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# Recent advances in surface decoration of nanoparticles in drug delivery

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Nanoparticulate delivery systems have been attracting attention in pharmaceutical sciences for enhanced drug bioavailability and targeted delivery. Specifically, these systems can enhance the solubility of poorly water-soluble drugs, protect therapeutic agents from degradation, prolong circulation time in the body, control drug release, and facilitate the precise targeting of drugs to specific tissues or cells. However, once administered into the body, nanoparticles often encounter significant challenges that can affect their efficacy and safety, such as issues with stability, biocompatibility, and targeting. The surface properties of nanoparticles are one of the most important features as they can greatly influence the interactions between nanoparticles themselves and between nanoparticles and biological targets. Key surface characteristics, such as charge, hydrophobicity, and the presence of functional groups, determine how nanoparticles behave in biological environments, thereby influencing their stability, cellular uptake, and ability to avoid immune clearance. Modification of the nanoparticle surface has been shown to be an effective approach to modulate the physicochemical and biological properties of nanoparticles, achieving desired therapeutic efficacy *in vivo*. This review aims to summarize recent advances in surface decoration of nanoparticles, with an emphasis on improved colloidal and biological stability, reduced toxicity, and enhanced drug targeting. The challenges and future perspectives of nanoparticle surface modification approaches are also discussed.

KEYWORDS

**nanoparticles, surface modification, targeted delivery, stability, toxicity**

## 1 Introduction

Nanoparticles are generally defined as particles with diameters ranging from 1 to 100 nm; however, in the field of pharmaceutics and medicine, submicron particles are also termed nanoparticles (Wu et al., 2011). The use of nanoparticles in drug delivery is driven by their ability to improve the solubility and/or stability of active pharmaceutical ingredients (APIs), thereby enhancing drug bioavailability. Nanoparticles can also be designed to release their payload in a controlled manner over a prolonged period, allowing for sustained drug release and reducing the frequency of dosing. Additionally, nanoparticles can be engineered to achieve targeted delivery, thereby minimizing side effects and enhancing the drug efficacy. Their small size facilitates the penetration through biological barriers, enabling efficient targeting of tissues and cells (Sharma et al., 2018).

There are different types of nanoparticles, including polymeric nanoparticles, lipid-based nanoparticles, inorganic nanoparticles, and biological nanoparticles. Each type possesses specific characteristics that can be employed for various drug delivery purposes (Yetisgin et al., 2020). Polymeric nanoparticles can be synthesized from a variety of natural or synthetic materials, offering diverse structures and characteristics. They can be manufactured using different techniques including emulsification, nanoprecipitation, ionic gelation, and microfluidics. Therapeutics can be encapsulated within, entrapped in, conjugated to, or bound to the nanoparticle surface, allowing delivery of various payloads including hydrophobic and hydrophilic compounds with differing molecular weights (Zielińska et al., 2020). Polymeric nanoparticles are excellent for drug delivery due to their water solubility, biocompatibility, and storage stability. However, they can pose risks of particle aggregation and toxicity (Beach et al., 2024). Lipid-based nanoparticles typically feature spherical structures with one or more lipid bilayers encapsulating an aqueous core. They offer numerous advantages such as simplicity in formulation, self-assembly, biocompatibility, high bioavailability, and the ability to carry large payloads. Their physicochemical properties can be controlled to modulate biological characteristics. The most common lipid-based nanoparticles are liposomes and lipid nanoparticles (Mehta et al., 2023). Inorganic materials, such as gold, iron, and silica, are used to create nanostructured materials for drug delivery, diagnostics, and imaging. These nanoparticles can be precisely engineered in various sizes, structures, and geometries (Mitchell et al., 2021). Biological nanoparticles, often derived from natural biological materials, such as proteins, lipids, and polysaccharides, exhibit inherent biocompatibility and biodegradability. These nanoparticles can be engineered to carry therapeutic agents, enhancing drug delivery by leveraging their natural cellular interactions. Common examples include exosomes, virus-like particles, and protein-based nanoparticles (Stanley, 2014).

Upon administration into the body, nanoparticles often face significant challenges that can compromise their efficacy and safety, including stability, biocompatibility, and targetability. Stability is a major challenge in nanoparticle-based drug delivery. Once administered, nanoparticles must remain stable in the bloodstream long enough to reach their target site. However, nanoparticles frequently encounter physical stability issues, primarily due to aggregation driven by van der Waals forces or hydrophobic interactions. This aggregation leads to particle clumping and sedimentation, which alters the size distribution of the nanoparticles and results in unpredictable behavior in biological environments (Wu et al., 2011). In addition to physical instability, biological instability of nanoparticles is another concern, typically caused by the adsorption of biomolecules, including proteins, lipids, and enzymes, onto the particle surface. This adsorption can alter the surface properties of nanoparticles, modifying their interactions with cells and leading to rapid clearance by the mononuclear phagocyte system (MPS). The biological instability of nanoparticles could also be attributed to enzymatic degradation that compromises the structural integrity of nanoparticles (Guerrini et al., 2018). The instability can lead to a reduction in the therapeutic effectiveness of the drug and can also cause unintended toxicity. Another challenge associated with nanoparticles is their limited biocompatibility, which can result in toxicity following administration. Nanoparticle-induced toxicity may stem from either the incompatible nature of the material or the small size of the nanoparticle. The latter factor can lead to strong interactions between nanoparticles and biological systems, potentially inducing toxicity. Parameters influencing nanoparticle toxicity include composition, size, shape, surface charge, and propensity for aggregation (Kyriakides et al., 2021). A significant concern with nanoparticles is their inability to specifically target tissues and cells. Physiological barriers, such as the immune system and the blood-brain barrier, prevent nanoparticles from selectively accumulating in target cells or tissues. Consequently, nanoparticles may exhibit suboptimal specificity, leading to a substantial portion of the therapeutic payload being distributed to non-target sites. This non-specific distribution can lead to off-target effects and reduced therapeutic efficacy (Debbage, 2009).

To address the issues associated with nanoparticles, a potential approach is to modify the nanoparticle surface, altering their physicochemical properties and bioactivity. For instance, functionalizing the nanoparticle surface with polymers such as polyethylene glycol (PEG) significantly improves stability by preventing aggregation and protein adsorption, thereby maintaining consistent size distribution and prolonging circulation time in biological environments—an effect known as stealth coating (Choi et al., 2003). Doxil® is the first approved PEGylated liposome loaded with doxorubicin for the treatment of some cancer types. The PEGylated liposome increased the drug bioavailability by 90-fold compared to the free drug and demonstrated a prolonged circulation half-life (Gabizon et al., 2003). Alternatively, surface modification of nanoparticles with chitosan can induce a positive surface charge, facilitating robust electrostatic interactions between the nanoparticles and mucin. This process extends the residence time of nanoparticles at the target site, consequently enhancing drug absorption (Gupta et al., 2011; Vieira et al., 2018). Additionally, surface modifications can mitigate toxicity by using biocompatible coatings that shield the nanoparticles from eliciting adverse immune responses and minimize interactions with non-target cells (Gamucci et al., 2014). In recent years, there has been a shift towards utilizing more specific and complex ligands for surface modification to improve targeting specificity. Nanoparticles can be conjugated with ligands, such as antibodies, peptides, or small molecules, that recognize and bind to specific receptors on the cell membrane, thereby facilitating uptake by target cells and enabling controlled drug release. This targeted approach, known as active coating, enhances the accumulation of nanoparticles in diseased tissues while reducing off-target effects and systemic toxicity (Patel et al., 2019). This underscores the necessity for continued development of surface decoration approaches to overcome the challenges of nanoparticle-based drug delivery systems as well as maximize their therapeutic potential. Recent studies have investigated surface modifications of various types of nanoparticles for both stealth and active coating purposes, as summarized in Table 1.

The purpose of this review paper is to explore and elucidate the significant advancements in the surface modification of nanoparticles. This paper focuses on the mechanism and approaches of surface modification to enhance physicochemical and biological stability, enable targeted delivery, and improve biocompatibility. By examining these key areas, we aim to

TABLE 1 A summary of recent research on surface modification of nanoparticles in drug delivery.

| Type of nanoparticles | Type of surface modification | Nanoparticle | Surface modifier | Outcomes | References |
|---|---|---|---|---|---|
| Polymeric nanoparticles | Stealth coating | Polybutylcyanoacrylate nanoparticle | Chitosan (3-20 kDa) | Enhanced nanoparticle stability | Lin et al. (2021) |
| | | Chitosan nanoparticle | PEG | Enhanced nanoparticle stability and prolonged blood circulation | Deng et al. (2021a) |
| | Active coating | PLGA nanoparticle | Folic acid | Improved cellular uptake into cervical cancer cells (HeLa) | Barnaud et al. (2024) |
| | | Polymeric micelles based on (mPEG-b-pHPMAmLacn) block copolymers | Cyclic arginine-glycine-aspartic acid (cRGD) peptide | Improved cellular uptake into tumour cells | De Lorenzi et al. (2023) |
| | | Poly ethyl-2-cyanoacrylate (PECA) nanoparticle | Di-arginine-histidine (RRH) | Improved cellular uptake into Caco-2 cells | Chiu et al. (2022) |
| Lipid nanoparticles | Stealth coating | Liposome | Chitosan-grafted polyhydroxy polymers | Improved circulation time *in vivo* | Miao et al. (2024) |
| | | Lipid nanoparticle | Albumin | Enhanced stability in serum and reduced non-specific cell interaction | Notabi et al. (2021) |
| | Active coating | Solid lipid nanoparticle | Polyoxyethylene stearyl ether (PSE) grafted PEG | Improved cellular uptake | Balenzano et al. (2024) |
| | | Liposome | Cholesteryl acetyl carnitine (CAC) | Improved cellular uptake | Zahednezhad et al. (2021) |
| | | Cubosome | Hyaluronic acid | Increased cytotoxic activity on liver cancer cells | Nisha et al. (2022) |
| Inorganic nanoparticles | Stealth coating | Mesoporous silicananoparticles | PEG | Enhaned colloidal stability and sustained drug release | Nguyen et al. (2024) |
| | | CeO2 nanoparticle | Alginate | Enhanced colloidal stability | Pramanik et al. (2022) |
| | Active coating | Iron oxide nanoparticle | HRH (HRHTKQRHTALH) peptide | Enhanced cellular uptake and cytotoxicity on lung cancer cells | Ngema et al. (2023) |
| Biological nanoparticles | Stealth coating | Extracellular vesicles (EVs) derived from mesenchymal stem cells (MSC) | Polyoxazoline | Improved plasma stability | Simon et al. (2025) |
| | | Exosome | Polydopamine and PEG | Improved colloidal stability | Wang et al. (2021a) |
| | Active coating | Exosome | AS1411 aptamer | Enhanced cellular uptake into colon tumour cells | Hosseini et al. (2022) |
| | | Exosome | Growth-associated protein-43 (GAP43) monoclonal antibody | Targeted drug delivery to impared neuron | Guo et al. (2021) |

provide a comprehensive understanding of the current strategies and technologies employed to optimize nanoparticle-based drug delivery systems for increased efficacy and safety.

## 2 Impact of surface on nanoparticle properties

The surface properties of nanoparticles are paramount in dictating their physicochemical and biological behavior, which in turn significantly impacts their effectiveness in drug delivery applications. The physicochemical properties of the nanoparticles, namely, the particle size, surface charge, hydrophobicity, and the presence of functional groups, can influence the stability, solubility, dispersibility, drug release rate, and toxicity of nanoparticles.

### 2.1 Particle size and surface charge

The particle size and surface charge of nanoparticles are critical determinants of their physicochemical and biological properties. Particle size affects several key aspects, including the stability, biodistribution, and cellular uptake of nanoparticles. Small nanoparticles, typically in the range of 10–100 nm, can penetrate

TABLE 2 Studies on surface modification of nanoparticles to reduce nanoparticle toxicity.

| Types of Nanoparticles | Surface moieties | Outcomes | References |
|---|---|---|---|
| Polymeric Nanoparticles | Metastatic tumour cell membrane | Reduced cytotoxicity in blood-brain barrier hCMEC/D3 and human glioblastoma U87MG cells | Wang et al. (2020a) |
| | MES23.5 neuronal cell membrane | Reduced cytotoxicity in murine microglial BV2, human neuroblastoma SH-SY5Y, and mouse embryonic fibroblast NIH-3T3 cells | Liu et al. (2020a) |
| | Neural stem cell/CXCR4 membrane | Enhanced biocompatible for intravenous use without tissue damage or liver toxicity (H&E staining) | Ma et al. (2019) |
| | Imidazole acetic acid | Reduced hematological and immune toxicity in C57/Bl6 mice | Toy et al. (2019) |
| | Thiol, carboxyl, and amino groups | No significant toxicity or liver and kidney function impairment through blood routine analysis, serum biochemical tests, and histopathological examination<br>Thiol and carboxyl modifications have better *in vivo* circulation and metabolic clearance than amino modification | Guo et al. (2023) |
| | Recombinant CD47 protein | Preferably reduced phagocytic activity by macrophage M1 phenotype compared to PEG-coated nanoparticles in C57BL/6J mice | Qie et al. (2016) |
| Metal-based Nanoparticles | Chitosan | Reduced cytotoxicity and reactive oxygen species (ROS) generation in human cervix carcinoma HeLa, human lung carcinoma A549, and human embryonic kidney HeK293 | Shukla et al. (2015) |
| | Chitosan | Reduced cytotoxicity with human fibroblast HS27 cells | Peng et al. (2017) |
| | Dextran | Reduced cytotoxicity in mouse fibroblast L929 cells | Shaterabadi et al. (2017) |
| | | Decreased mortality of Danio rerio zebrafish larvae | de Oliveira et al. (2017) |
| | | Minimal cytotoxicity and negligible impact on membrane integrity after 72 h of incubation with human T lymphocyte Jurkat cells | Balas et al. (2017) |
| | | No significant alterations in cell viability or apoptosis in human primary monocyte cells | Wu et al. (2018) |
| | | Increased *in vitro* hemocompatibility and no induction of complement activation-related pseudoallergy (CARPA) in healthy human volunteers | Unterweger et al. (2017) |
| | Red blood cell membrane (RBC) | Normal blood biochemistry, hematological testing, hematological staining in mice | Chen et al. (2021) |
| | Keratin | Did not affect growth, proliferation and temperature-dependent cellular viability of *E. coli* TG1 | Annesi et al. (2021) |
| | Alginate/gum acacia matrices | Reduced cytotoxicity in human adenocarcinoma Caco-2 cells | Manuja et al. (2022) |
| | Chitosan, polyethylene glycol, and alginate | Minimal cytotoxicity against normal cell lines (RAW264.7, 3T3-L1, and MCF10A) and MDA-MB-231 breast cancer cells<br>Nongenotoxicity through micronucleus assay, and hemocompatibility (only 2%–3% hemolysis) in mice | Malabanan et al. (2023) |
| | Fluorescent amorphous silica | Decreased acute cytotoxic effects in human cervix carcinoma HeLa cells | Navarro-Palomares et al. (2020) |

(Continued on following page)

TABLE 2 (*Continued*) Studies on surface modification of nanoparticles to reduce nanoparticle toxicity.

| Types of Nanoparticles | Surface moieties | Outcomes | References |
|---|---|---|---|
| | Poly (L-lysine) | Reduced cytotoxicity in neural stem cells | Pongrac et al. (2016) |
| | Meso-2,3-dimercaptosuccinic acid | Reduced cytotoxicity in human colorectal carcinoma HCT 116 cells | Gomez–Caballero et al. (2023) |
| | Human-like collagen | Reduced cytotoxicity in embryonic mouse fibroblast NIH3T3 cells | Liu et al. (2015) |
| | Nano-hydroxyapatite | Reduced cytotoxicity in murine calvarial pre-osteoblas MC3T3-E1 cells and decreased hemolysis in ICR mouse blood | Zhang et al. (2022) |
| Mesoporous Silica Nanoparticles | Polymixin B | Reduced ROS generation in human hepatoma cancer cells HepG2, human foreskin fibroblasts Hff-1 and human embryonic kidney Hek-293 cells | Gounani et al. (2018) |
| | Titania | Reduced ROS generation in solution | Farooq et al. (2018) |
| | Lipid bilayer composed of soybean lecithin and DSPE-PEG 2000 | Reduced cytotoxicity in human breast cancer MCF-7 cells, decreased non-specific protein absorption and hemolysis in rabbit red blood cells | Han et al. (2016) |
| Lipid-based Nanoparticles | Macrophage membrane | Reduced liver and kidney toxicity in spinal cord injury mice | Tang et al. (2021) |
| | Macrophage membrane | Reduced cytotoxicity in differentiated HT22 neurons, bEnd.3 cells, astrocytes Enhanced biocompatibility in healthy mice through H&E staining tests of the heart, liver, spleen, lung, kidney and brain | Han et al. (2021) |
| | Red blood cell membrane (RBC) | Reduced systemic toxicity in healthy mice throught H&E staining and haemogram assay | Fu et al. (2019) |

tissues more effectively and are less likely to be recognized and cleared by the reticuloendothelial system (RES), allowing for prolonged circulation time and enhanced accumulation at target sites. However, very small nanoparticles with less than 10 nm in size might exhibit rapid renal clearance, reducing their therapeutic efficacy (Sadat et al., 2016). Surface charge, on the other hand, plays a pivotal role in the interaction of nanoparticles with biological membranes and proteins. Positively charged nanoparticles often demonstrate enhanced cellular uptake due to the electrostatic attraction to the negatively charged cell membranes but may also exhibit higher toxicity and be rapidly cleared from the bloodstream due to opsonization and uptake by the RES. Negatively charged or neutral nanoparticles typically exhibit reduced protein adsorption and lower clearance rates, resulting in prolonged circulation time but potentially reduced cellular uptake (He et al., 2010).

## 2.2 Hydrophobicity

Hydrophilic surfaces tend to exhibit better dispersion in aqueous media, while hydrophobic-surfaced nanoparticles tend to aggregate due to their tendency to minimize contact with water molecules, which can lead to reduced stability and poor dispersion in biological fluids. This aggregation can hinder their ability to circulate effectively within the bloodstream and reach target sites (Sinani et al., 2005). Biologically, the hydrophobicity of nanoparticles plays a crucial role in their interaction with biological membranes and proteins. Hydrophobic surfaces can enhance the adsorption of plasma proteins, leading to opsonization and subsequent clearance by the RES, thereby reducing circulation time and limiting therapeutic efficacy (Verma and Stellacci, 2010). However, hydrophobic nanoparticles can also facilitate the encapsulation and controlled release of hydrophobic drugs, which are often challenging to deliver due to their poor solubility in water (Wischke and Schwendeman, 2008).

## 2.3 Surface functional groups

The incorporation of various functional groups can tailor the surface characteristics of nanoparticles, such as hydrophilicity, charge, and reactivity. Hydrophilic functional groups, such as hydroxyl or carboxyl groups, can enhance the solubility and physical stability of nanoparticles in biological fluids. Charged functional groups, whether positive (e.g., amine groups) or negative (e.g., carboxyl groups), significantly impact the surface charge of nanoparticles, resulting in changes in their physicochemical and biological properties (Verma and Stellacci, 2010). Functional groups can also be used to conjugate targeting ligands, such as antibodies, peptides, or small molecules, to the nanoparticle surface, thereby enabling active targeting of specific cells or tissues and improving therapeutic efficacy while minimizing off-target effects (Friedman et al., 2013).

# 3 Surface modification

To immobilize functionalities or ligands on the surface of nanoparticles, various approaches have been developed, which

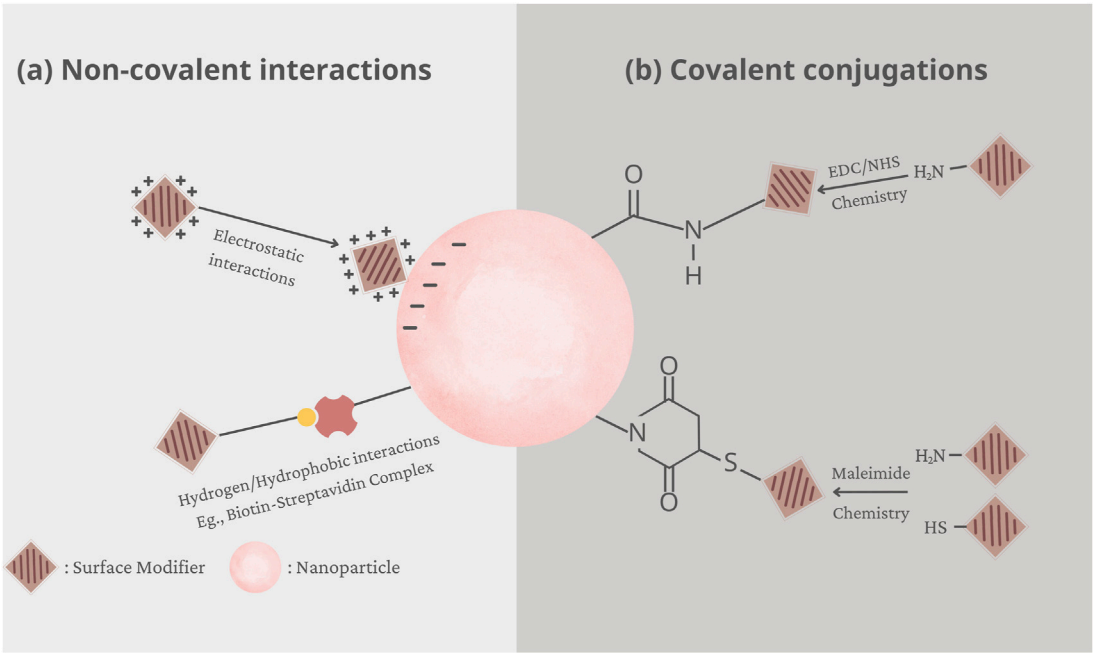


FIGURE 1
Graphical demonstration of two surface modification strategies: **(A)** electrostatic interactions and **(B)** covalent conjugations.

can be generally classified into two categories, i.e., covalent conjugation and non-covalent interactions (Moku et al., 2019). These two surface modification strategies are graphically demonstrated in Figure 1.

Covalent conjugation is a widely used method, which involves chemical immobilization of the functionalised moiety, such as the ligand or polymer, to the surface of nanoparticles. However, this process requires the presence of functional groups on the surface that can facilitate the attachment of functionalised moieties. A variety of functional groups have been immobilized onto the surface of nanoparticles, including carboxylic acids, amines, thiols, alcohols, or maleimides. For instance, 1-ethyl-3-(3-dimethylaminopropyl) carbodiimide hydrochloride (EDC) is a common coupling reagent that converts carboxyl or phosphate groups into amine-reactive forms, often in combination with N-hydroxysuccinimide (NHS) or sulfo-NHS to stabilize intermediates and enhance efficiency (Alcantara et al., 2024). Alternatively, maleimide coupling, which involves reactions between a primary amine and a thiol, or between two thiols, is also a prevalent technique for surface modification (Lee et al., 2020).

Noncovalent interactions offer another avenue for ligand attachment, showcasing the versatility of surface functionalization techniques. This method relies on the interplay of attractive forces between nanoparticle surfaces and functionalized moieties, encompassing electrostatic interactions, hydrogen bonding, hydrophobic interactions, and van der Waals forces. One prominent example is the biotin-(strept)avidin system, a paradigm of strong and specific molecular recognition. Avidin or streptavidin, proteins with a high affinity for biotin, form robust complexes, allowing for stable nanoparticle surface functionalization (Ehsani et al., 2021). Additionally, electrostatic interactions between oppositely charged species present another mechanism for stable ligand immobilization. By harnessing the inherent electrical properties of nanoparticles and ligands, electrostatic interactions can drive efficient binding, leading to effective surface modification (Nguyen et al., 2020). Furthermore, physical adsorption, facilitated by hydrogen bonding or hydrophobic interactions, offers a non-invasive approach for ligand attachment. For example, hydrophobically-modified dextran was physically adsorbed onto the surface of polystyrene nanoparticles via hydrophobic interactions (Delgado et al., 2000).

## 4 Surface modification for enhanced nanoparticle stability

The small size and high surface area of nanoparticles result in a strong tendency to adhere to each other and form aggregates, compromising their physical stability in biological fluids. This aggregation significantly reduces the circulation time of nanoparticles within the body, therefore limiting their pharmacological effectiveness. Additionally, nanoparticles tend to form a protein corona on their surface while circulating throughout the body, which alters their biological identity and impacts their biodistribution and targeting efficiency. Specifically, this protein corona can trigger the capture of nanoparticles by macrophages, thereby reducing the biological half-life. To address these challenges, surface modification of nanoparticles has emerged as a widely studied and effective strategy. Altering the surface properties of nanoparticles makes it possible to enhance nanoparticle stability, prevent agglomeration, and prolong circulation time.

## 4.1 Surface modification for stabilization of nanoparticles

Nanoparticles generally exhibit lower stability in aqueous media and biological fluids compared to microparticles due to several factors, which includes (Hotze et al., 2010):

- Size effect: Smaller particles have higher surface energy, making them more prone to agglomeration to reduce system free energy.
- Surface area to volume ratio: Nanoparticles have a higher surface area to volume ratio, increasing susceptibility to interactions and aggregation.
- Van der Waals forces: These forces are more significant at the nanoscale, causing nanoparticles to aggregate when in contact with each other or with the medium.
- Brownian motion: Pronounced Brownian motion in nanoparticles leads to collisions and aggregation.
- Electrostatic interactions: Nanoparticles may exhibit stronger electrostatic interactions with ions or molecules in the medium, influencing stability through attraction or repulsion.

These factors contribute to the reduced physical stability of nanoparticles in the liquid medium. Aoki et al. performed a study on the *in vivo* toxicity of high-dose intravenous nano-hydroxyapatite to Wistar rats and found that the observed health issues in the rats were due to nanoparticle aggregation, which caused drug blockage in pulmonary capillaries (Aoki et al., 2000). Other studies have also shown that nanoparticle aggregation can lead to diseases and toxicity in animals (Xie et al., 2010; Moore et al., 2013; Moore, 2014). These studies highlight the importance of stabilizing nanoparticles in biological fluids for enhanced drug bioavailability and reduced toxicity. Surface modification is one of the most effective methods used to improve nanoparticle stability. Materials used for surface modification of nanoparticles can be broadly classified into macromolecules and small molecules, each offering distinct advantages depending on the application's specific requirements. The distinction between macromolecules and small molecules is primarily based on molecular mass. Macromolecules are molecules with a high molecular weight, typically greater than 1 kDa, and are often large, complex structures formed by the polymerization of monomers through covalent bonds (Dkhar et al., 2022). In contrast, small molecules generally have a molecular weight ranging from 0.1 to 1 kDa (Chhabra, 2021). This difference in molecular weight also leads to differing characteristics in how they bind to the surface of nanoparticles.

### 4.1.1 Macromolecules

Macromolecules, such as polymers, polysaccharides, lipids, proteins, antibodies, or nucleic acids (aptamers), are frequently used for surface modification due to their large size and ability to introduce multiple functional groups. In general, macromolecules can be coated on nanoparticles via the formation of chemical bonds between biomolecules and the substrate surface either directly, through a spacer, or by noncovalent adsorption (Moku et al., 2019).

#### 4.1.1.1 Polymers

One of the effective methods to stabilize nanoparticles in biological fluids is to use polymeric ligands. Polymeric ligands provide a short physical barrier to the mutual interactions between nanoparticles. Many types of polymeric ligands have been used, but the most popular one is PEG because of its popularity and biocompatibility. Another reason for using PEG is the hydrophilic nature of this polymer. PEG forms a hydration layer around the nanoparticles, generating a repulsive force that prevents the nanoparticles from agglomeration. This steric stabilization enhances the stability of nanoparticles in biological fluids. Furthermore, PEG increases the stability of polymeric nanoparticles during storage and in aqueous dispersions by reducing the tendency of particles to aggregate (Suk et al., 2016). The distance between nanoparticles increases as the PEG chain length increases, thereby enhancing the steric repulsion of PEG and preventing the aggregation of nanoparticles (Shi et al., 2021). Kostiv et al. demonstrated that coating PEG-2000 to the surface of $Fe_3O_4$ and $SiO_2$ nanoparticles increased the biocompatibility and stability of these particles (Kostiv et al., 2017). Cyclic PEG, prepared through the etherification of PEG-3000, can also be used to modify the surface of gold nanoparticles, which significantly improved the nanoparticle's colloidal stability at 85°C for 48 h (Wang et al., 2020b). In addition to PEG, other polymers have also been used for steric stabilization of nanoparticles, including natural polymers (e.g., alginate, chitosan) and synthetic polymers (e.g., polyvinyl alcohol (PVA), polyvinyl pyrrolidone (PVP)). Jin Soon Han et al. used PEI (polyethylenimine) and PAA (polyacrylic acid) for surface functionalisation of $Fe_3O_4$ nanoparticles, resulting in reduced particle size distribution, mean particle size, and polydispersity index (PDI) compared to uncoated nanoparticles. The zeta potential increased by approximately tenfold, leading to electrostatic repulsion and reduced nanoparticle aggregation in suspension. Thus, PEI and PAA surface attachment significantly improved nanoparticle stability in the dispersion system (Han et al., 2018). Another work by Sabzi et al. modified the surface of $Fe_3O_4$ nanoparticles with PVA (72 kDa) and PEG-6000. The coated nanoparticles exhibited good colloidal stability in water for 72 h, while the uncoated nanoparticles showed agglomeration (Sabzi Dizajyekan et al., 2024).

#### 4.1.1.2 Polysaccharides

Polysaccharides or glycans are molecules that selectively bind to proteins and are essential for signaling between cells. An important property of glycans is their selectivity for specific cell types through carbohydrate receptors, which can be maintained regardless of the media used. The disadvantage of the glycan method is the complex chemical process on the surface of the nanoparticles. The stabilisation effect of polysaccharides when decorated onto the surface of nanoparticles is due to their steric protection, which prevents protein adsorption and uptake by macrophages (Lemarchand et al., 2004). For instance, Garcia et al. used thiol-terminated glycoconjugates either *N*-acetylglucosamine (GlcNAc) or disaccharide lactose to functionalize Au nanorods. The nanoparticles showed good stability in the standard cell culture medium (Dulbecco's modified Eagle's medium, DMEM) supplemented with 10% FBS for 2 h at 37°C (Garcia et al., 2015). Yang et al. studied the surface modification of nanoparticles using

heparosan polysaccharide (HEP) to produce colloidally stable HEP-conjugated gold nanoparticles. The resulting nanoparticles exhibited good stability in saline solutions with 0.3–0.7 M NaCl and within a pH range of 1.5–7 over a period of 4 days. The stability of the HEP-conjugated gold nanoparticles was also retained after six repeated centrifugation and washing cycles with water and PBS (Yang et al., 2022).

#### 4.1.1.3 Lipids

Another strategy used to improve the stability of nanoparticles in biological fluids is to use lipids as a coating layer for nanoparticles. The most important advantage of the lipid layer is to create a thin and uniform shell covering the nanoparticles, so it does not significantly change the hydrodynamic diameter of the nanoparticles. Besides, the uniformity of the lipid layer also helps the nanoparticles to be less susceptible to protein adsorption, making them more stable in biological fluids. However, media such as cultures containing high concentrations of cysteine or glutathione have been reported to cause aggregation of lipid-coated nanoparticles. Another downside of the lipid coating method is that they are not made from covalent bonds on the nanoparticle surfaces, so they are less durable and easy to separate. Natural phospholipids such as phosphatidylglycerol, phosphatidylcholine, phosphatidylinositol, phosphatidylserine, phosphatidic acid, phosphatidylethanolamine and their synthetic counterparts are often used to coat the surface of polymeric nanoparticles (Mandal et al., 2013). Bhowmik et al. simulated the cell membrane by using a lipid bilayer composed of POPC (1-palmitoyl-2-oleoyl-sn-glycero-3-phosphocholine), POPG (1-palmitoyl-2-oleoyl-sn-glycero-3 phosphoglycerol), and cholesterol. The coated nanoparticle suspension was shown to be highly stable in both PBS (pH 7.4) and 100 mM NaCl (Bhowmik et al., 2015). Märkl et al. utilized the phospholipid bilayer to coat the small core-shell upconversion nanoparticles of 12 nm, which demonstrated good colloidal stability in various media, including phosphate buffer (pH 7.4), high ionic saline solution (138 mM NaCl) and cell culture media supplemented with 5% fetal bovine serum (FBS) for 96 h (Märkl et al., 2020).

#### 4.1.1.4 Proteins

The formation of a protein corona can cause nanoparticles to become unstable and more susceptible to uptake by macrophages. Prior studies have, however, shown that coating nanoparticles with proteins enhances their stability in biological fluids. The protein coating, which contains many charged groups, helps stabilize the nanoparticles by maintaining their charge balance, thereby improving their spatial stability and reducing aggregation. Additionally, the protein coating creates a hydration layer around the nanoparticles, which prevents them from being absorbed by other free proteins, further enhancing their stability. Serum albumin is particularly suitable for this application because it carries cysteine groups that are highly reactive with the nanoparticle surface. Proteins can also be used to coat the surface of nanoparticles using the ligand exchange method, which involves replacing existing surface-bound ligands on the nanoparticles with protein molecules. Tebbe et al. investigated the ligand exchange of cetyltrimethylammonium bromide (CTAB) with bovine serum albumin (BSA) for gold nanorods. The obtained nanoparticles were demonstrated to be stable in biological media such as PBS or DMEM over a large pH range (pH 2–12). These nanoparticles could be freeze-dried and then redispersed in PBS without compromising their particle size (Tebbe et al., 2015). Chanana et al. used various proteins, i.e., insulin, β-lactoglobulin, and bovine serum albumin, to coat gold nanoparticles (Chanana et al., 2013). The colloidal stability of gold nanoparticles was tested by dispersing them in PBS (pH 7.4) with and without proteolytic enzymes (proteases), followed by incubation at 37°C for 3 days. The results showed that the nanoparticles remained stable at pH 7.4 throughout the incubation period. Bychkova et al. used bovine serum albumin (BSA), human serum albumin (HAS), and thrombin (TR) to coat magnetic nanoparticles. The obtained nanoparticles were stable in PBS at pH 6.5 (BSA, HSA) or pH 7.3 (TR) in the presence of hydrogen peroxide (Bychkova et al., 2013). Wenck et al. coated magnetic nanoparticles with casein, which resulted in enhanced colloidal stability compared to uncoated nanoparticles. This was evidenced by no change in particle size or magnetic behavior after incubation in solutions of NaCl, $Ca(CH_3COO)_2$ $(NH_4)_2SO_4$, and $MgSO_4$ for 18 h (Wenck et al., 2024).

#### 4.1.1.5 Aptamers

Aptamers are short sequences of DNA, RNA, XNA (i.e., xeno nucleic acids, a synthetic alternative to the natural nucleic acids DNA and RNA) or artificial peptides that bind to a specific target molecule or a family of target molecules. Aptamers can be considered natural antibodies, which can be used to replace antibodies in some applications such as identifying pathological markers or used in targeted therapy. Attaching aptamers to the surface of nanoparticles also renders these particles more stable and intact in biological fluids (Abdelkawi et al., 2023). Aptamers can be directly attached to the surface of nanoparticles via the thiol linkage (Catala et al., 2016). The disadvantage of the aptamer attachment method is the rarity and difficulty of obtaining this material (Guerrini et al., 2018). Delaviz et al. used cyanogen bromide in a sodium bicarbonate buffer to activate the hydroxyl groups of starch-functionalized magnetic nanoparticles and couple them with amino groups of aptamers (Delaviz et al., 2015). Additionally, Nair's group used a similar approach anchoring amino-modified aptamers onto carboxylated dextran-stabilized magnetic nanoparticles via EDC chemistry (Nair et al., 2010). In both above studies, aptamer functionalized magnetic nanoparticles have been shown to be stable in PBS upon incubation at 37°C for an hour.

### 4.1.2 Small molecule ligands

Small molecules, such as surfactants, ligands, and small organic compounds, stabilize the nanoparticles through various mechanisms, such as reducing surface tension or modifying surface charge. The major advantages of using a small molecule as the targeting ligand over macromolecules are their stability, ease of conjugation with nanoparticles, and low cost. The drawbacks associated with the use of small molecules as targeting ligands include the lack of an efficient approach to identify such ligands and their lower specificity and affinity for surface receptors on the target cells (Moku et al., 2019).

#### 4.1.2.1 Zwitterionic ligands

Zwitterionic ligands are molecules containing two or more functional groups carrying different positive and negative charges, but the total charge of the molecule is 0. Zwitterionic ligands, such as carboxybetaines or sulfobetaines, show a variety of positively and negatively charged groups allowing for the modulation of charge densities to optimize solubility and to avoid the interactions of the protein corona (Sanita et al., 2020). Because of this structure, zwitterionic ligands are less sensitive to solvents with high ionic concentrations. Therefore, zwitterionic ligands are good candidates for surface modification of nanoparticles and helping them stable in biological fluids. In addition, coating nanoparticles with zwitterionic ligands has been shown to produce nanoparticles with much smaller hydrodynamic diameters and lower degrees of opsonization compared to the corresponding polymers. Despite many advantages, zwitterionic ligands are not popular and the synthesis process is quite complicated. In addition, zwitterionic ligands are sensitive to pH changes, which increases the adsorption of proteins onto nanoparticles. Zhan et al. synthesized two compact multicoordinating (lipoic acid-appended) zwitterion ligands for the capping of luminescent quantum dots. The obtained quantum dots were tested for long-term colloidal stability in PBS at differing pH (pH 4-13), with the presence of excess electrolyte (1 and 2 M NaCl). The data obtained indicated that quantum dots photoligated with the zwitterion ligand were stable in those conditions for at least 2 months of storage at 4°C (Zhan et al., 2013). Wei et al. synthesized iron oxide nanoparticles via thermal decomposition of $Fe(CO)_5$ in dioctyl ether, then decorated the nanoparticle surface with the water-soluble zwitterionic dopamine sulfonate. These synthesized nanoparticles were highly stable in PBS (pH 7.4) over one-month of storage at room temperature, as evidenced by no significant changes in particle size and surface charge (Wei et al., 2012). Khunsuk et al. developed lipid nanoparticles by conjugating 1,2-dipalmitoyl-*sn*-glycero-3-phosphoethanolamine (DPPE) with an antifouling zwitterionic polymer, poly (2-methyacryloyloxyethyl phosphorylcholine) (PMPC). The obtained nanoparticles suspended in 150 mM HEPES buffer were spherical with a diameter of 144–255 nm, neutral in charge, and stable at 4°C for up to 28 days (Khunsuk et al., 2023). However, the absorption and biodistribution of nanoparticles may be affected by the surface charge distribution of zwitterionic nanoparticles. Han et al. demonstrated that zwitterionic nanoparticles with a positively charged outer layer are more sensitive to protein interactions than those with a negatively charged outer layer (Han et al., 2013).

#### 4.1.2.2 Mercaptoalkyl acid ligands

Mercaptoalkyl acid ligands are commonly used to decorate the surface of nanoparticles due to their strong affinity for metal surfaces. These ligands contain thiol (-SH) binding to metal atoms and carboxyl (-COOH) offering sites for further functionalization (Limongi et al., 2019). 11-Mercaptoundecanoic acid (MUA) is one of the most used mercaptoalkyl acid ligands for surface modification. Although MUA is less stable compared to other ligands, it can form a thin, single layer on the surface of nanoparticles. This layer provides effective protection and helps stabilize the nanoparticles in biological fluids. For instance, gold nanoparticles modified by MUA had good colloidal stability, which was proven by no changes in its colloidal state following multiple centrifugation steps at 20,000 ×g (Schulz et al., 2016). MUA molecules are usually short providing just a slight increase in the hydrodynamic diameter of the nanoparticles compared to PEG. This makes MUA inferior to PEG in terms of colloidal stability of nanosystems, but helps the nanoparticles to have lower degrees of opsonization, resulting in longer blood circulation time and the capability to escape from the capture by the phagocytic system (Guerrini et al., 2018).

## 4.2 Surface modification on enhancement the circulation time of nanoparticles—stealth effect

An important characteristic of an effective delivery system is its ability to stay in systemic circulation for a prolonged period. Phagocytic uptake by macrophages is the primary mechanism of particle clearance from systemic circulation. Stable nanoparticles are those that can circulate in the body for an extended period without being engulfed by macrophages. Most unprotected nanoparticles, regardless of their material composition, can be cleared from the blood circulation by the phagocytic system within seconds to minutes after introduction into the body (Fam et al., 2020). Modification of the nanoparticle surface with different types of molecules makes the nanoparticles "invisible" to cells of the immune system and not captured by macrophages. For this purpose, the researchers used hydrophilic polymers that bind water molecules, which creates a barrier on the nanoparticle surface. This water layer plays a role in reducing the interactions of nanoparticles with opsonin receptors and/or macrophages leading to reduced clearance of nanoparticles in the blood (Sanita et al., 2020). Hydrophilic polymers are often used as stealth coatings such as PEG, PVP, PVA, polyaminoacids, or poloxamer (Knop et al., 2010). PEG is a hydrophilic and neutral polymer that helps form barrier layers on the nanoparticle surface, leading to steric blocking, low opsonization and high blood circulation time (Papi et al., 2017). Lipka et al. demonstrated that gold nanoparticles (~5 nm) modified with PEG-10000 had a prolonged blood circulation time compared to uncoated nanoparticles in an *in vivo* study in rats. Twenty-4 hours after intravenous injection, over 18% of the coated nanoparticles remained in the blood, compared to just 0.1% of the uncoated ones (Lipka et al., 2010). The prolonged circulation time achieved by PEGylation of the nanoparticle surface has been shown to translate into an improved therapeutic effect in cancer treatment, as demonstrated in more recent studies using different types of nanoparticles (Kang et al., 2020; Mukherjee et al., 2020; Teng et al., 2020). In addition to PEG, other surface-modified materials have also been used to increase the circulation time of nanoparticles in the blood, such as chitosan, dextran, hyaluronic acid, or heparin (Abd Ellah and Abouelmagd, 2017). For instance, Miao et al. modified the surface of lipid nanoparticles with chitosan-grafted polyhydroxy polymer (PEO-PPO-PEO), which was shown to effectively reduce immunoglobulin adsorption onto the nanoparticles, leading to extended blood circulation *in vivo* (Miao et al., 2024). Another work by Simon et *al.* utilised polyoxazolines to modify the surface of liposomes and

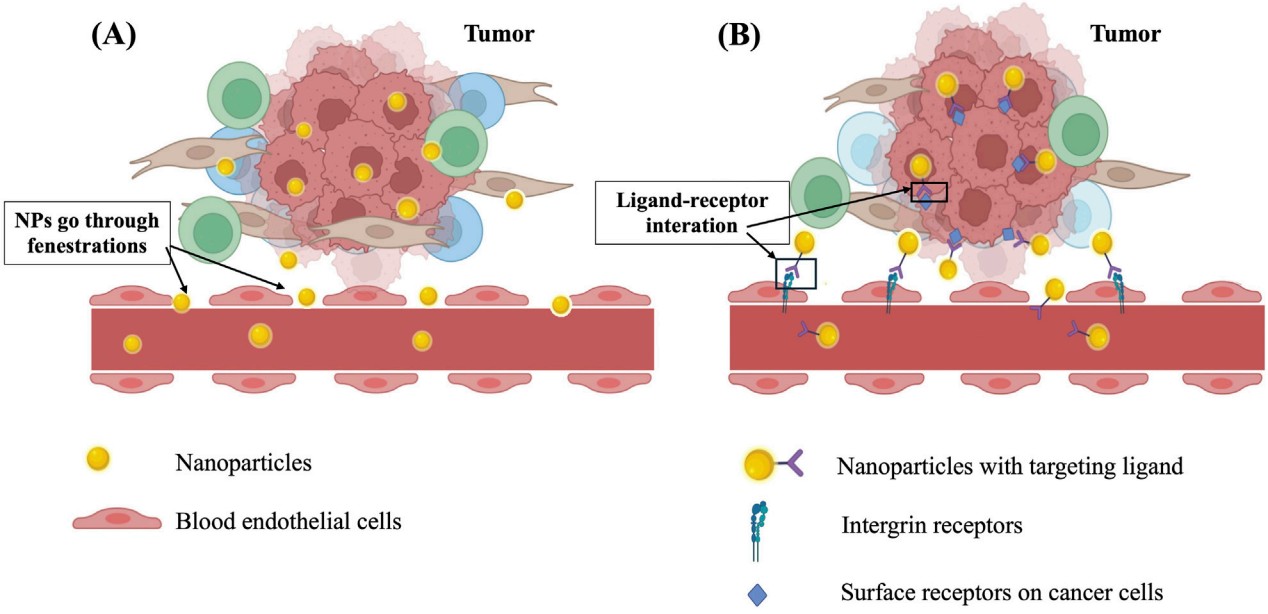


FIGURE 2
The mechanism of action of **(A)** passive targeting based on EPR effect and **(B)** active targeting based on interactions between targeting ligand and receptors.

extracellular vesicles (EVs), which also results in increased blood circulation time in an *in vivo* biodistribution study in mice (Simon et al., 2025).

## 5 Surface modification for drug targeting

To enhance bioactivity and minimize side effects of drugs, several surface modification strategies have been developed to enable targeted delivery. The concept of drug targeting was first suggested by Paul Ehrlich in the early 20th century and has been considered a "magic bullet" that can precisely reach biological targets. In principle, the formulations must be able to enter the target site, then selectively accumulate and elicit therapeutic actions (Hirsjarvi et al., 2011). Drug targeting is particularly valuable in the case of using highly toxic chemotherapeutics in cancer treatment because it can reduce cytotoxicity and immunogenic responses in healthy tissues. Furthermore, the dosage, frequency of administration, and cost of therapy will be reduced thanks to targeting efficiency (Hirsjarvi et al., 2011). There are two types of drug targeting, known as passive targeting and active targeting. Passive targeting, which was first discovered and applied in drug delivery, is based on the physiological features of the targeted area, particularly the enhanced permeability and retention (EPR) effect of the leaky vasculature in solid tumours. This is a pathophysiological phenomenon in which the intravascular structure is not structurally intact and complete due to the rapid growth of tumour cells. Such a condition unintentionally helps nanoparticles of 100–200 nm in size readily go through wide fenestrations between defective endothelial cells and accumulate in the tumour environment. Furthermore, tumour tissues usually lack effective lymphatic drainage, which keeps nanomedicine staying longer at the tumour site (Wu, 2021; Sun et al., 2022). While passive targeting is mainly applied in cancer treatment, active targeting can be utilized for a wider variety of disease settings, such as neurological disorders (Xu et al., 2021; Annu et al., 2022), osteoporosis (Niu et al., 2022), pulmonary diseases (Azarmi et al., 2008; Deng Z. et al., 2021) or cardiovascular diseases (Flores et al., 2019) in addition to cancer. For active targeting, nanomedicine is decorated with ligands that have high affinity to specific receptors over-expressed in targeted tissues. This approach utilizes the selective interactions between ligands and receptors, the receptor-mediated cellular uptake and transport to facilitate intended biodistribution. Common nanocarriers employed for active targeting include monoclonal antibodies (Tsao et al., 2021), liposomes (Liu et al., 2021), polymeric micelles (Kotta et al., 2022), polymeric nanoparticles (Begines et al., 2020), and mesoporous inorganic nanoparticles (Parra-Nieto et al., 2021). Figure 2 illustrates the mechanisms of passive and active targeting of nanoparticles to tumours. The main difference between these two mechanisms is that active targeting utilizes interactions between nanoparticles and over-expressed receptors on cancer cells and vascular endothelial cells, thereby enhancing nanoparticle accumulation in the tumour. In contrast, passive targeting does not involve receptor interactions but relies on the EPR effect of tumour vasculature, allowing for a higher concentration of nanoparticles in the tumour compared to other tissues.

In addition to the aforementioned drug delivery systems, stimuli-responsive prodrugs has been recently explored to control the drug release at the site of action, thereby enhancing drug perfusion into the tumour microenvironment (Rahim et al., 2021). Stimuli-responsive drug delivery systems contain "sensitive" moieties that undergo changes in response to exogenous (i.e., light, temperature, ultrasound) or endogenous

(i.e., pH, redox potential, enzymes) stimuli at the target site (Majumder and Minko, 2021). An example of an exogenous-triggered system is thermosensitive liposome, which can increase its lipid bilayer permeability under heating to a temperature above the average transition temperature of the lipid mixture (Dou et al., 2017). ThermoDox®, the first commercialized thermosensitive liposome contains a lysolipid component (i.e., 1-stearoyl-2-hydroxy-sn-glycero-3-phosphatidylcholine (MSPC or S-lyso-PC)) that becomes porous and releases approximately 80% of doxorubicin within 20 s upon heating to 42°C at the tumour site (Dou et al., 2017). pH-responsive prodrugs are systems belonging to endogenous triggered nanoplatforms. These systems contain either acid-cleavable linkers or ionizable groups that are stable at physiological pH 7.4 but susceptible to acidic pH. As a result, such prodrugs are degraded under the acidic condition in the tumour microenvironment (pH 6.5 – 7.0), leading to drug release at the targeted milieu (Xie et al., 2020).

## 5.1 Surface modification for passive targeting to the tumour

To achieve passive targeting, the physicochemical properties of nanomedicines should be favorable for the EPR effect. In the 1970s, Alec Bangham investigated the first liposome product as drug carriers, but researchers found that liposomes were quickly cleared by the RES, accumulating in the liver and spleen within minutes and reducing passive targeting effectiveness. PEGylation has emerged as a pivotal strategy for enhancing passive targeting in drug delivery systems. This modification imparts a hydrophilic stealth coating to the nanoparticles, significantly increasing their circulation time in the bloodstream by reducing opsonization and subsequent clearance by the MPS. The extended circulation time allows for enhanced accumulation of nanoparticles in tumour tissues through the EPR effect (Jokerst et al., 2011; Vllasaliu et al., 2014). In 1995, the first PEGylated nanomedicine was licensed to the market for the treatment of metastatic ovarian and breast cancer by the United States Food and Drug Administration (FDA), named Caelyx/Doxil® developed by Liposome Technology Inc., and recently sold by Johnson & Johnson. This product is doxorubicin-loaded liposome with a size less than 100 nm and stabilized with DSPE-PEG-2000 (Barenholz, 2012). Compared to the uncoated doxorubicin-loaded liposomes that were quickly cleared from human plasma before reaching the tumour, Doxil® circulates in the blood for up to 36 h and facilitates passive targeting to the tumour extended to 3-7 days (Barenholz, 2012). Following the success of PEGylated nano-liposomes, Genexol®, a product of Samyang Pharmaceuticals containing PEGylated poly (D, L-lactide) micelles loaded with paclitaxel, was approved in Korea in 2007 for the treatment of breast cancer and small cell lung cancer. This product demonstrated targeted biodistribution to malignant tissues, resulting in reduced toxicities of paclitaxel and promoted antitumour effect (Werner et al., 2013). The approval of these two PEGylated nano-products on the market for cancer treatment has strongly demonstrated the tumour targeting effect of PEGylation. Besides liposomes and micelles, the PEGylation technology has also been extensively studied on a wide range of nanocarriers. Studies on the tumour-directed effects of PEGylation in the past 5 years include research on solid lipid nanoparticles (Arduino et al., 2020; Smith et al., 2020; Korake et al., 2023), polymeric nanoparticles (Baião et al., 2020; Bobde et al., 2020; Guo et al., 2020), inorganic nanoparticles (Samadian et al., 2020; Sadalage et al., 2021), and dendrimers (Yadav et al., 2023) for cancer therapy. For instance, 5-fluorouracil-loaded solid lipid nanoparticles composed of PEGylated lipids and surfactants demonstrated a significant inhibition on tumour growth in mice bearing subcutaneous colorectal cancer cells, compared to the free form of 5-fluorouracil. At a dose of 20 mg/kg, 5-fluorouracil-loaded solid lipid nanoparticles remarkably suppressed HER2 receptor expression without causing toxicity in kidney and liver cells. This effect could be attributed to the passive targeting of the tumour due to PEGylation (Smith et al., 2020).

## 5.2 Surface modification for active targeting

While the EPR effect facilitates passive targeting of nanoparticles, it is often insufficient for achieving optimal therapeutic outcomes due to the heterogeneous and variable nature of tumour vasculature. To address the limitations of passive targeting, active targeting mechanisms have been developed, which are based on the selective and specific interactions of targeting ligands with specific receptors over-expressed in the target tissues. Attaching these targeting ligands to the surface of nanoformulations helps enhance targeting efficiency, increase cellular uptake and reach a wider range of targets than passive targeting. It is feasible to graft both PEG chains and targeting ligands on the surface to achieve both passive and active targeting effects. The common targeting moieties used in prior studies include transferrin, peptides, antibodies, carbohydrates, and aptamers (Vllasaliu et al., 2014).

### 5.2.1 Transferrin

Transferrin is a serum β-globulin with reversible binding properties to iron, first isolated by Schade and Caroline in 1946 (Giansanti et al., 2016). Transferrin plays an important role in transport and uptake of iron in the cells, and keeps the balance between the release of iron by RES and the absorption of iron by the bone marrow. When iron binds to transferrin, it will be transported by transferrin to the bone marrow to produce hemoglobin and part of red blood cells. In drug delivery, transferrin has been attached on the surface of nanoformulations to promote the interaction with the transferrin receptor 1 (TfR1), also known as CD-71 receptors, which are abundantly expressed in many types of maglinant cells. After binding to the receptors, the cellular uptake of these nano-formulations is improved through the receptor-mediated endocytosis pathway. Several nanocarriers, including polymeric micelles (Sun et al., 2020), dendrimers (Hu et al., 2020), polymeric nanoparticles (Zhang et al., 2021), nanocomplexes (Su et al., 2022) and liposomes (dos Santos Rodrigues et al., 2020; Fernandes et al., 2021; Mojarad-Jabali et al., 2022) have been successfully grafted with the transferrin ligand. Nanoformulations attached with transferrin showed a great cytotoxicity effect in several types of cancer cells *in vitro* and *in vivo*, including human breast carcinoma MCF-7ADR cells (Gao et al., 2017), human alveolar

cancer cell lines (Singh et al., 2016), HepG2 human hepatoma cell line (Zhang et al., 2016), colon cancer cell line (Varshosaz et al., 2017), and glioblastoma cells (Jhaveri et al., 2018; Sandbhor et al., 2022). Among the aforementioned cancer cells, brain tumour cells receive the most attention due to the significant challenge of delivering drugs across the blood-brain barrier. Thanks to the abundance of transferrin receptors in brain endothelial cells, the nanoformulations attached with transferrin becomes a potential cargo for glioblastoma treatment (Ramalho et al., 2022). For example, quercetin lipid nanoparticles attached with transferrin showed enhanced brain permeability on human cerebral microvascular endothelial cells and offered great benefits on reverting amyloid-beta fibrillation in Alzheimer´s disease in vitro (Pinheiro et al., 2020). Alternatively, a curcumin–loaded solid lipid nanoparticle modified with transferrin also demonstrated an enhanced permeability across blood-brain barrier, providing greater efficacy on neuroprotection (Neves et al., 2021).

### 5.2.2 Peptides - tumour-homing peptides and cell-penetrating peptides

Tumour-homing peptides, particularly those containing the RGD (arginine-glycine-aspartic acid) motif, have emerged as a powerful tool for targeted cancer therapy. The RGD sequence is known for its strong affinity to integrins, especially αvβ3 and αvβ5 integrins, which are overexpressed on the surface of tumour cells and tumour vasculature. These integrins play a crucial role in tumour growth, angiogenesis, and metastasis by mediating cell adhesion and signaling. Nanoparticles modified with peptides containing the RGD motif, such as iRGD (CRGDKGPDC), on the surface can specifically bind to these integrins, thereby facilitating the targeted delivery to the tumour (Wang et al., 2014a). Previous studies have prepared liposomes, solid lipid nanoparticles and polymeric micelles attached with the RGD motif-containing peptide, which have shown enhancement in drug accumulation in tumour cells (Dubey et al., 2004; Wang et al., 2009; Sanati et al., 2023). For liposomes, the RGD peptides are typically conjugated to PEG-linked lipid ingredients prior to the formation of liposomes. For instance, liposomes can be prepared using distearoylphosphatidylcholine (DSPC), cholesterol and distearoylphosphatidylethanolamine–polyethyleneglycol–RGD peptide conjugate (DSPE–PEG–RGD) in a molar ratio of 56:39:5. This cyclic RGD-PEG-liposome formulation was significantly more effective against both primary and metastatic tumours than the non-targeted PEGylated liposome (Dubey et al., 2004). In another study, cyclic RGD molecules containing a free amine group (-$NH_2$) were conjugated with DSPE-$PEG_{2000}$-COOH via EDC/NHS chemistry to form cRGD-modified solid lipid nanoparticles. The cellular uptake studies of these cRGD-SLN on U87MG glioma cells has shown an enhancement in the uptake efficiency compared to the uncoated nanoparticles. The surface modification with cRGD is therefore considered an important factor in promoting the antitumour activity of solid lipid nanoparticles on malignant glioblastoma cells (Wang et al., 2021b). In addition to its benefits in cancer treatment, the tumour-targeting effect of RGD also offers diagnostic applications. Polydopamine nanospheres, which are utilized in photothermal imaging due to their high absorbance in the near-infrared region, were modified with RGD to target αvβ3 integrin-overexpressing tumour cells, thereby successfully enhancing the visualization of tumour position and borders *in vivo* (Liu et al., 2023).

Cell-penetrating peptides (CPPs), also known as peptide transduction domains, are short peptides that are able to pass through a wide range of tissues and cell membranes. The internalization mechanism of CPPs occurs via either direct penetration through the cell membrane or through the endocytosis and macropinocytosis pathways, but not through interactions with specific receptors (Palm-Apergi et al., 2012). There are nearly 20 types of CPPs that have been tested in preclinical and clinical studies for their transporting capability into cells, including transactivator of transcription (TAT) protein of HIV-1, short arginine-rich sequence of TAT, penetratin pAntp (43-58), and polyarginines. Most of them comprise 5 – 30 amino acids, which are either cationic, amphiphilic, or hydrophobic (Guidotti et al., 2017). Thanks to these unique properties, CPPs have been used as surface ligands of nanomedicines to increase their ability to penetrate into target cells. This enhanced cellular uptake can address the limitation that although nano-carriers can reach the tumour environment via the EPR effect, they are not able to enter the cells (Desale et al., 2021). The first attempt of producing CPP-NP conjugates was described by Weissleder et al. in 1999, who reported a 100-fold higher internalization into lymphocytes compared to nonmodified particles (Josephson et al., 1999). Since then, numerous efforts have been made to conjugate CPP with mesoporous silica nanoparticles (Shadmani et al., 2023), liposomes (Yu et al., 2021), or hybrid magnetic nanoparticles (Zhang W. et al., 2020). CPP is also known as an emerging tool for the delivery of mRNA, siRNA, and pDNA, as it can improve endosomal escape efficiency and modulate endocytosis pathways in dendritic cells (Falato et al., 2021; Kurrikoff et al., 2021; Yokoo et al., 2021). This capability is crucial because, upon internalization, nucleic acid-based therapeutics often become trapped within endosomes, leading to their degradation and reduced therapeutic efficacy. CPPs facilitate the disruption of endosomal membranes, allowing the therapeutic cargo to escape into the cytoplasm where it can exert its intended biological function. For instance, the addition of CPP to poly (lactide-co-glycolide) (PLGA) nanoparticles containing pDNA enhanced the internalization and endosomal escape in Beas-2B and A549 cells, making the NP–DNA–CPP delivery system a promising approach for gene delivery to the lung (Gomes dos Reis et al., 2020).

### 5.2.3 Monoclonal antibodies (mAb) and antibody fragment (Fab)

Monoclonal antibodies (mAb) are large, Y-shaped glycoproteins, which are divided into two domains, the upper part is the Fab fragment and the lower part is the Fc fragment. The antigen binding site, known as the variable region, is at the top of the Fab fragment to specifically recognize and bind to the antigen. mAbs and Fab fragments are extensively studied for active targeting, especially tumour targeting. In addition, single-chain variable fragments (scFv), minibodies, diabodies, and nanobodies are other variants also used in drug targeting (Sanna et al., 2014). The choice of ligands depends on the compatibility between the structure and size of the ligand in the drug delivery system, and the features of the target tissues. Particularly, to target cancerous tissues that often over-express epidermal growth factor receptors (EGFR) and epidermal growth factor receptor-2 (HER-2 receptor), nanocarriers can be grafted with EGFR antibodies or HER2 antibodies on the surface to enhance the accumulation of

nanocarriers in the tumour environment. For example, PLGA nanoparticles loaded with the anticancer agent, camptothecin was conjugated with mAb against EGFR (cetuximab) showed the targeting distribution of nanoparticles to mutant KRAS PANC-1 tumours and reduced tumour growth *in vivo* (McDaid et al., 2019). Besides tumour treatment, the targeting effect of antibodies is also useful for breast cancer imaging at the early stage. Recently, 5-poly (amidoamine) dendrimers conjugated with gold nanoparticles, chelated gadolinium, and anti-human HER-2 antibody (trastuzumab) enhanced MRI signal intensity by ~ 20% and improved CT resolution and contrast by two-fold (Chen et al., 2020).

### 5.2.4 Carbohydrates

Carbohydrates are highly biocompatible and have low immunogenicity as ligands for active targeting. Among ligands such as dextran, mannose, and hyaluronic acid (HA), HA is widely studied in drug delivery systems. HA is an anionic, nonsulfated glycosaminoglycan, widely distributed in the extracellular matrix and recognized as a natural ligand for CD44, a cell surface adhesion molecule that is overexpressed in cancer cells, particularly in tumour-initiating cells (Wang et al., 2014a). Nanomedicine modified with HA is thus a potential targeted delivery system to tumour cells including liposomes (Park et al., 2014), mesoporous silica nanoparticles (Yu et al., 2013), and solid lipid nanoparticles (Shen et al., 2015). Recently, a biocompatible glycosaminoglycan layer of hyaluronic acid was attached to the surface of gene-loaded nanoparticles to selectively interact with CD44 receptors and thus increase the biodistribution of nanoparticles into cancer cells (Zhang et al., 2020a).

### 5.2.5 Aptamers

Aptamers are 3D conformations of DNA or RNA oligonucleotides that are potentially used as therapeutic agents in clinical applications or as targeting ligands to enhance active targeted delivery (Gao et al., 2022). Aptamers are commonly conjugated with potent chemical drugs or biological medicines via cleavable linkers, which can be broken down to release the payloads upon exposure to environmental conditions such as low acidic pH, high redox, or high enzymatic activity. The aptamer AS1411 was conjugated to proteolysis-targeting chimeras (PROTACs) to improve tumour-specific targeting. In an MCF-7 xenograft model, imaging assays showed that 8 h after administration, a high concentration of aptamer-modified PROTACs was observed in tumour tissues, while no signal was detected from the unmodified PROTACs. This result demonstrated the targeting effect of the aptamer *in vivo* distribution to breast cancer cells (He et al., 2021).

## 6 Applications of surface modifications on nanoparticle toxicity

Surface altering techniques have been employed extensively to reduce the toxicity of nanoparticles since the translation of nanomedicine from bench to bedside has encountered many toxicity-related problems. The harmful effects of nanoparticles predominantly depend on their physical and chemical properties, including dimensions, configuration, surface area, electric charge, catalytic potential, and coatings (Sukhanova et al., 2018). Aiming to reduce the toxicity of nanoparticles, one must first and foremost carefully examine the surface charges of nanoparticles. Naturally, cell membranes exhibit negative charges because of the lipid bilayer. Thus, nanoparticles with positive surface charges or zeta potential could interact with the cell membranes. Many studies have indeed demonstrated higher toxicity of positively charged nanoparticles compared to neutral or negatively charged counterparts (Kedmi et al., 2010; Jones et al., 2012; Hühn et al., 2013; Bozich et al., 2014). Wang et al. modified the surface charge of injected nano drug vehicles containing doxorubicin, a positively charged drug, to negative by utilizing poly (carboxybetaine methacrylate) (pCBMA) and negatively charged monomer sodium methacrylate (SMA). This strategy effectively mitigated toxicity, enhanced resistance to non-specific protein adsorption, and prolonged circulation time (Wang et al., 2014b). In the intestinal epithelial cell model, surface charge modification has also been demonstrated to reduce cytotoxicity, and between two factors, size and surface charge, the latter plays a more decisive role in the interaction of nanoparticles with these cell models (Bannunah et al., 2014). Surface charge modification not only decreases cytotoxicity of the nanoparticles but also enhances their haemocompatibility. Generally, cationic particles or polymers induce more adverse effects on blood cells and coagulation processes (Boas and Heegaard, 2004). Aisina et al. indicated that cationic polyamidoamine dendrimers prolonged prothrombin time and decreased endogenous thrombin generation, whereas anionic dendrimers did not impact these factors. Thus, cationic dendrimers exhibit a more pronounced inhibition of the overall hemostatic potential in plasma compared to anionic dendrimers (Aisina et al., 2020).

Another emerging approach to tackle toxicity-related challenges is to employ highly biocompatible molecules to coat the surface of nanoparticles. Commonly used coating moieties range from synthetic derivatives (e.g., PEG, silica, dextran) to nature-inspired derivatives (e.g., chitosan, red blood cell membrane, albumin) (Table 2). To illustrate, surface modification of zinc oxide nanoparticles with ε-polylysine (ε-PL) via mussel-inspired methods and "Michael addition" reactions significantly reduces toxicity, as indicated by improved cell viability at a high concentration (500 μg/mL) (Luo et al., 2023). The surface modification strategy can also mitigate the toxicity of nanoparticles by enhancing immunocompatibility. To evade detection by the immune system, nanoparticle surface can be modified with various molecules, commonly hydrophilic polymers, which form a protective shield by binding water molecules. This outermost water layer diminishes interactions with opsonins and macrophage receptors, thus rendering nanoparticles invisible to immune system cells (Pinzaru et al., 2018).

## 7 Summary, challenges and future directions of surface modifications on drug delivery

In recent decades, there has been a growing interest in developing strategies for surface modification of nanoparticles for drug delivery purposes (Priya et al., 2023). A wide range of ligands have been used to reduce toxicity, improve stability, and enhance

drug bioavailability (Newhouse et al., 2023). By harnessing the specific interactions between the surface ligands of nanoparticles and receptors overexpressed on target cells, the modified nanoparticles can be customized to actively target these cells and enhance cellular internalisation (Ying et al., 2022; Priya et al., 2023).

While surface modifications of nanoparticles offer significant promise for drug delivery, numerous challenges persist in this field (Gessner, 2021). First, the orientation and density of ligands on the nanoparticle surface are critical factors in affecting cellular uptake. The modification of nanoparticles with large molecules can significantly increase nanoparticle size and affect cellular uptake. Therefore, it is essential to examine the size distribution and morphology of modified nanoparticles to identify changes and their impact on cellular uptake. Secondly, the effectiveness of surface modification largely depends on the type of ligands and the methods employed to incorporate them onto the nanoparticle surface. Therefore, ligands should be carefully screened, and selecting an appropriate method is crucial for achieving effective modification. Thirdly, the non-covalent bonds between the nanoparticles and ligands are susceptible to changes in environmental conditions, including temperature, pH, and ionic strength. Therefore, it is essential to investigate the stability of surface-modified nanoparticles under various physiological conditions to ensure their integrity (Zou et al., 2023). Fourthly, during the functionalisation process, some ligands may undergo changes in their three-dimensional structure. This could potentially compromise the targeting ability of active ligands. Fifthly, the fate of modified nanoparticles in the body, including their absorption, biodistribution, metabolism, and excretion, requires thorough investigation to assess their delivery to target tissues or organs (Maheshwari et al., 2019; Liu et al., 2020b). Finally, it is essential to assess the biocompatibility, toxicity, and long-term effects of surface-modified nanoparticles on the body. This evaluation should include thorough assessments of adverse reactions and immunogenic responses resulting from the surface modifications (Kozma et al., 2020b; Duong, 2023). For instance, the production of anti-PEG antibodies in response to PEG exposure may increase clearance from the body and reduce the efficacy of the nanoparticles (Kozma et al., 2020a).

The regulatory approval process for nanoparticle-based drug delivery systems, including those with surface modifications, involves rigorous evaluation by the US FDA and the European Medicines Agency (EMA). These agencies assess different factors to ensure the safety, efficacy, and quality of the product. For instance, the pharmacokinetics and biodistribution of the drug can be altered after surface modification of the nanoparticles and should be evaluated. The modification can lead to an extended half-life and reduced immunogenicity (Gabizon et al., 2003). Therefore, a thorough investigation should be conducted to understand potential long-term effects, including immunogenic reactions to the ligands. Several detailed characterisations of the surface modifications may be required, including studies on the stability of the modification in the bloodstream and the potential for interactions with other components in the body. Through these comprehensive preclinical studies, the nanoparticles with surface modifications must demonstrate safety and efficacy before they proceed to clinical trials. The regulatory review will also focus on the reproducibility of the surface modification process and the consistency of the nanoparticle production. This involves strict adherence to Good Manufacturing Practice (GMP) and thorough documentation to ensure the final product maintains its intended characteristics. Variations in surface decoration could lead to inconsistent therapeutic outcomes or unexpected side effects. Once the preclinical data demonstrate the safety, efficacy, and reproducibility of the surface-modified nanoparticles, they will be evaluated in the clinical phases. Some surface-modified nanoparticles have led to successful clinical outcomes (Table 3), such as Doxil (Choi et al., 2003), Genexol (Werner et al., 2013), Onivyde (Passero et al., 2016), ThermoDox (Dou et al., 2017), Onpattro (Hoy, 2018), Comirnaty (Lamb, 2021), and mRNA-1273 (Graña et al., 2022). However, some clinical trials may fail due to unexpected immune responses, off-target effects, or insufficient targeting specificity. On the other hand, the outcomes of these trials may influence regulatory guidelines, pushing for more detailed preclinical testing and more models to predict clinical behavior.

Currently, several clinical trials involving surface-modified nanoparticles in tumour immunotherapy are underway. For example, surface-modified liposomes targeting mucinous glycoprotein-1 (MUC1) have been investigated for their potential to induce T-cell immune responses in managing non-small cell lung cancer (NSCLC) (NCT00409188) (Butts et al., 2014), colon carcinoma (NCT01462513), rectal cancer (NCT01507103), and prostate cancer (NCT01496131) (Chen and Cong, 2023). These trials highlight the promising role of surface modification of nanoparticles in drug delivery, offering enhanced

TABLE 3 List of approved nanoparticles with surface modification.

| Brand name | Drug agent | Structure | Surface modifier | Administration route | References |
|---|---|---|---|---|---|
| Doxil | Doxorubicin | Liposomes | PEG | IV | Choi et al. (2003) |
| Onpattro | Patisiran | Lipid nanoparticles | PEG | IV | Hoy (2018) |
| Comirnaty | BNT162b2 | Lipid nanoparticles | PEG | IM | Lamb (2021) |
| mRNA-1273 | mRNA-1273 | Lipid nanoparticles | PEG | IM | Graña et al. (2022) |
| Genexol | Paclitaxel | Polymeric micelles | PEG | IV | Werner et al. (2013) |
| ThermoDox | Doxorubicin | Liposomes | PEG | IV | Dou et al. (2017) |
| Onivyde | Irinotecan | Liposomes | PEG | IV | Passero et al. (2016) |

biocompatibility, stability, uptake, and targeting ability. During the development of surface-modified nanoparticles, it is essential to evaluate their impact on nanoparticle size distribution, morphology, stability, toxicity, and *in vivo* fate. In the coming years, we anticipate a surge in research on surface-modified nanoparticles, especially in the field of cancer immunotherapy. Future investigations will likely prioritize the utilisation of a wide range of ligands with tailored properties to target specific cells or tissues effectively. Furthermore, comprehensive biodistribution studies will be conducted to validate the efficacy of the designed surface-modified nanoparticles. Another promising trend is multi-functionalisation, where nanoparticles are engineered to carry multiple functional groups, allowing for the attachment of targeting ligands, imaging agents, and therapeutic molecules on the same nanoparticle. This trend is particularly important for creating drug delivery systems that can simultaneously diagnose and treat diseases, which are often referred to as theranostic nanoparticles (Hosseini et al., 2023). We anticipate more advances in the adoption of bioinspired and biomimetic approaches to develop nanoparticles that mimic natural biological processes. For instance, coating nanoparticles with cell membranes or utilizing endogenous molecules for surface decoration can enhance biocompatibility and reduce immune system recognition, thereby prolonging circulation time and improving the therapeutic index. These bioinspired nanoparticles can better navigate the complex biological environment, increasing their efficiency in targeting specific tissues (Chen et al., 2019). We also expect the future advancement of surface-modified nanoparticles for nose-to-brain delivery. Given the direct anatomical link between the nasal cavity and the central nervous system, nanoparticles administered intranasally have the potential to penetrate the central nervous system (Nguyen and Maeng, 2022). Surface modification of nanoparticles with mucoadhesive polymers can prolong the residence times of the nanoparticles in the nasal cavity, consequently enhancing drug absorption and accumulation in the brain (Singh et al., 2018; Qureshi et al., 2019; Kaur et al., 2021). The utilisation of Angiopep-2, a peptide capable of traversing the blood-brain barrier, in the modification of nanoparticles enables their transportation from the bloodstream to the brain (Wei et al., 2018; Duong et al., 2023). This represents another promising application for future development in surface-modified nanoparticles.

## Author contributions

P-DL: Conceptualization, Writing–original draft, Writing–review and editing. K-NL: Conceptualization, Writing–original draft, Writing–review and editing. H-LP: Writing–original draft, Writing–review and editing. HuN: Supervision, Writing–review and editing. V-AD: Writing–original draft, Writing–review and editing. HiN: Conceptualization, Writing–original draft, Writing–review and editing, Visualization, Resources, Supervision.

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## Conflict of interest

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

## Publisher's note



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