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Review Article

Phytosynthesized Nanoparticles Against Viral Diseases: Current Updates

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Abstract

Advancements in nanomedicine have effectively overcome the issues of solubility, absorption, and cytotoxicity of conventional drugs. In recent years, phytoproducts rich in bioactive constituents have been exploited as green-, herb-, or phytosynthesized metal or nonmetal nanocarriers. Of these, alkaloids, flavonoids, polyphenols, sterols, lignans, tannins, and saponins efficiently contribute to the enhanced stability of such nanocarriers or nanoparticles by reducing metal ions. In addition, phytosynthesized silver and gold nanoparticles have received much interest due to their less hazardous, eco-friendly, and cost-effective properties. Owing to these properties, phytosynthesized silver and gold nanoparticles also have been developed as effective antiviral drug delivery carriers against human immunodeficiency virus, herpes simplex virus, influenza virus, dengue virus, chikungunya virus, hepatitis B virus, bovine diarrhea virus, and foot and mouth disease virus infections. Although experimental studies have shown that such phytonanoparticles can inhibit viral replication in infected cells, the underlying mechanism of their antiviral activities is poorly understood. Importantly, compared to herbal antivirals or metal-based antiviral nanoparticles, the novel approach of phytosynthesis of antiviral nanoparticles seems to be in its infancy. In view of the emerging viral outbreaks and pandemics like coronavirus disease 2019, this area of drug research needs special attention.

Introduction

In modern research, nanotechnology has become an important field dealing with the synthetic strategies and manipulation of metallic or nonmetallic substances of <100 nm in size. The physical, chemical, and biological properties of such nanoparticles, either atom or molecule, can be controlled or changed in a fundamental way. The growing applications of nanoparticles are rapidly transforming numerous fields of research such as environmental science, chemical industries, electronics, optical devices, cosmetics, health care, and biomedical instruments, etc.[1] Further, the application of nanobiotechnology requires hygienic, safe, and eco-friendly methods of synthesizing such nanoparticles. In view of this, the use of substances of biological origin, nonhazardous environmentally friendly solvents, and renewable materials have become key to the development of green-, herb-, or phytosynthesized nanoparticles.[2,3] Phytosynthesis of nanoparticles includes the exploitation of various biological materials of bacterial, fungal, algal, or plant sources, collectively called as biogenic nanoparticles.[4]

Nanotechnology has emerged as a significant technology in biomedical science, including drug or gene delivery systems.[5,6] In nanomedicine, this technology allows the development of new classes of bioactive macromolecules for their cellular or targeted delivery of therapeutic molecules for their enhanced bioavailability and activities.[7]

Nanoparticles or nanocarriers are nanoscale spacious structures (1–100 nm) of metallic or nonmetallic materials prepared as a powder, suspension, or colloidal form. The nanoparticles are morphologically classified on the basis of a high or low aspect ratio, where the former class includes tubes and wires, while the later class includes spherical, oval, or capsular nanostructures.[8] Recently, nanoparticles have emerged as the preferred delivery system against important chronic and infectious diseases due to their properties, which reduce the cytotoxicity and side effects of some drugs. In addition, several biological substances such as albumin, gelatin, liposomes, polymers, metals, nonmetals, and phytoproducts have been developed to synthesize promising drug-delivery nanoparticles.[9]

Nanoparticles or carriers as drug delivery vehicles

A nanocarrier is a nanosized spacious vehicle for another sub-

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Abbreviations: AgNPs, silver nanoparticles; AuNPs, gold nanoparticles; HSV, herpes simplex virus.

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stance such as a drug or therapeutic molecule. The most commonly used materials to synthesize such nanocarriers are lipid micelles, liposomes, protein polymers, carbon, silver, gold, etc. Because the human body contains mostly water, the materials used in therapeutic nanocarriers should allow the efficient delivery of both hydrophobic and hydrophilic drugs to the cells.[10,11] Nonetheless, a potential problem with inorganic or synthetic nanocarriers is their unwanted toxicity if they accumulate in certain cell organelles compared to protein-based nanocarriers, which generally demonstrate less cytotoxicity.[12] Furthermore, in nanomedicine, such nanocarriers are employed to deliver therapeutic agents to specifically targeted sites in a controlled manner. Nanomedicine manages the nanoparticle size, surface properties, and discharge of bioactive molecules to achieve their site-specific delivery and action under the optimum conditions. In contrast to nanoliposomes, polymeric nanoparticles have some precise advantages; for example, they help to enhance the stability of drugs and possess suitable controlled release in the body.[13–15]

Phytosynthesis of therapeutic nanoparticles

Although therapeutic herbs or phytoproducts can easily dissolve in nonpolar solvents, they are poorly soluble in water, resulting in their partial absorption when taken orally. In recent years, therefore, phytoproducts rich in bioactive constituents have been reported as green-, herb-, or phytosynthesized lipid, polymer, lipid–polymer hybrid, carbon, and silver or gold nanoparticles.[8] Moreover, phytochemicals, such as alkaloids, flavonoids, polyphenols, sterols, lignans, tannins, and saponins effectively contribute to the reduction of gold and silver ions, thereby enhancing their stability. In addition, such phytosynthesized silver nanoparticles (AgNPs) or gold nanoparticles (AuNPs) have received much attention due to their less biohazardous, eco-friendly, and cost-effective properties.[16] Furthermore, several recent studies have suggested that such phytosynthesized AuNPs can also act as effective antiviral drugs.[17]

In herbal medicine or phytotherapy research and development, phytosynthesized nanoparticles have gained much attention. Even though marginal or no side effects have made natural products a potential therapeutic alternative, there exist important issues of their poor delivery, solubility, permeability, bioavailability, instability, and metabolism. These restrictions can be overcome by their attachment with or encapsulation within appropriately studied and selected nanomaterials for their significant enhancement in the pharmacokinetics index.[18,19] In view of this, the most important features for nanoparticle synthesis include the selection of phytoproducts, sustainable or eco-friendly solvent, a good reducing agent, and a safe or noncytotoxic material.[20] In contrast to the chemical methods that are very costly and use hazardous chemicals,[21] the phytosynthesized nanoparticles are safe, biocompatible, and environmentally friendly.[22]

For the biogenic synthesis of nanoparticles, the use of plant extracts is a very simple and easy process to synthesize metal or metal-oxide nanoparticles at a large scale compared to bacteria or fungi.[4,20,23] Higher plants are a very rich source of bioactive phytoconstituents like alkaloids, flavonoids, saponins, steroids, tannins, and phenolic acids, which act as stabilizing and reducing agents for metal ions as well as inhibit their aggregation and agglomeration by nonhazardous means.[24–26] Moreover, the phytosynthesis of nanoparticles based on biological precursors depends on various reaction parameters such as the solvent, temperature, pressure, and pH conditions. Also, while the type of plant product and its concentration affect the morphology of the herb-synthesized nanoparticles, the temperature and pH of the medium control their growth and size.[27]

Metabolism of phytonanoparticles

Bioactive phytochemicals have a high-water solubility but low absorption capacities due to their large molecular sizes that inefficiently permeate the cell membrane, resulting in poor bioavailability. Phytosynthesized nanoparticles have advanced due to their efficient targeted drug delivery without the further need for conjugating ligands; additionally, they demonstrate enhanced solubility, absorption, bioavailability, and safety.[28–30] They have enhanced permeation through obstacles because of their nanosize as well as their increased retention time owing to poor lymphatic drainage.[31] In targeting hepatocytes, though the *in-vivo* uptake of lipid-nanoparticles is limited, a reduction in the accumulation of antiviral siRNA vectors in sinusoidal endothelial cells, including hepatotoxicity, has been reported.[32]

Recent approaches with solid-lipid nanoparticles, liquid-crystal systems, precursor systems for liquid-crystals, or microemulsions with new substances having dissimilar properties in the same formulation could allow further alterations in their properties and behavior in a biological environment. Furthermore, other parameters like selectivity and efficacy, defending against thermal degradation or photodegradation, fewer side effects, and the controlled release of active constituents can be further improved before commercialization.[33–35]

Phytosynthesized antiviral nanoparticles

Viral diseases are among the most serious global public issues. In recent decades, several cases of viral epidemics and pandemics, notably, coronavirus disease 2019, have caused significant increases in mortality and morbidity rates worldwide.[36,37] In addition to conventional drugs, several phytoproducts and isolated metabolites have been extensively reported for their antiviral properties against several viruses.[38] Natural bioactive compounds have a high chemical diversity and biochemical specificity; therefore, exploring natural products could be an effective strategy to develop new and potential antiviral drugs.

In the past decade, ample of studies has reported that phytosynthesized metal nanoparticles like AuNPs can also inhibit human immunodeficiency virus, influenza virus, herpes simplex virus (HSV), chikungunya virus, hepatitis B virus, bovine diarrhea virus, foot-and-mouth disease virus.[17] Notably, its further modifications or functionalization as multivalent-, tannic acid-, gallic acid-, or curcumin-AuNP also have been suggested for enhanced antiviral activities.[39,40] The notable examples include *Astragalus membranaceus*-derived tannic acid-modified AgNPs against HSV;[41] *Tinospora cordifolia*, *Phyllanthus niruri*, and *Andrographis paniculate* extract-synthesized AgNPs against chikungunya virus;[42] *Lampranthus coccineus* and *Malephora lutea* extract-synthesized AuNPs against HSV, influenza virus, and hepatitis B virus;[43] and *Plumbago indica*-synthesize zinc oxide nanoparticles against HSV (Table 1).[41,43–47] Although further experimental studies have shown that such phytonanoparticles can inhibit viral replication in infected cells, the underlying mechanism of their antiviral activities is poorly understood.

Future directions

Compared to conventional herbal antivirals or metal-based antiviral nanoparticles, the novel combined approach of plant-mediated synthesis of metal-based antiviral nanoparticles seems to be in its infancy. Therefore, in view of the emerging viral outbreaks and pandemics like coronavirus disease 2019, this area of research

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Table 1. Synthesis of antiviral nanoparticles using various plant products.

Plant/product	Metal	Virus	Reference
Astragalus membranaceus	Ag	HSV	41
Lampranthus coccineus	Ag	HSV-1, HAV-10, CoxB4	43
Malephora lutea	Ag	HSV-1, HAV-10, CoxB4	43
Plumbago indica	Zn	HSV-1	44
Portulaca oleracea	Se	HAV, Cox-B4	45
Cinnamomum cassia	Ag	Influenza A subtype H7N3	46
Tinospora cordifolia	Ag	CKV	47
Phyllanthus niruri	Ag	CKV	47
Andrographis paniculate	Ag	CKV	47
Cinnamon, curcumin, pepper	Se_2S	Influenza A subtype H1N1, HCoV-OC43.	46

Cox-B4, Coxsackievirus B4; CKV, chikungunya virus; HAV-10, hepatitis A virus 10; HCoV-OC43, human coronavirus OC43; HSV, herpes simplex virus.

needs special attention towards the development of more effective, nonhazardous, biodegradable, and cost-effective antiviral drugs.

Conclusions

Nanomedicines employing different carrier materials have effectively resolved the issues of delivery, solubility, absorption, and cytotoxicity of conventional drugs. Therapeutic herbal or phytoproducts can easily dissolve in nonpolar solvents, but they are poorly soluble in water, resulting in partial absorption. Therefore, owing to their ability to efficiently reduce and stabilize metal ions, several herbal products or bioactive phytochemicals have been exploited as plant-mediated or phytosynthesized gold and silver nanoparticles, which are less biohazardous, eco-friendly, cost-effective, and easily scalable. Recently, phytosynthesized gold and silver nanoparticles have been developed as effective drug-delivery vehicles against infectious diseases, including pathogenic viruses.

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Conflict of interest

The authors declare no conflicts of interest.

Author contributions

Conceptualization, literature search, data acquisition, and preparation of the first draft (MKP), literature search, data acquisition, and preparation of the final draft (SA), review and approval of the final manuscript (MKP and SA).

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