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Plant-based silver nanoparticles ecotoxicity: Perspectives about green technologies in the One Health context

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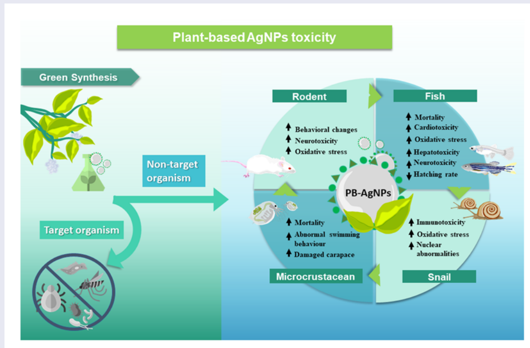
ABSTRACT
Silver nanoparticles (AgNPs) have extensive applications in nanomedicine and parasitology, particularly as antifungal, bactericidal, antiviral, larvicidal, mosquitocidal, and tick-killing agents. Plant-based AgNPs (PB-AgNPs) have been studied as a safer and biocompatible strategy to collaborate in disease control. However, knowledge concerning the toxicity of PB-AgNPs in non-target organisms is still limited. A scientometric and systematic review was conducted to comprehensively understand the potential toxicity associated with these nanoparticles. In brief, the assessment of PB-AgNPs toxicological and ecotoxicity aspects needs to be aligned with their development for target organisms. Our review demonstrates that different PB-AgNPs can cause lethal and sublethal effects like increased oxidative stress, cardiotoxicity, neurotoxicity, hepatotoxicity, hematotoxicity, and, DNA damage, alongside others, particularly in aquatic organisms. Besides, the toxicity of PB-AgNPs for terrestrial and some aquatic organisms remains poorly understood. Additionally, the similar LC_{50} range between non-target aquatic organisms and target organisms highlights the potential ecological impact of PB-AgNPs. Comprehensive toxicological assessments and further research are crucial to ensure the safe and sustainable use of PB-AgNPs in a One Health context.



KEYWORDS Ecotoxicity; health risks; model system; nanotoxicity; sustainable nanotechnology

HANDLING EDITORS Peng Gao and Bradford Scott

1. Introduction

Plant-based AgNPs (PB-AgNPs) have been widely indicated as eco-friendly nanotechnology for a sustainable future in nanomedicine (e.g., diagnostics, biomedicine, and molecular imaging) (Pala et al., 2019), food packaging (Kumar et al., 2021) and textiles (Hebeish et al., 2011). In agriculture, PB-AgNPs can be used in disease control and smart sensors to optimize the allocation of water and agrochemicals (Partila, 2019). The PB-AgNPs use may provide an efficient means of controlling disease transmission and mitigate the environmental and health concerns

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associated with traditional chemical insecticides. In parasitology, these NPs have been shown to control vectors and intermediate hosts of neglected tropical diseases, such as ticks, mosquitoes, and snails (Araújo et al., 2022), offering a promising alternative to conventional methods of vector and intermediate host control.

Moreover, the shift toward green synthesis represents a significant step toward sustainable and economically viable NP synthesis methods (F. Khan et al., 2022). The adoption of greener approaches reduces the reliance on hazardous chemicals, energy-intensive processes, and costly purification steps (Ahmad et al., 2019). This, in turn, contributes to a more efficient and environmentally responsible NP manufacturing industry.

Plant extracts have emerged as a prominent method for the biosynthesis of NPs, owing to the abundant presence of phytochemicals with excellent reducing and stabilizing capabilities. Various parts of plants, including leaves, roots, fruits, flowers, bark, and stems, can be utilized for this purpose, eliminating the need for microorganism cultivation (Ahmad et al., 2019; Mohamad et al., 2013). The underlying principle of this synthesis approach lies in the utilization of secondary metabolites, proteins, and diverse low molecular weight compounds such as terpenoids, alkaloids, amino acids, alcohols, polyphenols, glutathione, polysaccharides, antioxidants, organic acids, quinones, and others, which are naturally present in the plant extracts (Marslin et al., 2018). This strategy enables harnessing the inherent chemical diversity of plants to facilitate the reduction and stabilization of NPs, presenting an efficient and versatile alternative to traditional methods of NP biosynthesis in a One Health context.

The One Health approach recognizes the interconnectedness between human, animal, and environmental health (Sleeman et al., 2017). It emphasizes the interdependence of these three domains and aims to promote collaboration and communication among various disciplines to address health challenges (Sleeman et al., 2017). By considering the health of humans, animals, and the environment as interconnected and interdependent, One Health seeks to improve overall well-being, prevent and control disease spread, and ensure the ecosystems's sustainability for future generations (Destoumieux-Garzón et al., 2018).

Toxicology safety evaluation plays a crucial role in the One Health context by providing essential insights into the potential risks and impacts of several substances on human, animal, and environmental health. It helps us understand the effects of chemical, biological, and physical agents on living organisms, allowing for informed decision-making and risk assessment. By studying the toxic effects of substances across different species and ecosystems, toxicology contributes to the overall understanding of health risks and assists in the strategies developed to mitigate and prevent adverse health outcomes (Buttke, 2011; Shi et al., 2023).

Despite the advantages of green PB-AgNPs, these NPs are not exempt from toxicity toward non-target organisms (NTO). Thus, a literature review on the toxicity of green PB-AgNPs allows for a comprehensive understanding of the potential risks and impacts associated with these nanoparticles (Owsianiak et al., 2023). We hypothesize that PB-AgNPs induce toxic effects in non-target animal models. Here, a bibliometric and systematic review was conducted to comprehensively understand the potential toxicity induced by PB-AgNPs in non-target organisms (microcrustacean, snails, fish, and rodents). Also, safe concentrations of these nanoparticles for the environment, human and animal health in the One Heath perspective were discussed.

2. Methodological approach

A scientometric and systematic review was performed in Scopus, ScienceDirect, Web Of Science, and PubMed databases with the keywords “Plant-based silver nanoparticles,” “Green silver nanoparticles,” “Biosynthesized silver nanoparticles” and “Biogenic silver nanoparticles” combined with “ecotoxicity” “toxicity” or “safety,” both in the singular and plural, until December 2022 (Figure 1). The search resulted in 11,195 articles. Books, theses, dissertations, book chapters, review articles, articles in non-English languages, technical reports, abstracts, and protocols were

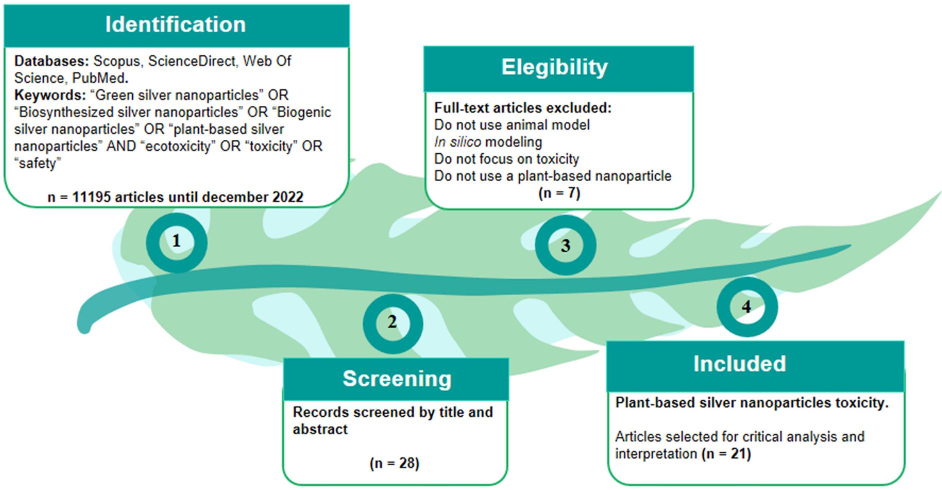

Figure 1. Methodological approach of a systematic and bibliometric review on the toxicity of plant-based silver nanoparticles (PB-AgNPs) toward non-target animals.

excluded. The other articles were evaluated according to the following inclusion criteria: (i) using at least one animal model system in the experiments; (ii) using silver nanoparticles with a plant-based synthesis; (iii) focusing on the assessment of toxicological or ecotoxicological safety. Articles that fulfilled all inclusion criteria ($n = 21$) were further evaluated for publication history and geographic distribution (corresponding author address), methodological aspects, and toxicological results (Figure 1). The geographic map was plotted in the Infogram software and graphics were plotted in Prism 9 GraphPad® software.

3. Distribution of the publications

Environmental concerns about the safety of PB-AgNPs are relatively recent. The first study was reported in 2012, aimed to evaluate the toxicity of these NPs in NTO, particularly the toxicity of PB-AgNPs obtained from the aqueous extract of *Pergularia daemia* latex in the freshwater fish *Poecilia reticulata*. These NPs exhibited toxicity against *Aedes aegypti* and *Anopheles stephensi* mosquito larvae. However, when exposed to PB-AgNPs (6.18–14.08 mg L^{-1}) for 48 h, no notable effects were observed in *P. reticulata*, indicating that these NPs could be considered for use alongside predatory fish without apparent safety concerns (Patil et al., 2012). Sarkar et al. (2014) exposed juveniles of the freshwater fish *Danio rerio* to PB-Ag NPs derived from an aqueous extract of *Psidium gujava* leaves for 96 h. Mortality rate increase (LC_{50}, 96 h = 0.4 mg L^{-1}) and damage to ovarian tissues occurred. Subsequently, from 2014 to 2022, the number of scientific papers investigating the safety of PB-AgNPs increase (Figure 2A,B). Upon reviewing the available literature on the toxicity of PB-AgNPs, a lack of consistent information regarding the efficacy of PB-AgNPs against target organisms (TO) and their corresponding toxicity to NTO was detected. This inconsistency makes it challenging to assess and compare the toxicological safety of PB-AgNPs.

Research focused on PB-AgNPs toxicity were conducted in nine countries (Figure 2C). India has the highest number of studies dedicated to the toxicological evaluation of PB-AgNPs ($n = 10$; 47.6%). Similarly, India stands out in the production of research assessing the efficacy of these NPs against target organisms, particularly mosquitoes and tick vectors (Araújo et al., 2022). South Korea, China, and Pakistan rank second with two research papers each ($n = 2$; 9.52%). Interestingly, countries that stand out in terms of scientific production on nanomaterial toxicity, such as the United States, Italy, and Germany (Anlar, 2019), have no published work on PB-AgNPs.

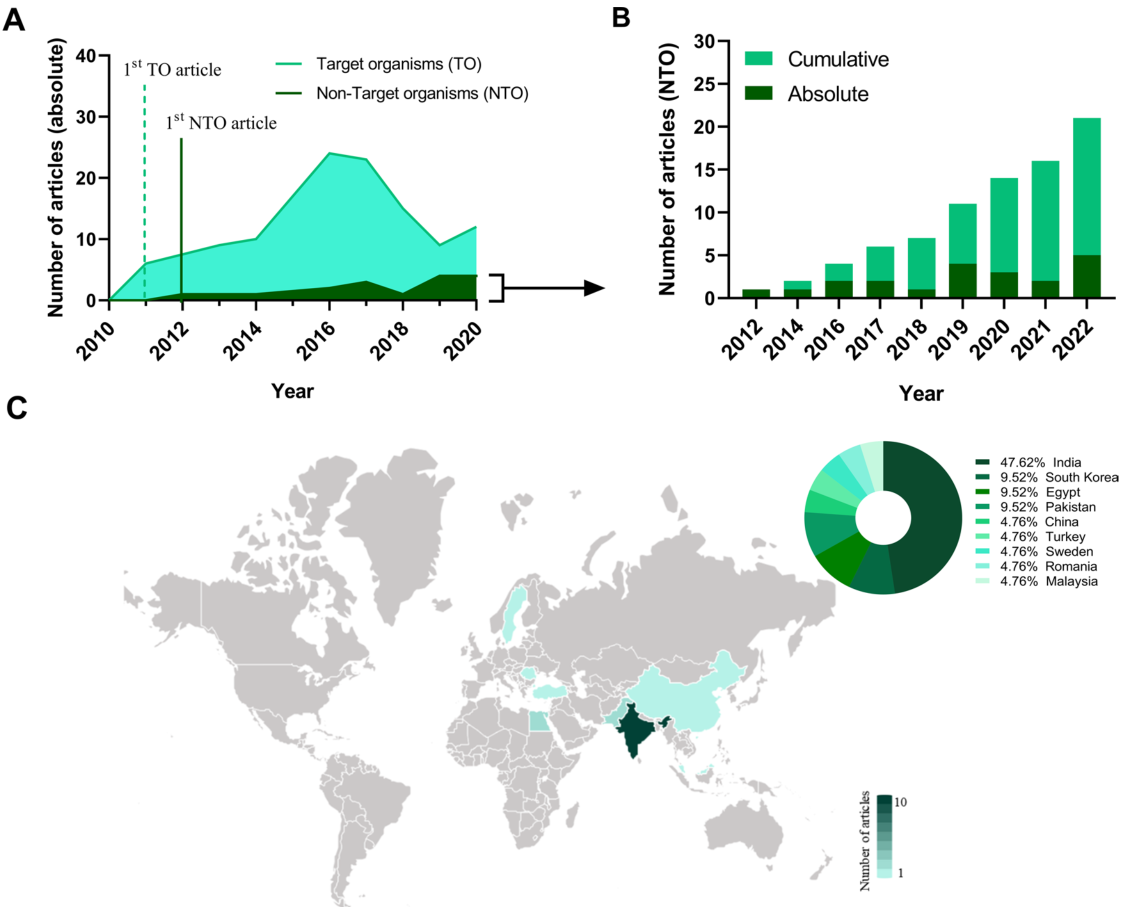

Figure 2. Distribution of the absolute number of articles exploring the toxicity of PB-AgNPs in target (TO) and non-target organisms (NTO) (A). Absolute and cumulative historical distribution of articles exploring the toxicity of NPs in non-target organisms (B). Geographical distribution map of studies on the toxicological safety and ecotoxicity of PB-AgNPs.

In South America and many other emerging African countries, where there are high levels of arboviral and other vector-borne diseases (WHO, 2019), no publications on this topic were found (Figure 2C), indicating that further research on the effects of PB-AgNPs in neotropical species, especially under field conditions, is needed.

4. Synthesis and characterization

To synthesize PB-AgNPs using a plant extract, a mixture of the extract and a silver precursor solution, typically silver nitrate ($AgNO_3$ 1 mM), is subjected to diverse reaction conditions, including temperature, pH, and incubation time (Makarov et al., 2014). These conditions can affect the size, shape, and stability of the resultant PB-AgNPs. The phytochemicals in the plant extract work as reducing agents, promoting the conversion of silver ions into AgNPs. Furthermore, the bioactive compounds in the extract contribute to NP stabilization (Dwivedi & Gopal, 2010; Mittal et al., 2013). Twenty-one plant species seems to have a potential for stable synthesis of PB-AgNPs (Table S1). Among these plants the Acanthaceae family emerged as the most popular ($n = 3$; 14.3%), with three representatives: *Andrographis peniculata*, *Barleria cristata*, and *Pergularia daemia*.

The most utilized plant parts were leaves ($n = 14$; 66.6%), followed by stem, clove, fruit, gum, latex, peel, and starch ($n = 1$; 4.7% each one) (Figure 3A). Most of the syntheses used solely

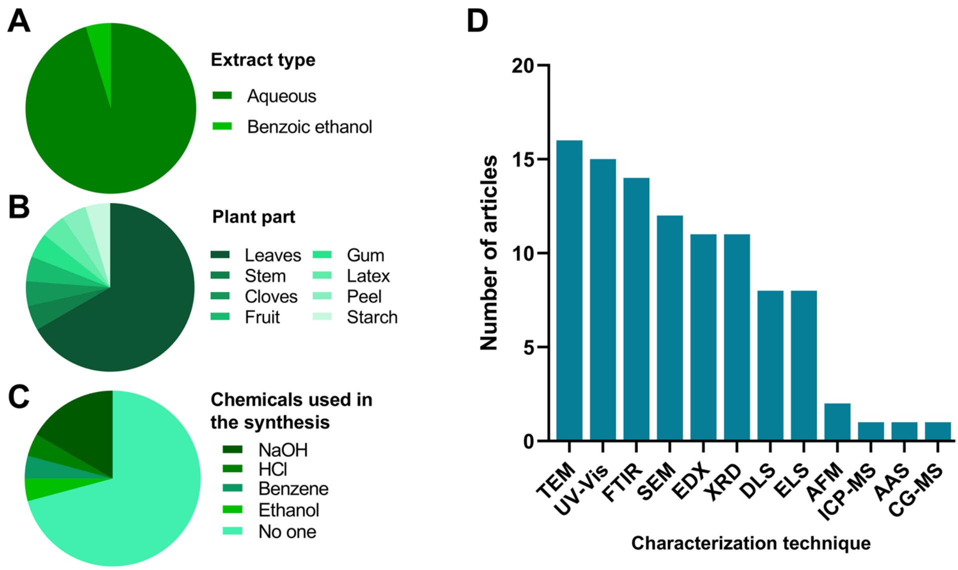

Figure 3. Synthesis of PB-AgNPs concerning of plant part extract (A), extract type (B) and chemicals used (C), and characterization techniques (D). TEM: Transmission Electron Microscopy; UV-Vis: Ultraviolet-Visible Spectroscopy; FTIR: Fourier Transform Infrared Spectroscopy; SEM: Scanning Electron Microscopy; XRD: X-Ray Diffraction; DLS: Dynamic Light Scattering; ELS: Electrophoretic Light Scattering; EDX: Energy-Dispersive X-Ray Spectroscopy; EDS: Energy-Dispersive X-Ray Spectroscopy; AFM: Atomic Force Microscopy; ICP-MS: Inductively Coupled Plasma Mass Spectrometry; AAS: Atomic Absorption Spectroscopy; GC-MS: Gas Chromatography-Mass Spectrometry.

aqueous extract ($n = 20$) (Figure 3B) without the addition of sodium hydroxide (NaOH) ($n = 4$; 19%) or hydrochloric acid (HCl) ($n = 1$; 4.8%) for pH regulation (Figure 3C). The use of benzoethanolic extract was reported (Figure 3B). The green synthesis approach employing only the aqueous plant extract adheres to the principle of green chemistry, minimizing the use and disposal of chemical reagents in the environment (Li & Trost, 2008).

Many plants used in the PB-AgNPs synthesis possess medicinal properties or are already applied in biological insect control. For instance, *Azadirachta indica* (Meliaceae), known as Neem, is renowned for its insecticidal and repellent properties (Benelli et al., 2017; Saleem et al., 2018). The aqueous extract of the root bark of *A. indica* exhibited moderate toxicity to *Artemia salina* nauplii after 24 h of exposure (LC_{50} = 285.8 mg L^{-1}) (Mwangi et al., 2014) and no effects were observed in *D. rerio* larvae following exposure to the methanolic extract of green callus concentrations (below 4000 µg mL^{-1}) after 5 days of exposure (Ashokhan et al., 2020). *A. indica* was identified as a plant with the potential for more sustainable insecticides based on nanotechnology development (Iqbal et al., 2022; Murugan et al., 2016) and is well-known for its antimicrobial, anti-inflammatory, and anthelmintic properties.

AgNPs obtained from *A. indica* extracts has demonstrated activity against water-borne pathogens such as *Escherichia coli* and *Vibrio cholerae*, as well as fungal plant pathogens including *Alternaria alternata*, *Sclerotinia sclerotiorum*, *Macrophomina phaseolina*, *Rhizoctonia solani*, *Botrytis cinerea* and *Curvularia lunata* (AgNPs ranging from 10 to 50 nm) (Krishnaraj et al., 2012). The toxicity of *A. indica* extracts was attributed to a cyanogenic glycoside called Acalyphin, which can be degraded by heat during the extract preparation (Hungeling et al., 2009; Zahidin et al., 2017). Hence, it is crucial to consider the toxicity of different extract types, concentrations, and the sensitivity of each organism when selecting the optimal PB-AgNPs synthesis approach.

Intrinsic characteristics of NPs can influence their toxicity, such as size, coating, functionalization, stability in aqueous media, and surface charge, among others (Levard et al., 2012; Tortella et al., 2020; Windell et al., 2023). A comprehensive characterization of PB-AgNPs can provide essential information regarding their dynamics and toxicity to organisms. Transmission electron microscopy (TEM) and High-Resolution TEM (HR-TEM) ($n = 16$; 76.19%) was the most widely used characterization technique. TEM provides information about the dry size and morphology of the particles (Mourdikoudis et al., 2018). Several shapes of PB-AgNPs, ranging in size from 5 to 60 nm in dry diameter (Table S1) were identified. UV-Vis spectroscopy technique ($n = 15$; 71.42%) was also used, particularly for monitoring the synthesis of AgNPs. Changes in the absorption spectrum over time indicate the formation of NPs, providing real-time information on the synthesis process or potential instability issues (Baghizadeh et al., 2015).

Fourier Transform Infrared Spectroscopy (FTIR) ($n = 14$; 66.7%), is another technique commonly used for the NPs characterization. FTIR analysis is valuable for elucidating the chemical composition of plant extracts, identifying phytochemicals acting as reducing agents, and determining the functional groups responsible for capping the nanoparticles (Ijaz et al., 2020).

However, the most employed methodology was scanning electron microscopy (SEM) or field-emission SEM (FESEM) ($n = 12$; 57.1%). SEM/FESEM provides detailed information on the sample morphology and topography, offering valuable insights into the characteristics and features of the material (Vladár & Hodoroaba, 2020). Both the TEM and SEM techniques can be coupled with energy-dispersive X-ray spectroscopy (EDX) analysis ($n = 11$; 52.4%). By combining EDX with electron microscopy, valuable information can be obtained about the elemental composition and distribution within the analyzed samples (Joudeh & Linke, 2022). The X-ray diffraction (XRD) ($n = 11$; 52.4%) is also valuable for the analysis of nanomaterials, as it can provide information into crystallinity and NPs phase (I. Khan et al., 2019).

Interestingly, less than half of the information on the behavior of PB-AgNPs in aqueous media used dynamic light scattering (DLS) ($n = 8$; 38.1%), as well as their zeta potential using electrophoretic light scattering (ELS) ($n = 8$; 38.1%). Dispersion stability is important for NP interactions with biological systems and their potential toxicity. Unstable or agglomerated NPs can have different effects on cellular uptake, distribution, and toxicity (Fabrega et al., 2011; Tomankova et al., 2015). Overall, it is strongly recommended that the characterization of PB-AGNPs be made by multiple techniques, as well as their behavior and fate in the environment for a better understanding of their ecotoxicological impacts.

5. Model systems and exposure conditions

The evaluation of the toxicity of NPs necessitates a comprehensive approach encompassing multiple model systems and trophic levels. A robust analyze ensures a holistic understanding of toxicity across various complexity levels. In this study, research papers that explore the toxicity of PB-AgNPs within four distinct complexity levels: microcrustaceans, snails, fish, and rodents compiled and categorized (Figure 4A). Notably, the majority primarily focus on aquatic organisms such as fishes and copepods, while the number of terrestrial species is limited (see Figure 4B).

Fish were the more representative group ($n = 16$; 68.0%) on the ecotoxicity of PB-AgNPs (Figure 4A). Out of this total, 47% used the zebrafish (*D. rerio*) as a model system, followed by *P. reticulata* (17.6%) and *Gambusia affinis* (11.7%). *D. rerio* has been widely employed as a gold standard in toxicity research for various substances and has been recommended as a robust model system for assessing the toxicity of nanomaterials (Jia et al., 2019; Pereira et al., 2019). The microcrustacean group ($n = 4$ studies) was represented by the species *Ceriodaphnia cornuta* ($n = 3$; 75%) and *Daphnia magna* ($n = 1$; 25%). Daphnids, mainly *Daphnia magna*, are frequently used in acute toxicity and reproductive toxicity tests and are a sensitive model organism for the ecotoxicological assessment of many substances, including nanomaterials (Lekamge et al., 2020; Boros & Ostafe, 2020).

The exposure duration to PB-AgNPs varies depending on the model system, the developmental stage of the animal, and the research question at hand. In the case of fish, acute exposures of two ($n = 3$ articles) and four days ($n = 7$ articles) have been commonly employed, particularly for determining median lethal and sublethal concentrations for subsequent chronic tests lasting

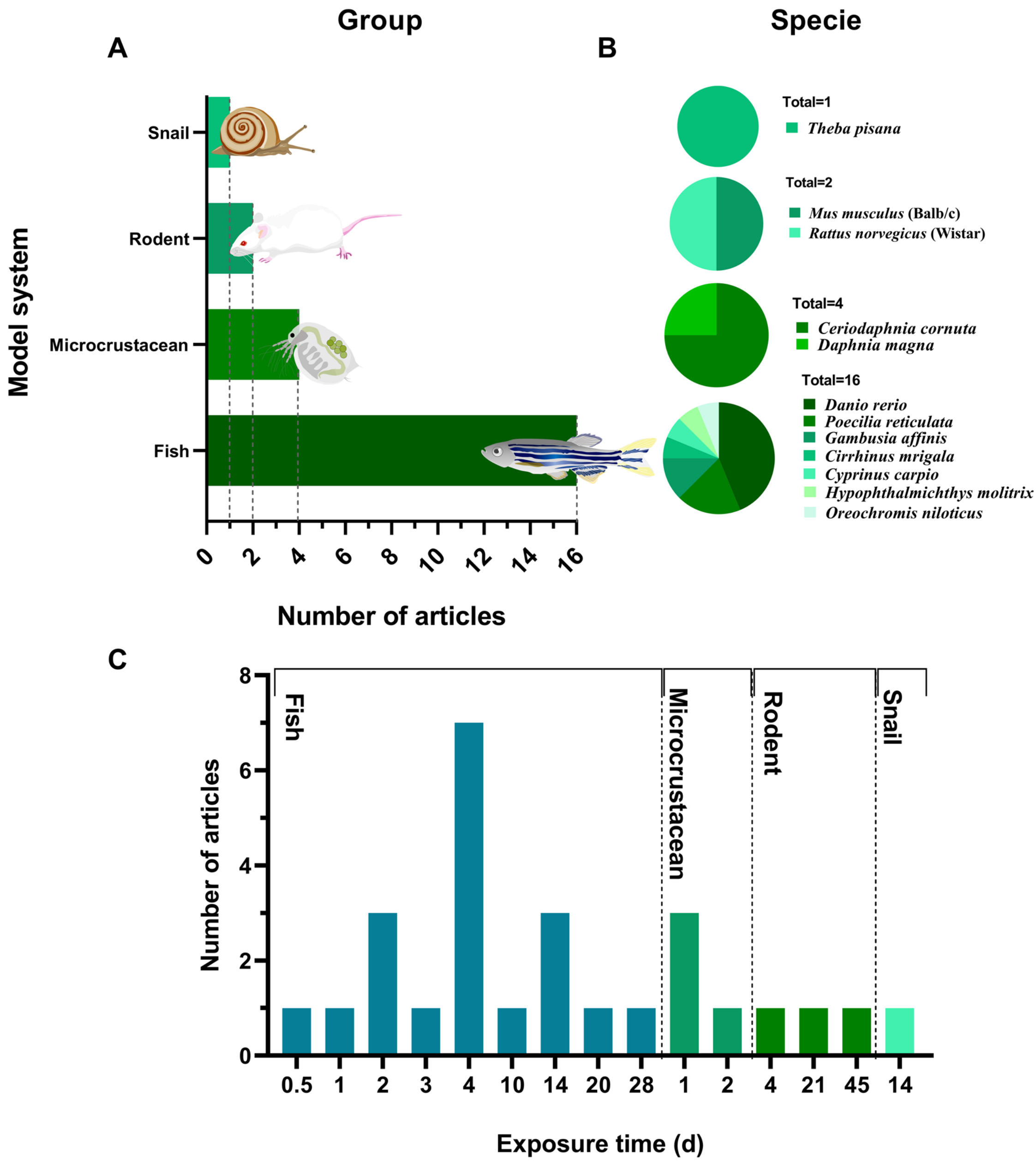

Figure 4. Animals used (A), corresponding model systems for each group (B), and exposure durations for each group (C). d: Days.

more than one week. The OECD 236 guideline (OECD, 2013) addresses acute toxicity testing on fish embryos and establishes the acute exposure time for determining the LC_{50} within 96 h of exposure.

The microcrustaceans *C. cornuta* and *D. magna* were exposed for either 24 ($n = 3$ articles) or 48 h ($n = 1$ article). Acute exposure tests with daphnids are the most commonly used, as recommended by the OECD 202 (2004b) guideline for Acute Immobilization Test, which suggests exposure and calculation of the EC_{50} within 24 or 48 h (Figure 4C). These timeframes allow for short-term assessment effects and the identification of potential adverse outcomes over an extended period. However, it is important to note that the specific exposure duration may vary based on the study goals and the organism's characteristics. Furthermore, more studies concerning the toxicity of PB-AgNPs after long-time and chronic exposure are needed.

Only three studies (14.3%) reported the toxicity of PB-AgNPs to terrestrial animals. Mammalian models have been decreasingly utilized in early toxicological assessments, always aiming for the principles of the 3 R's. Only two studies investigated the toxicity of PB-AgNPs in the mouse *Mus musculus* with an acute exposure of 96 h and a chronic exposure of 21 days (Yaqub et al., 2019) and the rat *Rattus norvegicus* for 45 days (Opris et al., 2021). Only one study reported the use of the terrestrial snail *Theba pisana*. Given that terrestrial animals can be exposed to NPs through distinct pathways compared to aquatic animals, more studies are essential to thoroughly understand the potential adverse effects and ecological implications of PB-AgNPs on terrestrial organisms.

5.1. Microcrustacean

Daphnia magna and *C. cornuta* are widely recognized and extensively studied freshwater crustacean for assessing nanoparticle toxicity (Liu et al., 2022). Its rapid reproduction, short lifespan, and sensitivity to various toxic substances make it an ideal species for ecotoxicological studies. Moreover, they occupy a crucial position in aquatic food chains, serving as a primary consumer and playing a vital role in nutrient cycling (Ebert, 2005). *D. magna* and *C. cornuta* were used as model organisms to assess the ecotoxicity of AgNPs obtained from three plant species (Table S1).

The most common effects of daphnids exposed to PB-AgNPs included increased mortality, abnormalities in swimming behavior and accumulation of NPs in the gut. Exposure of *C. cornuta* neonates to *Solanum nigrum* aqueous extract PB-AgNPs (10–50 nm) induced mortality (LC_{50} = 23.5 mg L^{-1}), erratic swimming behavior, migration to the bottom or surface, blackening of the intestine, rupture of the abdomen, and reduced carapace development (Jenifer et al., 2020). The blackening of the intestine was caused by the accumulation of NPs after ingestion. The exposure to 4–20 mg L^{-1} of PB-AgNPs derived from *Cissus quadrangularis* aqueous extract also caused mortality increase and accumulation in the gastrointestinal tract in *C. cornuta* (Ishwarya et al., 2017). In contrast, *C. cornuta* exposed to concentrations of up to 250 µg L^{-1} of AgNPs (22.21 nm) synthesized with aqueous extract of *Allium sativum* cloves did not show increased mortality or significant morphological alterations. However, there was an increase in the percentage of abnormalities in swimming behavior (Vijayakumar et al., 2019). Similar effects were found in *D. magna* exposed to AgNPs (49.05 ± 25.34 nm, hydrodynamic) derived from *Alcea rosea* aqueous leaf extract. In addition to increased mortality (LC_{50} = 1.86 µg L^{-1}), the presence of brown pigments in the gill area and on the trunk limbs was observed, indicating possible accumulation (Khoshnamvand et al., 2020) (Figure 5; Table S1). No work analyzed the influence of PB-AgNPs toxicity on daphnid reproductive success, indicating that further research needs to go beyond acute toxicity.

5.2. Snail

Land snails can be exposed to and absorb pollutants through ingestion, dermal contact, or inhalation (De Vaufleury et al., 2006). Therefore, they can provide valuable information regarding the toxicity of pollutants such as NPs (Besnaci et al., 2019; Caixeta et al., 2020). Adult snails *Theba pisana* were exposed to 1 mM of AgNPs (18–19.87 nm) synthesized from the aqueous extract of *Raphanus sativus*. Two weeks of dietary exposure did not cause mortality. However, sublethal effects such as oxidative stress indicated by increased lipid peroxidation and decreased levels of glutathione, catalase, and glutathione s-transferase, were observed. There was also an increase in the number of micronuclei and binucleated cells present in the hemolymph

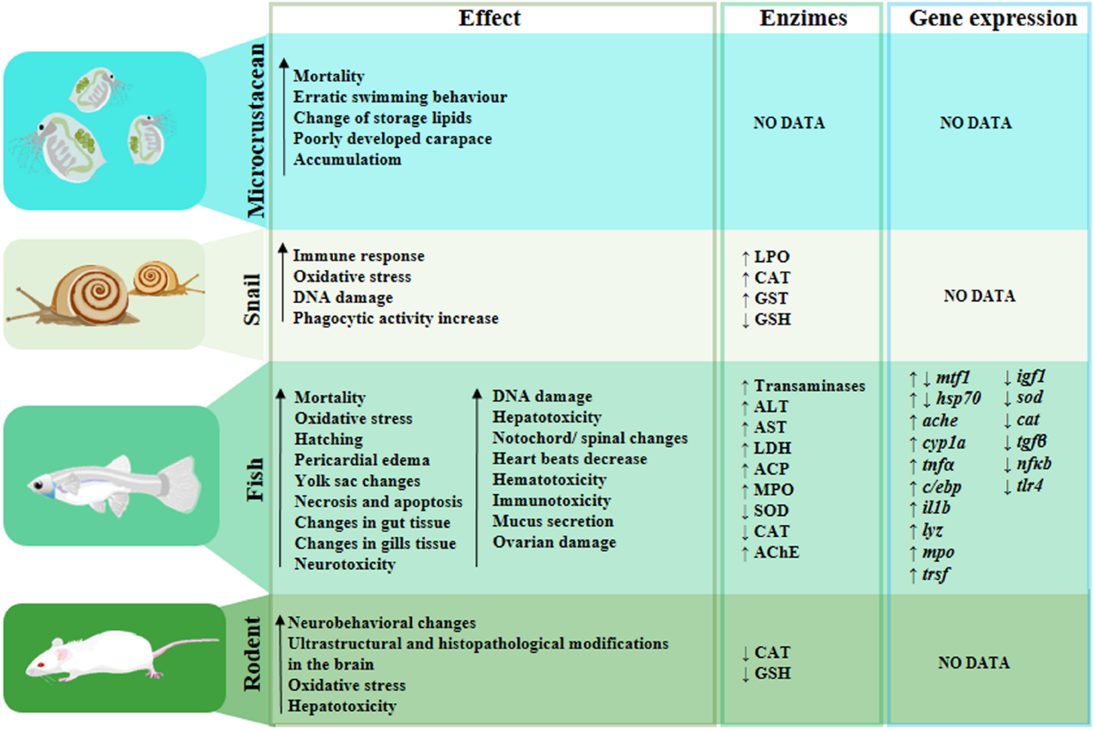

Figure 5. Lethal and sublethal effects of PB-AgNPs on different trophic levels of non-target organisms. LPO: Lipid Peroxidation; CAT: Catalase; GST: Glutathione S-Transferase; GSH: Glutathione; ALT: Alanine Aminotransferase; AST: Aspartate Aminotransferase; LDH: Lactate Dehydrogenase; ACP: Acid Phosphatase; MPO: Myeloperoxidase; SOD: Superoxide Dismutase; *mtf1*: Metal-Responsive Transcription Factor 1 gene; *hsp70:* Heat Shock Protein 70 gene; *ache*: Acetylcholinesterase gene; *cyp1a*: Cytochrome P450 1 A gene; *tgfβ*: Transforming Growth Factor Beta gene; *tnfα*: Tumor Necrosis Factor Alpha gene; *igf-1*: Insulin-like Growth Factor 1 gene; SOD: Superoxide Dismutase; CAT: Catalase; *c/ebp*: CCAAT-enhancer binding protein gene; *trsf*: transferrin gene; *lyz*: lysozyme gene; *tlr4*: Toll-like receptor 4 gene; *tlr22:* Toll-like receptor 22 gene; *nfkb*: Nuclear factor-κB gene; *il1b:* interleukin 1 beta gene.

(mutagenic effects), as well as a decrease in lectin levels and an increase in hemocyanin levels (Radwan et al., 2019) (Figure 5). Even after one week of recovery, these changes persisted, indicating the long-term effects of PB-AgNPs on gastropods.

5.3. Fish

Fish are essential organisms in the food chain and can be exposed to pollutants such as engineered NPs through absorption, adsorption, or direct feeding from the aquatic environment (Callaghan & MacCormack, 2017; Handy et al., 2008). Besides being bioindicators of environmental pollution, they can be crucial organisms in understanding the toxicity of NPs in the one health context, as they are an important source of human nutrition (Tacon & Metian, 2013). In this review, we described toxicity studies of PB-AgNPs to seven fish species (Figures 4 and 5).

Increased mortality, decreased hatching rate, pericardial edema, and alterations in the notochord or spinal curvature were common effects observed following the exposure of zebrafish embryos to PB-AgNPs (Figure 5; Table S1). Zebrafish exposed to PB-AgNPs synthesized from *Miscanthus sinensis* leaves extract (25 ± 10 nm) at 5–100 µg mL^{-1} for 72 h showed increased mortality, cardiotoxicity (pericardial edema and decreased heart rate), decreased hatching rate, and abnormalities in the notochord (Panda et al., 2022). Exposure to AgNPs (hydrodynamic diameter = 80 nm) derived from *Andrographis peniculata* extract at 10–250 µg mL^{-1} also caused mortality, cardiac edema, decreased hatching, and notochord bending increasing. Additionally, there was an elevation in reactive oxygen species (ROS) levels and increased apoptosis (Kumari et al., 2020). The effects also included neurotoxicity, as evidenced by an increase in degeneration and necrosis of neurons (Kokturk et al., 2022).

For adult zebrafish, commonly observed effects included increased mortality, hepatotoxicity, histopathological changes in the gills, and nuclear abnormalities (Table S1). Adult zebrafish were exposed to sublethal concentrations (15.5–31 µg L^{-1}) of AgNPs (<30 nm) derived from the aqueous leaf extract of *Acalypha indica* for two weeks. The effects were increased mortality, higher levels of liver marker enzymes, liver intracellular ROS, nuclear abnormalities, and changes in CCAAT-enhancer binding protein (*c/ebp*), interleukin 1 beta (*il1b*), lysozyme (*lyz*), myeloperoxidase (*mpo*), Toll-like receptor 22 (*tlr22*), nuclear factor-κB (*nfκb*), Toll-like receptor 4 (*tlr4*), Metal-Responsive Transcription Factor 1 (*mft1*), Transferrin (*trsf*) and Heat Shock Protein 70 *(hsp70)* gene expression (Ramachandran et al., 2018), indicating oxidative stress, hepatotoxicity, mutagenicity and immunotoxicity. AgNPs (5–50 nm) derived from *Malva crispa* Linn. at 71.1 µg L^{-1} caused notable effects, including cytological changes in the gills and increased expression of transaminases in the liver (Krishnaraj et al., 2016).

PB-AgNPs biosynthesized from the aqueous extract of *Pergularia daemia* (Patil et al., 2012), *Cissus quadrangularis* (Ishwarya et al., 2017), and *Solanum nigrum* (Jenifer et al., 2020) were tested in the *P. reticulata* model system. AgNPs (44–255 nm, hydrodynamic) from *P. daemia* latex (6.18–14.08 mg L^{-1}) caused no toxic effects. However, increased mortality, DNA damage, hepatotoxicity, decreased heart rate, and increased mucus secretion were observed in animals exposed to PB-AgNPs from *C. quadrangularis* (4–20 mg L^{-1}) and *S. nigrum* (1–50 mg L^{-1}; 10–50 nm).

Exposure of *Oreochromis niloticus* fingerlings to AgNPs (40 nm) synthesized from rice starch (3.31–26.50 mg L^{-1}) resulted in increased mortality. Sublethal effects associated with chronic exposure (28 days) included elevated Red Blood Cells (RBCs) and White Blood Cells (WBCs) counts, as well as decreased hemoglobin levels, indicating hematotoxicity associated with prolonged exposure to PB-AgNPs. Additionally, hepatotoxic, and nephrotoxic effects were observed, as evidenced by impaired liver and kidney functions marked by increased levels of Aspartate Aminotransferase (AST), Alanine Aminotransferase (ALT), Acid Phosphatase (ACP), and Alkaline Phosphatase (ALP), as well as elevated creatinine and urea levels. The 28-day chronic exposure also led to sublethal effects, including reduced growth and altered expression of genes involved in the inflammatory response. Specifically, there was a decrease in Transforming Growth Factor beta (*tgfb*) expression and an increase in Tumor Necrosis Factor alpha (*tnfα*) gene expression (Mansour et al., 2021), suggesting an impact on the regulatory mechanisms of the inflammatory response.

Only the mortality rate of *G. affinis* species exposed to AgNPs (25–30 nm) derived from the aqueous leaf extract of *Barleria cristata* (Govindarajan & Benelli, 2016) and *Trewia nudiflora* (Esan et al., 2022) was evaluated. The estimated LC_{50} values are essential for comparing lethal effects between model systems and determining environmentally safe concentrations. However, the importance of conducting concurrent assessments of sublethal effects, which can provide equally relevant insights into environmental impact, is crucial.

5.4. Rodent

Although there is limited information about the toxicity of PB-AgNPs in mammalian models (Figure 5), Wistar rats exposed orally to 0.8 and 1.5 mg kg^{-1} of PB-AgNPs (5–30 nm) obtained from *Cornus mas* L. fruits extract (Opris et al., 2021) showed neurobehavioral changes (e.g., general locomotor activity and anxiety-like behavior), ultrastructural changes in neurons from the frontal cortex and hippocampus (e.g., nuclear and mitochondrial polymorphism, abundant endoplasmic reticula, few/rare lysosomes, lysis of astrocyte end-foots and proliferation of capillary endothelium), and histopathological alterations (e.g., apoptotic neurons, pericellular edema, myelin vacuolization, heterogeneous neuropil and astrogliosis) in brain tissue. High doses (500–1200 mg kg^{-1}) of green AgNPs (40–60 nm) from aqueous leaf extract of *Ocimum tenuiflorum* L. also led to mortality of Balb/c mice and increased oxidative stress after 96 h of exposure (Yaqub et al., 2019). Thus, further studies concerning the toxicity of PB-AgNPs to mammal models are needed, especially for understanding the effects of green nanotechnology on human health.

6. Comparative toxicity

The LC_{50} values for fish ranged from 0.01 to 3162 mg L^{-1}. The species *G. affinis* and *Hypophthalmichthys molitrix* exhibited the lowest sensitivity to PB-AgNPs (25–40 nm) exposure, with LC_{50} values ranging from 867 to 3162 mg L^{-1}. For *D. rerio* embryos, the LC_{50} values ranged from 47.2 to 127.8 mg L^{-1} (15–35 nm), indicating lower sensitivity compared to adult individuals of the same species (LC_{50} = 0.01–0.14 mg L^{-1}; 5–50 nm) (Figure 6A). These findings highlight species-specific and developmental stage variations in sensitivity to PB-AgNPs, with certain species showing higher tolerance to NP exposure while others, like *D. rerio* embryos, demonstrate comparatively lower sensitivity than their adult counterparts. For instance, in acute exposures of embryos, fish are protected by the chorion barrier, which selectively allows some NP sizes to reach the embryo (Chen et al., 2020; Duan et al., 2020). Additionally, zebrafish embryos cannot be orally exposed as they rely on yolk reserves for nutrition. From the larval stage onwards, there is increased susceptibility to NP exposure through skin contact, ingestion, and direct exposure to the gills (Dube & Okuthe, 2023; Handy et al., 2008; Pereira et al., 2019). PB-AgNPs obtained from *Baleria cristata* extract showed activity against larvae (3rd instar) of *A. subpictus* (LC_{50} = 12.46 µg mL^{-1}), *Aedes albopictus* (LC_{50} = 13.49 µg mL^{-1}), and *Culex tritaeniorhynchus* (LC_{50} = 15.01 µg mL^{-1}). The mosquito larvae appear to be more sensitive to *Baleria cristata* AgNPs than the fish *G. affinis*, which exhibited an LC_{50} of 866.92 mg L^{-1} after 48 h of exposure (Govindarajan & Benelli, 2016). PB-AgNPs with potential for field application are expected to exhibit reduced sensitivity to NTOs, as they can be applied in the field at lower concentrations while still maintaining effectiveness against TOs.

PB-AgNPs from *Azadirachta indica* also exhibited larvicidal activity (III instar; 24 h) against *Anopheles stephensi* (ethanolic seed extract; LC_{50}, 24 h = 5.6 ppm) (Murugan et al., 2016), *Anopheles stephensi* (aqueous leaf extract; LC_{50}, 24 h = 2 ppm), *Culex quinquefasciatus* (LC_{50}, 24 h = 10 ppm) (Soni & Prakash, 2014), and *Aedes aegypti* (aqueous leaf extract; LC_{50}, 24 h = 0.006 mg L^{-1}) (Poopathi et al., 2015). It also showed toxicity against *Rhipicephalus (Boophilus)* microplus tick larvae (aqueous leaf extract; LC_{50}, 24 h = 35.40 ppm) (Avinash et al., 2017). These PB-AgNPs

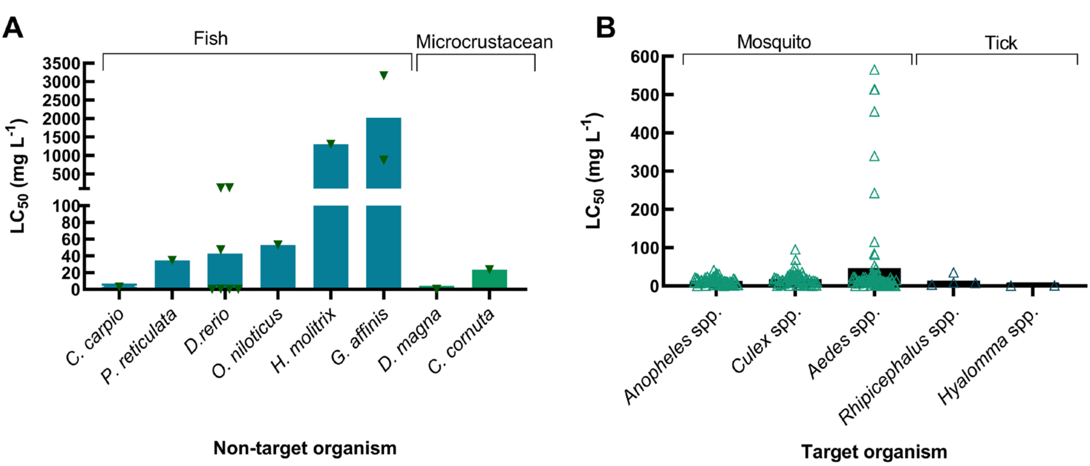

Figure 6. Comparison of median lethal concentrations (LC_{50}) of PB-AgNPs for non-target organisms (A) and target organisms (B).

(50 nm) exhibited nontoxic properties when tested on *Cirrhinus mrigala* fish through immersion and intramuscular injection. However, they did demonstrate significant immunomodulatory effects, including increased responses against pathogens, myeloperoxidase activity, and phagocytic activity (Rather et al., 2017).

Leaves and fruits of *Solanum nigrum* were used for the biosynthesis of PB-AgNPs, and their activity was tested against mosquitoes *A. stephensi* and C. *quinquefasciatus*. The species *C. quinquefasciatus* was more sensitive than *A. stephensi*. Overall, NPs synthesized from fresh or dried leaves and fruits showed similar levels of toxicity (Rawani et al., 2013). Ag NPs obtained from the aqueous extract of *S. nigrum* were toxic to the fish *P. reticulata* (LC_{50}, 48 h = 38.3 μg mL^{-1}), leading to increased mortality, hepatotoxicity, and decreased heart rate.

Only two studies presented the LC_{50} values of PB-AgNPs for *D. magna* and *C. cornuta* (0.0018 mg L^{-1}; 10–50 nm and 23.5 mg L^{-1}, respectively) (Figure 6A). It is important to note that the range of LC_{50} values found for mosquito larvae *Anopheles* spp., *Aedes* spp., and *Culex* spp. (III instar) exposed to PB-AgNPs was 0.06–565 mg L^{-1} (Figure 6B). These data emphasize the need for careful consideration of the environmental impacts and potential risks associated with the use of PB-AgNPs as larvicidal agents, ensuring that the concentrations used are within safe limits to mitigate adverse effects on NTO and preserve the integrity of the aquatic ecosystem.

Only one study determined the median lethal dose (LD_{50}) of PB-AgNPs (40–60 nm) for a terrestrial animal, *M. musculus*, to be 812 mg kg^{-1}. Interestingly, the LC_{50} values reported for larvae of *Rhipicephalus* spp. and *Hyalomma* spp. ticks ranged from 0.7 to 35.4 mg L^{-1} (Figure 6B). However, even though these concentrations may be considered safe for non-target terrestrial organisms, it is important to consider the potential for NPs to enter the aquatic environment. It is crucial to assess the environmental fate and transport of PB-AgNPs to prevent unintended exposure to aquatic organisms, as they may be sensitive to even lower concentrations.

7. PB-AgNPs toxicity from the One Health perspective

The One Health approach is an interdisciplinary approach that links human, animal and environmental health. In this context, the environment plays a crucial role because in this approach it is particularly important to address environmental pollution and its impact and propose solutions such as early warning mechanisms on risk related chemical pollutants to reach a toxic free environment. Moreover, for applying the One Health perspective, it is crucial to consider the risks posed by chemicals on ecosystems, ecosystem services and human health (Brack et al 2022; Rabinowitz et al., 2018) and for this purpose, it is essential to have sound scientific data on the effects of chemical compounds in humans and animals. Undoubtedly, the development of new technologies for the control of neglected diseases is necessary and urgent (Engels & Zhou, 2020; Weng et al., 2018). In addition to vector control, as mentioned earlier in this review, the etiological agents are also targets of PB-AgNPs. AgNPs synthesized with extracts from *A. indica* seeds have shown promise in eliminating the protozoa *Plasmodium berghei* and *Plasmodium falciparum* (Murugan et al., 2016). PB-AgNPs from *Artemisia abrotanum* and *Artemisia arborescens* have also demonstrated *in vitro* activity against *P. falciparum* (Avitabile et al., 2020). These findings reinforce the antimalarial potential of PB-AgNPs and open new venues for addressing the lack of vaccines and the growing resistance to conventional antimalarials.

The helminth *Schistosoma mansoni* was effectively treated *in vivo* with PB-AgNPs fabricated using *Calotropis* extract. Both isolated treatment and the combination treatment with the drug praziquantel showed considerable antischistosomal effects, suggesting a potential combined application for a more efficient schistosomiasis treatment (Hamdan et al., 2023). Given the applications of PB-AgNPs aimed at controlling parasitic diseases and interrupting the vector life cycle (Araújo et al., 2022), it is evident that their toxicity should be seen as an interconnected network that encompasses human and animal health, and environmental impact (Figure 7).

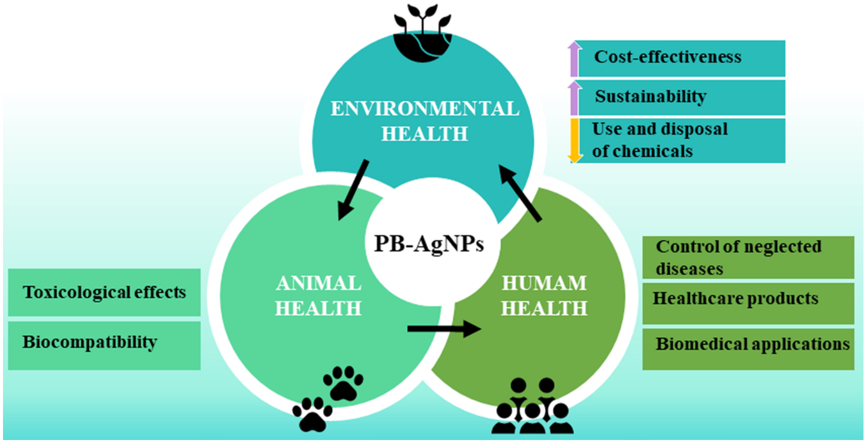

Figure 7. Uses of plant-based AgNPs in the One Health perspective.

8. Conclusions

In this review, we assessed the current knowledge regarding the safety and ecotoxicity of PB-AgNPs in animal model systems. Revised data showed that the lethal and sublethal effects of PB-AgNPs are influenced by various factors such as species, developmental stage, exposure route, and PB-AgNP characteristics, including size, extract type, functionalizing molecules, and stability.

The reviewed current knowledge is mainly based on the ecotoxicity of PB-AgNPs synthesized from aqueous leaf extracts on fish models. Despite the limited diversity of studies, we shed light on the LC_{50} values found for NTO and compare them with different disease vector genera. There is very limited information on toxicity for mammalian models, making it even more challenging to extrapolate the results to humans and other large mammals. Furthermore, the One Health perspective will be extremely useful in developing approaches that effectively reduce the ecological risk of using PB-AgNPs and developing new clean technologies.

9. Perspectives

Here are some suggestions that could be considered in future studies:

a. Analyze the efficiency of PB-AgNPs from the One Health perspective, considering the preservation of plant biodiversity, adverse effects on non-target organisms, and ecosystem-level toxicity;
b. Characterize the physical, chemical and environmental transformations of PB-AgNPs;
c. Develop robust studies to elucidate the toxicity of PB-AgNPs in terrestrial organisms;
d. Conduct studies that examine the trophic transfer and biomagnification of PB-AgNPs;
e. Describe other ecotoxicological metrics in addition to LC_{50}, such as EC_{50} (Effective Concentration), NOEC (No-Observed-Effect Concentration), and LOEC (Lowest-Observed-Effect Concentration), which help determine a safe concentration for the use of PB-AgNP-based technologies;
f. Study of the toxicokinetics of PB-AgNPs in organisms of different trophic levels;
g. More research on ecotoxicity of PB-AgNPs in more environmentally relevant conditions and field studies.

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