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Learning lessons from nano-medicine to improve the design and performances of nano-agrochemicals

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Sharing concepts and knowledge between medical and agricultural fields can promote the development of improved nano-enabled technologies. A central idea behind drug delivery systems is that the active substances are encapsulated in nanoparticles (nano-medicines) to protect the drugs from premature degradation and allow them to be transported to the target site within the body. After three decades of development, nano-medicines are now used in many practical applications, including clinical oncology, infectious disease, cosmetics, and vaccines. Nano-agrochemicals are increasingly considered to tackle challenges associated with food production, sustainability and food security. Despite obvious differences between nano-medicines and nano-agrochemicals in terms of uptake mechanisms, target and environmental and economic constraints, the principles behind nanoparticle design share many similarities. This article hopes to share experiences and lessons learnt from nano-medicines that will help design more effective and safer nano-agrochemicals.

The development of nano-medicines over the last three decades has offered new hope for a range of disease from cancer to Covid-19. Cancer is the largest field of study in nano-medicine. The currently approved nano-medicines include liposomal, polymer, albumin, iron oxide, silica, gold and hafnium oxide nanoparticles[1]. Despite 30 years of research, the uptake mechanisms of nanoparticles into tumours are still debated. One view is that the nanoparticles are transported through gaps between endothelial cells in the tumour blood vessel, whilst an opposing view suggests the nanoparticles enter tumours using an active process through endothelial cells[2,3]. This lack of understanding of the uptake mechanisms limits the efficiency and clinical outcomes of current nano-medicines. For instance, a recent meta-study demonstrated that only about 0.7% of the administered nanoparticles could get into solid tumours and only 0.0014% of nanoparticles actually entered cancer cells in mouse models[4].

After two decades of nano-pesticide research, the efficacy of nano-pesticides is on average 30% higher than conventional pesticides[5,6], but it often comes with higher expected costs. Both the efficacy and efficiency of nano-pesticides should be further improved to ensure attractive cost-benefits for growers[7]. To achieve this, nano-materials can be designed to (1) reduce premature loss of nano-particles and active substances and (2) control the uptake and translocation into the target organism via the most effective pathway to shorten their journey to the target. Based on the lessons learnt from nano-medicines, we considered several scenarios for nanoparticle design for foliar and root applications based on the uptake mechanisms. This strategy contrasts with the most common approach that currently consists of synthesising the nanoparticles first and then studying the relevant uptake pathway to the target organism. Box 1 presents and clarifies some of the differences in the terminology commonly used in nano-medicine and nano-agrochemistry to promote knowledge transfer between the two fields.

Designing nanoparticles to reduce premature loss and increase bioavailability: lessons learnt from hydrophobic anticancer drugs

About half of anticancer and pesticidal active substances exhibit poor water solubility and are unstable in biological

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BOX 1

Technical terms used in nano-medicine and nano-agrochemical

	In nano-medicine	In nano-agrochemical
Uptake pathway	The pathway that materials use to enter the human body, tissues, tumours, or cells. For example, nanoparticles enter tumours via an active pathway through endothelial cells[4].	The pathway that materials use to enter target organisms such as pathogens or plants (via root, stem, or leaf tissue). For example, nanoparticles enter leaves via cuticular and/or stomata uptake pathways[66,67].
Cuticle		The cuticle is a barrier coating the outer surface of the leaf and consists of cutin polyester and waxes.
Stomata		Stomata are natural surface openings on leaves that regulate water and gas exchange.
Endocytosis pathway	The main active pathway to cross the cell membrane and enter cells.	The pathway to cross the cell membrane of plant or plant pathogen cells and enter the cells.
Energy-independent endocytosis	A cellular uptake pathway that does not require energy. Nanoparticles can passively penetrate the membrane of human or plant cells.	
Energy-dependent endocytosis	A cellular uptake pathway that requires energy from biologically regulated events for nanoparticles to cross the membrane of human or plant cells. For example, **clathrin-mediated endocytosis** requires clathrin proteins to assist the internalisation of materials into human or plant cells[36,68].	
Endocytosis inhibitor	Chemicals or genetic tools that inhibit or block the cellular uptake of nanoparticles into cells. They are used to confirm the endocytosis pathway of nanoparticles. For example, hydroxychloroquine[68] and ikarugamycin[69] inhibit the clathrin-mediated endocytosis of human and plant cells, respectively.	
Biodistribution	Materials are distributed through the body fluids in human body after administration.	
Translocation		The movement of materials throughout the plant after foliar or root application.
Active targeting approach	The surface modification of nanoparticles with charges and ligands to target overexpressed receptors of target cells. For example, human epidermal growth factor receptor 2 (HER2) is overexpressed in breast cancer cells[70].	The surface modification of nanoparticles with charges and ligands to target specific regions of a plant. For example, LM6-M, a biomolecule with affinity for α-1,5-arabinan-a chemical moiety found on stomatal cell[71].

environments[8–10]. Paclitaxel is a hydrophobic anticancer drug whose nanoformulation is a good example for nanoparticle design. Paclitaxel prevents cell division of rapidly dividing tumour cells[11]. Paclitaxel was encapsulated in albumin nanoparticles (*nab*-paclitaxel) to increase its solubility. Patients receiving *nab*-paclitaxel had significantly improved clinical effectiveness compared with paclitaxel[12]. *Nab*-paclitaxel obtained Food and Drug Administration (FDA) approval in 2005[1].

In agriculture, encapsulating poorly water-soluble active substances, such as insecticide and fungicide into nanoparticles, potentially eliminates the use of surfactants whilst reducing premature loss of active agent from the surface of plant leaves. Currently, surfactants are added to conventional pesticide formulations to increase the solubility of active substances, and enhance droplet deposition and retention on leaves to increase the uptake into plants[13,14]. Despite the use of surfactants, the amount of active substance adhering to the leaves and reaching the target remains very low[15]. Moreover, some surfactants are toxic to non-target organisms including natural enemies of pests and pollinators. For example, the surfactant *N*-methyl-2-pyrrolidone that is widely used in fungicide formulation is highly toxic to bee larvae[16]. For post-emergence application of pesticides, nano-delivery systems should be designed to increase the adhesion of nano-agrochemicals onto leaves, increase their uptake into the leaves and increase bioavailability for the target organisms. Exposure to non-target organisms can also be reduced by the more efficient delivery to the plant host and target organisms. To achieve these goals, key nanoparticle design characteristics such as amphiphilicity, morphology and roughness are discussed in more detail below.

Amphiphilicity

Nanoparticle structure should have amphiphilic properties in which the hydrophobic portion of the particle can hold hydrophobic active substances and increase the adhesion to the leaves whilst the hydrophilic portion helps improve the dispersibility of nano-agrochemicals in water for practical use[17]. For example, the amphiphilic polymer nanoparticles (copolymer poly-(2-(dimethylamino)ethylmethylacrylate)-bpoly(ε-caprolactone) without the use of surfactants showed excellent wetting effect compared to commercial formulations[17]. The degree of amphiphilicity of polymer materials is relatively easy to adjust by controlling the ratio of hydrophilic and hydrophobic precursors[18]. Sustainable raw polymers such as zein, cellulose and chitin are suitable for such applications[19,20]. Inorganic nanomaterials such as copper and silica can also have amphiphilic properties by using ligand surface modification to enhance their adhesion to the leaves and reduce premature losses (Fig. 1a)[21].

Morphology

We hypothesise that adjusting the morphology of nanoparticles can optimise the adhesion of nanoparticles to leaves. One lesson learnt from nano-medicines is that rod-shaped nanoparticles can provide greater binding affinity to cell surface compared to spheres[22]. Mathematical modelling showed that nanorods exhibited higher avidity and specificity originating from the balance of polyvalent interactions that favoured adhesion and entropic losses compared to nanospheres (Fig. 1b)[23]. However, there are very limited reports on the impact of nanoparticle shape on the binding affinity to leaves. Kah et al. found that smaller nanoparticles were less easily washed off compared to

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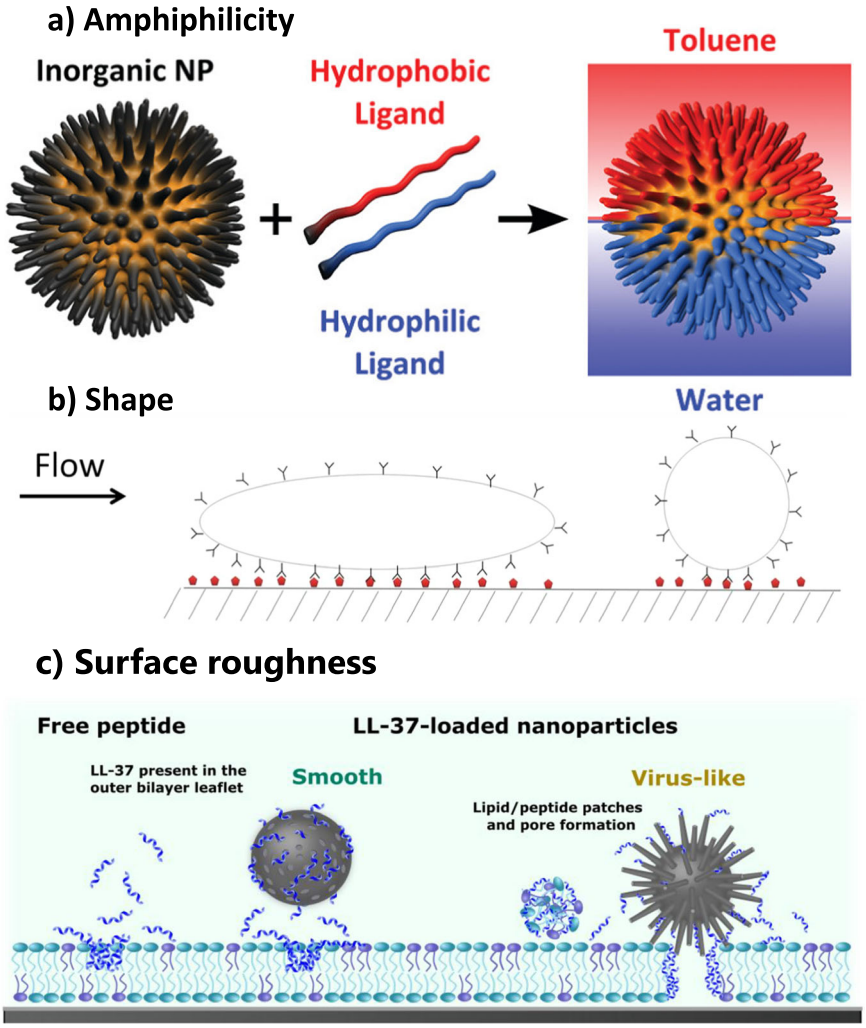

Fig. 1 | Designing nanoparticles to reduce premature loss and to increase bioavailability. a Amphiphilicity of nanomaterials to enhance their adhesion to leaves. The hydrophobic part is used to load hydrophobic active substances and increase the adhesion to leaves. The hydrophilic part helps improve the dispersibility of the nanoparticles in water. **b** Using the shape of nanoparticles to optimise the adhesion to leaves. Rod-shaped nanoparticles show favoured adhesion and entropic losses compared to nanospheres. **c** Surface roughness of nanoparticles is expected to increase the binding affinity to the target. **a** Reprinted with permission from Dickson et al.[21], copyright 2012 American Chemical Society. **b** Reproduced with permission from ref. 23, PNAS. **c** Reproduced with permission from ref. 28, American Chemical Society.

larger nanoparticles, but other factors such as the particle shape also played an essential role[24].

As well as changing the ahesion properties of nanoparticles changing the morphology of materials can also change the loading capacity of active substances into nanoparticles. For example, mesoporous silica nanorods can carry an amount of active substances four times greater than that of nanospheres with similar diameter and surface chemistry[25]. Designing nanoparticles with high active substance-loading capacity can reduce the production cost for nano-agrochemicals and reduce the amount of active ingredients needed for plant protection[26]. Various nanoparticle morphologies are encouraged to optimise adhesion and loading. Knowledge from medical research in this specific area can serve as an excellent source of inspiration (see for instance the review by Kinnear et al.[27]).

Roughness

Learning from nature, the spike protein of the virus, like SARS-CoV.2, increase surface roughness, enhance adhesion and transmission efficiencies into the host. Virus-like nanoparticles are also known to have stronger influences on the membrane of bacteria, cattle hair and tick larvae compared to smooth nanoparticles (Fig. 1c[28,29]). In nano-agrochemical research for animals, pesticide loaded into silica nanoparticles with a rough surface enhanced their adhesion to cattle hair, which led to significantly higher tick mortality compared to smooth surface nanoparticles and a benchmark commercial product[29]. In nano-agrochemical research for plants, nanoparticles with high surface roughness had a 5.9 times higher adhesion capacity on the surface of plant leaves compared to smooth surface nanoparticles, resulting in a 2.3 times improved uptake for the rough nanoparticle[30]. Increased surface roughness led to lower contact angle on the leaf, improved wettability on the hydrophobic surface of the leaves, thus reducing wash-off compared to smooth nanoparticles[30]. The surface roughness of nanoparticles should thus be considered as a potentially important factor to increase retention and uptake in plant leaves.

Using the uptake pathway to design nanoparticles

Once the nanoparticles bind to the leaves, the nanoparticles can enter plant leaves via cuticular and/or stomata uptake pathways. Each uptake pathway if favoured based on specific sizes, shapes and surface chemistry of materials. Nanoparticles enter cuticular pathway via the cuticle- a barrier coating the outer surface of the leaf consisting of cutin polyester and waxes. The cuticle has very small hydrophilic pores

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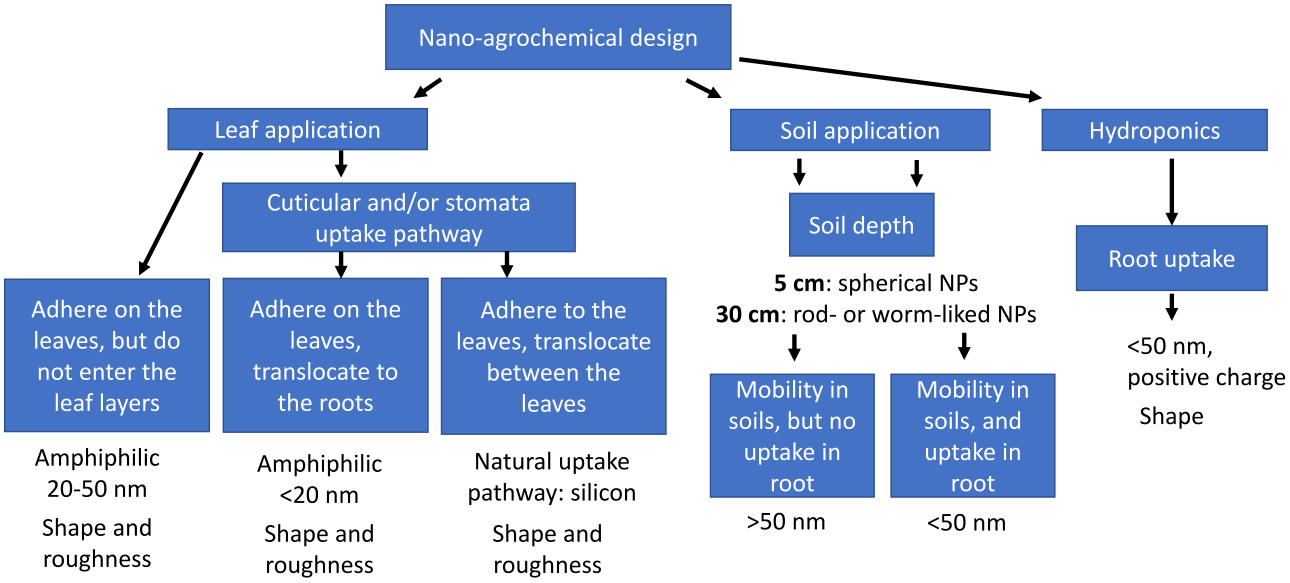

Fig. 2 | Suggestion for nano-agrochemical designs for leaf, soil and hydroponics applications. The nanoparticle physiochemical parameters should be included in the nanoparticle design to maximise the benefits. Adjusting the composition, size, shape (length and width) and roughness, and surface chemistry of nanoparticles allows an increase in the adhesion of nanoparticles to the leaves and improves the uptake and translocation to the targets.

with an upper limit of ~15 nm[31,32]. Therefore, nanoparticle design for the cuticular pathway should be less than 15 nm, and amphiphilic nanoparticles are recommended. The stomata pathway can take larger nanoparticles up to a few micrometres[33], but only when the stomata are open. The density and location of stomata on leaves are species-dependent[34], which should be carefully considered in the nanoparticle design.

The next critical question nano-agrochemical developers need to address is whether the nanoparticles need to enter the leaf (systemic) or not (non-systemic)? And if systemic, do the nanoparticles need to enter the plant cells (endocytosis) or not (non-endocytosis)? Below we consider three scenarios for nanoparticle design for foliar application to maximise efficacy.

Design nano-pesticide for non-systemic applications

This nanoparticle type is specifically designed for preventive pesticides such as fungicides. The preventive fungicide is often applied before the spores deposit on the leaves or begin to develop[35]. Here, nanoparticles could work as an interface between the leaves and active substances. We suggest designing amphiphilic nanoparticles with a size from 20–50 nm. Note that nanoparticles larger than 50 nm can generally be easily washed off the leaves[24]. The 20–50 nm nanoparticle size could possibly exclude their uptake via the cuticular pathway, and the amphiphilic properties could increase the binding affinity to the waxy layer of the leaves so it could slow down the uptake via the stomata pathway.

Design nano-pesticide for systemic application: nanoparticles enter the leaf, and translocate to the roots

Strategies applied in nano-medicine to increase the biodistribution of nanoparticles in the human body can be applied to improve the translocation of nanopesticides in plants. It has been learned from nano-medicine that particles with a size in the range of 150–200 nm were mostly excluded from cellular internalisation and often got removed from the body by phagocytic cells[36]. Highly positive charged nanoparticles (~40 mV) exhibit a strong affinity for the negatively charged cell membrane, accounting for higher cellular uptake and higher toxicity[37]. Highly negative particles (−40 mV) are also attractive to phagocytic cells. Nano-medicine researchers nowadays often design smaller sizes (under 150 nm) and slightly negatively charged nanoparticles to prolong blood circulation time and increase the accumulation in tumours more efficiently.

A practical application is the targeted delivery of fungicide and bactericide that are needed in the root zone, but which do not translocate easily on their own, for example carabrone[38]. Such active substances are typically applied directly on soil, which is home to both beneficial and pathogenic microorganisms. Overapplications of fungicides and bactericides to soil can negatively affect the soil microbiome, whose important functions are increasingly recognised[39]. This nanoparticle design offers opportunities to treat root diseases via foliar application. With this goal, amphiphilic nanoparticles with a diameter of 10–20 nm are recommended to allow penetration inside the leaf via cuticular and/or stomata pathways (Fig. 2). Insights into the uptake pathways could be obtained using strategies previously used for nano-medicines, e.g. blocking or inhibiting one pathway to study another (Box 1). For example, the inhibitor abscisic acid applied to the leaves causes the stomata to remain closed, whilst fusicoccin causes the stomata to remain open[40]. The incorporation of fusicoccin or similar molecules in the nano-agrochemical design to promote uptake by stomata could be also considered. However, the efficiency of such approach is uncertain because stomata opening is also regulated by the amount of water inside the plants, environmental temperature and carbon dioxide. At this stage, we believe that abscisic acid and fusicoccin will mainly help confirm whether the nanoparticles can enter the leaf via the stomata pathway.

Nanoparticle morphology also impacts translocation and needs to be considered. For example, when nanoparticles were applied to leaves using a drop cast method, 20 × 60 nm rods translocated to the roots to the greatest extent (49.2%) as compared to the translocation of 35 nm spheres (13.4%), 30 nm cubes (7.3%), and 65 nm rhombic dodecahedra (8.3%)[41]. It is believed that the differences in the translocation of nanoparticles with different morphologies from the leaf to root is affected by the pressure gradient of photosynthate in leaves driven a flow stream from leaves, to stems and roots.

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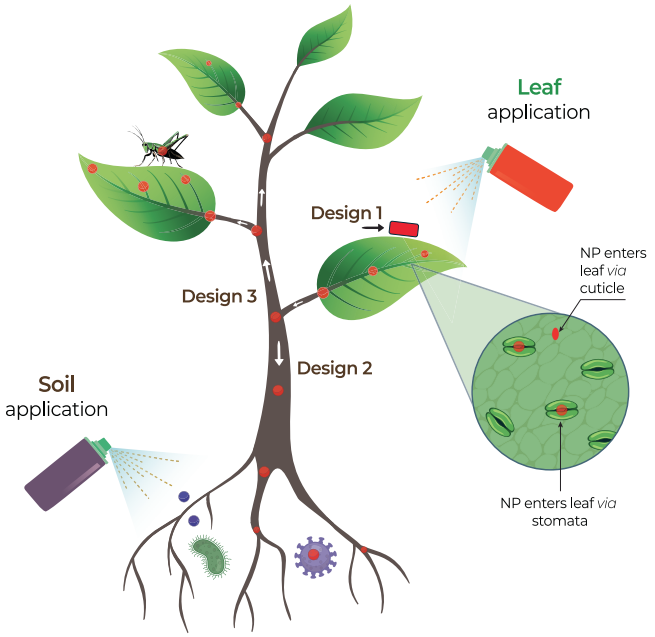

Fig. 3 | Nanoparticle designs for foliar and soil applications. For foliar application there are three designs; design 1: nano-pesticide for non-systemic applications; design 2: nano-pesticide for systemic application: nanoparticles enter the leaf, and translocate to the roots; design 3: nano-agrochemical for systemic application: nanoparticles enter the leaf, and translocate between the leaves.

Design nano-agrochemical for systemic application: nanoparticles enter the leaf, and translocate between the leaves

Controlling the distribution of active substances among young leaves and shoots via foliar application could be a game changer for the agrochemical industry and growers (Fig. 3). This would provide more effective protection and avoid the need for repetitive applications that is common with conventional agrochemicals. For this design objective, we suggest taking advantage of natural pathways, such as the silicon uptake pathway in the plant. It was found that, unlike zinc oxide nanoparticles, zinc oxide coated with mesoporous silica shell can selectively deliver zinc not only to root, stem and lower leaves, but also to upper leaves, and shoots[42], which can be used for emergent needs of zinc of young leaves. The silicon uptake pathway can also be used to reduce the uptake of contaminants in soil. For instance, the accumulation of cadmium in rice is a serious problem in agriculture. Foliar application of silica nanoparticles reduced the uptake of cadmium in rice because silica nanoparticles were able to accumulate in the walls of the rice cells and inhibited the uptake and accumulation of cadmium in soil[43]. Besides the silicon uptake pathway, there are several other uptake pathways that are worth exploring[44], such as the manganese pathway.

Protein corona and artificial intelligence

Once nanoparticles enter the leaves, biomolecules that bind onto the surface of nanoparticles (protein corona) will change the surface properties, translocation pathways and destination of the nanoparticles. The formation of protein corona is an important process that should not be ignored. Early research into nano-medicines considered coating nanoparticles with antifouling polymers such as polyethylene glycol (PEG) in order to prevent the formation of protein corona. However, PEGylated nanoparticles triggered anti-PEG antibodies and resulted in accelerated blood clearance with repeated administration in vivo[45]. Research has now moved to controlling the formation of protein corona on nanoparticles to improve delivery. For example, the approved Onpattro lipid nanoparticles were designed to interact with apolipoprotein-E in the blood[46], which are highly effective in targeting hepatocytes in the liver. Recently, machine learning was successfully used to predict the formation of protein corona to design safer nano-medicines to be used in vivo[47].

The formation of protein corona on nano-agrochemicals may be an even more complicated process than in animals. Different types of plants have different protein contents[48], and our current knowledge of the protein corona related to nano-agrochemicals is limited due to analytical challenges. Ideally, databases suitable for the application of machine learning can be built for nano-agrochemicals. Experiments could consider (1) the uptake of nanoparticles applied to plants, followed by (2) the extraction of protein corona modified nanoparticles, (3) the characterisation of the protein corona, and (4) an assessment of the influencing variables (nanoparticle type, size, shape, surface chemistry, plant species, exposure pathway, and measured plant tissues). Step 2 is extremely challenging, and as an alternative to in situ experiments, nanoparticles could also be dispersed in reconstituted plant protein solutions to monitor how protein corona form and evolve under well-controlled conditions that are particularly suitable for machine learning algorithms. An improved understanding of the formation and functions of protein corona inside the plants will help in designing nano-agrochemicals more precisely and effectively.

Controlled-release nanoparticles

Cancer nano-medicines can trigger the release of anticancer drugs inside the cancer cells, which significantly reduces the side effects of anticancer drugs for cancer patients[49]. The design of nano-medicines can have more than one stimuli for precisely controlling the release of drugs to avoid premature loss or unexpected release of the cargo before cell internalisation. For example, a drug can be released from a responsive nanocarrier with both pH and enzyme triggers[50]. This lesson can be applied for insecticide delivery. Dual responsive controlled-release nano-insecticides could be designed to release active substances only in the stomach of insect pests, not in plants or bees. The pH of the midgut tract of insect pests is alkaline[51], whilst the pH of the plant is about 5–7[52], and of bees is about 7[53]. In addition, the stomach of insect pests contains an abundance of digestive enzymes including α-amylase[54]. Taking advantage of α-amylase, low-cost carbohydrate-based polymeric nanoparticles such as glycopolymers and glyconanoparticles can be used as nano-carriers, which can be degraded by α-amylase in the insect midgut.

Active targeting nanoparticles

The surface of nano-medicines can be modified with charges and ligands to target overexpressed receptors of cancer cells. This strategy is called active targeting nano-medicine[55]. In the human body the nanoparticles can travel and find the cancer cells; however, in an open field the nano-agrochemical may not be able to be transported to find the pests. We thus suggest that active targeting nano-agrochemical could be designed to attract pests to nanoparticles. One of the approaches is to encapsulate a pests' sex pheromones in a nanoparticle formulation. Sex pheromones are chemical signals emitted by an organism that elicit the opposite sex of the same species. In fact, sex pheromones have been used to trap insect pests for high value crops[56]. Here, pheromones can be modified to attach on the outer surface of nano-insecticide or co-loaded with insecticidal active substances to attract insect pests. This design could potentially reduce the area of spraying insecticides and reduce the negative impact of insecticides on non-target insects such as bees.

Facilitating nanoparticle mobility in soils: lesson learnt from nucleus-targeted drug delivery

Nanomedicine research suggests that unlike spherical nanoparticles, rod-shaped and worm-like nanoparticles could pass the nuclear pore

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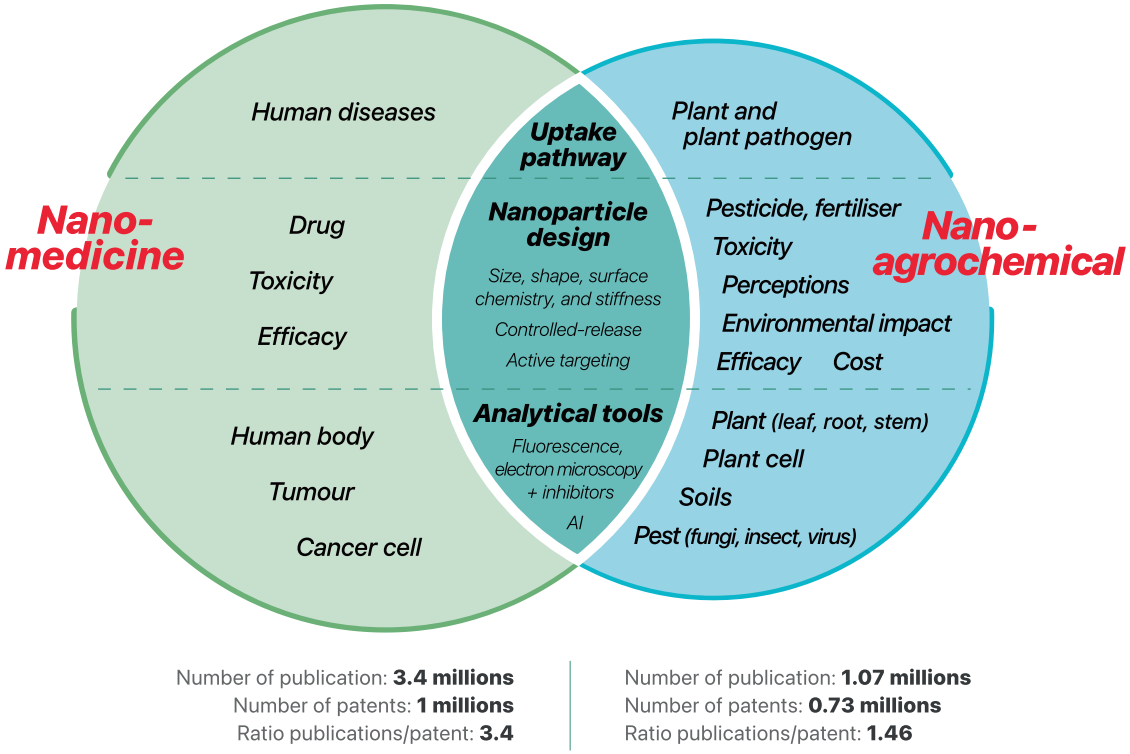

Fig. 4 | Key similarities and differences between nano-medicine and nano-agrochemical designs. Starting from the top, the uptake pathway of the target drives the nanoparticle design based on a range of different criteria; then analytical tools are used to study the uptake pathway. A SciFinder search with key words 'nano-medicines', 'nano-pesticides' and 'nano-fertilisers' was conducted in April 2024 to compare the number of publications and patents in two areas.

complex of the nucleus of cancer cells resulting in more anticancer drug release inside the nucleus and correlation with greater cytotoxicity[57]. The inability of the spherical nanoparticles to pass through the nuclear pore complex was linked to their negligible accumulation in the nucleus. A parallel to agriculture is the possible transport of active substances to where the targets are located within a soil profile and also potentially reducing exposure of soil organisms in other locations. For instance, plant-parasitic nematodes tend to be located 30 cm below the soil surface[58], therefore, nanoparticles need to be delivered to that depth to be most efficient (Fig. 2). Nematicide active substances tend to be hydrophobic and tend to accumulate at the soil surface. In contrast, herbicides work best when they are about 5 cm below the soil surface, but herbicide active substances tend to be quite mobile in the environment, and they are likely to move down the soil profile where they are not needed and risk contaminating groundwater. We suggest further exploring the impact of the size and shape of nanoparticles on their mobility in soils. Unlike nanospheres, nanorods were reported to penetrate the soil up to 30 cm below the soil surface[58]. Additionally, nanorods enter the root faster than other morphologies, which can reduce stress damage for plants[59]. Nanoparticle size <50 nm can enter root system via root cells or wounds[60,61] and positively charged nanoparticles are attracted to the roots more than the negatively charged nanoparticles due to the electrostatic attraction/repulsion of the negatively charged root surfaces (Fig. 2).

The uptake pathway of nanoparticles into roots should be further investigated. Nanoparticles can enter root tissues and cells via energy-independent and/or dependent endocytosis pathway(s). Energy-independent and/or dependent endocytosis can be confirmed by pre-cooling the root at 4 °C before exposure to nanoparticles. If the nanoparticles can cross the root tissue and enter the root cells, the uptake happens mainly based on physical penetration or energy-independent. However, if the uptake only occurs at temperatures higher than 4 °C, this is the energy-dependent uptake. If nanoparticles physically penetrate the plasma membrane, the nanoparticles are likely to reach the cytoplasm or nucleus of the root cells, which can be explored to deliver DNA to the cytoplasm and nucleus[62]. A practical example is mesoporous silica nanoparticles designed with the size of ~50 nm, charge reversal based on pH that could enter the root cells via energy-independent pathway and effectively deliver DNA to the cells (US Patent 2013/0185823A). However, if the nanoparticles are wrapped by cell membrane, the nanoparticles are transported into internal vesicles inside the cells, and potentially transported between cells, which can be applied for agrochemical delivery.

Outlook

Nano-medicine has had a head start with over 3 million publications whilst nano-agrochemical area reported about 1 million of publications so far (Fig. 4). The ratio of publications/patents in nano-medicines is 3.4, compared to 1.5 for nano-agrochemicals. Nano-agrochemicals can be tested directly on the target organisms whilst nano-medicines have to pass several layers of pre-clinical trials before attempting human trials. The commercialisation and adoption of nano-agrochemicals is thus likely faster and will strongly depend on the flexibility of the regulatory framework, costs and public perception. Understanding and exploring the uptake pathways to design effective and safe nano-agrochemicals are the critical goals.

A lesson learnt from nano-medicine development is the necessity to understand the uptake pathways early in the product development as this supports the strategic design of nano-delivery platforms that are fit for purpose. Current nano-agrochemical research includes studies on the translocation and accumulation in plants, but lacks reports on quantifying translocation and accumulation at cellular or sub-cellular levels. These knowledge gaps may challenge the registration and commercialisation of nano-agrochemicals. Studying endocytosis

at cellular or subcellular levels will also provide information about the potential negative effects of nanoparticles on plants (e.g. endocytosis may damage organelles, cell division and functions) and support the design of safer nano-agrochemicals. Analytical approaches based on mass spectrometry, fluorescence and electron microscopy in combination with endocytosis inhibitors should be further applied to elucidate the uptake mechanisms of nano-agrochemicals.

Regarding the nanoparticle design, nanoparticle size and surface chemistry have been intensively studied; however, a significant knowledge gap remains in the impact of nano-agrochemical shape, which is not very surprising as the same was observed in the early stages of nano-medicine development. The shape can be adjusted to adhere on the leaves, increase the uptake and translocation to the target. We recommend that all of the nanoparticle physiochemical parameters including morphology, surface chemistry and roughness are included in the nanoparticle design to maximise benefits. It is particularly important to prioritise materials that are sustainable, degradable, low cost, and low toxicity (including degrading to benign compounds), such as silica, cellulose, chitosan, or carbohydrate-based polymeric nanoparticles.

Public perception and the cost also need to be carefully considered for commercial success. Despite their advantages relative to conventional approaches, nano-agrochemicals may be perceived as unnecessary or even unsafe and they risk public rejection compared to nano-medicines that can show direct benefits to human health[63]. Applications to non-food crops and/or confined spaces (e.g. hothouses, hydroponics) could be prioritised to demonstrate the benefits and safety of nano-agrochemicals, and build the confidence of regulators, users and consumers before deploying the technology to larger scales. Targeting currently unsolved problems for high-value crops is also likely to be more successful in addressing issues of cost and perception. For example, Fusarium wilt caused by the soil-borne fungal pathogen *Fusarium oxysporum* is almost impossible to eradicate for high-value crops such as cotton (Fusarium Wilt.pdf (cottoninfo.com.au) and tomato (fusarium-wilt-of-tomato.pdf (ct.gov)). Greenhouse trials showed that fungicide loaded mesoporous silica nanoparticles controlled Fusarium crown and root rot in tomato four times better than conventional fungicide owing to the smart pH responsive system of nanoparticles[64]. The higher cost of nano-agrochemicals can also be justified by cost saving associated with the combination of several agrochemicals and the ease to use for farmers from mixing, spraying and cleaning the tank, which translates in saving on labour and fuel. Co-designing nano-agrochemicals with future users and actively engaging with diverse disciplines including nano-medicine will help harness the full potential of nanotechnology in agriculture.

It is vital to recognise that performant nano-delivery platforms may not be transferable from one field to the other. The portion of nano-medicines that is not reaching the target organs/tumour, can be excreted out of the human body with no further consequences on human health. The undelivered portion of nano-agrochemicals remains in the environment, and may represent a risk to non-target organisms in the shorter or longer term. Nano-agrochemicals that are designed for soil application will interact with soil proteins (eco-corona protein) before they can get into the plants (plant corona protein)[65]. Nano-agrochemicals that are applied in the open environment need to comply with stringent environmental safety criteria compared to nano-medicines.

References

1. de Lazaro, I. & Mooney, D. J. Obstacles and opportunities in a forward vision for cancer nanomedicine. *Nat. Mater.* **20**, 1469–1479 (2021).
2. Sindhwani, S. et al. The entry of nanoparticles into solid tumours. *Nat. Mater.* **19**, 566–575 (2020).
3. Ikeda-Imafuku, M. et al. Strategies to improve the EPR effect: a mechanistic perspective and clinical translation. *J. Control Release* **345**, 512–536 (2022).
4. Nguyen, L. N. M. et al. The mechanisms of nanoparticle delivery to solid tumours. *Nat. Rev. Bioeng.* **2**, 201–213 (2024).
5. Wang, D. et al. Nano-enabled pesticides for sustainable agriculture and global food security. *Nat. Nanotechnol.* **17**, 347–360 (2022).
6. Kah, M., Kookana, R. S., Gogos, A. & Bucheli, T. D. A critical evaluation of nanopesticides and nanofertilizers against their conventional analogues. *Nat. Nanotechnol.* **13**, 677–684 (2018).
7. Su, Y. et al. Cost–benefit analysis of nanofertilizers and nanopesticides emphasizes the need to improve the efficiency of nanoformulations for widescale adoption. *Nat. Food* **3**, 1020–1030 (2022).
8. Umetsu, N. & Shirai, Y. Development of novel pesticides in the 21st century. *J. Pestic. Sci.* **45**, 54–74 (2020).
9. Phillips, M. W. A. Agrochemical industry development, trends in R&D and the impact of regulation. *Pest Manag. Sci.* **76**, 3348–3356 (2020).
10. Tran, P. et al. Overview of the manufacturing methods of solid dispersion technology for improving the solubility of poorly water-soluble drugs and application to anticancer drugs. *Pharmaceutics* **11**, 132 (2019).
11. Weaver, B. A. How taxol/paclitaxel kills cancer cells. *Mol. Biol. Cell* **25**, 2677–2681 (2014).
12. Mahtani, R. L. et al. Comparative effectiveness of early-line nab-paclitaxel vs. paclitaxel in patients with metastatic breast cancer: a US community-based real-world analysis. *Cancer Manag. Res.* **10**, 249–256 (2018).
13. Mesnage, R., Benbrook, C. & Antoniou, M. N. Insight into the confusion over surfactant co-formulants in glyphosate-based herbicides. *Food Chem. Toxicol.* **128**, 137–145 (2019).
14. Bao, Z. et al. The simple strategy to improve pesticide bioavailability and minimize environmental risk by effective and ecofriendly surfactants. *Sci. Total Environ.* **851**, 158169 (2022).
15. Damak, M., Hyder, M. N. & Varanasi, K. K. Enhancing droplet deposition through in-situ precipitation. *Nat. Commun.* **7**, 12560 (2016).
16. Zhu, W., Schmehl, D. R., Mullin, C. A. & Frazier, J. L. Four common pesticides, their mixtures and a formulation solvent in the hive environment have high oral toxicity to honey bee larvae. *PLoS ONE* **9**, e77547 (2014).
17. Tang, J. et al. Deposition and water repelling of temperature-responsive nanopesticides on leaves. *Nat. Commun.* **14**, 6401 (2023).
18. Zhao, M. et al. pH/redox dual responsive from natural polymer-based nanoparticles for on-demand delivery of pesticides. *Chem. Eng. J.* **435**, 134861 (2022).
19. Ristroph, K. D., Astete, C. E., Bodoki, E. & Sabliov, C. M. Zein nanoparticles uptake by hydroponically grown soybean plants. *Environ. Sci. Technol.* **51**, 14065–14071 (2017).
20. Singh, R. P., Handa, R. & Manchanda, G. Nanoparticles in sustainable agriculture: an emerging opportunity. *J. Control Release* **329**, 1234–1248 (2021).
21. Dickson, M., Andala, S. H. R. S., Lee, H.-Y. & Kyle, J. M. B. Templated synthesis of amphiphilic nanoparticles at the liquid liquid interface. *ACS Nano* **6**, 1044–1050 (2012).
22. Cong, V. T., Gaus, K., Tilley, R. D. & Gooding, J. J. Rod-shaped mesoporous silica nanoparticles for nanomedicine: recent progress and perspectives. *Expert Opin. Drug Deliv.* **15**, 881–892 (2018).
23. Kolhar, P. et al. Using shape effects to target antibody-coated nanoparticles to lung and brain endothelium. *Proc. Natl. Acad. Sci. USA* **110**, 10753–10758 (2013).

24. Kah, M. et al. Impact of (nano)formulations on the distribution and wash-off of copper pesticides and fertilisers applied on citrus leaves. *Environ. Chem.* **16**, 401–410 (2019).
25. You, Y., He, L., Ma, B. & Chen, T. High-drug-loading mesoporous silica nanorods with reduced toxicity for precise cancer therapy against nasopharyngeal carcinoma. *Adv. Funct. Mater.* **27**, 1703313 (2017).
26. Su, Y. et al. Cost-benefit analysis of nanofertilizers and nanopesticides emphasizes the need to improve the efficiency of nanoformulations for widescale adoption. *Nat. Food* **3**, 1020–1030 (2022).
27. Kinnear, C., Moore, T. L., Rodriguez-Lorenzo, L., Rothen-Rutishauser, B. & Petri-Fink, A. Form follows function: nanoparticle shape and its implications for nanomedicine. *Chem. Rev.* **117**, 11476–11521 (2017).
28. Haffner, S. M. et al. Membrane interactions of virus-like mesoporous silica nanoparticles. *ACS Nano* **15**, 6787–6800 (2021).
29. Zhang, J. et al. Nanobiopesticides: Silica nanoparticles with spiky surfaces enable dual adhesion and enhanced performance. *EcoMat* **2**, e12028 (2020).
30. Li, W. et al. Improving the utilization rate of foliar nitrogen fertilizers by surface roughness engineering of silica spheres. *Environ. Sci. Nano* **7**, 3526–3535 (2020).
31. Schonherr, J. Characterization of aqueous pores in plant cuticles and permeation of ionic solutes. *J. Exp. Bot.* **57**, 2471–2491 (2006).
32. Popp, C., Burghardt, M., Friedmann, A. & Riederer, M. Characterization of hydrophilic and lipophilic pathways of Hedera helix L. cuticular membranes: permeation of water and uncharged organic compounds. *J. Exp. Bot.* **56**, 2797–2806 (2005).
33. Zeng, Y., Himmel, M. E. & Ding, S. Y. Visualizing chemical functionality in plant cell walls. *Biotechnol. Biofuels* **10**, 263 (2017).
34. Bertolino, L. T., Caine, R. S. & Gray, J. E. Impact of stomatal density and morphology on water-use efficiency in a changing world. *Front. Plant Sci.* **10**, 225 (2019).
35. Ayres, M. R., Billones-Baaijens, R., Savocchia, S., Scott, E. S. & Sosnowski, M. R. Critical timing of fungicide application for pruning wound protection to control grapevine trunk diseases. *Aust. J. Grape Wine Res.* **28**, 70–74 (2021).
36. Cong, V. T. et al. How can we use the endocytosis pathways to design nanoparticle drug-delivery vehicles to target cancer cells over healthy cells? *Chem. Soc. Rev.* **51**, 7531–7559 (2022).
37. He, C., Hu, Y., Yin, L., Tang, C. & Yin, C. Effects of particle size and surface charge on cellular uptake and biodistribution of polymeric nanoparticles. *Biomaterials* **31**, 3657–3666 (2010).
38. Wang, L.-Y. et al. The efficacy and translocation behavior of carabrone in wheat and cucumber. *Crop Prot.* **100**, 87–95 (2017).
39. Edlinger, A. et al. Agricultural management and pesticide use reduce the functioning of beneficial plant symbionts. *Nat. Ecol. Evol.* **6**, 1145–1154 (2022).
40. Guzman-Delgado, P., Laca, E. & Zwieniecki, M. A. Unravelling foliar water uptake pathways: the contribution of stomata and the cuticle. *Plant Cell Environ.* **44**, 1728–1740 (2021).
41. Raliya, R. et al. Quantitative understanding of nanoparticle uptake in watermelon plants. *Front. Plant Sci.* **7**, 1288 (2016).
42. Gao, X., Kundu, A., Bueno, V., Rahim, A. A. & Ghoshal, S. Uptake and translocation of mesoporous SiO2-coated ZnO nanoparticles to solanum lycopersicum following foliar application. *Environ. Sci. Technol.* **55**, 13551–13560 (2021).
43. Ahmed, S. et al. Foliar application of silicon-based nanoparticles improve the adaptability of maize (Zea mays L.) in cadmium contaminated soils. *Environ. Sci. Pollut. Res. Int* **30**, 41002–41013 (2023).
44. Dimkpa, C. et al. Effects of manganese nanoparticle exposure on nutrient acquisition in wheat (Triticum aestivum L.). *Agronomy* **8**, 158 (2018).
45. Schottler, S. et al. Protein adsorption is required for stealth effect of poly(ethylene glycol)- and poly(phosphoester)-coated nanocarriers. *Nat. Nanotechnol.* **11**, 372–377 (2016).
46. Akinc, A. et al. The Onpattro story and the clinical translation of nanomedicines containing nucleic acid-based drugs. *Nat. Nanotechnol.* **14**, 1084–1087 (2019).
47. Zhu, M. et al. Machine-learning-assisted single-vessel analysis of nanoparticle permeability in tumour vasculatures. *Nat. Nanotechnol.* **18**, 657–666 (2023).
48. Yu, Y., Dai, W. & Luan, Y. Bio- and eco-corona related to plants: understanding the formation and biological effects of plant protein coatings on nanoparticles. *Environ. Pollut.* **317**, 120784 (2023).
49. Bosetti, R., Ferrandina, G., Marneffe, W., Scambia, G. & Vereeck, L. Cost-effectiveness of gemcitabine versus PEGylated liposomal doxorubicin for recurrent or progressive ovarian cancer: comparing chemotherapy with nanotherapy. *Nanomedicine* **9**, 2175–2186 (2014).
50. Chen, X. et al. Dual bioresponsive mesoporous silica nanocarrier as an "AND" logic gate for targeted drug delivery cancer cells. *Adv. Funct. Mater.* **24**, 6999–7006 (2014).
51. Kan, Q. et al. An alkali-triggered polydopamine modified mesoporous silica nanopesticide for smart delivery of chlorpyrifos with low loss. *ACS Agric. Sci. Technol.* **2**, 501–511 (2022).
52. Cornelissen, J. H. C., Sibma, F., Van Logtestijn, R. S. P., Broekman, R. A. & Thompson, K. Leaf pH as a plant trait: species-driven rather than soil-driven variation. *Funct. Ecol.* **25**, 449–455 (2011).
53. Muresan, C. I. & Buttstedt, A. pH-dependent stability of honey bee (Apis mellifera) major royal jelly proteins. *Sci. Rep.* **9**, 9014 (2019).
54. Dong, J. et al. Cyclodextrin polymer-valved MoS2-embedded mesoporous silica nanopesticides toward hierarchical targets via multidimensional stimuli of biological and natural environments. *J. Hazard. Mater.* **419**, 126404 (2021).
55. Rosenblum, D., Joshi, N., Tao, W., Karp, J. M. & Peer, D. Progress and challenges towards targeted delivery of cancer therapeutics. *Nat. Commun.* **9**, 1410 (2018).
56. Wang, H.-L. et al. Insect pest management with sex pheromone precursors from engineered oilseed plants. *Nat. Sustain.* **5**, 981–990 (2022).
57. Hinde, E. et al. Pair correlation microscopy reveals the role of nanoparticle shape in intracellular transport and site of drug release. *Nat. Nanotechnol.* **12**, 81–89 (2017).
58. Chariou, P. L. et al. Soil mobility of synthetic and virus-based model nanopesticides. *Nat. Nanotechnol.* **14**, 712–718 (2019).
59. Djanaguiraman, M., Nair, R., Giraldo, J. P. & Prasad, P. V. V. Cerium oxide nanoparticles decrease drought-induced oxidative damage in sorghum leading to higher photosynthesis and grain yield. *ACS Omega* **3**, 14406–14416 (2018).
60. Yusefi-Tanha, E., Fallah, S., Rostamnejadi, A. & Pokhrel, L. R. Root system architecture, copper uptake and tissue distribution in soybean (Glycine max (L.) Merr.) grown in copper oxide nanoparticle (CuONP)-amended soil and implications for human nutrition. *Plants* **9**, 1326 (2020).
61. Sharma, S. et al. A non-classical route of efficient plant uptake verified with fluorescent nanoparticles and root adhesion forces investigated using AFM. *Sci. Rep.* **10**, 19233 (2020).
62. Chang, F. P. et al. A simple plant gene delivery system using mesoporous silica nanoparticles as carriers. *J. Mater. Chem. B* **1**, 5279–5287 (2013).
63. Siimes, N., Sharp, E. L., Lewis, N. & Kah, M. Determining acceptance and rejection of nano-enabled agriculture: a case study of the New Zealand wine industry. *NanoImpact* **28**, 100432 (2022).
64. Mosa, M. A. et al. Smart pH responsive system based on hybrid mesoporous silica nanoparticles for delivery of fungicide to control Fusarium crown and root rot in tomato. *J. Plant Pathol.* **104**, 979–992 (2022).

65. Mahmoudi, M., Landry, M. P., Moore, A. & Coreas R. The protein corona from nanomedicine to environmental science. *Nat. Rev. Mater*. **8**, 422–438 (2023).
66. Lowry, G. V. et al. Towards realizing nano-enabled precision delivery in plants. *Nat. Nanotechnol*. **19**, 1255–1269 (2024).
67. Zhang, H.-Y. & Su, W.-H. Classification, uptake, translocation, and detection methods of nanoparticles in crop plants: a review. *Environ. Sci. Nano* **11**, 1847–1870 (2024).
68. Cong, V. T. et al. Can the shape of nanoparticles enable the targeting to cancer cells over healthy cells? *Adv. Funct. Mater.* **31**, 2007880 (2021).
69. Zhang, H. et al. Nanoparticle cellular internalization is not required for RNA delivery to mature plant leaves. *Nat. Nanotechnol.* **17**, 197–205 (2022).
70. Zhang, L. et al. Transformable peptide nanoparticles arrest HER2 signalling and cause cancer cell death in vivo. *Nat. Nanotechnol.* **15**, 145–153 (2020).
71. Spielman-Sun, E. et al. Protein coating composition targets nanoparticles to leaf stomata and trichomes. *Nanoscale* **12**, 3630–3636 (2020).

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Author contributions

V.T.C. initiated the idea. V.T.C., J.J.G. and M.K. conceived the scope of the manuscript. V.T.C. wrote the first draft of the manuscript. J.J.G. and M.K. revised and provided suggestions to the manuscript. All the authors read, revised, and approved the final version.

Competing interests

All authors declare no competing interests. V.T.C. is the founder of NanoSoils Bio. J.J.G. is scientific advisor of NanoSoils Bio.

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