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Nano-enabled pesticides for sustainable agriculture and global food security

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Abstract

Achieving sustainable agricultural productivity and global food security are two of the biggest challenges of the new millennium. Addressing these challenges requires innovative technologies that can uplift global food production, while minimizing collateral environmental damage and preserving the resilience of agroecosystems against a rapidly changing climate. Nanomaterials with the ability to encapsulate and deliver pesticidal active ingredients (AIs) in a responsive (for example, controlled, targeted and synchronized) manner offer new opportunities to increase pesticidal efficacy and efficiency when compared with conventional pesticides. Here, we provide a comprehensive analysis of the key properties of nanopesticides in controlling agricultural pests for crop enhancement compared with their non-nanoscale analogues. Our analysis shows that when compared with non-nanoscale pesticides, the overall efficacy of nanopesticides against target organisms is 31.5% higher, including an 18.9% increased efficacy in field trials. Notably, the toxicity of nanopesticides toward non-target organisms is 43.1% lower, highlighting a decrease in collateral damage to the environment. The premature loss of AIs prior to reaching target organisms is reduced by 41.4%, paired with a 22.1% lower leaching potential of AIs in soils. Nanopesticides also render other benefits, including enhanced foliar adhesion, improved crop yield and quality, and a responsive nanoscale delivery platform of AIs to mitigate various pressing biotic and abiotic stresses (for example, heat, drought and salinity). Nonetheless, the uncertainties associated with the adverse effects of some nanopesticides are not well-understood, requiring further investigations. Overall, our findings show that nanopesticides are potentially more efficient, sustainable and resilient with lower adverse environmental impacts than their conventional analogues. These benefits, if harnessed appropriately, can promote higher crop yields and thus contribute towards sustainable agriculture and global food security.

Global food production has more than tripled over the past half century during the Green Revolution[1]. It has benefited from the intensive use of pesticides, fertilizers, water (~70% of global freshwater use)[2] and energy (6–30% of global energy consumption)[3] in agriculture. Yet, this period of agricultural intensification has also caused problems[4]. Of particular concerns are the inefficient overuse of pesticides and thus ineffective control of agricultural pests. Nearly 4 million tonnes of pesticides are used annually, with often only a small amount (1–25%) reaching the target organisms, leaving a large proportion released into the environment as a potential hazard[5]. Ineffective control of agricultural pests and plant diseases can account for ~20–40% of global crop losses, causing an economic drop of around US$220 billion per year[6]. Changes in global climate, desertification and escalating land degradation, in combination with other global change stresses, are likely to exacerbate these losses[7].

Breakthroughs in scientifically sound and evidence-driven technologies offer new opportunities to address the challenges associated with sustainable agriculture. Nanotechnology and nanomaterials have the potential to boost the agriculture industry through their nanospecific properties (for example, small size, rich and tunable surface chemistry, high efficiency and more resilience)[8]. A systematic analysis of technology-readiness and the performance of nanotechnology-enabled products in the agriculture industry demonstrated that nanopesticides could benefit sustainable agriculture practices, particularly responsive nanopesticides with stimuli-responsive delivery platforms[9]. A 2018 analysis integrating laboratory studies and field trials on pest control efficacy indicated that responsive nanopesticides are, on average, 24% more efficient than their non-nanoscale analogues[10]. Responsive nanopesticides are therefore seen as one of the key drivers in accelerating sustainable agriculture in the future.

The development of responsive nanopesticides enables key nanospecific properties to be exploited[8]. For instance, the responsive nanoscale delivery platform (RNDP) of nanopesticides can increase active ingredient (AI) solubility, reduce premature AI loss and improve AI adhesion on plant foliage. Notably, the RNDP can provide controlled, targeted and synchronized release of AIs to maintain available long-term optimal concentrations against agricultural pests (increased efficacy to target organisms with less exposure to non-target organisms). Together, these benefits can enhance crop growth and yield quantity and quality (for example, sugar, organic acid and protein contents). Collateral benefits behind these opportunities include the need for less resources (raw materials, processing energy and costs)[11] and reduced environmental footprints.

Global crop yield decline is often a result of an overall reduction of plant vigour and resilience to biotic and abiotic stresses (for example, heat, drought and salinity) in a rapidly changing climate[7,12]. This is partially due to the loss of the soil's ability to suppress disease (that is, soil suppressiveness) and rhizosphere microbiome diversity and balance, which compromises plant health and increases opportunistic soil-borne pathogen activity[7,12]. Responsive nanopesticides may have the potential to resume soil suppressiveness in counteracting root colonization by soil-borne pathogens through harnessing the rhizosphere microbiome (for example, enhancing microbial abundance, structure and diversity)[12]. This could improve soil health and rhizosphere microbiome resilience, enhance plant immunity against stresses and ultimately benefit crop production.

Here, we provide a comprehensive analysis of the key properties of a wide range of nanopesticides compared with their non-nanoscale analogues in combating agricultural pests (Box 1). The analysis includes comparisons of efficacy (direct inhibition efficiency) against target organisms, toxicity toward non-target organisms, premature loss, foliar adhesion and leaching potential of the AIs in soil. Special focus is on the RNDP to overcome various emerging biotic and abiotic stresses in a rapidly changing climate. In this Analysis, we define nanopesticides as pesticidal particles with a size less than 500 nm. Thus far, no consensus has been reached on the size definition of nanopesticides, but an analysis of the literature suggests that nanopesticides up to 500 nm in size can retain nanoscale-typical properties and functions[10,13,14].

Classification of nanopesticides

We analysed 36,658 patents (Fig. 1) and 500 peer-reviewed journal articles (Supplementary Tables 1 and 2, see also Methods section), through which we identified two major types of nanopesticides. Type 1 are metal-based (for example, Ag, Cu and Ti) nanopesticides (Fig. 1a), and Type 2 include materials in which the AIs are encapsulated by nanocarriers (for example, polymers, clays and zein nanoparticles (NPs); Fig. 1b). For Type 1 nanopesticides, Ag-, Ti- and Cu-based nanomaterials (NMs) are the most common analytes (Fig. 1a). These NMs have strong antimicrobial activity rendered by adhesion, dissolution (for example, Ag^+ and Cu^{2+} ions), cytotoxicity and oxidative stress (reactive oxygen species, ROS), and genotoxicity-induced cell death (Fig. 2)[15]. These nanopesticides can control plant pathogens, including bacteria (for example, *Escherichia* (N = 172) and *Staphylococcus* (N = 148)) and fungi (for example, *Candida* (N = 64) and *Fusarium* (N = 24); Supplementary Table 1). For example, the fungus *Fusarium* poses a great threat to various crop plants, including wheat, soybean, tomato and radish[16]. The strong antimicrobial activity of these nanopesticides is manifested by low minimum inhibitory concentration (MIC) values, for example, the 75th and 25th percentiles of Ag-based nanobactericide MIC values against *Escherichia coli* and *Staphylococcus aureus* are in the ranges 4–65.5 and 8–100 μg ml^{-1}, respectively.

Type 2 nanopesticides focus more on the RNDP, showing potential to meet sustainable agriculture goals. Most nanocarriers are biocompatible, cost-effective and stimuli-responsive, and are categorized into two major groups: polymer- and clay-based (Fig. 1b). Chitosan, cellulose and polylactide are common natural polymers for making nanocapsules, nanospheres, nano(hydro)gels and nanomicelles for AIs. Mesoporous silica NPs (MSNs) and montmorillonite are typical clay-based NMs with demonstrated high AI encapsulation capacity. Other emerging nanocarriers include advanced nanocomposites and two-dimensional (2D) NMs with large specific surface areas that facilitate AI loading (Fig. 1). For Type 2 nanopesticides, most AIs are conventional pesticides, such as the insecticides avermectin (N = 32) and essential oils (that is, botanically derived oils; N = 32), as well as the herbicides atrazine (N = 13), 2,4-dichlorophenoxyacetic acid (2,4-D) and glyphosate (Supplementary Table 2). Taken altogether, we identified 569 Type 1 and 1,094 Type 2 nanopesticides (Fig. 1 and Supplementary Tables 1 and 2).

Physicochemical properties of nanopesticides

The advantage of nanotechnology is its ability to maximize the performance of NMs by harnessing their unique nanoscale properties (for example, large specific surface area and tunable surface chemistry), while minimizing potential nanospecific risks. The physicochemical properties of NMs affect their efficacy, fate, transport and environmental and human health impacts. Both types of nanopesticides have shared properties of interest, such as size, uniformity, surface area and surface charge. Type 2 nanopesticides have additional novel properties that impact AI release for pest control, including encapsulation efficiency (EE), loading efficiency (LE) and release efficiency (RE) of AIs.

The size of nanopesticides generally varies from a few to 500 nm (N = 900; Fig. 3 and Supplementary Fig. 1). The mean sizes of Ag- and Cu-based (Type 1) nanopesticides measured by transmission electron microscopy (TEM) and dynamic light scattering (DLS) are 22.8 and 53.5 nm and 59.2 and 153.2 nm, respectively (Fig. 3). Compared with Type 1 nanopesticides, the mean TEM and DLS sizes of Type 2 nanopesticides are much larger, lying in the ranges 166.7–251.5 and 273.0–358.6 nm, respectively (Fig. 3 and

Supplementary Fig. 1b). In particular, the 75th percentile size of Type 2 nanopesticides reaches ~450 nm.

The polydispersity index (PDI) reflects the degree of uniformity of particle size distribution in a suspension. A PDI value below 0.2 indicates particles with a narrow size range[17]. Type 2 nanopesticides with nanocarriers often have lower PDI values than Type 1 nanopesticides, which is particularly true for polymer-enabled nanoformulations (Supplementary Fig. 1c). Chitosan, cellulose and polylactide (Supplementary Tables 1 and 2) can stabilize the nanoformulations by electrostatic and/or steric repulsion, resulting in stable colloidal suspensions for months (up to a year) with a minor alteration to their PDIs (generally <10%)[18].

EE, LE and RE characterize the degree of assemblage and release of AIs (two opposite processes) from nanocarriers. High EE values (70.0–84.6%; Supplementary Fig. 1d) are reported due to the large specific surface area of these nanocarriers (194.1–426.2 $m^2 g^{-1}$; Supplementary Table 2). Among these, zein NPs, a prolamin class protein found in maize with diverse non-polar amino acids[19], have the highest EE value (84.6%). The hydrophobic properties of zein NPs enable a high degree of encapsulation of various hydrophobic AIs (for example, essential oils). Compared with EE, the LE values are much lower, ranging between 13.0% and 27.6% (Supplementary Fig. 1d). Note that the mean and 75th percentile RE values of AIs vary between 52.1% and 90.3% (Supplementary Fig. 1d), indicating that nanocarriers cannot release 100% of the AIs. This suggests that nanopesticides may present a lower collateral risk to the environment than their non-nanoscale analogues (with complete release of unencapsulated AIs). Nonetheless, more research is still needed to improve the overall potential of the RE for nanopesticides on site, given that 9.7–47.9% of AIs are not released to reach the target organisms. Also, data need to be collected in field conditions to better characterize AI release regimes from different nanocarriers.

Our analysis shows that the 100-nm upper-size limit often assumed for NMs is not suitable for nanopesticides[10], because nanoformulations larger than 100 nm can still retain the novel properties and functions claimed at the nanoscale. An upper-size threshold of 500 nm is proposed here for nanopesticides (Fig. 3), which is consistent with the recent regulation of nanopesticides by the European Union[20]. Although nanopesticides do exist with sizes above 500 nm, they are the exception, because research efforts have typically been focused on the sub-500-nm regime (Fig. 3). There is currently a lack of data for nanopesticides above 500 nm, which may artificially skew the results. As such, these data should be analysed cautiously until more data are available. In terms of size characterization, a combination of different techniques, preferably TEM ($N = 367$) and DLS ($N = 446$; Fig. 3 and Supplementary Fig. 1), is recommended to better characterize the size and uniformity of nanopesticides in complex environmental matrices. Large datasets and essential characterization under more realistic field conditions are critically needed to decipher the underlying mechanisms of nanopesticide action to unlock the efficacy of nano-agrochemicals by enhancing their nanospecific effects[9,10].

Nanopesticides show improved ability to control agricultural pests

Among the 500 papers that we analysed, we identified 314 studies comparing the overall efficacy of nanopesticides and their non-nanoscale analogues against target organisms (Fig. 4a). Various indices, such as inhibition efficiency, mortality efficiency, repellent efficiency and disease incidence against target organisms, were monitored (Supplementary Tables 1 and 2), so normalized efficacy was used for comparison (Fig. 4a). The target organisms tested included insects, weeds, bacteria and fungi, which are responsible for blight, powdery mildew and black rot canker in plant crops such as rice, maize and tomato.

Our analysis reveals that nanopesticides are, on average, 31.5% ($N = 314$) more efficient than their non-nanoscale analogues (Fig. 4a). The independent samples *t*-test results show that the efficacy difference is significant ($p < 0.05$; Supplementary Table 3). A similar but lower efficacy increase (24%) was reported by Kah et al.[10] when comparing the efficacy between 42 pairs of non-nanoscale and nanopesticides in 2018. The higher efficacy (31.5% versus 24%) reported here (314 versus 42 comparisons) is partly because Type 2 nanopesticides, which were not included by Kah et al.[10], exhibit improved properties and performance for pest control. For example, an amphiphilic chitosan nanocarrier (168–214 nm) with octadecanol glycidyl ether as the hydrophobic group and sulfate as the hydrophilic group was used to encapsulate rotenone (botanical insecticide) using a reverse-micelle approach[21]. The self-assembled chitosan@rotenone nanoinsecticide contained 20.6–26.0 mg ml^{-1} rotenone due to micelle encapsulation of the insecticide in the nanocarrier, leading to a fourfold higher rotenone concentration than unencapsulated rotenone in water (0.002 mg ml^{-1})[21]. The nanoinsecticide exhibited controlled and sustained release of rotenone by altering the micelle structure and diffusion rate (that is, an initial slow release between 0 and 110 h, followed by a burst release between 110 and 150 h, followed by another slow release thereafter until 230 h; the proposed mechanisms are illustrated in Supplementary Fig. 2). Another biosafe polymer, polylactide (approved by the US Food and Drug Administration), was used to fabricate larger-sized polylactide@avermectin nanoinsecticides (344, 460, 615 and 827 nm)[22]. The nanoinsecticides showed sustained (240 h) and size-dependent release of AI, that is, the avermectin release rate correlated inversely with particle size. These benefits contributed to a higher insecticidal efficacy against aphid larvae (median lethal concentration, LC_{50} = 4.8, 8.8, 10.6 and 12.5 mg l^{-1} for particle sizes of 344, 460, 615 and 827 nm, respectively) as compared with non-nanoscale avermectin (LC_{50} = 23.5 mg l^{-1})[22]. These findings show the potential of nanotechnology to tune particle size and other properties to achieve better and more sustainable integrated pest management (IPM).

Nanopesticides can enhance crop yield and nutritional value

Nanopesticides, if used appropriately, have the potential to enhance crop yield, food safety and nutritional value. This has been demonstrated in a recent study that analysed the biomass, yield and nutritional quality of crop plants after exposure to Type 1 metal-based nanopesticides[23]. The results showed that the nutritional value of vitamin, organic acid, protein, amino acid and antioxidant content of crops, including their edible tissues, was enhanced by 2.8%, 9.6%, 9.9%, 10.8% and 18.0%, respectively[23]. Enhancements in sugar, fatty acid, chlorophyll, carotenoid and essential element (for example, P, K, Ca, Mg, S, Fe, Si, Mn, Cu and Zn) content have also been increasingly reported for various plants with Type 1 nanopesticides (for example, Ag-, Ti-, Cu- and Zn-based NMs; Fig. 1a)[24–30]. Potential factors contributing to these enhancements include[8] (1) increased light absorption and electron-transfer efficiency by improving the structure and function of chlorophyll, (2) improved CO_2 assimilation and water uptake during photosynthesis, (3) efficient scavenging of excess ROS (Figs. 2g), (4) suppression of pathogenic activity (Fig. 2a–f) and (5) enhanced plant immune response through beneficial modulation of metabolite profiles in plants.

More importantly, understanding the nexus of nanopesticides, soil, the rhizosphere microbiome and nutrients in a plant–soil system (Fig. 5) is needed to maximize their full benefits. Adding metal-based nanopesticides to soil can alter the bioavailability and recycling of macronutrients (for example, C, N, P and S) by modifying the abundance, structure and network functioning of the rhizosphere microbiome (for example, archaea, bacteria and fungi)[31]. The bioavailability of micronutrients (for example, Fe, Mg, Cu and Zn) can also be improved by nanopesticides through the modulation of cell signalling, composition and rhizosphere microbiome function[24]. These benefits can improve plant performance, for example, enhanced yield and nutritional value[25], which, in turn, can benefit soil health and agroecosystem resilience and biodiversity. However, a recent study probing long-term (117 days) impacts of Ag nanopesticides (100 mg kg^{-1}) on the maize rhizosphere microbiome showed undesirable effects on microbial abundance, the nitrogen cycle and crop yield[32]. Future work is needed to understand how realistic concentrations of nanopesticides affect the rhizosphere microbiome, crop production and agroecosystem health in field conditions over the long term.

High efficacy of nanopesticides in field trials

Although field studies ($N = 47$) represent a minority of all comparisons ($N = 314$) made against target organisms (Fig. 4a), they provide valuable insights for their future large-scale applications. Most field trials examined Type 1 nanopesticides, such as Cu-based NMs (for example, Cu, CuO, $Cu_3(PO_4)_2$ and $Cu(OH)_2$), while only eight tested Type 2 nanopesticides. Disease suppression reflected by the reduction in disease incidence or the area under disease progress curve (AUDPC) is commonly used for comparing efficacy.

The overall efficacy of nanopesticides (23 Type 1 and 24 Type 2) against target organisms in field tests is on average 18.9% higher than the non-nanoscale analogues (Fig. 4a), although the difference is not significant at the $p < 0.05$ level ($p = 0.223$; Supplementary Table 4). For Type 1 nanopesticides, foliar spraying of 150 nm $Cu_3(PO_4)_2$ nanosheets suppressed AUDPC by 26% and increased fruit yield by 46% (when compared with $CuSO_4$ salt treatment) in full life cycle (14 weeks) field trials. This is largely a result of the modulation of crop nutrition, which activates plant defence and antioxidant systems against *Fusarium* wilt disease[33]. Seedling foliar treatment with 30 nm CuO nanopesticides also reduced AUDPC by 69%, induced by *Fusarium oxysporum* and *Verticillium dahlia*, while increasing eggplant and tomato yield by 64% (ref. [34]). These observed benefits are partly due to the fact that Cu-based nanopesticides behave as nanofertilizers and thus can enhance plant immunity against pathogens through an increase in essential micronutrient (Cu) supply[34]. These findings are at the centre of sustainable nanopesticide development; tuning NM properties (for example, size, morphology, composition and dissolution behaviour)[16] to suppress soil pathogens during an entire season (through early seedling foliar treatment) could truly maximize agricultural benefits.

For Type 2 nanopesticides, similar improvements in disease control and crop growth are also reported. An ~27% decrease in AUDPC and ~70% increase in fruit yield were observed when watermelon seedling foliar tissue was immersed in a chitosan-coated mesoporous silica nanopesticide suspension (500 mg l^{-1})[35]. Mechanistically, both chitosan and Si can stimulate plant defence and antioxidant systems against diseases. Other Type 2 nanopesticides tested include nanoherbicides and nanoinsecticides in which conventional herbicide (2,4-D)[36] and insecticide (abamectin)[37] were encapsulated within nanocarriers, respectively. The nanocarriers offered sustained and controlled release of AIs against biotic stresses from weeds and insects. These nanopesticides, when applied at a lower dose (a third lower)[36,38], exhibited greater efficacy against target organisms for a longer period than the conventional pesticides. These approaches enable sustainable and cost-effective control (low material and labour costs due to lower dose and use frequency)[35] of agricultural pests, while minimizing collateral environmental damage from excessive release of AIs.

Through a personal communication with the crop protection industry, Kah et al.[39] stated that an improvement in efficacy, productivity or cost-saving of 20% is seen as a benchmark threshold to ensure the competitiveness of a nanoformulation. Our analysis shows the potential of nanopesticides (on average 18.9% increment in efficacy; Fig. 4a) in field experiments. Nonetheless, more rigorous performance tests with well-designed comparisons are critically needed in geographically diverse regions with robust variation in soil type, water regime and climatic conditions over multiple plant growth seasons. Those nanopesticides already showing high efficacy in small-scale field experiments (for example, 47% higher in pesticidal efficiency compared with non-nanoscale pesticides)[37] are good candidates for initiating large-scale field demonstrations under different climatic scenarios.

Stress resilience of nanopesticides in a rapidly changing climate

Global agricultural productivity is increasingly compromised by climatic constraints, such as the increasing frequency of heatwaves, droughts, flooding and other weather extremes[40]. These abiotic stresses can reduce global crop yield by over 50% (ref. [41]). Among these, heat and drought garnered unprecedented warnings in the 2020 IPCC Climate Change and Land Report (https://www.ipcc.ch/srccl). Models forecast that warmer climates would reduce yields of soybean, maize, rice and wheat by 10.6%, 7.1%, 5.6% and 2.9%, respectively, not even considering other indirect losses associated with warmer climates (more pests and plant diseases)[42]. Therefore, agriculture practices must bolster resilience to confront the rapidly changing climate. Responsive nanopesticides have the potential to enhance system resilience and adaptation to biotic and abiotic stresses.

Responsive nanopesticides, particularly Type 2 nanopesticides, can be tuned to deliver AIs upon heat stress. Our analysis ($N = 30$) on thermosensitive nanopesticides shows that when the temperature is increased from 10 to 50 °C, the cumulative release of AIs from nanocarriers is increased by 25.8% ($p = 0.001$; Fig. 4b and Supplementary Table 6). For example, the thermosensitive poly-dopamine–graphene oxide nanocarrier was used to encapsulate hymexazol[43]. The dispersion temperature of the nanocarrier can rapidly reach 50.9 °C within 10 min (compared with 28.8 °C for technical hymexazol). This indicates that the nanofungicide may release hymexazol in a temperature-controlled fashion, even when the temperature is above 28.8 °C (ref. [43]). This is important as the nanofungicide may potentially enhance crop growth by releasing AI during fast-growing summer months (for example, 28.8 °C < T < 40 °C), when the threat from target pathogens (fungi, although these are also sensitive to humidity) and the competition for resources among competing organisms (weeds) are both high.

Also, responsive Type 2 nanopesticides can effectively deliver AIs in high-salinity environments. A faster and greater release of 2,4-D was observed for MSN@2,4-D nanoherbicide in a background solution of 0.1 M NaCl compared with in pure water (98% versus 57% release)[44]. This is due to the electrostatic attraction between negatively charged chloride ions (NaCl) and positively charged trimethylammonium groups on MSNs that promotes the release of 2,4-D. The MSN@2,4-D nanoherbicide also showed temperature (20–40 °C) and pH (3–10) responsive release, contributing to a strong inhibition of target organisms with no phototoxicity toward non-target organisms (wheat)[44]. Additionally, MSNs can promote plant growth by enhancing photosynthesis[45]. MSN-enabled nanopesticides are thereby seen as a competitive alternative to mitigate multiple abiotic stresses (heat and salt), while potentially maintaining or promoting crop growth.

Similarly, Type 1 nanopesticides can also strengthen plant immunity to or tolerance against various stresses (through defence molecules, secondary metabolites, ROS and phytohormones; Fig. 6)[46]. Depending on the physicochemical properties (for example, size, charge and hydrophobicity), application modes (foliar delivery, hydroponics and soil) and applied concentrations, Type 1 nanopesticides can augment plant tolerance and resilience against various stresses, while promoting plant growth and yield[47]. For example, low concentrations of Ag, CuO, TiO_2 and ZnO nanopesticides have been documented to enhance plant growth and augment plant resistance against viruses and fungi (*F. oxysporum*)[33,48], drought[49], cold[50], salinity[51] and heavy metal contamination[52]. Drought reduced grain yield of sorghum and wheat by 76% and also compromised crop quality by reducing nutrient (N, P, K and Zn) acquisition by 22–63% (ref. [49]). However, soil amended with 1–5 mg kg^{-1} ZnO nanopesticides (which also act as nanofertilizers) under the same drought conditions enhanced crop grain yield by 22–183% and increased nutritional quality by 11–123%, respectively[49]. Such data exemplify the potential of Type 1 nanopesticides in mitigating various stresses and facilitating crop yield.

Overall, our analysis shows that Type 2 nanopesticides are more mature in curbing abiotic stresses (for example, heat and salinity). Conversely, Type 1 nanopesticides perform better against biotic (pathogen) and other abiotic stresses (for example, drought), albeit with fewer published studies. A desirable approach will be the development of next-generation nanopesticides based on a combination of Type 1 (metal-based NMs as AIs) and Type 2 nanopesticide components (with an RNDP that tunes AI release). This could provide potential to mitigate multiple overlapping stresses (heat, drought and pathogen) and thus bolster agricultural productivity in a changing climate. Nonetheless, field trials evaluating the responsive releasing behaviours of AIs under more climatically relevant conditions (for example, temperature variation by climate change) are needed.

Reduced adverse impacts from nanopesticides on non-target organisms

To meet sustainable agriculture goals, nanopesticides should render equivalent, or ideally less, adverse impacts (toxicity) toward non-target organisms. Our analysis ($N = 59$) shows that nanopesticides exhibit 43.1% less toxicity at the $p < 0.05$ level ($p = 0.001$; Fig. 4a and Supplementary Table 5) when compared with their non-nanoscale analogues. This is primarily due to the RNDP, which delivers AIs to target organisms and releases AIs in response to certain stimuli (for example, biotic and abiotic triggers), both of which minimize the exposure to non-target organisms. For example, chitosan-grafted essential oil bio-nanopesticides showed lower cytotoxicity to cell lines (3T3 and V79), less ecotoxicity toward fish species and lower phototoxicity to maize and bean (for example, <5% inhibition on seed germination)[53]. Long-term (365 days) repeated exposure of a target soil agroecosystem and a non-target wetland system to $Cu(OH)_2$ nanopesticides showed limited deleterious effects on soil biodiversity (bacteria and fungi communities)[54]. Nevertheless, marked shifts in microbial communities (protists and algae) occurred in the wetland system. These observations suggest that non-target aquatic communities are likely more sensitive to long-term exposure to nanopesticides than target terrestrial ecosystems. Future environmental risk assessment for nanopesticides should consider non-target organisms and unanticipated secondary effects in various terrestrial and aquatic ecosystems.

Minimized premature loss and enhanced foliage adhesion of AIs

Premature loss of conventional pesticides occurs through ultraviolet (UV) radiation, photolysis, volatilization and spray drift, which lowers use efficacy of conventional pesticides for plant leaves (10–30% or lower) and target organisms (~0.1%)[14]. Compared with conventional pesticides, the RNDP can reduce AI premature loss due to UV radiation, photolysis and volatilization by 41.4% ($N = 105$; Fig. 4b and Supplementary Table 7). Depending on the type of nanocarrier (Fig. 1b), they exhibit varying degrees of UV-shielding and antiphotolysis ability. For instance, chitosan@carbon (shell@ core) nanostructures prolonged the durability of emamectin benzoate 208-fold (time for 50% degradation (T_{50}) is 666.5 h compared with 3.2 h) against UV radiation[55]. MSNs improved the anti-UV properties of AIs in nanoformulations (AI loss in nanopesticides versus conventional pesticides is 8.5% versus 100%)[56]. These findings show the potential of these nanocarriers to be biosafe and cost-competitive in protecting AIs against premature loss.

Inadequate adhesion and retention of conventional pesticides on plant foliage further restrict use efficacy. The RNDP can improve AI use efficacy by enhancing their adhesion (lower contact angle) and antiwashing properties[14]. The contact angle on plant foliage is lowered by 16.0° ($N = 69$; Fig. 4b) when AIs are encapsulated within nanocarriers. AI adhesion can also be enhanced by tuning nanocarrier surface chemistry and functional groups (NH_2, CH_3CO and COOH). Positively charged amine groups interact with leaves through strong hydrogen bonding, covalent bonds and electrostatic attraction, whereas carboxy groups interact through hydrogen bonds and electrostatic repulsion. Thereby, the adhesion propensity follows the following order: NH_2 > CH_3CO > COOH (ref. [57]). MSNs can increase AI adhesion on plant foliage and also improve AI anti-washing properties[58]. Compared with uncoated cyantraniliprole, MSNs increased the anti-washing efficiency of cyantraniliprole by 82% after nine cycles of simulated rainwater washing tests[58]. These observations suggest that by tuning the surface properties of nanocarriers, foliar adhesion and antiwashing attributes of AIs on plants under extreme conditions can be optimized.

The RNDP can also limit the vertical leaching and lateral run-off of nanopesticides in agricultural soils, reducing the collateral damage to surface water and groundwater. Nanocarriers can lower the transport and leaching potential of conventional pesticides by 22.1% in soil (Fig. 4b and Supplementary Table 8). The high leaching potential of 2,4-D (97.3% breakthrough) was reduced more than a half in soil-packed columns once embedded into MSNs (48.4% breakthrough)[44]. The cumulative leaching of atrazine in the soil after 20 rinses decreased from ~46% to ~10% by incorporation into graphitized carbon, because graphitized carbon immobilizes atrazine through physical interactions, chemical bonding and **π–π** interactions[59]. These findings have important implications for sustainable agriculture. However, the dataset is relatively small ($N = 9$) and additional robust tests under field conditions are required.

Fate and transport of nanopesticides in a plant–soil system

Understanding how nanopesticides interact with plant species, as well as their transport and transformation in a plant–soil system, is important to ensure successful IPM. After foliar spray or root application, nanopesticides can enter plant tissues through shoot or root openings (Fig. 5). For instance, the cuticle and epidermis facilitate fast entry of small (14–32 nm) polymer-based nanobactericide into the mesophyll and phloem tissues of tomatoes[60]. Hydathodes (a few to several micrometres) allow direct entry of large (256–345 nm) polymer@atrazine nanoherbicide into weed mesophyll and vascular tissues[61]. After entering plant tissues, nanopesticides can translocate through apoplastic (in extracellular spaces, for example, cell walls and xylem vessels) and symplastic (for example, plasmodesmata and sieve plates) pathways (Fig. 5b,c). Although biological barriers routinely possess size-limited structures (for example, 5–20 nm cell walls), thus allowing smaller NPs to pass through[62], large nanopesticides (~80–200 nm)[63,64] can still be internalized into cells. This is due to their interactions with cell walls that facilitate nanopesticide internalization by processes such as endocytosis, pore formation and others (for example, crack-entry mode at lateral root junctions; Fig. 5d). Damaged junctions or tissues due to stresses or diseases are also target passages for nanopesticides. Once entering the cell cytoplasm, nanopesticides can interact with cellular organelles (chloroplasts and mitochondria), proteins and DNA (Figs. 2g and 6e), likely affecting the physiological, biochemical and metabolic reactions or processes of plants.

Nanocarriers can be tuned to release AI before and after entering the plant (a smart-release process by the RNDP; Fig. 5b,c) by altering the interaction between the analyte and biological tissues. Nanocarriers can facilitate AI entry and subsequent translocation across plant compartments by enhancing the affinity to leaf/root cuticles and organelles[65]. For example, AIs can be delivered to targeted locations within a plant at the subcellular level (inhibiting the photosynthesis of the chloroplasts of weeds)[66] by tuning their physicochemical properties (for example, shape). Hexagonal and rod-shaped clay nanocarriers can deliver AIs to different cellular destinations (cytoplasm and nucleus)[67]. The RNDP can also enhance plant photosynthesis and growth by delivering nutrients (N and P) to specific cellular organelles, such as chloroplasts and mitochondria (that is, by acting as nanofertilizers).

In a typical plant–soil system, rhizosphere microbes, symbiotic microorganisms, organic matter and rhizosphere deposits can affect nanopesticide uptake and translocation in plants. Organic matter and root exudates may associate with the nanopesticide surface, displacing or overcoating the outer layer by the nanocarriers[68]. Root exudates can also facilitate nanopesticide accumulation in root epidermis (Fig. 5b). The accumulated nanopesticides at the epidermal layer can then be translocated by the apoplastic route to the endodermis, xylem and other plant tissues (Fig. 5c). Applying nanopesticides to soil can alter the rhizosphere microbiome, depending on the agricultural practice (for example, cultivation and row crop agriculture)[69] and nanopesticide type (Fig. 5f). A microbial network analysis can elucidate ecological interactions of rhizosphere microbiomes and their response to environmental changes (abiotic and biotic stresses). Harnessing new knowledge on how nanopesticides affect the rhizosphere microbiome through network analysis may aid the development of effective nanopesticides for pest management, while preserving microbiome integrity and soil health[12].

The translocation and transformation of nanopesticides (for example, Ag-based) in plants can be identified at the subcellular level by integrating multiscale techniques such as three-dimensional micro-/nano-X-ray computed tomography, micro-X-ray fluorescence and micro-X-ray absorption near-edge structure analyses (Fig. 5e). These synchrotron-based techniques can differentiate distribution and speciation changes (for example, by dissolution, redox and chelation reactions) of nanopesticides (compared with their non-nanoscale analogues) in plants[70]. Although accessibility to these types of analytical platforms can be limited, the information gathered is highly useful for evaluating the risk and ecotoxicological implication of nanopesticides.

The location of nanopesticides within plants may affect their trophic transfer in the food chain and associated impacts on the ecosystem and human health. Nanopesticides that move along the phloem will likely accumulate in plant organs such as fruits and grains; caution should be exercised to minimize the ingestion of these tissues by animals and humans. Trophic transfer of TiO_2 nanopesticides in the algae–*Daphnia* food chain has been reported to increase with decreasing particle size (from 100 to 25 nm, and to 5 nm)[71]. This may indicate a higher trophic transfer potential and associated ecological risk of smaller particles in aquatic ecosystems. Human exposure to nanopesticides could occur through the consumption of nanopesticide-containing food (crops and aquatic products). Future research should focus on using mesocosms and field experiments under agriculturally relevant conditions to assess the trophic transfer potential of nanopesticides, as well as their potential impacts and environmental transformations (for example, sorption, photoreaction and hydrolysis)[72] on ecosystem function and human health.

Adverse effects and toxicity of nanopesticides

Nanopesticides have obvious pesticidal activity and as such can exhibit toxicity toward non-target organisms. The observed adverse impacts and toxicity vary depending on, for instance, nanopesticide properties, species of non-target organisms, exposure route, concentration, duration and environmental matrices. Commercial Ag- (Zerebra Agro) and Cu-based (Kocide 3000) nanopesticides can cause negative impacts on plants, microcrustaceans and soil microbiota at the physiological, metabolic and genetic levels. These include structural changes of plant tissues, reduction of chlorophyll content, alteration of the antioxidant defence system, metabolic reprogramming and genetic over-regulation (Fig. 6)[73]. Nanopesticides can also impair soil microbial activity. Nonetheless, these adverse effects are reported to be limited at agriculturally relevant concentrations (0.2 and 0.1 mg kg^{-1} for Zerebra Agro and Kocide 3000, respectively) in long-term trials (1 year), potentially due to inherent soil self-recovery and resilience[74]. However, more research is needed for other nanopesticides and exposure scenarios with a relatively high market potential (for example, see Fig. 1). The adverse impacts and toxicity of nanopesticides are also likely to occur outside of terrestrial systems (for example, aquatic ecosystems). Studies examining the adverse effects of a Cu-based nanopesticide in marine systems demonstrated that the bioavailable form of the nanopesticide was present when treated lumber (used as a nanofungicide) was introduced into seawater[75,76]. Further, when the same Cu-based nanopesticide was exposed to benthic communities in laboratory studies, statistically significant adverse effects were detected[77]. Therefore, despite the benefits of nanopesticides, when they are transported beyond agricultural systems, they may have negative ecological impacts, highlighting the presence of data gaps that should be addressed.

The effects of certain Type 2 nanopesticides on soil microbiota at the genetic level have recently been reported. Type 2 nanopesticides did not substantially alter soil microbiota based on real-time quantitative polymerase chain reaction (qPCR) analysis of N-cycling genes, particularly under long-term (300 days) exposure. Importantly, treating soil with nanocarriers alone (without AIs) can stimulate beneficial N-cycling bacterial growth[78]. This underscores that field application of encapsulated nanopesticides may introduce additional benefits, because AIs and nanocarriers will be separated in soil over time. Compared with metal-based nanopesticides, encapsulated nanopesticides exhibit reduced negative impacts on soil microbiota, such as N-cycling bacteria[79]. This may be due to the larger size (Fig. 3) and size-dependent response (less dissolution and less concentrated release of metal ions) of encapsulated nanopesticides, making these safer towards soil biota and the rhizosphere microbiome that control nutrient cycling and plant growth. Nonetheless, caution is needed due to the potential of Type 2 nanopesticides crossing biological barriers in the human body, and thus the potential risk to human health from occupational exposure[13]. The comprehensive framework illustrated by Kah et al.[13], using a tiered approach, is useful for assessing the potential human health risk of nanopesticides.

Toxicity evaluation of nanopesticides using multiomics

Multiomic[80] techniques have emerged as a robust platform to advance mechanistic understanding of the toxicity of nanopesticides (including nanocarriers; Fig. 1a) at molecular, genetic, cellular and organismal levels under the adverse outcome pathway framework (Fig. 6a)[81]. The multiomics approach integrates genomics, transcriptomics, proteomics and metabolomics analyses to characterize stress responses, tolerance pathways and mechanisms of action of biota upon nanopesticide exposure and biotic and abiotic stresses (Fig. 6c).

Arabidopsis thaliana is commonly used as a model plant to assess stress and toxicity responses to Type 1 metal-based nanopesticides (for example, Ag[82] and CuO[83]). Venn networks (Fig. 6b), heatmaps (Fig. 6c) and gene correlation network analyses (Fig. 6d) enable identification of the proteins and genes associated with altered metabolic function, stress response and detoxification (DNA repair, protein synthesis and ROS production) upon nanopesticide exposure. For example, plant defence responders of phytohormones, such as ethylene, abscisic acid and salicylic acid, are encoded by *SUB1*, *DRO1* and *HKT1* genes[40]. The identified candidate hormones, proteins and genes can potentially be used as molecular biomarkers for assessing the ecotoxicity of nanopesticides toward more complex organisms, such as crop species (wheat, rice, maize and soybean), wildlife and even humans.

Cellular assays of fungi, plants and cultured human tissues exposed to metal-based nanopesticides showed that mitochondria and chloroplasts are primary targets of nanopesticides (Fig. 6e). These two organelles maintain primary energetic and metabolic functions and modulate ROS (Fig. 2) and reactive nitrogen species ($NO_2^{\bullet-}$ and $ONOO^-$)[84] for cellular detoxification. Notably, these organelles exhibit a high degree of conservation in response to metal-based nanopesticides (similarly conservative gene ontology classes; Fig. 6e), ranging from simpler eukaryotic models (yeast *Saccharomyces cerevisiae*) to higher eukaryotes (*A. thaliana*) and human cells[85]. Therefore, integrating the omics data enables a mechanistic understanding of the toxicity of nanopesticides toward complex organisms in a plant–soil system, as well as in aquatic and other terrestrial ecosystems.

Convergence of nanotechnology and plant biotechnology

Precise delivery of nanopesticides to targeted plant cells and their subcellular compartments (chloroplasts, mitochondria and nuclei) can be achieved by integrating nanotechnology with plant bioengineering[86]. The delivery efficiency of nanopesticides to targeted subcellular compartments can be optimized by tuning the physicochemical properties of nanopesticides (for example, size, charge, shape and hydrophobicity), and thus modulate nanopesticide–lipid interactions within plant cells[86]. For example, by tailoring the size and surface charge of CeO_2 and SiO_2 nanopesticides, their delivery efficiency to targeted guard cells, extracellular spaces and chloroplasts in cotton and maize can reach 100%, 90.3% and 55.8–78.8%, respectively[87].

The convergence of nanotechnology with plant biotechnology approaches, such as CRISPR–Cas9 technology, also enables the co-delivery of nanopesticides and CRISPR–Cas9 cargoes into plants[88]. This could confer plant tolerance against biotic (pathogens) and abiotic (for example, heat and drought) stresses[89]. Potential plant candidates include commodity crops with large markets, such as maize, soybean and cotton[40]. Furthermore, nanotechnology can facilitate targeted co-delivery of nanopesticides and exogenous double-stranded RNA into plants using the RNDP (for example, polymer and clay; Fig. 1b)[90,91]. Additionally, plant nanobiotechnology can easily deliver gene silencing using microRNAs[92] to different plant species as a pest management platform, targeting improved nutrient profiles and enhanced crop productivity[93]. Nonetheless, prior to marking the bioengineered plants, studies must be conducted to ensure that their genes are not inadvertently transferred to native species.

Regulatory aspects and public perception

Estimates suggest that years of dedicated efforts with an estimated cost of US$0.25–1.2 billion are necessary to develop a complete quantitative risk assessment for engineered NMs and nano-enabled products[94]. More efforts and costs are required if nanopesticides are included, because these also involve co-formulants and other adjuvants. Like all pesticides under the Federal Insecticide, Fungicide and Rodenticide Act and the Toxic Substances Control Act, regulatory assessment is necessary for all aspects of pesticidal nanoformulations, including fate, transport, transformation, bioaccumulation, adverse effects and risk to the environment and human health[95].

Given that a large number of nanopesticides are or will soon be on the market (Fig. 1), it is essential to build a robust framework that can pre-screen, classify and group nanopesticides with similar hazard properties for adequate risk characterization and assessment[96]. Seeking similarities in the physicochemical properties (for example, particle size, nanocarrier type and release efficiency; Fig. 3 and Supplementary Fig. 1), toxicokinetic behaviours (for example, cellular pathways and responses to nanopesticides; Fig. 6) and ecotoxicological implications (for example, transfer in a plant–soil system; Fig. 5) of nanopesticides is crucial. This is because these characteristics will guide the development of a nanopesticide risk-assessment framework, pioneered by Kookana et al. using a tiered exposure–hazard–risk approach[97]. An exposure–hazard–risk chain evaluation that includes different life-cycle stages of nanopesticides in typical environmental matrices (water, soil, air and biota) is needed[95]. The gathered information will assist regulatory agencies in adopting an appropriate framework for nanopesticide risk assessment and management.

Public perception and consumer acceptance ultimately determine the success or failure of nano-enabled food products. Safety concerns surrounding nanopesticide-produced food closely link government regulators, policymakers, farmers, consumers and other stakeholders[9]. A multi-agency effort is needed to coordinate and address food safety concerns associated with nanopesticide applications. Effective risk communication will be a critical tool in this effort. In this regard, biosafe AIs (essential oils) and nanocarriers (chitosan, cellulose and zein NPs) of natural origin are perceived by the public as safer candidates for making nanopesticides; these will also encounter lower regulatory scrutiny as many of these materials are generally recognized as safe. Biogenic metallic (Ag and Cu) NMs that are synthesized by microorganisms (bacteria, fungi and algae) or plant extracts are also seen as safer alternatives for IPM and have higher levels of public acceptance[98].

Perspectives

Our results do not demonstrate that nanopesticides can achieve the 50/50 targets proposed by Cassman and Grassini[99], with a 50% increase in crop yield and 50% decrease in negative environmental externalities toward sustainable agriculture. However, based on the data included in this Analysis, our findings demonstrate a 31% increase in pesticidal efficacy and 43% decrease in toxicity, paired with other tangible benefits of nanopesticides, compared with their non-nanoscale analogues. These benefits (for example, enhanced foliar adhesion, improved crop nutrition, reduced leaching potential and RNDP) are essential for better combating biotic and abiotic stresses in a rapidly changing climate. Moving forward, we anticipate that nanopesticides will continue to be developed and optimized for best field applications. Cross-sectoral collaborations involving agriculture, agronomy, food, water, health and education are critical for meeting the United Nations Sustainable Development Goals[1]. Enhancing cross-disciplinary connection between plant biology and pathology, microbiology, soil science, materials synthesis and nanotechnology is crucial for continued development of nanopesticides towards sustainable agriculture and global food security. Future research priorities, recommendations and concluding remarks are provided below.

- Select safe and ecosustainable nanotechnology approaches to develop efficient nanopesticides for field applications, merging ‘safer-by-design’ synthesis and sustainable agriculture. To this end, designing bionanopesticides using materials of ‘natural’ origin (for example, essential oils, chitosan, MSNs and zein NPs) to combat agricultural pests, while minimizing the adverse evolution of pest resistance is desirable.
- Tune the controlled and targeted release of AIs at the right time and dose based on crop needs and other biotic and abiotic stresses under field conditions.
- Emphasize the field testing of encapsulated nanopesticides (Type 2), given the expected high growth rates of encapsulation technology (that is, compound annual growth rate of 11.8%)[74].
- Nanopesticides show the potential to enhance plant resilience against various stresses, but reported findings primarily focus on the laboratory or greenhouse scale. Large-scale field demonstrations under agriculturally relevant conditions are needed to understand the limitations that will be imposed by a rapidly changing climate.
- Understand the fate, adverse impacts and risk aspects of this new type of materials (compared with conventional pesticides), along with public and societal acceptance. The long-term adverse impacts of metal nanopesticides and nanocarriers (Fig. 1) on the rhizosphere microbiome and the effects of particulate metallic nanopesticides on aquatic systems are not fully understood, suggesting that research needs to be performed to fill these knowledge gaps.
- Computational ‘in silico’ strategies that integrate chemometrics (molecular dynamics simulations), machine learning (artificial neutral networks), statistics (nanoquantitative structure–activity relationships) and bioinformatics

(multiomics; Fig. 6) are needed. Also, there is a strong need for a more standardized approach that can generate the needed information for ‘big data’ computational analyses. These enable advancing the prediction of nanopesticide properties, their interactions with biological entities, hazards and risks to ecosystems and human health, particularly for the more complicated Type 2 nanopesticides. Nonetheless, for the moment, we recommend nanopesticide-based assessment on a case-by-case basis because currently no fixed commonality exists.

- Trade-offs between the benefits (for example, enhancement in crop yield and nutritional value) and risks (for example, adverse impacts on non-target organisms and the environment) of nanopesticides need to be carefully weighed, particularly when large-scale field trials are planned.
- Current nano-enabled products, including nanopesticides, mostly target crops (for example, wheat, rice and maize) that are already approaching their maximum attainable yield primarily in developed countries. Much work is required involving crops currently showing relatively low productivity but having high-yield potential (for example, cassava, yam and sweet potato)[39], particularly in impoverished areas with high food demands (for example, sub-Saharan Africa). For high-yield crops, focus should be on maximizing the tangible benefits (for example, less toxicity toward non-target organisms and improved crop nutrition) of nanopesticides.

Methods

Nanopesticide patents were compiled using Google Patents (https://patents.google.com/) with the search term ‘nano-pesticides’. The search yielded 36,658 applied and granted patents (recorded on 3 October 2021). A further detailed screening removed duplicate and irrelevant patents and generated 1,163 records of interest. Web of Science (https://www.webofscience.com/), with the search terms ‘nano-pesticides’ and ‘nanopesticides’, was used to obtain the 500 peer-reviewed articles. The physicochemical properties and efficacy data of the nanopesticides were extracted from each paper for analysis. Given that particle size is one of the key properties in judging whether the pesticide is nano or not, the papers reporting two or more types of particle size measurements (for example, TEM, SEM, DLS and atomic force microscope) were included. The independent samples *t*-test of the overall efficacy between non-nanoscale pesticides and nanopesticides at the 95% confidence interval percentage was performed using SPSS software (IBM).

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data availability

Large datasets were extracted from the 500 peer-reviewed journal articles, as shown in Supplementary Tables 1 and 2. These data are available from the corresponding author upon reasonable request. Source data are provided with this paper.

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Box 1 |

Terminology relevant to sustainable agriculture and global food security

- Sustainable agriculture: sustainable agriculture seeks to provide safe and nutritional food on existing agricultural land using less resources, while preserving the function, service and resilience of the ecosystem.
- Global food security: global food security aims to meet human food and nutrition needs, while preferably maintaining environmental health. This involves stable and predictable access to safe and nutritious food, despite limitations imposed by a highly changing climate and other co-limiting factors (for example, water and energy).
- Agricultural pests: ‘agricultural pests’ (also known as target organisms) is a ‘composite’ term that includes weeds, insects, rodents, mites, nematodes, pathogens (for example, bacteria, fungi and viruses) and other higher organisms that compromise crop growth, yield, quality and nutrition.
- Responsive nanopesticides: ‘responsive nanopesticides’ is a ‘composite’ term that represents nanoscale bactericides, insecticides, fungicides, herbicides and nematicides that have an RNDP of AIs. Upon biotic and abiotic stimuli or stresses (for example, heat, drought and salinity), the RNDP enables the responsive delivery of AIs to a desired target area within a required time and dose in a controlled, targeted and synchronized manner to combat agricultural pests. The platform is primarily composed of nanocarriers and AIs.
- Integrated pest management: IPM prioritizes crop growth with the least possible disruption of the agroecosystem to combat agricultural pests and can include the use of responsive nanopesticides to preserve ecological function and service.

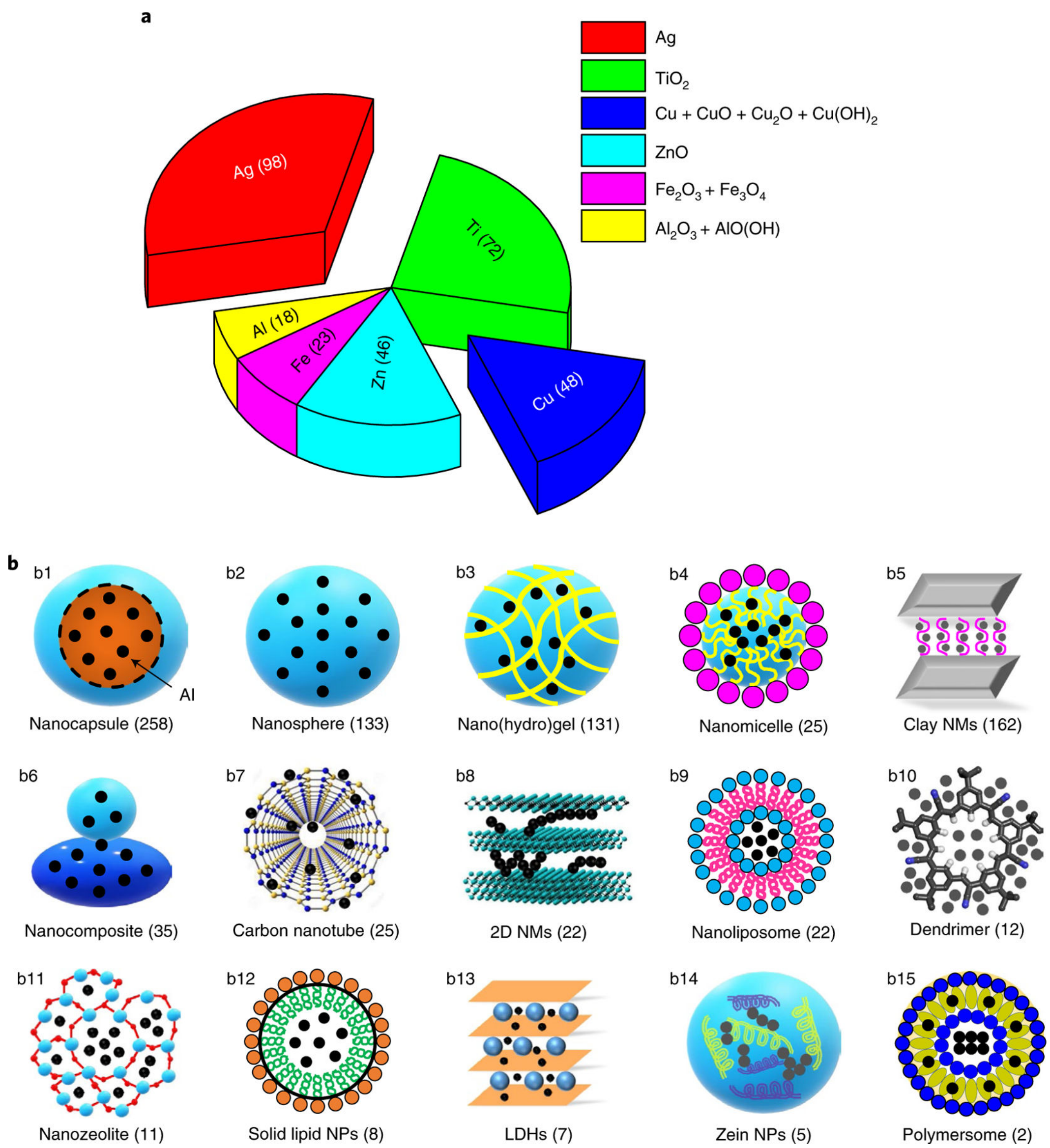

Fig. 1 |. Classification of nanopesticides.

Nanopesticides were classified by analysis of 36,658 patents (among which 1,163 are nanopesticides of interest; see Methods section). **a**, In Type 1 nanopesticides, NMs are used directly as AIs. Metal-based NMs are the most widely applied Type 1 nanopesticides and they include Ag-based NMs (as nanobactericides, nanofungicides and nanoinsecticides), Ti-based NMs (as nanobactericides and nanofungicides), Cu-based NMs (as nanofungicides and nanobactericides) and Zn-, Fe- and Al-based NMs. **b**, In Type 2 nanopesticides, NMs serve as nanocarriers to encapsulate AIs to achieve controlled, targeted and synchronized release of AIs at the right target, time and dose (that is, through the RNDP). The AIs in Type 2 nanopesticides are mainly conventional pesticides, such as atrazine, avermectin and glyphosate. The common nanocarrier types include polymers (b1–b4) such as chitosan, cellulose and polyethylene existing in the forms of nanocapsules (b1), nanospheres (b2), nano(hydro)gels (b3) and nanomicelles (b4), clay NMs (for example, silica, montmorillonite

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and kaolinite; b5), nanocomposites (b6), carbon nanotubes (CNTs; b7), 2D NMs (for example, graphene; b8), nanoliposomes (b9), dendrimers (b10), nanozeolites (b11), solid lipid NPs (b12), layered double hydroxides (LDHs; b13), zein NPs (b14) and polymersomes (b15). The numbers in parentheses indicate the number of patents indexed by Google Patents (https://patents.google.com/), which showed 305 Type 1 nanopesticide patents and 858 Type 2 patents, some of which are projected to hit the market very soon or are already on the market (for example, Nu-Clo silvercide (EPA registration number 7124–101, approved in 2007) and DuPont Kocide 3000 (EPA registration number 352–662, approved in 2007) in which nano-Ag and nano-$Cu(OH)_2$ are the AIs, respectively).

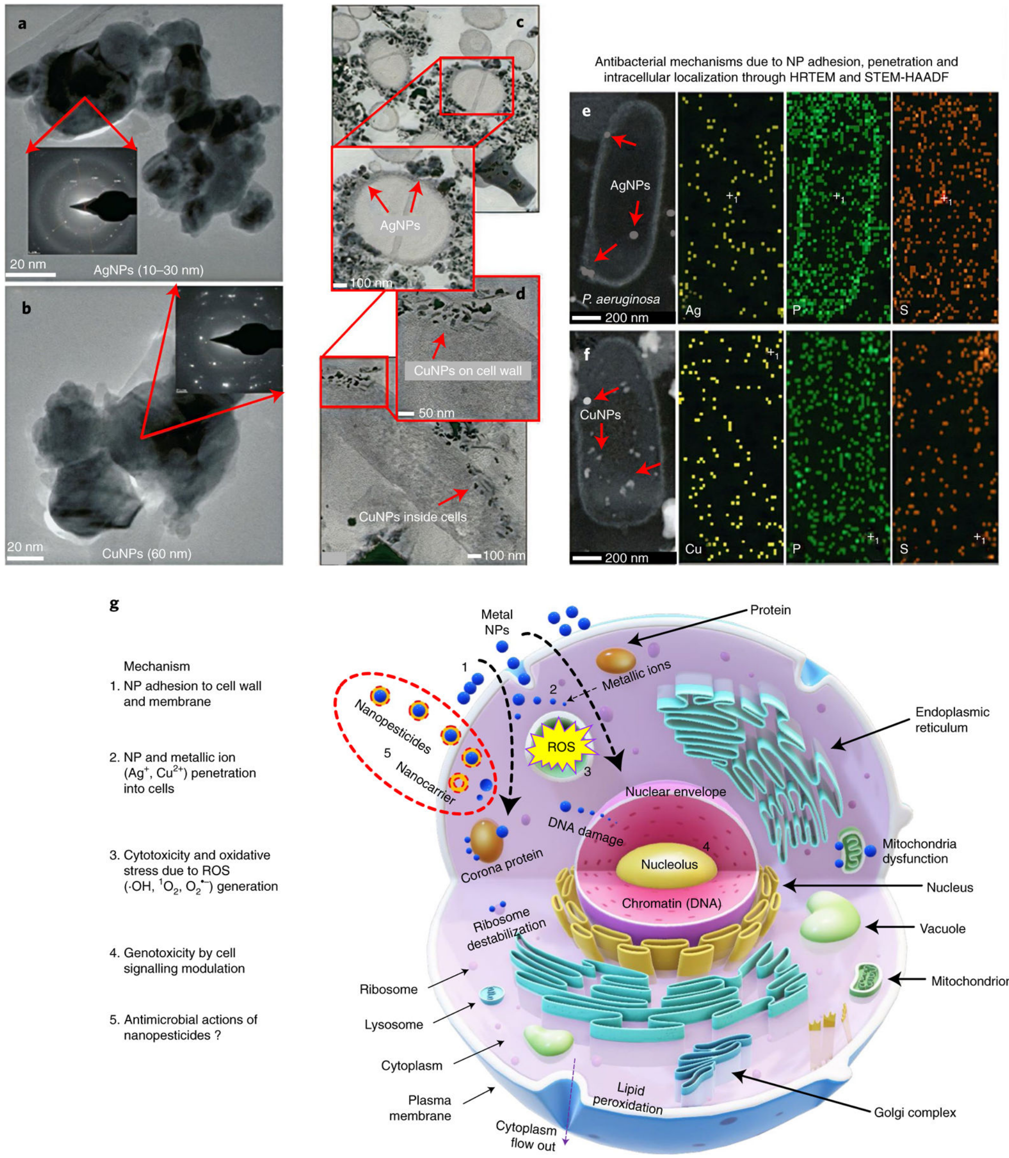

Fig. 2 |. Characterization of Ag- and Cu-based nanopesticides against *Pseudomonas aeruginosa*.
The antimicrobial properties of Ag- and Cu-based nanopesticides (AgNPs and CuNPs) against bacteria (*P. aeruginosa*) are revealed by high-resolution TEM (HRTEM) and scanning TEM high-angle annular dark-field (STEM-HAADF) measurements. **a**,**b**, TEM images of spherical 10–30 nm AgNPs (**a**) and semi-spherical 60 nm CuNPs (**b**). The insets show the selected area electron diffraction patterns. **c**,**d**, TEM images of cross-sections of *P. aeruginosa* interacting with AgNPs (**c**) and CuNPs (**d**). AgNPs and CuNPs cluster around the cell walls, penetrate (shown by red arrows) and are internalized into the cells. The CuNPs in **d** are not semi-spherical and exhibit a mean size of 30 nm (compare with semi-spherical 60 nm CuNPs in **b**). This suggests the transformation of CuNPs in liquid cell media (for example, partial dissolution to form Cu^{2+}). **e**,**f**, STEM-HAADF images and elemental mapping of Ag, Cu, P and S in *P. aeruginosa* after interacting with AgNPs (**e**) and CuNPs (**f**). Integrating HRTEM and STEM-HAADF observations enables

direct visualization of the morphological and structural changes in both bacterial cells and NPs (CuNP transformation; **d**). **g**, Proposed antimicrobial mechanisms of action of nanopesticides. Type 1 nanopesticides follow steps 1–4, whereas Type 2 nanopesticides follow steps 1–5. Step 1: NP adhesion causes cell wall and membrane damage due to lipid peroxidation, altered structure and permeability of the membrane and leakage of the cellular components. Step 2: the penetration of NPs and metallic ions (for example, Ag^+ and Cu^{2+}) into cells damages intracellular organelles and biomolecules (for example, protein denaturation, DNA damage, ribosome destabilization and mitochondrial dysfunction). Step 3: cytotoxicity and oxidative stress due to the generation of ROS (for example, ·OH, $^1O_2$ and $O_2^{\bullet-}$) and other radical-related agents (H_2O_2 and HOCl). Step 4: genotoxicity by modulation of microbial signal transduction pathways, ultimately causing cell death. Step 5: possible antimicrobial actions of nanopesticides due to interior metal NPs, exterior nanocarriers and transformed species from metal NPs and nanocarriers within the cells. Panels a–f adapted with permission from ref. [100], Bentham Science Publishers.

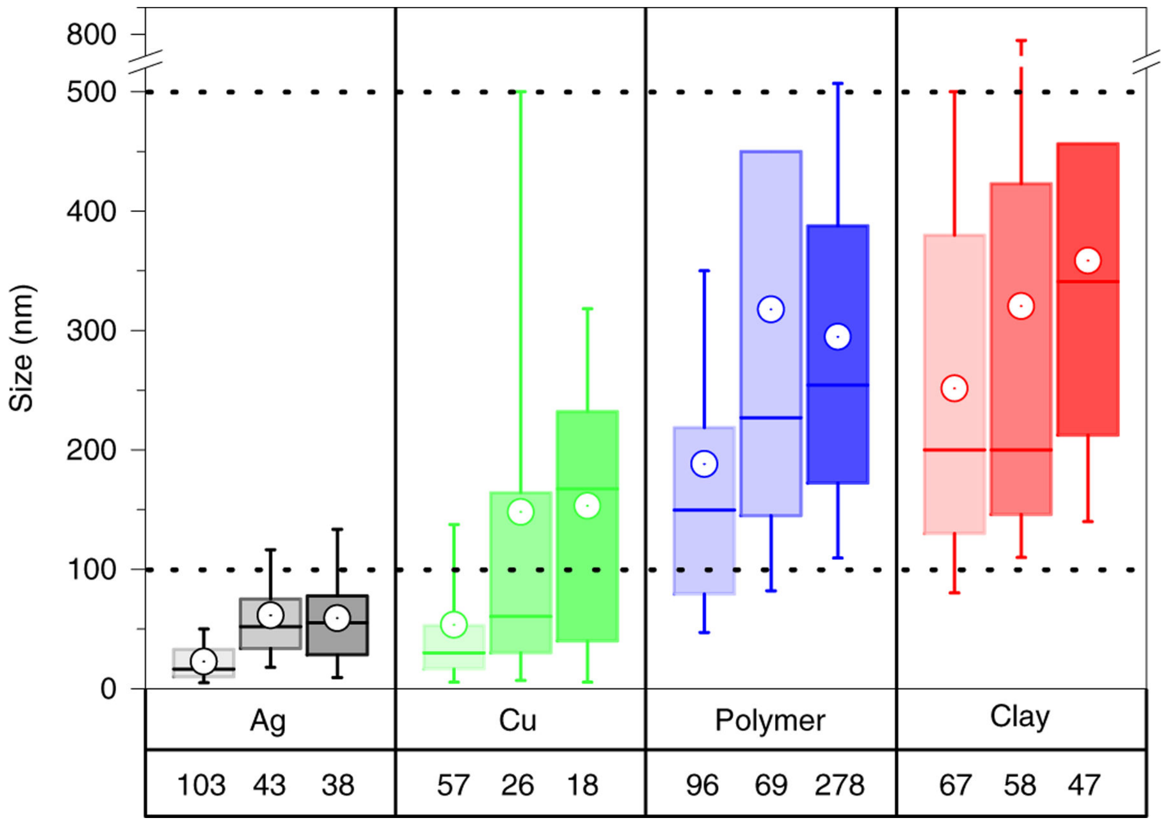

Fig. 3 |. Comparison of the particle sizes of nanopesticides.

Comparison of the sizes of the most common Type 1 (Ag- and Cu-based) and Type 2 (polymer- and clay-based) nanopesticides measured by TEM, scanning electron microscopy (SEM) and DLS. In total, 900 comparisons were made. Colour scale: lightest shading, TEM; medium shading, SEM; darkest shading, DLS. The bottom and top ends of the boxplots indicate the 25th and 75th percentiles, the bottom and top whiskers indicate the 10th and 90th percentiles, and the solid line and circle within each boxplot mark the median and mean values, respectively. The numbers below the boxplots indicate the number of nanopesticides analysed by TEM, SEM and DLS. The two dashed horizontal lines indicate thresholds of 100 and 500 nm. The datasets were extracted from 500 published papers (Supplementary Tables 1 and 2).

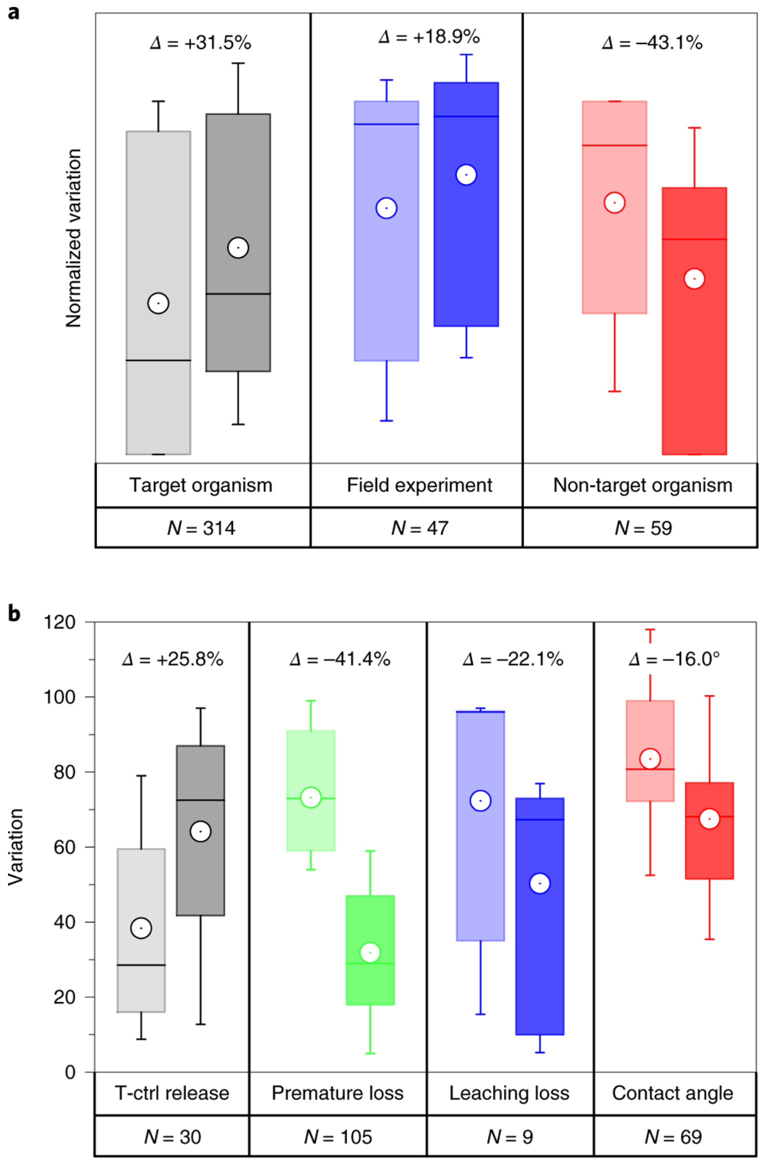

Fig. 4 |. Comparison of the overall efficacy of nanopesticides and non-nanoscale pesticides.
Efficacy comparison (586 comparisons) between non-nanoscale pesticides (left boxplot) and nanopesticides (right boxplot). The non-nanoscale pesticides are metal-based bulk materials (primary particle size above 1,000 nm) and conventional pesticides (for example, atrazine, avermectin and glyphosate). **a**, Normalized efficacy variation of non-nanoscale pesticides and nanopesticides includes their efficacy against target organisms (314 results, including 47 field trials) and non-target organisms (for example, toxicity; 59 comparisons). **b**, Efficacy variation of non-nanoscale pesticides (conventional formulations) and Type 2 nanopesticides includes temperature-controlled (T-ctrl) release of AIs, premature loss of AIs, leaching loss of AIs and foliar contact angle of AIs. The lower and higher ends of the boxplots indicate the 25th and 75th percentiles, the lower and higher whiskers indicate the 10th and 90th percentiles, and the solid line and circle within the boxplots mark the median and mean values, respectively. **Δ** indicates the efficacy variation of mean values between

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non-nanoscale pesticides and nanopesticides. *N* indicates the number of comparisons. The datasets were extracted from 500 published papers (Supplementary Tables 1 and 2). The independent samples *t*-test results are shown in Supplementary Tables 3–8.

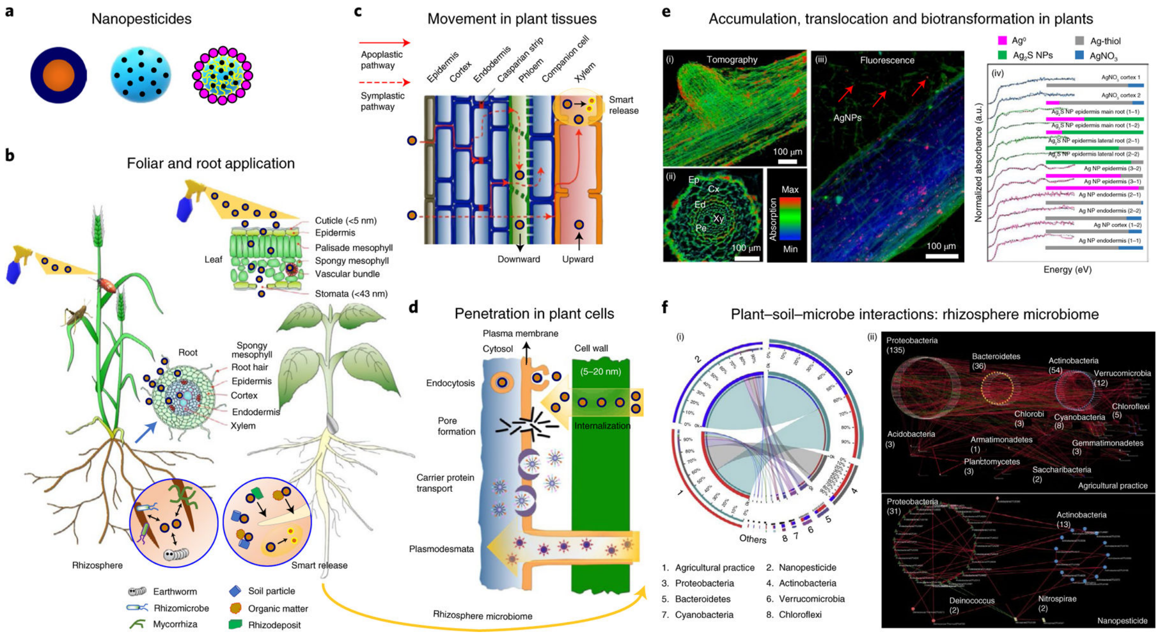

Fig. 5 |. Uptake, translocation and transformation of nanopesticides in a typical plant–soil system, and their impacts on the rhizosphere microbiome.

a, Type 2 nanopesticides. **b**, Nanopesticides can enter plants through openings in the above-ground shoots (for example, cuticle, epidermis and stomata) and below-ground roots (for example, cortex and lateral root junction). Soil invertebrates (earthworm), rhizosphere microbes (bacteria and fungi), symbiotic microorganisms (mycorrhiza), soil particles (clay), organic matter and rhizosphere deposits (root exudates) can affect nanopesticide uptake and translocation in plants. **c**, Nanopesticides can translocate vertically and radially across plant tissues through apoplastic and symplastic pathways. In **b** and **c**, a smart release of AIs from the RNDP can alter the fate and transport of nanopesticides. **d**, The internalization pathways of nanopesticides into cells include endocytosis and facilitated transport through pore formation, carrier proteins and plasmodesmata. **e**, The accumulation, translocation and transformation of nanopesticides in a plant can be differentiated by integrating multiscale techniques such as micro-/nano-X-ray computed tomography (i,ii), micro-X-ray fluorescence (iii) and micro-X-ray absorption near-edge structure (μ-XANES; iv) techniques. The images in (i,ii) and (iii) show wheat roots exposed to non-nanoscale ($AgNO_3$) and nanopesticides (AgNPs), respectively. The red arrows in (iii) show the preferential accumulation locations of AgNPs. The associated μ-XANES spectra in (iv) were collected from root tissues and show Ag speciation in different root tissues and the transformation of AgNPs (Ag^0, Ag_2S NPs, Ag-thiol and $AgNO_3$) in plants. Numbers in parentheses in (iv) indicate the nodes from operational taxonomic units analysis. Ep, epidermis; Cx, cortex; Ed, endodermis; Xy, xylem; Pe, pericycle; Max, maximum; Min, minimum. **f**, Nanopesticide exposure to soil affects the rhizosphere microbiome (archaea, bacteria and fungi): relative abundance (i) and co-occurrence network (ii) analyses of the bacterial community at the phylum level under different scenarios (agricultural practice and nanopesticide exposure). In image (ii), the nodes indicate major phyla (for example, proteobacteria, actinobacteria and bacteroidetes), and the red and blue edges indicate positive and negative correlations, respectively, between two nodes. Panels adapted with permission from: **b–d**, ref. [101] under a Creative Commons license CC BY 4.0; **e**, ref. [102], American Chemical Society; **f**, ref. [103], Elsevier.

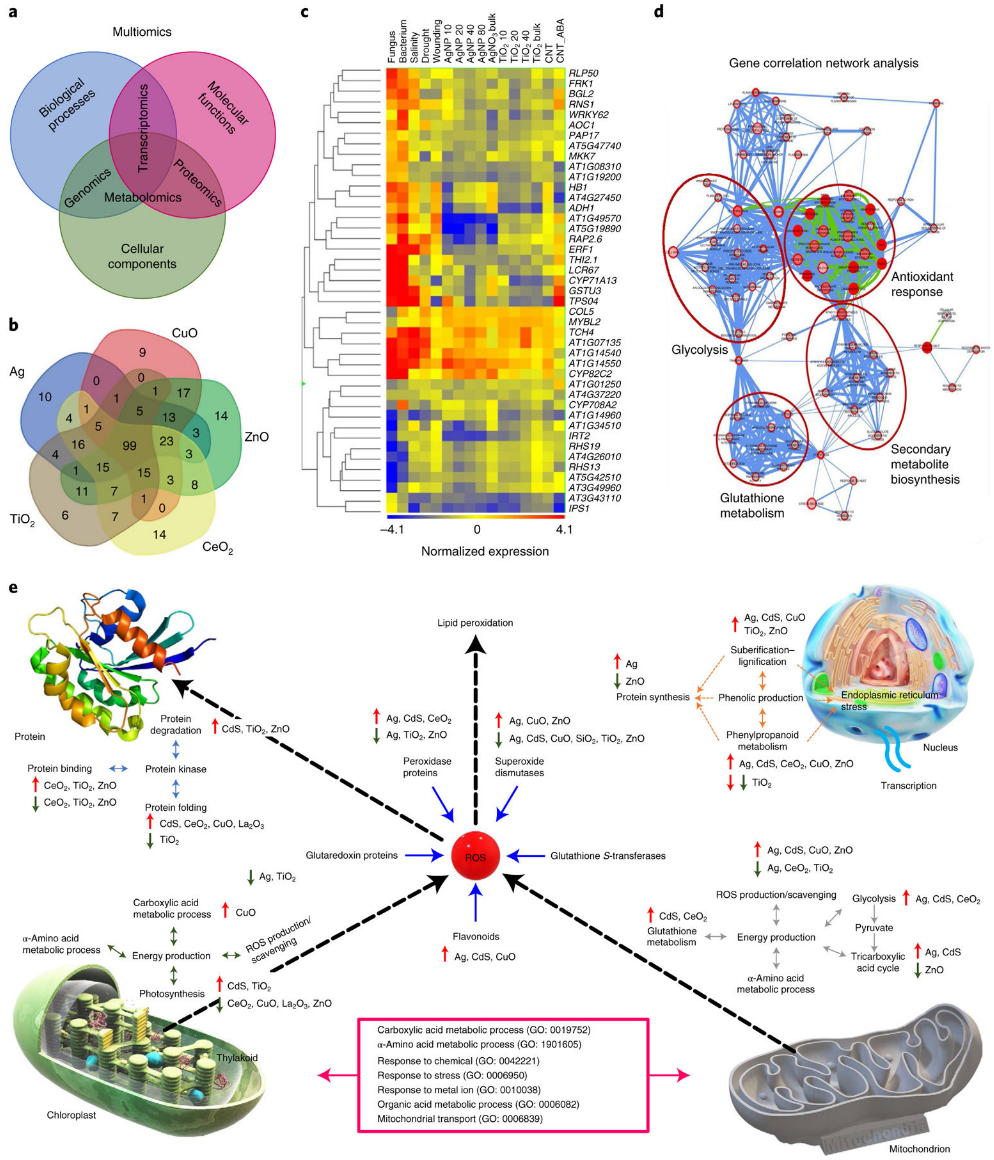

Fig. 6 |. Multiomics strategies to unveil stress responses, tolerance pathways and modes of action of biota upon nanopesticide exposure.

a, Multiomics strategies integrate genomics (DNA level), transcriptomics (messenger RNA), proteomics (protein) and metabolomics (metabolite) to unveil stress responses, tolerance pathways and modes of action of biota upon nanopesticide exposure at molecular, genetic, cellular and organismal levels. **b**, Venn network diagrams can group genes with structural, functional and responsive similarities upon stimuli. The numbers in the Venn diagram in **b** indicate the number of similarly (reside at the intersection) and uniquely (outside the intersection) regulated proteins of a model plant (*A. thaliana*) exposed to Type 1 metal-based nanopesticides. **c**, Heatmaps can also group genes based on their expression patterns and identify up- and downregulated genes and biological signatures upon nanopesticide exposure. Shown in **c** is the multicoloured hierarchical gene clustering heatmap of *A. thaliana* exposed to biotic stress (fungus and bacterium), abiotic stress (salinity, drought and wounding), nanopesticide exposure (10, 20, 40 and 80 nm AgNPs,

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10, 20 and 40 nm TiO_2 NPs, CNTs and CNTs with abscisic acid (CNT_ABA)) and others ($AgNO_3$ and TiO_2 bulk materials). **d**, Gene correlation network analysis identifying shared biological responses to metal-based nanopesticides. Highly redundant (over-expressed) gene sets are grouped together as clusters to highlight enriched metabolic processes upon stimuli, including antioxidant response, biosynthesis of secondary metabolites, glutathione metabolism and glycolysis. **e**, A comprehensive illustration of cellular pathways, metabolic processes and modes of action mediated by metal-based nanopesticides. These include interference with cell organelles (for example, chloroplasts and mitochondria), oxidative stress (ROS generation) and protein/DNA damage. The primary response relates to ROS generation, which is negatively correlated with the activity of flavonoids, glutaredoxin proteins, peroxidase proteins, superoxide dismutases and glutathione *S*-transferases (shown by blue arrows). Up- and downregulated genes upon nanopesticide exposure are indicated by red and green arrows, respectively. Notably, gene ontology (GO) analysis indicates that chloroplasts and mitochondria share similar, conservative GO classes involved in metal-based nanopesticide responses (pink box). Panels adapted with permission from: **c**, ref. [104] under a Creative Commons license CC BY 4.0; **d**, ref. [85], American Chemical Society[105].