A Scientific Review over Silver Nanoparticles as a Potential Alternative Broad Spectrum Antiviral Agent

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Abstract

The emergence of Nanotechnology in the field of medicine has led to new horizons since 1990s, which also widely used in pharmaceutical industry, chemical industry, bio-sciences, textiles industry etc. Viral infections are severely effecting global population and causing hazards to life. SARS-CoV-2 has badly affected human beings worldwide and also including economic distress. Silver nanoparticles having potential antiviral, antibacterial and antifungal property through different mode of actions. Virus replicates by using host cells, therefore it is so challenging to develop safe and effective antiviral agents. However, targeting virus without harm to host cell is very difficult to design such a safer and effective drug. The research is continuing for the evaluation of antiviral property of silver nanoparticles and several studies had scientifically claimed the potential antiviral property of silver nanoparticles against different species of virus and viron. In this review, we discuss the antiviral property of silver nanoparticles, mechanism of action, method of synthesis, their characterization methods, safer dose and toxicity, application in different fields.

Keywords: Antiviral activity, Silver nanoparticles, SARS CoV2, Zika Virus, Polio Virus, SEM, XRD, TEM, EDXS, DLS,

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Introduction

In recent years viral diseases are very crucial to control their final outcomes and a greatest threat to entire world. Many millions of people were affected globally due to SARS-CoV-2 pandemic. Throughout the history, diseases due to the viral infection are one of the major threats for entire community worldwide. Viruses are thought to have generated from multiple ancient cells and co-existed with the ancestors of modern cells [1]. They are existed in nature with a variety of shapes, sizes ranging from 20 -900 nm. Viruses are also able to act as vector in bacteria, fungus, animals and plants; they may transmit through person to person, mother to child. They are also responsible to spread highly contagious and communicable diseases in our community and may led to pandemic [2]. Virus can also spread through coughing, sneezing, direct contact, exchange of saliva, sexually, oral and faecal route. Sometimes virus may cause persistent infections which may lead to HIV, cancer or Hepatitis etc. An effective antiviral drug is most important and prevalence to overcome the threats due to viral attacks [3]. They also play a role to increase the rate of morbidity and mortality worldwide. Globally more than 2 millions of population face death due to viral attack in a year. The control over the spread and growth of viruses is not much effective due to lack of efficient processes and also because of their highly contagious nature [2, 3]. However, the pharmaceutical sciences have grown up with the time and with the help of vaccines development against few viruses, we got success to eradicate some diseases due to viral infections like smallpox in 1979. But still there is a high demand to develop vaccines and new anti-viral drugs against viruses which recently causes pandemic worldwide [4]. Nano-medicine is a ray of hope to develop such antiviral agents in the battle against viruses. Several nano-medicines already has been developed to increase the effectiveness of antiviral property through targeted delivery [5]. The metallic nano particles like silver, gold, copper, zinc, iron, titanium widely used in a variety of consumer goods like drugs, cosmetics, disinfectants, personal protective equipments [6]. Silver nano particles are most considerable among metal nanoparticles because of their unique properties. When we compared Silver nano particles with conventional chemical drugs, we found several advantages of silver nano particles which only target viruses; specifically they can bind to viral surface glycoprotein and enter host cells where they interact with viral genome and causes virucidal activity[3,6]. In this review, we discuss the antiviral property of silver nanoparticles, mechanism of action, method of synthesis, their characterization methods, safer dose and toxicity, application in different fields.

Methods of development of metal nanoparticles: There are two major techniques used for the synthesis of silver nanoparticles, bottom up and top down approaches, Fig.01 summarized the methods of metal nanoparticles development [6,7]. The bottom up approach uses nucleation and growth process to build clusters from molecular components for the synthesis of silver nanoparticles, biological and chemical process of nanoparticles synthesis are very widely used in bottom – up approach which synthesize nanoparticles by lowering the precursor salt. In chemical synthesis process the alternative energies can be used i.e. microwave assisted, electrochemical, photochemical, Sonochemical etc. [6,9]. With the help of the above techniques, the nanoparticles of different sizes ranges from 1-400 nm can be produce which shows antiviral properties. The biological approach for the synthesis of nanoparticles is easy, convenient, eco-friendly and cost effective. However the physical characterization of nanoparticles must be taken into account. The top – down approach refers to the preparation of silver nanoparticles by using physical forces like milling, crushing, grinding, laser ablation, electrical arc discharge etc. Another process of nanoparticles synthesis is popular named vapour condensation by using thermal energy [7,10]. The nanoparticles synthesized from the top-down approach with different size ranges from 10 to 120 nm and there is no need to add any chemical which allows the synthesis of homogeneous size of nanoparticles with high purity. But in this technique there is a significant problem in preventing agglomeration in absence of capping agents or stabilizers and also required external energy as well as highly precise and sophisticated equipments [8,11].

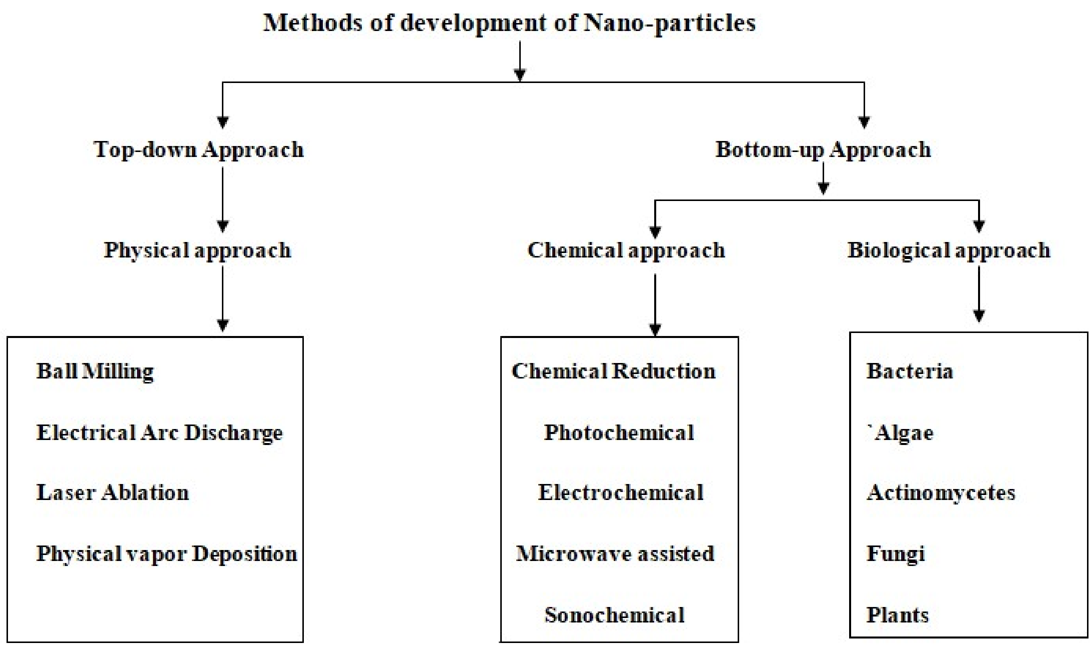

Fig.01 Methods of Silver Nanoparticles Development

Characteristics of Silver nanoparticles Silver nanoparticles having some unique properties comparatively bulk materials. The characterization of nanoparticles includes chemical composition, morphological phenomena and surface properties. Now a day's nanoparticles are significantly used in a variety of products manufacturing applied in the field of medical diagnosis, bio-imaging, targeted drug delivery on the basis of morphological and surface properties [7,25]. The specific characteristics and properties of silver nanoparticles are as given below:

a) **Crystallinity and shape:** The crystallinity and shape of silver nanoparticles depends on the process of synthesis such as spherical, plates, wires, prisms, rods etc. [7,26]. A study claimed that an altered polyol process where ethylene glycol plays a role of solvent as well as reducing agent to synthesize silver nanoparticles of different shapes includes nano-cubes, nano-wires, pentagonal, bi-pyramids etc.

b) **Optical Properties:** Silver nanoparticles efficiently interact with visible range of light which is an unique phenomena as compared with any organic and inorganic chromophores [18]. They have a great capability to capture light and having significant light interaction cross sections up to 10 times larger than their geometric cross section [7,19].
c) **Electrical Properties:** The electrical losses from samples made from silver nanoparticles are lower than those of similar conductors made from thick film silver conductors fired at very high temperature [8,19].
d) **Melting Temperature:** Melting temperature of Silver nanoparticles is substantially lower comparatively bulk silver. The melting temperature of bulk silver is 960 ◦C and it is lower for silver nanoparticles which depend on the diameter of silver nanoparticles [19,24]. The Gibbs – Thomson effect explained this phenomenon, the higher tendency of smaller particles to sinter or Ostwald ripen such that total free energy is reduced causes melting of nanoparticles at a lower temperature [3,20].

Characterization of Silver Nanoparticles: Evaluation of morphological character, surface property, size and shape of silver nanoparticles is an important step which has a significant effect on their biological application [6,21]. Characterization of silver nanoparticles is also very important due to safety issues before application in any drug. UV-visible is the basic technique of silver nanoparticles characterization. But some highly sophisticated techniques also used for the characterization of silver nanoparticles i.e. Scanning electron microscopy, transmission light microscopy, dynamic light scattering, atomic force microscopy, Fourier transform infrared spectroscopy, X-ray diffraction, energy dispersive X-ray spectroscopy, energy dispersive spectroscopy, X-ray photoelectron spectroscopy, diffuse reflectance spectroscopy, zeta potential analysis etc. [9,22]. UV-visible spectroscopy basically confirms the formation of silver nanoparticles from the colour shift resulting from SPR which turns yellowish brown. When using light in the wavelength between 300 – 800 nm, an absorption peak at around 430 nm indicated the presence of silver nanoparticles. To obtain the structure and topography of silver nanoparticles, scanning electron microscopy has been used where a high energy electron beam is used over a larger area of sample to get a high resolution image [10,23]. To obtain the chemical structure and topographical phenomenon of nano particle, the scanning electron microscopy is widely used where a high energy electron beam is used over a large area of sample to get a high resolution image [24]. Transmission light microscopy is applied to obtain morphological characteristics of silver nanoparticles arranged in a thin film. By producing lattice images, this technique also provides insight into the chemical structure along with their size related information with 1000 fold higher resolution [10,25]. Atomic force microscopy is also beneficial to find out the result about surface morphology of nano particles [26]. With the help of Dynamic light scattering technique we can get the average diameter and size of nanoparticles and their surface charges. DLS is based on the principal of Brownian motion where a scattering laser light is passed through the colloidal sample solution containing silver nanoparticles [27]. FTIR help to identify the functional groups attached to the surface of the silver nanoparticles. X-Ray diffraction technique is useful to find out the crystal structure of nanomaterials where the diffraction patterns observed after a beam of X-rays incident on sample. Based on the strong signals corresponding to silver nanoparticles, elemental analysis is performed by EDS or EDXS [11,28].

Anti-viral property of Silver nanoparticles: The specific anti-viral property and mechanism of action of Silver nanoparticles is uncertain but they can be used to prevent the multiple viral infections by preventing the infection in cells or directly by inhibiting viruses such as respiratory Syntical virus (RSV), Herpes simplex virus (HSV), adenovirus etc. The antiviral activity of Silver nanoparticles is due to the large surface area facilitates to make the attachment with virus [3,29]. Most of the antiviral substances act on viruses directly by binding to viral coat proteins and interfere with structural interaction and their functions [30]. The size of silver nanoparticles also plays an important role in viral-silver nanoparticles interaction. Fig. 02 is illustrated the anti-viral mechanism of silver nanoparticles [7]. Silver nanoparticles first interact with surface of virus and lead to the destruction of genomic material of virus and also inhibit the penetration in to the host cell membrane. Silver nanoparticles completely prevent the interaction of virus with the host cell membrane after making a attachment with the viral entity and also interact with viral genome which inhibit its replication inside the host cell [31]. Finally they break the chain of viral protein synthesis resulting in inhibition of the replication of the viral entity [11,32]. Although the silver nanoparticles have shown a greater efficacy against most of the viral, bacterial and fungal species when compared with the other metal nanoparticles. Many researchers and scientist have proven the efficacy of silver nanoparticles against different species of viruses [33]. In this review we discuss the antiviral property of silver nanoparticles against different viral entities. The antiviral effect of Silver nanoparticles against different species of virus is summarized in Table 01.

a) **SARS-CoV-2:** It is a member of Coronaviridae family and genus Beta corona virus which affected the humankind globally [34]. Due to its rapid mutation in a short period of time, this is very difficult to develop an effective vaccine or therapy to control the spread of virus and limit the death count [11,35]. It was basically discovered in the month of December 2019, in Wuhan city of Hubei province of China causing pandemic worldwide. Millions of people got infected by SARS-CoV-2 with a ~32-kb genome comprised of (+) single strand RNA. Corona virus enters in to the body through the epithelial cells of human trachea which contains carbohydrate with α-2,6 bond where it linked to epithelial cells contains sialic acids on the surface and bind to galactose α-2,6. Recent studied revealed that the various sizes and concentrations of silver nano particles are capable to inhibit SARS-CoV-2 [36]. The silver nono particles size ranges up to 10 nm with concentration between 1-10 PPM are effective for inhibition of extracellular SARS-CoV-2 with cytotoxic effect at the concentration above 20 PPM. Another study showed that the silver nano particles also effective against MERS-CoV with 48.3 % viral suppression[5,37].

b) **Influenza A:** Influenza-A virus is categorised into hemagglutinin (HA) and neuaminidase (NA) which further classified in to 18 HA and 11NA subtypes. There is possibility of several combination of HA and NA proteins [5,38]. The birds are infected by subtype H7N2 of Influenza A virus. Influenza virus infection in human is accompanied by mild fever, headache, fatigue, chills, non-productive cough, stuffy or runny nose, sore throat, muscular pain and body ache [39,40]. It has been proven by HA inhibition tests & embryonated inoculation assays that silver nanoparticles prevents HA of chickens red blood cells infected with subtype H7N2 of Influenza A virus [12,41]. With the help of cytometry and TEM characterization technique it has been clarified that silver nanoparticles reduces the virus induced apoptosis of Madin-Darby canine kidney cells. In such experiments the silver nano particles were used up to the size ranges between 5 to 20 nm with an average 10 nm diameter [42]. The study found that the silver nano particles without coated may destroy the glycoproteins of viral membrane which is the key substance uses by virus to infect the host cells [13,43].

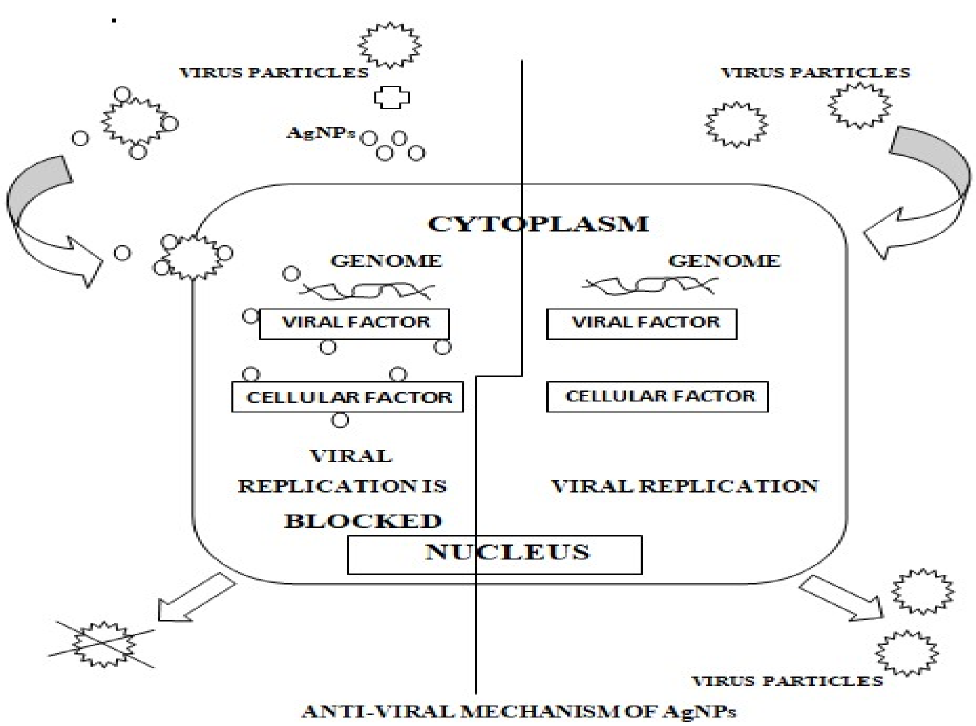

Fig.02 Anti-viral mechanism of Silver nanoparticles

c) **Respiratory Syntical Virus (RSV):** RSV is a member of family Paramyxoviridae and genus Orthoneumovirus which target lower respiratory passage for infection and also the major cause of bronchitis and pneumonia among neonates and infants. The researchers are trying to develop several effective remedies against RSV and may be available in commercial market very soon [2,44]. Few researchers focus on silver nano particles and revealed after successful experiments that RSV infection can prevent up to 44% by PVP coated silver nanoparticles. During the experimental study it was that the small size ranges between 4-8 nm and PVP coated silver nano particles allowed binding to the G protein of RSV virus compared with to the BSA and RF conjugated nono particles (3-38 nm), this capability of binding was considerable for viral inhibition [45,46]. The studies showed about the cytotoxicity of silver nano particles had less than 20 % up to the concentration of 100 PPM [5,47].

Table 01 List of Virus and their characters included in Anti-viral study of Silver nanoparticles

Sr. No.	Virus	Family	Genetic Material	Capsid / Coat	Genome Size	Diameter of Viron
1	SARS-CoV-2	Coronaviridae	ssRNA	Coiled Helix/Enveloped	~32-kb genome	50–200 nm/Positive-sense
2	Influenza A	Orthomyxoviridae	ssRNA	Helical Complex/Enveloped	~7.12–18.73 kb	10–15 nm/Negative-sense
3	Respiratory Syntical Virus (RSV)	Paramyxoviridae	ssRNA	Helical/Enveloped	~15.2 kb	100–1000 nm/Negative-sense
4	Hepatitis B Virus (HBV)	Hepadnaviridae	dsDNA-RT	Icosahedral/Enveloped	~3.2 kb	22–4 nm
5	Herpes Simplex Virus (HSV)	Herpesviridae	dsDNA	Icosahedral/Enveloped	~152 kb	155 to 240 nm
6	Adenovirus	Adenoviridae	dsDNA	Icosahedral/Non-Enveloped	~30–40 kb	~70 to 100 nm
7	Human Immunodeficiency Virus-1 (HIV-1)	Retroviridae	ssRNA	Conical/Enveloped	~775 kb	~100 nm
8	Zika Virus (ZIKV)	Flaviviridae	ssRNA	Spherical/Enveloped	~10 kb	50 nm/Positive-sense
9	Chikunguniya Virus	Togaviridae	ssRNA	Icosahedral/Enveloped	~11.8 kb	~11.8 kb
10	White Spot Syndrome Virus (WSSV)	Nimaviridae	dsDNA	dsDNA	~300 kb	70–167 nm
11	Poliomyelitis Poliovirus	Picornaviridae	ssRNA	Icosahedra/Naked	~7.5 kb	~7.5 kb

d) **Hepatitis B Virus (HBV):** HBV belongs to the family Hepadnaviridae and genus orthohepadnavirus which is a double stranded DNA virus infect to the lever cells causes chronic or acute Hepatitis B disease [48]. The WHO claimed that the millions of people died annually due to HBV infections including hepato-cellular carcinoma and liver cirrhosis. Silver nanoparticles of size ranges between 10-50 nm in HEPES buffer from AgNO3 attached to HepAD38 cell line to produce HBV pgRNA, as confirmed by TEM, which is responsible for successful inhibition of HBV genome replication [5,49].

e) **Herpes Simplex Virus (HSV):** HSV type 1 infects people worldwide of any age group which is considered a very common agent responsible for viral infection. HSV type 1 is also causes asymptomatic severe encephalitis and for orolabial ulcers. Millions of population between age of 0-50 years infected in western pacific region, Southeast Asia, Africa, America, and Europe were estimated to have HSV type 1 infection. HSV type 1 has a 152 – kb double stranded DNA genome encapsulated within an icosahedral capsid with a lipid bilayer envelop [50]. HSV type 1 interaction with host cells is due to heparin sulphate moieties on the surface of cells and the glycoproteins on the HSV-1 envelop. Silver nanoparticles enveloped with mercaptoethane sulfonate mimic the heparin sulphate and finally prevent the interaction between HSV type 1 and host cells [10,51].

f) **Adenovirus:** These are non-enveloped, double stranded DNA viruses causes infection and resulting GIT disease, ocular disease, respiratory disorders and may ne endemic for infants [52]. Throughout the year adenovirus causes infections, and the available drugs against adenovirus are limited therefore it is a market requirement to develop few more advance modern drugs. In-vitro results have shown the antiviral activity of silver nanoparticles against adenovirus type-3 [14,52].

g) **Human Immunodeficiency Virus-1 (HIV-1)** which is transmitted through malpractice of medical procedures and unsafe sexual activity. Worldwide sexually transmitted infections are considered major health issues [53]. HIV-1 can be transmitted from one to another through the infected mother to child, infected blood, and semen, rectal and vaginal fluids. HIV-1 causes acquired immune deficiency syndrome (AIDS). After treatment, human body can not eliminate HIV completely which harm to T cell or CD4 cells responsible for human immune system [54]. Silver nanoparticles also having antiviral activity against HIV-1 and widely used to make coating on polyurethane condoms. Silver nanoparticles coated with poly N-vinyl-2-pyrrolidone (PVP) attached to the gp120 receptors of HIV-1 envelop. Silver nanoparticles compete with virus attach to a disulfide bond in the CD4 binding domain of gp120 [55,56]. The inhibitory activity of silver nanoparticles against gp120 –CD4 cells is confirmed by ELISA, which proves the antiviral property of silver nanoparticles in cells infected by HIV-1 [14,56].

h) **Zika Virus (ZIKV):** ZIKV belongs to the family Flaviviridae and genus Flavivirus. Zika virus is an enveloped, spherical in shape, single stranded RNA virus with positive – sense consist of 10kb of genetic material which is surrounded by capsid proteins [57,58]. Zika virus is spread by Aedes mosquitoes active in day time so it is very crucial to prevent mosquito-borne disease outbreaks [59]. Few insecticides like pyrethroids and organophosphates are being utilized to control the growth of mosquitoes but these synthetic chemicals have resulted in slew of human health and environment concern [60]. The use of silver nanoparticles for the mosquito control can play a vital and environment friendly role at low cost. At very lower concentration silver nanoparticles demonstrated effective pupicidal and larvicidal toxicity against Aedes mosquitoes [3,61].

i) **Chikunguniya Virus:** It is a member of Togaviridiae family and genus Alphavirus with ~11.8-kb genomic material. Chikunguniya virus is an enveloped single strand RNA virus which is a transmitted through the mosquitoes and infects human population worldwide [62]. The research showed that the billion of people worldwide were affected annually and causes death. The disease has larger impact and the scientist suggested monoclonal antibodies to control infection but still there is no specific cure for chikunguniya [63]. However the studies revealed that the biologically synthesized silver nanoparticles from tinospora cordifolia, Andrographis paniculata and Phyllanthus niruri have antiviral effect against Chikunguniya virus. The experimental studies claimed that the green synthesized silver nanoparticles as an anti viral drug is viable and may prove an alternative option to fight against chikunguniya virus [15,64].

j) **White Spot Syndrome Virus (WSSV):** WSSV is a member of family Nimaviridae and genus Whispovirus are enveloped, pleomorphic, negative sense single strand RNA virus consist of approximate 300 kb of genetic material surrounded by capsid proteins [65]. The studies revealed that the single treatment with a small amount of silver nanoparticles were capable to enhance the response of the shrimp immune system without causing harmful effects in health shrimp [7,66].

k) **Poliomyelitis Poliovirus:** Poliovirus is a member of Picornaviridae family and Enterovirus genus are single strand RNA virus with ~7500 nucleotides in size and consist of capsid proteins (VP1, VP1 and VP3). It infect to the nervous system resulted paralysis and transmitted through fecaloral route [67]. The study showed that silver nanoparticles had activity against poliovirus infected human rhabdomyosarcoma (RD) cells and without cytopathic effect on RD cells up to 100 PPM. Silver nanoparticles at concentration 3.13 PPM after 30 min. revealed as antiviral at the viral concentration of 1 tissue culture infectious dose 50 [16,68].

Safety and Toxicity majors of Silver nanoparticles: Silver nanoparticles interacts with biomolecules and produces reactive oxygen causes harm to DNA, lipids and proteins by oxidation therefore considered cytotoxic to mammalian cells [68]. The cytotoxic effects of silver nanoparticles basically characterised as per their route of administration, level of concentration, duration of exposure, inherent toxicity with silver molecules, accumulation in the body and the bioavailability [17,69]. The major choice of silver nanoparticles administration is oral route, cutaneous and inhalation. Silver nanoparticles larger in size eliminated from the body but smaller particles deposited in the lungs and reaches to the other organs through the blood stream [70]. The research observations claimed that the concentration of Silver nanoparticles at the concentration 0.5-381 g/m3 of size 15-30 nm shows no significant histopathological effect when applied in liver, lungs and nasal cavity [70,71]. However Silver nanoparticles at very high concentration above 2.9 mg/m3 cause brain damage. Silver nanoparticles at the size range 20-100 nm and 0.1-1000 mg/kg through parentral route gives cytotoxic effect on brain, liver, kidneys and lungs [14,72].

Future Prospects and Conclusions: The researchers have been investigated the physical, chemical, electrical and optical properties of silver nanoparticles particularly related to their shape and size. It was concluded through the various scientific studies that the size of silver nanoparticles less than 20 nm is important for better effective results. The recent studies suggest that silver nanoparticles are most capable to inhibit Influenza virus. On the basis of recent studies, silver nanoparticles can be regarded as a viable option in the development of antiviral drugs. Their effectiveness as antiviral agent is impressive but still there is also need to further researches about the mechanism of action and the pharmacological studies. Nano treatment of broad spectrum viral infection has been studied widely and proven successful enough. The viral diseases are also been examined intensively including the life cycle, replication, complexities in different organs or cellular / sub-cellular levels, evolution of drug resistance, latent infection potentiality, kinetics and dynamics. The advancement in Nanomedicine, silver nanoparticles have considered as an effective therapeutic agent against broad spectrum viral infections. Several issues related to toxicity, adverse effect, biocompatibility, allergic reactions, potential side effects etc. need to overcome before the application of silver nanoparticles as therapeutic agents in human beings. More scientific research are required for the development of an effective broad-spectrum antiviral drug containing silver nanoparticles as a major active constituent.

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