

# Noble Metal Chitosan for the Medication of Herpesvirus Infection

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## Abstract

Neuroinfections caused by herpesviruses, primarily HHV-1, pose a significant challenge for modern medicine due to the scarcity of therapeutic substances in the pharmaceutical industry. Furthermore, HHV-1 infection has been linked to neurodegenerative processes like Alzheimer's disease, justifying the search for new effective treatments. The advancement of nanotechnology opens up new avenues for treating neuroinflammation. Gold and silver nanoparticles are becoming increasingly popular, and the number of clinical trials involving metallic nanoparticles is growing all the time. The research on gold and silver nanoparticles and their potential use in the treatment of herpesvirus neuroinfection is reviewed in this paper.

**Keywords:** Noble metal nanoparticles • HHV-1 • Neuroinfection

## Introduction

Infections of the central nervous system (CNS) are sporadic; they primarily affect paediatric patients as well as people with weakened immune systems due to immunosuppression or congenital immune system dysfunction. CNS infection can manifest itself in a variety of ways, depending on the biology of the virus; it can be acute, chronic, or latent. DNA and RNA viruses can both cause neurological diseases such as meningitis, encephalitis, meningovascularitis, radiculitis myelitis, cranial neuritis, and neuritis, potentially affecting all neurological and anatomical sites. Many neurotropic viruses have been identified as causing a variety of CNS diseases, but herpesviruses are the most common cause of neuropathogenic infections due to their ability to establish latency in neuronal tissue (neuronal ganglia) or in the CNS. B cells in lymphatic tissue. The Herpesviridae virus family causes minor dysfunction during primary infection, including fever and skin or mucous membrane rash. Following primary infections, the virus enters a latency state in which virus particles are not recognised by the immune system, giving the virus a "advantage" over the host cell's defence mechanisms.

The mechanisms by which herpesviruses enter the CNS are not fully understood. Some believe that these viruses can spread along with the ganglia or enter the frontal and temporal lobes of the brain directly from the upper respiratory tract mucous membranes. Human herpesvirus type 1 (HHV-1) is an alpha-herpesvirus with double-stranded DNA. HHV-1 can cycle effectively and create a state of latency within the CNS. The infection is mostly spread through direct contact, but it can also spread through blood transfusions or transplants. During infancy, children are usually infected by their parents. The interaction of viral glycoproteins with host membrane receptors initiates the disease. The oral epithelium, conjunctiva, and genital mucosa are the most common sites of HHV-1 infection. The virus's productive cycle manifests as vesicular lesions around the mouth and nose. Symptoms may be accompanied by an elevated temperature. Furthermore, as previously stated, the virus establishes latency in the trigeminal ganglia following the productive cycle. Only specific

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viral genes, such as LATs, are detected during the latency period (latency-associated transcripts). Immunosuppression, physical stress, and ultraviolet radiation are just a few examples [1].

## Standard antiviral treatment

Treatment strategies for herpesvirus infection have remained unchanged since the discovery of nucleoside analogues. Acyclovir (ACV), famciclovir, and valacyclovir are antiviral drugs for HHV-1 infection that are analogues of viral thymidine kinase, which phosphorylates nucleotides incorporated into viral genetic material. Acyclovir has the highest in vitro activity against HHV-1 and HHV-2 and is the most widely used antiviral medication. Famciclovir and valacyclovir, on the other hand, have higher oral bioavailability than acyclovir. The widespread use of nucleoside analogues, primarily acyclovir, has been linked to an increase in HHV-1 drug resistance. Dexamethasone, in addition to acyclovir, is used to treat herpesviral encephalitis in cases of extensive inflammatory changes in the brain. As a result, new therapies that inhibit the productive cycle and prevent its reactivation are required. There is a wealth of information in the literature on natural treatments for HHV-1 infection using polyphenols isolated from plants. El-Toumy et al. investigated the antiviral activity of plant extracts derived from Egyptian plants in vitro. Out of 25 plant extracts tested, they discovered that eight plant extracts and seven pure phenolic compounds had strong anti-HHV-1 activity [2].

The phenolic compounds gallic acid and curcumin demonstrated the most potent anti-HHV-1 activity. Another study found that four plants used traditionally by women of the Tacana tribe in the Bolivian Amazon could prevent HHV-2 infection in vitro and in vivo. Plant extracts inhibited HHV-2 binding and entry but not viral replication after entry. There were no clinical signs observed in mice infected with HHV-2 and treated with these extracts, no virus replication was found in the reproductive organs or spinal cord. Antiviral polyphenols have also been used in the chemical modification of nanoparticles (NPs). There has recently been a lot of discussion about NPs synthesised using photosynthesizing organisms, also known as 'green synthesis.' Algae, such as cyanobacteria, are primarily used to synthesise such NPs. Mostafa M. El-Sheekh et al. synthesised gold (AuNPs) and silver (AgNPs) nanoparticles using two cyanobacteria species: *Oscillatoria* sp. and *Spirulina platensis*. The obtained compounds were tested for virucidal activity against HHV-1 in a Vero cell line. The green synthesis produced AuNPs and AgNPs that reduced the cytopathic effect of HHV-1 [3].

## Noble metal nanoparticles as antiviral drugs

Nanotechnology employs particles with a diameter of 100 nm. Noble metal NPs have distinct chemical, physical, and biological properties due to their small size. As a result, they can be used as drug carriers and undergo various chemical modifications. The use of gold nanoparticles, which are chemically inert and biologically compatible, appears to be particularly beneficial.

Nanotechnologies for antiviral treatment have been extensively researched and developed in recent years. Nanoscale antiviral therapies have many advantages over traditional antiviral therapies. Nanomaterials can be used to improve current treatments as well as to develop new strategies to inhibit viral replication. Several strategies for NP antiviral action have been proposed thus far. These include NP interactions with viruses, blocking viral transport in the cell, blocking attachment by blocking the cellular receptor, and NP interaction with virus components. The mechanism by which NPs enter the CNS appears to be critical for the treatment of neuroinfections. Ag and AuNPs can both cross the blood-brain barrier (BBB). The size and surface modifications of NPs affect their penetration into the brain. Most of the time, NPs overcome the barrier with the help of immune cells, causing local barrier disruption [4].

The BBB is critical for CNS homeostasis and acts as a link between the brain and the body. It is in charge of allowing nutrients, ions, and vitamins into the body. Brain microvascular endothelial cells, tight junctions, astrocytes, pericytes, and the basal membrane comprise the BBB. Tight junctions play an important role in the BBB's continuity. Several studies show that claudin 5 and occludin have a significant influence on the maintenance of a normal BBB. He et al. discovered a significant decrease in claudin 5 and occludin protein levels during HSE. The treatment of neurodegenerative diseases such as Alzheimer's or Parkinson's disease, as well as HHV-1 neuroinfections, is difficult due to the complex structure of the BBB and selective permeability. The majority of the proposed therapeutic substances have little ability to cross the BBB. Water, some gases, and lipid-soluble compounds are the only molecules that can easily cross the BBB via simple diffusion. Large molecules with a high electrical charge, polarity, and hydrophilicity, such as glucose, amino acids, and most drugs, are actively transported and require the participation of specialised proteins.

## Discussion

Silver has long been known to have antimicrobial properties. It is less chemically stable and has a higher toxicity than gold. Cellular toxicity is primarily determined by the size and type of modification of silver nanoparticles (AgNPs). Their neurotoxicity is poorly understood. Many researchers find the use of AgNPs to be counterintuitive due to their cytotoxicity: AgNPs with diameters of 20 nm are thought to be the most toxic. Small AgNPs can directly pass through cellular membranes, whereas larger nanoparticles (>30 nm) are actively internalised by cells via processes such as phagocytosis, micropinocytosis, caveolin-dependent, and clathrin-dependent endocytosis. Gaiser and colleagues' research has shown that 20 nm AgNPs cause inflammation, cytotoxicity, and an increase in levels of oxidative stress in a human hepatocyte cell line and in female Wistar rats in vivo. In both in vitro and in vivo models, AgNPs increased inflammatory cytokines such as IL-8, MIP2, IL-1RI and TNF. AgNPs have been shown to disrupt mitochondrial function and

stimulate the formation of reactive oxygen species (ROS), ultimately leading to cell apoptosis/necrosis. Furthermore, in vivo studies on rodents treated with AgNPs revealed an increase in the expression of oxidative stress-related genes. That AgNPs with sizes of 50-60 nm could cause myelin damage [5].

## Conclusion

Neuroinfections of herpesvirus aetiology are a major problem in modern medicine, owing to their association with neurodegenerative diseases. Due to other comorbidities associated with herpesvirus infections (such as encephalitis) and a lack of effective vaccination strategies, available therapies based on nucleotide analogues may be insufficient. We can influence their ability to cross the BBB and become internalised by different neuronal cell types by using different substances to modify the surface of nanoparticles or by steering their sizes. Because herpesvirus infection, both primary and latent, involves neuronal cells in the skin, we should consider the possibility of influencing the outcome of HHV-1/HHV-2 local infection through topical use of modified Au/AgNPs. Further research, as well as more in-depth analysis, are required for good refinement. In vivo research on the bioaccumulation, biodistribution, and cytotoxicity of noble metal nanoparticles.

## Acknowledgement

None.

## Conflict of Interest

None.

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