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Review

New Insights for Exploring the Risks of Bioaccumulation, Molecular Mechanisms, and Cellular Toxicities of AgNPs in Aquatic Ecosystem

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Abstract: Silver nanoparticles (AgNPs) are commonly used in numerous consumer products, including textiles, cosmetics, and health care items. The widespread usage of AgNPs results in their unavoidable discharge into the ecosystem, which pollutes the aquatic, groundwater, sediments, and marine environments. These nanoparticles (NPs) activate the production of free radicals reactive species in aquatic organisms that interrupt the functions of DNA, cause mitochondrial dysfunction, and increase lipid peroxidation, which terminates the development and reproduction both in vivo and in vitro. The life present in the aquatic ecosystem is becoming threatened due to the release and exploitation of AgNPs. Managing the aquatic ecosystem from the AgNP effects in the near future is highly recommended. In this review, we discussed the background of AgNPs, their discharge, and uptake by aquatic organisms, the mechanism of toxicity, different pathways of cytotoxicity, and bioaccumulation, particularly in aquatic organisms. We have also discussed the antimicrobial activities of AgNPs along with acute and chronic toxicity in aquatic groups of organisms.

Keywords: AgNPs; marine ecosystem; toxicity; bioaccumulation; pollutants; molecular mechanisms

1. Introduction

Water is the most important natural resource on the planet, and its existence in its purest form is essential for all living organisms since life would be unimaginable without water [1]. Physical, chemical, and biological factors and their interactions significantly impact water quality [2]. According to recently released United Nations (UN) statistics, about 60% of the world's population may be living in water-stressed areas by 2025 [3]. It may severely impact many areas of contemporary life, including food and energy shortages, which could lead to increased disease rates. As the world's population and activities grow, so does wastewater production. Excessive discharge of toxic pollutants into water bodies has adverse effects on human health, aquatic organisms, and ecosystems because they change the physical and chemical characteristics of the water, rendering it unfit for use by people, animals, and plants [3].

Nanotechnology has become a significant scientific and economic development in water conservation. However, the widespread use of nanomaterials, toxic compounds, and effluents released from industrial processes has ultimately negatively affected the different modes of life [4]. Nanomaterials are synthesized in various forms, sizes, shapes, and functionalities with their extensive applications. Nano-sized products have been established in drug delivery, tissue engineering, diagnostics, energy, environmental remediation, chemical sensors, and agricultural sciences [5]. They have exceptional physicochemical properties in comparison to the bulk metals from which they are extracted and have made numerous advances in various fields [6,7]. The most micro-genic approach to AgNP synthesis gained attention because of its wide biocompatibility and good stability [8].

AgNPs' broad-spectrum antibacterial activity has been exploited in several marketable products such as textiles, household appliances, food packaging, shampoos, toothpaste, water filters, and medical devices; all of these contribute to the excessive discharge of AgNPs into the aquatic ecosystem through use and manufacturing [9,10]. This substantial rise in the number of products available in the market, including AgNPs, raises the risk of their release and aggregation in the environment and triggers harmful effects on the organisms continuously exposed to these materials [11]. Recent advances in designing novel engineered nanomaterials have expanded social and environmental awareness, making it much more essential to consider the future consequences of synthesis and the use of AgNPs [12].

In daily life, nanomaterials are widely used and readily discharged into the aquatic ecosystem, a significant source of water pollution [13]. About 2500 metric tonnes of silver are discharged into the environment each year as a result of industrial waste and emissions, with an additional 150 metric tonnes ending up in sewage sludge and 80 metric tonnes going into surface waterways [14]. They can cause environmental pollution with different particle morphology and composition of an element, intentionally or unintentionally.

In terms of heavy metal toxicity, silver ion is second only to mercury and is thus classified in the highest toxicity class along with cadmium, chromium (VI), copper, and mercury [15]. For all the metals, the interaction of adjacent locations influences the connection of silver ions through different ligands, and these impacts persuade the toxicity and bioavailability [16–18]. AgNPs cause multiple toxic effects on aquatic groups of organisms because of their exposure conditions (e.g., pH, conductivity, media composition, and temperature) and physicochemical properties, i.e., size and surface coating [19–21]. For example, sulfide and organic matter have strong silver sensitivity in freshwater environments, and possibly control of silver ions speciation decreases silver bioavailability. Along with all the discussion of AgNPs and their toxicity processes, we have noticed that no work has been done to identify the agent that detoxifies the nanoparticles (NPs) [22]. So, there is also a need for urgent attention to establishing the biological control and bioremediation of AgNPs to reduce silver toxicity through microorganisms such as bacteria, fungi, protozoa, or algae to save the ecosystem and the lives of aquatic organisms.

This review discussed the background of AgNPs, their discharge and uptake by aquatic organisms, the mechanism of toxicity of AgNPs, and bioaccumulation in the aquatic ecosystem and its life. The present study discussed the antimicrobial activity of AgNPs, along with acute and chronic toxicity. The present study also highlighted the toxic effects of AgNPs on aquatic groups of organisms.

2. Discharge of AgNPs into the Aquatic Environment

Global production of AgNPs currently ranges between 420 and 500 tonnes per year [22,23]. Silver nanoparticles can be released directly and indirectly into the environment throughout their life cycle (manufacture, transport, use, and disposal). An example of direct release could be discharged from transport accidents and all types of spills. The indirect release could be due to discharge from wastewater treatment plants which receive discarded nanoparticles at the end of their life cycle [20]. The surface water compartment (rivers, seas) receives the discharge of AgNPs either directly effluents from wastewater treatment plants or from other environmental compartments. Several ways, like residual industrial material, chemical spills, runoff, or washing machines, increase the discharge of AgNPs into the aquatic ecosystem, including synthesis, the integrating of NPs inside the products, using different things containing NPs, and recycling/disposing of things [21]. Silver nanoparticles can be highly toxic to aquatic organisms due to the same mechanisms of toxicity for terrestrial species. Marine invertebrates and small fish make good indicators of aquatic toxicity due to their small size and high degree of susceptibility to environmental pollutants. Zebrafish (*Danio rerio*) are a model organism for aquatic studies since the number of available materials and data on these fish make them efficient for streamlining ecotoxicological testing. Hence, aquatic ecosystems receive an important amount of the released AgNPs [22]. In that case, the possibility of silver ion concentration in the natural environment may rise locally to a level of mass that may typically match or surpass the peak rates of dissolved silver ions found in the polluted waters [24], which would intensify apprehensions around environmental hazards [25].

In the aquatic environment, the fate of AgNPs is determined by their capping agents [26]. Polyvinylpyrrolidone (PVP) and polymer-based citrate are the most commonly used capping agents that increase the risk of heavy metal toxicity in aquatic organisms. PVP and citrate-based AgNPs induced metal toxicity in the gut epithelial tissues of *Mytilus galloprovincialis* [27]. It is demonstrated that the accumulation of PVP and citrate in coelomocytes of *Nereis diversicolor* increased DNA damage and lysosomal membrane permeability. Environmental exposure to PVP and citrate also damages the pancreatic tissues in *Litopenaeus vannamei* [28]. Another study investigated that exposure of 200 μg/L PVP-AgNPs to *Cyprinus carpio* increased the damage to the brain and gills [29]. Uptake of PVP and citrate-based AgNPs by *Ampelisca abdita* and *Americamysis bahia* also damages their skin epithelial tissues [4]. PVP and citrate-based AgNPs also aggregate with the microalgae, *Raphidocelis subcapitata,* causing faster segmentation of filaments [30]. The antioxidant defense system arises from glutathione peroxidase and catalase in aquatic organisms that lower the toxic effects of PVP and citrate AgNPs [31].

Dissolution and Toxicity in Fresh and Marine Water

A recent study reported the toxicity of silver ions and Ag-NPPVP for *Ceramium tenuicorne* and *Tisbe battagliai*. It was found that *Ceramium tenuicorne* exhibited EC_{50} values of 2312.2 and 26.6 mg/L against silver ions and Ag-NPPVP, while *Tisbe battagliai* showed only EC_{50} values of 90.9 and 7.9 mg/L, respectively 27. The EC_{50} values for *Scenedesmus* sp. and *Thalassiosira* sp. were 89.92 ± 9.68 and 107.21 ± 7.43 μg/L, respectively [20,32]. A low EC_{50} value (0.055 mg/L) for *A. salina* was also determined with AgNPs (2–18 nm) at concentrations between 0 and 1.5 mg/L [33]. The toxicity of PVP-coated AgNPs in *Daphnia* sp. from different boreal lakes was evaluated and found to have an LC_{50} ranging from 34 to 292 μg/L [34]. In contrast to silver ion, the toxicity of Ag-NPPVP enhanced substantially

with increasing salinity. However, despite extensive characterization, it was not feasible to link particle behaviour with an increase in toxicity and salinity. The findings indicate that the observed toxicity is caused by free ionic silver complexing in solution and an unknown possible particle-related impact [35]. Pham [36] estimated the effect of AgNPs on the algal species in marine (*Thalassiosira* sp.) and freshwater (*Scenedesmus* sp.) environments, and his findings described that AgNPs are more hazardous in freshwater than in marine environments. At a specific concentration, AgNPs caused a change in cell width, a decrease in chlorophyll-a content, and an increase in total lipid synthesis in the studied microalgae. The morphological properties of microalgae may be utilized as an efficient method for monitoring NPs in water. Table 1 shows the Percentage of dissolved silver ions in different aquatic ecosystems (freshwater and marine water). It has been demonstrated that one of the main mechanisms of toxicity of AgNPs is related to Ag dissolved from AgNPs, which in both media has a relationship with the size and exposed surface of the AgNPs [24,37]. The dissolution of silver ions from AgNPs and their ionic membrane potential are discussed in Table 1. The dissolution of silver ions from AgNPs in freshwater is 1.8–4% ppb (20 nm), 24.5(40 nm), 75(30 nm), 27(42 nm), and <0.1% (100 nm), and in fresh marine water 35–95% ppb (20 nm) and 0.38–1.25% ppb (100 nm).

Table 1. Percentage of dissolved silver ions in different aquatic ecosystems (freshwater and marine water).

Nanoparticles	Size (nm)	Dissolution of Silver Ions from AgNPs over Time (ppb)			Ionic Membrane Potential (mV)		
Type of Nanoparticles	Size of Nanoparticles	Time (h)	Freshwater (%)	Marine Water (%)	Freshwater	Marine Water	References
AgNPs	40	0–24	24.5	30–38	−25.3	16.5 ± 2	[27]
AgNPs	20	0–48	1.8–4	35–95	−17.5	−6.5 ± 1	[37]
AgNPs	30	0–48	118	15–30	−19.6	−15.8 ± 2	[30]
AgNPs	50	0–48	0.3–1.4	14–23	−16.2	−5.6 ± 2	[37]
AgNPs	30	0–48	75	32.38	−32.5	−11.7 ± 1	[24]
AgNPs	42	0–72	45	20–38	−17.8	−15.8 ± 1	[29]
AgNPs	100	0–48	<0.1	0.38–1.25	−21.7	−12.6 ± 2	[37]
AgNPs	20	0–96	200	35–45	−23.4	−19.4 ± 1	[35]
AgNPs	42	0–48	27	40–55	−16.5	−2.5 ± 2	[6]

3. Uptake and Bioaccumulation of AgNPs

3.1. Bioaccumulation of AgNPs in Aquatic Organis

Bioaccumulation is a primary method for determining the risks and hazards of AgNPs. Hazard evaluation needs analysis of all consequences and exposure. The xenobiotic consequences of bioaccumulation and exposure are frequently a condition for toxicity because the organism must preserve the chemical until it can show toxic behavior. Bioaccumulation is the simple method of evaluating the developments that affect bioavailability, the concentration of pollutants an organism absorbs from the ecological medium [38].

The structural and physicochemical features of AgNPs reflect the particles' ability to remain suspended in a solution that is isolated from the dissolved organic matter and microbes due to their interaction with aquatic biota [33,34]. The literature review we observed about the uptake and bioaccumulation of AgNPs in living organisms is provided in Table 2. Algal cells can accumulate NPs due to the permeability of NPs to the outer cell wall. Adsorption (or connection) of AgNPs to zooplankton is believed to include respiratory epithelium, appendages, digestive tract epithelium, and exoskeleton, and these NPs usually bioaccumulate in the consumers of zooplankton. Isolated hepatopancreatic digestive cells from mussels were seen to endocytose NPs, while invaginated cell membrane particles were produced in the lysosomal degradative compartment of cells [39]. Almost 70% of the AgNPs contained in Daphnia are obtained through food consumption. Silver ion makes zooplankton sick when they eat algae that have been exposed to AgNP [40].

About 63 tons of nano-silver are annually projected to flow into stream water bodies throughout the globe, with concentrations in aquatic environments predicted to range from 0.03 to 0.32 micrograms per liter [41]. Although the extra consumption of AgNPs released into the aquatic environment will rise in the coming years. It is estimated that the predicted environmental concentrations (PECs) for AgNPs in surface water ranged from 0.088 to 10,000 ng/L[42]. AgNPs provide an excessive amount of attention in the aquatic ecosystem because ionic silver is considered to be one of the most harmful metals for aquatic life (prokaryotes, small fishes, marine and freshwater invertebrates), where the range of lethal concentration is low, like 1.25–10 μg/L (see Table 2) [43,44].

Table 2. Uptake concentration of AgNPs by aquatic organisms.

Aquatic Organisms Isolated Strains		NP Size (nm)	Concentration Range	Duration	Uptake Endpoints	Reference
Diatom	*Thalassiosira weissflogii*	10	10 mg/L	48 h	Cellular distribution	[45]
Aquatic bacterium	*Pseudomonas fluorescens*	30–50	0.002–2 mg/L	24 h	Aggregation by nanoscale film formation	[9]
Eastern mud snails, Juvenile hard clams, Grass shrimp, Cordgrass, Biofilms	*Vibrio harveyi*	20–80	1.62 mg/L	60 d	Bioaccumulation and trophic transfer	[34]
Nematode	*Caenorhabditis elegans*	<100	up to 0.5 mg/L	24 h	Uptake/adsorption to body	[46]
		7–25	5–50 mg/L	24 h	Uptake/transgenerational transfer to body	[47]
Earthworm	*Eisenia fetida*	30–50	10–20 mg/L	28 d	Bioaccumulation in a concentration-dependent manner	[48]
		10–50	<0.1 mg/L	48 h	Unpredictable	[48]
		29–39	1 mg/L	28 d	Possible body distribution	[49]
Water flea	*Daphnia magna*	40–50	up to 5 mg/L	8 h	Uptake and bioaccumulation	[40]
Zebrafish embryos	*Danio rerio*	5–15	1.62 mg/L	120 h	Uptake in embryos through chorion pore canals	[50]
		11.3	0.48 mg/L	21 h	Adsorption to embryos	[51]
		20–30	1×10^{-8}-2×10^{-8} mg/L	24 h	Penetrated skin and blood tube as aggregated particles	[52]
		20–30	0–4 mg/L	10 d	Bioaccumulation in muscle and intestine	[53]
		20–30	10 mg/L	48 h	Possible body uptake	[54]
Eurasian perch	*Perca fluviatilis*	30–40	0.000063–0.0003 mg/L	25 h	Possible to adsorb into gill	[55]
Rainbow trout	*Oncorhynchus mykiss*	5–15	10–20 mg/L	48 h	Cellular compartmentalization, transport over epithelial layers	[56]
Japanese medaka	*Oryzias Latipes*	30–50	20 mg/L	7 d	Bioaccumulation in liver and gill	[57]
Zucchini	*Cucurbita pepo*	100	1000 mg/L	12 d	Translocation through shoots	[58]
Thale cress	*Arabidopsis thaliana*	20–80	10–20 mg/L		Uptake and accumulation of roots	[59]
Common grass	*Lolium multiflorum*	6–25	0–40 mg/L	24 h	Uptake into roots and shoots	[60]

Mechanisms of Bioaccumulation

In aquatic organisms such as fishes, the NPs enter across gills or external surface epithelia [61]. The NPs enter the cell through the cell membrane at the cellular level. The plasma membrane has a complex system that allows selective substances into the cells; the translocation of substances inside the cell membrane occurs through pores and protein carriers. NPs are transported inside the plasma membrane through the invagination and vesicle formation that enclose material and transport these vesicles inside the membrane, whereas other translocating NPs enter via endocytosis [62]. If the uptake of AgNPs is prevailed by endocytosis, producing a nano environment of silver ions concentration becomes favorable for fast ion absorption [63]. These NPs can generate reactive oxygen species (ROS) that cause damage to cells by attacking membrane, protein, and DNA [64].

3.2. Ecological and Biological Toxic Effects of AgNPs

The toxicity of AgNPs directly correlates with their alteration within ecological and biological media and the release of silver ions with surface oxidation [65,66]. Silver ions are highly susceptible to bioconcentration in organisms as they are consistent with chemical reactions through cell membrane transporters of ions [67]. In aquatic invertebrates, some evidence suggests that silver ions increase toxicity if it is present in NPs due to subsequent release as ionic silver ions from NPs [68]. Studies demonstrated that AgNPs are less harmful than silver ions, remaining in the ionic form [69,70].

Various studies reported that AgNPs conjugated with the protein of the membrane and trigger signaling pathways, which leads to inhibition and proliferation of cells [71,72]. AgNPs often reach inside the cell through endocytosis or diffusion to induce mitochondrial disruption, producing ROS that damage proteins and inhibit cell proliferation [73,74]. Oxidative stress as ROS production reaches the capacities of antioxidant cellular defense mechanisms [75]. Oxidative disruption is always concerned with the degradation of glutathione, sulfhydryl group-containing protein, and improvements in the functioning of multiple antioxidant enzymes [76]. The toxicity significance for AgNPs is the association of nano and ionic silver with sulphur comprising macromolecules like proteins [77,78].

Algae play a vital role in all aquatic ecosystems and produce oxygen in aquatic habitats; thus, AgNPs pollution may severely impact algae functions [79]. NPs often cause harm to multicellular organisms via their respiratory system or skin, while unicellular organisms such as microalgae may be harmed generally by NPs [80]. AgNP toxicity, includes the collapse of proton pumps, membrane adhesion, increased cell porosity, DNA damage, inactivation of proteins and enzymes, destruction of lipopolysaccharide molecules, ribosome denaturation, production of ROS, and suppression of DNA synthesis [81,82].

Daphnia magna died after exposure to AR-AgNPs and silver ions, and the higher the concentration, the higher the death rate. The 48-h LC_{50} of AR-AgNPs and silver ions to daphnids was 1.86 ± 0.12 and 1.30 ± 0.07 mg/L, respectively, suggesting silver ions' higher toxicity in Daphnia, leading to mortality than AR-AgNPs. After 24 h of acute toxicity testing and removing dead zebrafish from a medium containing AR-AgNPs, two distinct abnormalities in the deceased zebrafish were identified. Ascites (fluid build-up in the belly) and colour alteration (fading colour) were among the abnormalities seen in fish exposed to 25 mg/L of AR-AgNPs [83]. This added to the evidence that AR-AgNPs had a negative impact on zebrafish development. The toxicity of AgNPs to aquatic species is typically caused by the release of free Ag ions [84]. The toxicity of silver ions to organisms may be attributed to ion regulatory disruption and competitive suppression of potassium or sodium ion-dependent adenosine triphosphate (Na+, K+-ATPase), which hindered absorption of Na+ by Daphnia. When AgNPs get into living cells, they may cause ROS and oxidative stress, which can lead to detrimental consequences such as membrane lipid peroxidation, mitochondrial damage, DNA damage, and cell death [85].

3.3. Toxicity of AgNPs on Algal Cells

The cytotoxic effects of AgNPs are based on their size, environmental influences, concentration, exposure time, and other cell properties. The cell wall in algae is a binding site for any reciprocal action with AgNPs since it serves as a barrier to the entry of the AgNPs from the surroundings. The majority of the algal cell wall is composed of proteins, carbohydrates, and cellulose (polysaccharides and glycoproteins) [86]. The algal cell wall acts as a semi-permeable sieve and also filters the large NPs via a smaller particle transition. The smaller size and broader surface area of the AgNPs make it possible to pass through the cell wall pores to the plasma membrane [78]. Cell reproduction may affect the permeability of cell walls, and newly manufactured holes may become more permeable to AgNPs. It was observed that newly formed holes are more prominent than previous ones

owing to the effect of AgNPs on algal cells that may lead to an increase in nano-silver absorption in algal cells [87].

Some recent studies have shown the toxicity concerns of AgNPs. AgNPs are incredibly toxic in in-vitro studies at concentrations of 5–10 µg/L and particle sizes of 10–100 nm [88,89]. The surface coating agents of AgNPs like amino acids, sodium dodecyl sulfate, citric acid, and acetyl trimethyl ammonium bromide are non-covalently bound to AgNPs and discharged into the biological and environmental medium [90,91]. The formation of silver oxide through surface oxidation of AgNPs and silver oxide discharge into silver ions occurs in various biological and ecological media [92]. Due to this property, these particles enter the cell via passive and active transport and get assembled into silver oxide, causing mitochondrial dysfunction [93].

From previous studies, it can be inferred that AgNPs can enter the cell membrane, particularly inside the mitochondria. However, it is unclear whether nanomaterials can cause damage to the mitochondria across the cell or invade secondary organelles for oxidative impairment [94]. AgNPs can contact the cell membrane protein, triggering the cell signalling pathways to produce ROS, leading to protein and nucleic acid damage. The initiation of the strong attraction of Ag for sulfur of protein eventually causes apoptosis and inhibits cell proliferation [95]. The anti-proliferative action of AgNPs and the toxicity mechanism of AgNPs are shown in Figure 1. Wu and Zhou determined the toxicity of AgNPs to freshwater fish cell lines and their embryos [96]. This example is based on research work that used sub-chronic toxicity procedures to assess AgNPs bioaccumulation and its impact on adult medaka's histology and antioxidant protection mechanisms. Purified AgNPs were well dissolved in water, and after 14 days of exposure to the fish, a significant accumulation of Ag in the gills, liver, and intestinal tissues was observed. The functions of lactate dehydrogenase and antioxidant enzymes in the liver were dose-dependent. Reduction in glutathione and lipid peroxidation was dose-dependent both in the liver and gills. Exposure to AgNPs also caused histological lesions in fish tissues. Toxicological endpoints and metal transport analysis showed that AgNPs caused tissue-specific toxicity, especially in the liver.

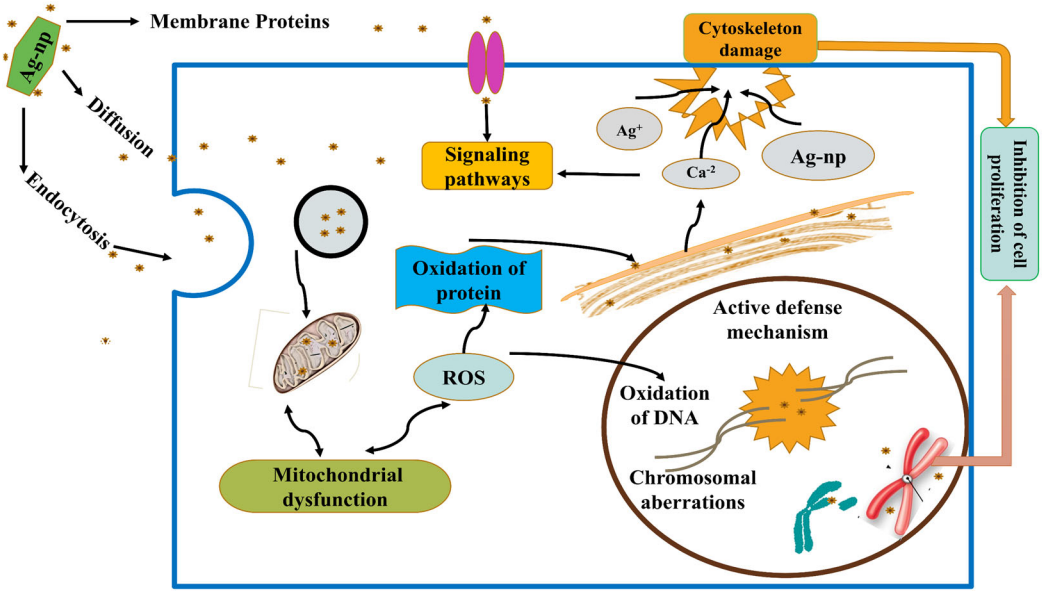

Figure 1. Proposed mechanism of AgNPs toxicity. This figure is reproduced from Asharani et al. [97].

3.4. Different Toxicological Pathways of AgNPs

Cell death mechanisms are broadly classified into necrosis and apoptosis. Apoptosis is an uncontrolled cellular explosion that is dependent on the enzyme caspases, whereas

necroptosis and autophagy are caspase-independent. Programmed cell death is a natural process in which cells commit suicide in respond to precise signals, including exogenous cell-damaging (infectious or physical) and endogenous tissue-specific mediators depending upon the critical physiological situation. The apoptosis mechanism consists of three pathways: intrinsic or mitochondrial-mediated, extrinsic or DR-mediated, and execution [98]. Mitochondrial-mediated apoptotic or intrinsic pathways elicited by intracellular and extracellular stress release cytochrome c from the inter-membrane space of mitochondria into the cytosol [99]. The extrinsic pathway is activated through apoptotic signals when extracellular ligands, including (TNF-related apoptosis ligand; TRAIL), (Fas ligand; Fas-L), (tumour necrosis factor ligand; TNF) are bonded to the extracellular domain of transmembrane death receptors; DRs such as TRAIL, CD95/Apo-1/Fas, type 1 TNF/TNFR1 receptors [100]. The extrinsic apoptosis phase is well defined by ligands and receptor association models (TNF-α; TNFR) and (FasL; FasR). Death-inducing signalling complex, DISC is expressed when specific death-ligand is triggered [98]. In the execution pathway, the intrinsic and extrinsic pathways are converged at the same point of the execution phase, the final approach of apoptosis [99].

3.4.1. AgNPs Regulate Apoptotic Pathways

The AgNPs cause cytotoxicity in various routes by inducing apoptosis and cell death [101]. In-vitro induction of AgNPs increases reactive oxygen free radicals inside the cell, which initiates apoptotic signalling through PKB (Protein Kinase B), TP53 (Tumor Protein 53) [102]. Overproduction of ROS causes PKB down-regulation and enhances p38 mitogen-activated protein kinase (p38 MAPK. Meanwhile, poly ADP ribose polymerase (PARP) declines in response to significant changes in caspase-3 and P53 proteins [103]. Thus, AgNPs can persuade apoptosis via subsequent TP53 signalling pathways (Figure 2).

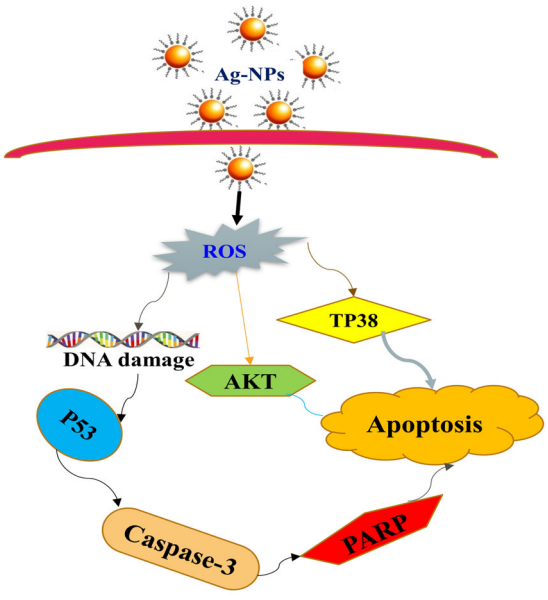

Figure 2. Apoptosis induced by tumor protein 53 (TP53) mediated signalling pathway, protein kinase B (PKB), p38 mitogen-activated protein kinase (p38 MAPK) activation suppresses the ROS produced by AgNPs. This figure is reproduced/modified from Li et al.; Akter et al. [103,104].

3.4.2. Mechanism of Apoptosis by AgNPs

The mitochondria are an important center of the apoptosis signal. AgNPs use mitochondria for signalling apoptosis. AgNPs affect the mitochondrial membrane's permeability, which damages the mitochondria's integrity, thus initiating apoptosis based on Jun amino-terminal kinases (JNK) facilitating cysteine-dependent aspartate specific-protease

[105,106]. Loss of mitochondrial membrane potential causes B cell lymphoma-2 (BCL-2) down-regulation, pro-apoptotic Bax protein (BAX) upregulation, and discharge of cytochrome C inside the cytosol. JNK may affect the downregulation of Bcl-2 by phosphorylation. The cascade caused by cytochrome C is released inside the cytosol, leading to cysteine-dependent aspartate specific-protease (caspase 3) initiated via apoptotic protease activating factor-1 (APAF-1) and cysteine-dependent aspartate specific-protease (caspase 9) [107]. Thus, AgNPs can persuade apoptosis through the JNK-mediated mitochondrial and caspase-dependent pathways (Figure 3).

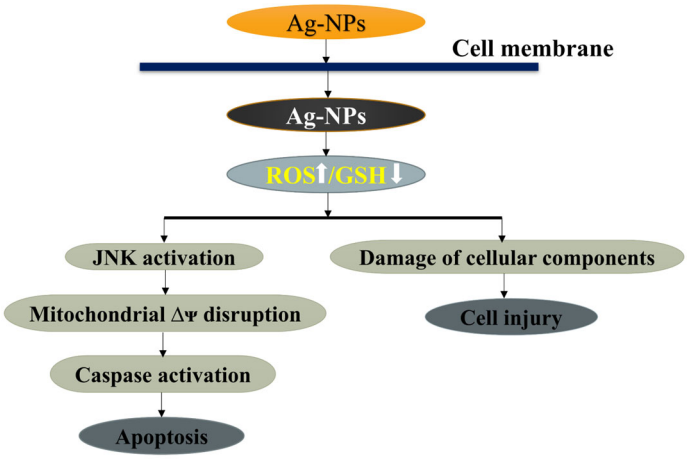

Figure 3. An anticipated pathway of AgNPs generates ROS production of intracellular glutathione (GSH) reduction, impairment to the cellular components, and eventually cell apoptosis. This figure is reproduced/modified from Akter et al.; Piao et al. [104,106].

3.4.3. Trojan-Horse Mechanism

In 2007, Limbach and colleagues proposed the Trojan-horse mechanism [108], further expanding as potential bioavailability and toxicity alterations linked to NP-pollutant associations [109]. The so-called "Trojan-horse" mechanism, in which NPs are incorporated inside cells and subsequently release large amounts of hazardous ions, has been suggested as a characteristic in AgNP cellular absorption [110]. Su et al. [111] investigated that Trojan horse greatly impacts several biochemical pathways involving substances adsorbed on NPs and present in cells simultaneously.

Interestingly, bacterial membranes often have negative charges that bind cationic silver but not AgNPs. As a result, silver ions may readily bind to bacterial membranes and produce a more severe toxicological reaction. Furthermore, larger AgNPs may survive in the environment; therefore, a Trojan-horse process transforms AgNPs into free silver ions pools, which can continually release silver ions [110]. In most cases, silver ions toxicity is caused by binding to proteins/peptides or DNA, inhibiting intracellular signal transmission. However, oxidative stress may be possible depending on the superoxide intermediates found during the oxidative dissolution processes [112]. Researchers found that O_2^- is more likely generated in the oxidative process of AgNPs with oxygen [113].

For example, RAW 265 cells phagocytose AgNPs; both in culture medium and cytosol, active cells are accessible rather than damaged cells. Trojan-horse mechanism promoted the discharge of NPs from the damaged cell [104]. The disappearance of AgNPs across the scratched cells proposes that NPs inside the cell ionize and cause cell damage. AgNPs phagocytosis can produce ROS, which stimulates inflammatory TNF-α (Tumor Necrosis Factor-alpha) signals. The cell membrane damage and apoptosis are due to the rising level of TNF-α. So, the hypothesis triggering the ionization of AgNPs across the cell is stated as a process of Trojan-horse mechanism [114].

Navarro and colleagues found that AgNPs' environmental toxicity is greatly influenced by their size and shape and the Trojan-horse mechanism, which promotes the

release of silver ions within cells [115]. Smaller AgNPs offer higher antibacterial/antifungal effectiveness than bigger AgNPs [116]. Several studies concluded that the AgNPs were more hazardous to nitrifying bacteria than silver ions or silver chloride colloids [13,117,118]. These findings support the Trojan horse mechanism, though the authors hypothesized that AgNPs could attach to the outside cell membranes and induce oxidative stress without compromising the membrane.

Moreover, silver ion release is a significant toxicological mechanism for AgNPs in the environment because toxicity has been found mainly in the aqueous phase and is related to the levels of free silver ions [119]. When distributed in aquatic environments, ionic silver is highly hazardous to some species, including bacteria, phytoplankton, and fish [120]. It is believed that the ion's toxicity stems from its attraction to thiols (HS-), which are found in proteins and enzymes [121]. Similarly, studies indicate that when sulfide and thiosulfate are present in water to bind with silver ions, their toxicity to microorganisms considerably decreases because silver is no longer accessible [121,122]. The Trojan-horse effect has been proposed as the mechanism for inhalation toxicity of AgNPs (Figure 4).

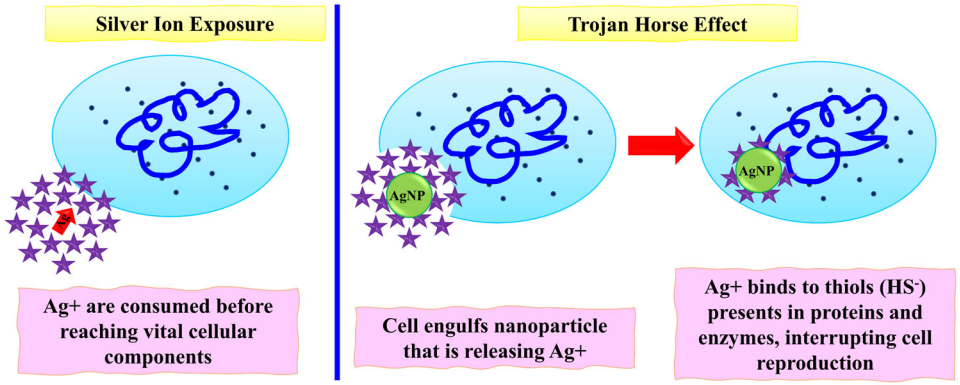

Figure 4. Silver ion exposure vs. Trojan-horse effect. This figure is reproduced/modified from Quadros and Marr [123].

4. Pharmacological Activities of AgNPs

4.1. Antimicrobial Activities of AgNPs

AgNPs possess excellent pharmacological activities against bacteria, fungi, and yeasts in aquatic groups of organisms. A study conducted by Moustafa et al. [124] investigated the antibacterial potential of AgNPs in marine organisms. They reported that these NPs showed excellent antibacterial properties against *S. agalactiae* and *V. alginolyticu* [124]. Another study conducted by Ghetas et al. [125] investigated that AgNPs possess antibacterial action against *S. agalactiae*, *A. hydrophila*, *V. alginolyticus,* and antifungal action against *F. moniliform*, and *C. albicans* [125]. AgNPs also possess antiviral activities in some aquatic organisms. White spot syndrome and hepatopancreatic parvoviruses are common viruses in aquatic organisms. A study conducted by Quinonez et al. [126] showed that a 1000 ng dose significantly reduced mortality by up to 50% and thus a potential role in controlling the White spot syndrome in striped harlequin, bumblebee red cherry shrimps. AgNPs also showed interaction with the envelope of hepatopancreatic parvoviruses and inhibited their viral replication in *A. japonicus* and *L. vannamei* [127].

Some recent studies have been reported about the antibacterial action of AgNPs in aquatic organisms. The larger surface area of AgNPs shows strong interaction with the biological membranes of microorganisms [128]. Therefore, these particles attach to the bacterial surface and enter the cell membrane due to their small size. It is also described as highly poisonous to bacterial species. Their antibacterial potency can be improved [129]. Free radical production mainly targets the membrane lipids in the living organism, occurs with dissociation and disruption, and ultimately inhibits microorganism growth [130]. The same mass of silver ions and AgNPs show an equivalent inhibition of bacteria,

Staphylococcus aureus, and *Escherichia coli* [131]. The silver ions are infused through the cell wall into bacteria; due to this cell wall breakdown, the cells' protein is denatured, and the organisms die [132,133]. The silver ions are small and positively charged and freely communicate negatively charged biomolecules in the bacterial cell wall [134,135].

Silver ions discharged from AgNPs and entered across the bacterial cell-like protein and peptidoglycan constituents, preventing them from additional replication [136]. Discharge of silver ions occurs through oxidizing agents, which oxidize the elemental silver and convert them into toxic forms. Organic groups such as protein and carbonyl inside bacteria's cell walls are donors of electrons instead of electrons acceptors. The silver atom cannot generate silver ions. Therefore, the production of silver ions approves oxidizing agents [137]. Rai et al. [138] have noted how AgNPs correlated with the *E. coli* cell wall, which interfered with all membrane sides, dissolved with the release of silver ions into the cell, and affected the transcriptional response. They also illustrated a new dimension of the target microorganism species' significance, as the antibacterial behavior of NPs often relies on the target microorganism species. Antibacterial activity is explained stepwise in the later section: (1) NPs attract electrostatically [139], (2) generation of the free radicals, permeability changes, respiration disturbance, intracellular contents linkage [140], (3) modulation of protein phosphotyrosine profiles, activated in the development of the cell cycle and the synthesis of capsular polysaccharides [141], (4) associations with SH-groups; synthesis of protein and its function inhibited [142], and (5) interact with DNA-phosphorus that contain phosphorus (Figure 5) [143,144].

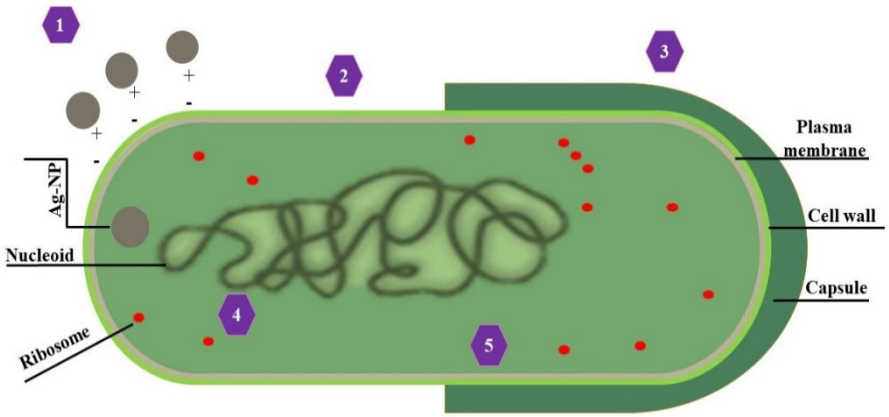

Figure 5. AgNPs mechanism proposed for antibacterial activity. This figure is reproduced/modified from Cui et al. [145].

4.2. Chronic and Acute Toxicity Effects of AgNPs

AgNPs influence the cellular processes in living organisms and increase the production of reactive species in aquatic organisms in both in vitro and in vivo. These reactive species disrupted mitochondrial DNA activity and lipid peroxidation, stopping embryonic development and reproduction [146]. When AgNPs are exposed at high concentrations by two folds, even with a slow time of exposure, the survival of organisms is reduced abruptly [147,148]. The generally established explanation for this phenomenon leads to silver ion blockage of the Na^+, K^+-ATPase and inhibits the incorporation of Na ions via the gill membranes. It triggers the failure of ion regulation and eventually leads to the organism's death [149]. The acute toxicity of AgNP exposure has both a direct and indirect effect. ROS generation, protein denaturation, membrane deformation, and DNA disruption are all direct effects of AgNP free radicals. In contrast, the indirect effect includes the discharge of Ag ions from the AgNP suspension [150].

Chronic toxicity tests utilizing minimal doses of exposure (ppb) and spanning the whole life cycle are required to accurately determine the toxicity of AgNPs in the aquatic environment. The chronic toxicity of AgNPs involves lipid peroxidation and oxidative

stress caused by these NPs as free radicals [151]. The supply of food and the hurdles of purifying these NPs form the gut lines of the aquatic organisms [152]. In the chronic toxicity experiments, the waterborne AgNPs substantially reduce the proliferation of daphnids at a low concentration, i.e., 5 mg/L, suggesting that AgNPs provoke chronic toxicity in animals. Daphnid replication significantly decreased under the borne AgNP exposure when the algae were loaded with 0.1 mg/L AgNPs, far lower than the existing freshwater requirements [153]. AgNPs are affecting the organism's life in the aquatic ecosystem, as some of them are described in Table 3.

Table 3. AgNPs toxicity and effects on different aquatic life.

Groups	Role of AgNPs in Toxicity/Malfunctioning of Cells/Organ/Organisms	Example	Reference
Protozoa	Ag ions destroy the sporozoites by entering the oocyst and ultimately break the oocyst wall	*Cryptosporidium parvum*	[154]
	The effects of protein-coated AgNPs (14.6 nm, Collargol) have shown in the viability, oxidative stress, and gene expression levels of ciliates species	*Tetrahymena thermophila*	[155]
Monera	AgNPs are highly toxic to bacteria, often associated with ion release and induction of oxidative stress. AgNPs serve as an antibacterial against bacterial tension and thus avoids its horrendous impact	Bacteria	[156,157]
	Inhibition of bacterial growth increased permeability due to the formation of "pits"	*Escherichia coli*	[134]
	The interaction of the bacterial cell with AgNPs causes Proton Motive Force dissipation leading to the death of the cell	*Staphylococcus aureus*	[158]
	Generation of ROS	Autotrophic nitrifying bacteria	[147]
	AgNPs caused toxicity in the membrane when they attached with less than ten nm-sized NPs	*Salmonella typhi*, *Pseudomonas aeruginosa* and *Vibrio cholera*	[159]
Fungi	AgNPs show antifungal activity, which suppresses the growth of fungal cells	*Aspergillus* Sp., Rhizoctonia solani, Sclerotinia sclerotiorum, S. Minor	[160]
Plant	AgNPs changed/inhibited seed's germination, the surface area of leaf, morphology, biomass, and growth potential	*Spirodela polyrhiza*	[161]
	Metabolic disorders arise, foliar proline accumulation is caused by a decrease in the contents of sugar. Total protein and chlorophyll, elongation of shoots and roots become reduced	*Lupinus termis*	[162]
	Repressed down-regulated induction of auxin receptor-related genetics, gravitropism of root, and reduction in root tips accumulation of auxins	*Arabidopsis thaliana*	[163]
	DNA damages when cytotoxicity enhances at lethal concentration; LC_{50}, i.e., up to 10 mg/L	*Allium cepa*	[164]
Animals	Apoptosis occurs when AgNPs directly contact the intestinal epithelium. In specific, typhlosole wherein the apoptosis impaired chloragogenous cells have a role like that of the liver invertebrate species or tissue in molluscs and arthropods	Oligochaetes, vertebrates, molluscs, arthropoda	[165]
	Acute toxicity/cause immobilization	*Daphnia magna*	[152]
Algae	AgNPs increase toxicity and disrupts the Photosynthetic system, cell metabolism, and cell membrane. The percentage of overall NPs absorbed by algae cells was 21% and 31%, respectively, for both species	*Chlorella vulgaris*, *Raphidocelis subcapitata*	[166]
	AgNPs cause inhibitory effects on algae species	*Chlorella vulgaris Dunaliella tertiolecta*	[79]
	Chronic toxicity/Growth inhibition	*Euglena gracilis*	[167]
	Chronic toxicity/Growth inhibition	*Chlamydomonas reinhardtii*	[167]
Fishes	AgNPs induce changes in haematology parameters such as the mean corpuscular haemoglobin (MCH) and mean corpuscular volume (MCV) become decreased. In contrast, red blood cells (RBCs) and white blood cells (WBCs) become increased as the concentration (Conc.) of AgNPs increased	Rainbow trout (*Oncorhynchus mykiss)*	[154]
	AgNPs decreased the concentration of albumin (Al), globulin (Gl), and total proteins (Tp). In contrast, the concentration of alkaline phosphatase (ALP), Aspartic aminotransferase (AST), Glucose (Glu), Alanine aminotransferase (ALT), and total lipids (Tl) increases. At tissue and cell levels, pyknotic nuclei, proliferation of hepatocytes, cytoplasmic vacuolation, hepatic necrosis, central vein wall rupture, infiltrations of inflammatory cells, melanoma-macrophages aggregation, and apoptotic cells occurs in the liver of AgNPs-exposed fish	*Clarias gariepinus*	[168]
	Acute toxicity/Abnormality	*Oryzias latipes*	[167]
	Recent findings revealed that AgNPs had influenced the fish behaviour at the highest concentration (0.09 mg/L). The bioaccumulation AgNPs was found high	*Cyprinus carpio*	[169]

	in the liver, intestine, gills, and muscles. Moreover, the results revealed that at the highest concentration (0.09 mg/L), the bioaccumulation of AgNPs led to histopathological alterations, including gill damage leading to necrosis		
	Acute toxicity/Abnormality in different functions	*Danio rerio*	[167]
Amphibians	The influence of AgNPs on stress and thyroid hormones is being studied with tadpole caudal fin cultures in vitro	*Lithobates catesbeianus*, *Rana catesbeiana*	[170,171]

Many microorganisms, including bacteria, fungi, algae, and protozoa, are used as bioremediation to reduce the toxicity of inorganic and heavy metals like cobalt (Co), lead (Pb), copper (Cu), chromium (Cr), nickel (Ni), and zinc (Zn), which contaminate the aquatic ecosystem. Bacterial species of *Cellulosi microbium*, *Pseudomonas*, *Staphylococcus*, and *Enterobacter cloacae* [172] and fungal species like *Aspergillus niger*, *Aspergillus vesicolor*, *Phanerochaete chrysosporium*, *Sphaerotilus natans*, *Saccharomyces cerevisiae*, and *Gloeophyllum sepiarium* are used to minimize the toxicity effect [173,174]. Similarly, many species of algae; *Chlorella vulgaris* [175], *Spirogyra*, *Spirulina*, *Nostoc* sp., [176] and protozoa; *Tetrahymena rostrata* are also reported to detoxify the heavy metal concentration in the aquatic ecosystem [177]. The toxicity of silver particles is a severe threat to all living organisms in the aquatic ecosystem. There is also a need for urgent attention to establishing the biological control and bioremediation of AgNPs to reduce the silver toxicity through microorganisms (bacteria, fungi, protozoa) and algae to save the ecosystem's living aquatic life. However, from literature databases, we found a minimal number of studies published providing little detail on overcoming excessive bioaccumulation in an aquatic ecosystem. *Chromobacterium violaceum* is used for bioremediation purposes. They found that bacteria efficiently absorbed AgNPs released during cloth washing [178]. The morphological changes were observed in bacteria upon uptake of AgNPs. However, after subsequent culture, the original shape was restored to it.

5. Different Methods for Silver Ions Detection

At the nanomolar (nM) level, several techniques are employed for the detection of silver ions. Several ways of detecting silver ions depend on a mix of metal ion analysis and enzymatic or oxidative amplification mechanisms. It was identified and developed as a significant technique for increasing metal ion detection sensitivity. The biosensor technique has gotten a lot of interest because of its great sensitivity, short processing time, and ease of use [179]. These methods are based on nucleic acid interaction with metal ions in very low concentrations, which can be detected.

5.1. Biosensor

Silver ions could selectively connect via coordinating bonds with cytosine (C) molecules to form a strong C–Ag^+–C framework and transform single-stranded DNA into a double-helix structure. The C–Ag^+–C interaction is highly selective because the C–C mismatching interaction with silver ions is stronger than with other metal ions. It was observed that a colorimetric approach for silver ion detection was based on the interaction between methylene blue (MB) and C-rich single-stranded DNA (ssDNA). When the MB was absorbed onto the ssDNA surface, the MB color changed from blue to purple. However, in the presence of silver ions, the specific C–Ag^+–C pair is formed and removes the interaction between SSDNA and MB, returning to the blue color. Based on this feature, a new method for detecting silver ions by adding cysteine that removes base pairs C–Ag^+–C because it binds to silver ions instead of cytosine has been developed. The amount of free cysteine was critical for colorimetric detection using ABTS–H_2O_2 [180].

A new biosensor based on electro-chem-luminescence (ECL) of Ru (bpy) 2 (mcbpy-O-Su-ester) (PF6)2 for highly sensitive and selective silver ion detection. Based on deoxyribonucleic acid (DNA tetrahedron TS primer (STTS), this process consists of three hybridized oligonucleotides forming three dual-stranded DNAs, close to a Y-shaped DNA

structure. The formation of DNA-TS makes the signal intensity change of Ru (bpy) 2 (mcbpy-O-Su-ester) (PF6) 2 at different concentrations of silver ions [181].

5.2. Chemical Sensor

The highly sensitive chemical colorimetric sensor approach for silver ions' detection in the picomolar (pM) range. This approach uses Pt nano-cubes coated with PVP as artificial peroxidases. The peroxidase substrates generate a colored signal that diminishes the existence of silver ions. This colorimetric approach will achieve an ultralow detection limit of 80 pM and a wide dynamic range of 102-104 nM. A colorimetric approach for silver ions' detection that measures the changes in SPR of modified AuNPs [182]. A colorimetric sensor based on ascorbic acid (AA) and AuNPs for silver ions' detection at concentrations of 2–28 μM in aqueous solutions. A nanocomposite membrane of Cu–(PAAc/PVA) by gamma radiation for Rapid Colorimetric Detection (RCD) of silver and mercury ions associated with significant changes of color of the Cu–(PAAc/PVA) membrane from yellow to dark green and pale gray color, respectively [183]. A carbon dot is another nonmetal ion used as a colorimetric sensor of silver ions. Carbon dots (CDs) have fluorescence emission properties that quench when their surface is attached to metal ions such as silver ions. The CDs have strong fluorescent emission at 479 nm when excited over 370 nm. This fluorescent emission was quenched by the existence of silver ions in an aqueous solution. Therefore, increased risks of AgNPs lead to health and environmental issues, cellular toxicities, and damage to the organisms in the aquatic system. It is urgently needed to discover novel detection methods that can control the increased discharge of heavy metals into human food items [184].

6. Conclusions

This review revealed the current significance of AgNPs as emerging environmental contaminants that can cause adverse effects on living tissues, damage vital organs, and pose a severe threat to aquatic life and their ecosystems. The widespread use of AgNPs results in their unavoidable discharge into the ecosystem, which pollutes the aquatic environment. With every passing day, the accumulation of AgNPs increases in the biological system, creating cytotoxicity in the normal cells of aquatic life. The genotoxic and cytotoxic effects of AgNPs are based on their size, environmental influences, concentration, and exposure time. These NPs produce the reactive species in aquatic organisms that interrupt the functions of DNA, cause mitochondrial dysfunction, and increase lipid peroxidation, which terminates development and reproduction both in vivo and in vitro. These reactive species interrupt mitochondrial, DNA activity, and lipid peroxidation, stopping embryonic development and reproduction. This review will be helpful for drawing attention to establishing the biological control and bioremediation of AgNPs to reduce the silver toxicity through microorganisms, bacteria, fungi, protozoa, or algae to save the ecosystem and for living aquatic life. It will also be helpful for identifying the organisms that denature the toxic NPs effect so that its toxicity mechanisms can be reduced.

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