.

6.5 Targeted delivery of phytochemicals in the body using nanotechnology.

Targeted delivery of phytochemicals in the body using nanotechnology involves the design of nanoscale drug delivery systems to deliver natural compounds derived from plants to specific tissues or cells, maximizing therapeutic effects while minimizing off-target effects. Nanotechnology provides various strategies for achieving targeted delivery of phytochemicals, enhancing their bioavailability and therapeutic efficacy. In active targeting, nanoparticles can be functionalized with targeting ligands, such as antibodies or peptides that specifically recognize receptors or markers overexpressed on the surface of target cells [123]. When administered, these targeted nanoparticles can selectively bind to the desired cells, facilitating the internalization of phytochemicals into the target cells. The targeting can also be passive, where nanoparticles exploit the enhanced permeability and retention effect, which occurs due to the leaky vasculature of tumor tissues and inflamed areas [123]. This passive targeting enables nanoparticles to accumulate preferentially in tumor or inflamed tissues, delivering phytochemicals to these sites.

The design of nanocarriers can be tailored to suit the characteristics of specific tissues or organs, enabling targeted delivery to those areas. For example, pH-sensitive nanoparticles can release phytochemicals in response to the acidic microenvironment of tumors or inflamed tissues [124]. Some nanoparticles can exploit receptor-mediated endocytosis to enter specific cells [125]. By incorporating specific ligands recognized by receptors on the cell surface, the nanoparticles can be internalized and deliver phytochemicals intracellularly. Nanoparticles can also be designed to release phytochemicals within the intracellular environment, ensuring that the compounds reach their intended targets inside the cells [126]. Interestingly, some nanocarriers can be engineered to combine multiple functionalities, such as targeting, imaging, and drug delivery, in a single platform. These multifunctional nanoparticles can enable simultaneous diagnostics and targeted drug delivery [127]. By utilizing nanotechnology for targeted delivery of phytochemicals, the therapeutic effects of these natural compounds can be optimized thereby enhancing patient outcomes and reducing potential side effects associated with non-targeted delivery.

7. Advancements made so far with nanomedicines in Africa.

While the field is still in its early stages, several notable achievements and initiatives are underway in various African countries. African researchers are actively investigating the use of nanocarriers, such as liposomes, polymeric nanoparticles, and micelles, for targeted drug delivery [128]. These nanoscale drug delivery systems aim to improve the bioavailability and therapeutic efficacy of drugs, especially for poorly water-soluble compounds. Nanomedicine research in Africa is focusing on cancer therapeutics, aiming to enhance treatment outcomes and reduce side effects. Nanoparticle-based drug delivery systems are being explored for the targeted delivery of chemotherapy agents to tumor tissues [129]. Furthermore, nanotechnologies are being employed to develop more effective and patient-friendly treatments for tuberculosis (TB) [130]. African researchers are investigating nanocarriers for delivering anti-TB drugs to improve treatment outcomes and combat drug-resistant TB [131]. In the fight against malaria, nanomedicines were being studied for targeted drug delivery to infect cells and vaccine development. Nanoparticles are being explored to improve the stability and delivery of antimalarial drugs [132]. In addition to these, researchers in Africa are also exploring nanotechnology-based wound dressings and scaffolds for tissue regeneration applications [133]. These nanomaterials aim to accelerate wound healing and promote tissue repair. Summarily, the field of nanomedicines in Africa is still growing, indicating a need for the allocation of more resources and expertise to nanotechnology-themed research areas towards the development of more effective plant-based medicines against diseases of public health significance.

8. Conclusion

It is essential to recognize that the field of nanomedicines is dynamic, and development efforts are still ongoing. While this is true, the achievements recorded so far can be suitably applied to the field of phytomedicines, with and beyond Africa. This will involve tapping into the many potentials of nanotechnologies. By fusing the discoveries in phytomedicine with innovations in nanotechnology, more novel and patient-focused dosage forms can be expected in the near future, as solutions to the various diseases of public health importance, that afflict us in this 21st century.

Conflict of Interest

The authors declare that there is no conflict of interest.

Submission declaration and verification

We confirm that this work is original and has not been published elsewhere, nor is it currently under consideration for publication elsewhere, there are no potential competing interests, and we both approved the manuscript for submission.

Author's contribution

A.T.O (Ajala, Tolulope Omolola), O.O.A (Omoteso, Omobolanle Ayoyinka) and G.Y.O (Ghazali, Yusuf Oluwagbenga)
Conceptualization, A.T.O; writing—review and editing, A.T.O, O.O.A, G.Y.O.; visualization, O.O.A.; supervision, A.T.O. All authors have read and agreed to the published version of the manuscript.

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