INTRODUCTION

Accidental poisonings from environmental pollutants, as well as intentional self- and chemical warfare-related poisonings affect millions of people worldwide each year. While many toxic agents, such as heavy metals (Li et al., 2015), organophosphorus (OP) pesticides (organophosphates) and nerve agents (organophosphonates) (Zorbaz et al., 2018) readily enter the central nervous system (CNS), it is estimated that <5% of pharmaceuticals are able to cross the blood-brain barrier (BBB) (Barbu, Molnár, Tsibouklis, & Górecki, 2009). The BBB is a semipermeable and selective reticulum at the junctions of capillary endothelial cells of the brain, which restricts the transport of substances to the brain from the blood flow (Sweeney, Zhao, Montagne, Nelson, & Zlokovic, 2019; Tsai, Chien, Lin, & Tsai, 2011). Generally, only small hydrophilic compounds with the molecular mass <150 Da or highly hydrophobic compounds with the mass <400-600 Da can cross the BBB by passive diffusion (Alam et al., 2010; Kang, Cho, & Ko, 2019; Pardridge, 2010; Santaguida et al., 2006). Consequently,
most poisoning antidotes cannot reach their site of action in the brain in therapeutically relevant concentrations, and thus only provide effective protection to the peripheral nervous system (Löschner & Potschka, 2005; Pardridge, 2010; Tsuji & Tamai, 1997).

Aiming to overcome delivery restrictions presented by the BBB, recent advances in CNS-targeted delivery suggest the application of therapeutics in the form of nanomedicines, which exploit the advantages of size reduction. It is important to note, that according to the strict definition of the core field of nanotechnology, nanomaterials are entities that have the size of 1-100 nm at least in one dimension. On the contrary, in biomedical applications, any natural or synthetic particle with the dimension of a few nanometers to 1000 nm can be considered as a nanocarrier (Wong, Wu, & Bendayan, 2012; Kobrlova, Korabecny, & Soukup, 2019). In nanomedicinal applications, drugs with poor CNS distribution are loaded into nanocarriers that can enhance their brain penetration via one of the following mechanisms (Kreuter, 2004) (Figure 1):

- Nanoparticles (NPs) accumulate inside and on the walls of brain blood capillaries, which enhances drug permeation through the endothelial cell layer by creating a higher drug concentration gradient between the blood stream and the CNS.
- NPs open the tight junctions between the endothelial cells of the brain, which enables the transport of the drug via the openings either in its free form after being released from its carrier matrix, or together with the NP.
- Nanocarriers are endocytosed by the endothelial cells, and then the drug is released, still within the endothelial layer, and diffuses to the brain.
- NP-drug complexes are transcytosed through the endothelial cell layer to the brain.
- In case of surfactant containing nanocarriers, the surfactant enhances the drug permeability of the BBB by solubilizing the lipids of the endothelial cell membrane. Certain coating agents, such as polysorbate 80, can also inhibit components of the efflux system, particularly P-glycoproteins.

![FIGURE 1 Possible mode of action of nanoparticle-mediated drug delivery via the blood-brain barrier. A. Enhancement of drug permeation by increasing the concentration gradient between blood and brain. B. Opening of tight junctions between endothelial cells. C. Endocytosis and release of drug within endothelial cells. D. Transcytosis. E. Surfactants on nanoparticles induce endothelial cell membrane solubilization.](image-url)

2 | CENTRAL NERVOUS SYSTEM DELIVERY OF DRUGS BY POLYMERIC NANOPARTICLES

Among nanocarriers, considerable benefits of polymer-based NPs for CNS transport of various therapeutic agents have been demonstrated both in vitro and in vivo (Lockman, Mumper, Khan, & Allen, 2002; Masserini, 2013). Compared with other NPs, such as liposomes and micelles, polymeric NPs are more stable, easier to produce and scale-up, and usually exhibit much higher (80%-100%) encapsulation efficacy (Barbu et al., 2009; Chigumira et al., 2015). Polymers can be designed to be intrinsically multifunctional as well as being modified relatively easily with targeting ligands to enhance BBB transport or to direct the loading drug to specific CNS tissues. Polymeric NPs are also ideal to obtain a sustained drug release profile or enable controlled release via the incorporation of stimuli-responsive polymeric building blocks (Domján, Manek, Geissler, & László, 2013). Furthermore, polymers can be biologically active themselves, which can be utilized to control the activity of endogenous transport systems in the body to improve drug targeting (Kabanov & Batrakova, 2017). Another benefit of polymeric nanocarriers is that even if they exhibit a variety of geometries (e.g., polymeric conjugates, micelles, dendrimers, polymersomes) (Panyam & Labhasetwar, 2003), in most cases, their size and structure are fundamentally similar to those of natural carrier systems, such as serum lipoproteins (Lavasanifar, Samuel, & Kwon, 2002). Despite their benefits, polymeric nanocarriers may unquestionably exhibit disadvantages as well. The production of polymeric NPs often requires the use of organic solvents, which raises environmental questions and can cause the degradation of the loading pharmaceuticals, particularly biomacromolecules. Another key problem is that it is practically impossible to determine the fate of polymers in vivo, particularly in brain tissues (Patel, 2014).

Polymeric carriers can bind drugs both covalently and non-covalently, as well as are able to carry both hydrophilic and hydrophobic therapeutic compounds (Ghosh, Mandal, Sarkar, Panda, & Das, 2009; László, Manek, Vavra, Geissler, & Domján, 2012). Encapsulation of drugs into polymeric NPs was reported to enhance water
solubility, bioavailability, cellular uptake, tissue retention and BBB penetration (Anand et al., 2010; Tsai et al., 2011; Yadav, Lomash, Samim, & Flora, 2012). Polymeric nanocarriers are also able to protect drugs that normally would be subject to degradation by blood proteins or by enzymes of the BBB (Kabanov & Batrakova, 2017). These enhancements of drug pharmacokinetics upon encapsulation in polymer NPs are usually attributed to the masking effect of the polymeric matrix, which shields the physicochemical properties of the drug. As a result, drug stability and pharmacokinetics will be predominantly determined by the characteristics of the NP delivery system itself (Chigumira et al., 2015).

For pharmaceutical applications, both natural and synthetic polymers can be utilized (Lockman et al., 2002). The ideal polymer for brain delivery is biodegradable, biocompatible, nontoxic, non-thrombogenic, nonimmunogenic, noninflammatory and stable in blood. In addition, polymeric NPs have to withstand aggregation, and should be produced in an inexpensive and scalable manner (Gaillard, Visser, de Boer, Appeldoorn, & Rip, 2014; Lockman et al., 2002). For brain delivery of drugs, the most commonly used polymers are poly(lactic-co-glycolic acid) (PLGA), chitosan, polyvinyl alcohol (PVA) and poly(butyl cyanoacrylate) (PBCA). Recently, diblock copolymers such as Pluronic®, PEG-phospholipid conjugates, PEG-polymesters, poly(l-lysine)-graft-poly(ethylene oxide) (PLL-g-PEG) or PEG-b-poly (l-amino acid) are also suggested as building blocks of nanocarriers (Andrieux & Couvreur, 2009; Hrkach et al., 2012).

PLGA is a polyester, which is composed of biodegradable, biocompatible and nontoxic polymers (Park, 1995) (Figure 1). PLGA NPs typically exhibit a well-controllable release kinetics and higher encapsulation efficacy than most other polymeric NPs (Gaillard et al., 2014). PLGA is the most commonly used polymer for pharmaceutical nanoformulations, as it is approved both by the Food and Drug Administration (FDA) and by the European Medicines Agency (Chigumira et al., 2015; Sankar et al., 2016; Tsai et al., 2011). Owing to its lipid-soluble nature, PLGA can also easily cross the BBB (Park, 1995) and thus is widely suggested as matrix material for the improvement of brain penetration of drugs that show poor CNS distribution (Anand et al., 2010; Ankola, Viswanad, Bhardwaj, Ramarao, & Kumar, 2007). As PLGA mainly degrades to water and carbon dioxide, it could also be a safer choice for brain delivery than other, nonpolyester-based polymers (Wong et al., 2012) (Figure 2A).

Chitosan is a polysaccharide, which is biocompatible, biodegradable and has low immunogenicity (Patel, Zhou, Piepmeier, & Saltzman, 2012) (Figure 2). Chitosan was shown to have an acceptable toxicological profile (Rao & Sharma, 1997) and is approved by the FDA as an animal nutrition additive. Chitosan can also be obtained from natural origins and be available in various molecular weights (MW) (Gaillard et al., 2014). PVA is a water-soluble polymer that is often used to stabilize NPs that are composed of other polymers (Cao et al., 2017; Tsai et al., 2011) (Figure 2B).

PVA is blood compatible (Chowdhury, Kunjappan, Panneerselvam, Somasundaram, & Bhattacharjee, 2017), shows low toxicity (Demerlis & Schoneker, 2003) and is approved by the FDA; however, it is not biodegradable (Chowdhury et al., 2017) (Figure 2C).
PBCA NPs were also reported to deliver a wide variety of drugs to the CNS successfully, either attached on to the surface or incorporated inside the NPs (Calvo et al., 2001; Kreuter, 2004) (Figure 2D). PBCA NPs can also be manufactured easily; however, they exhibit a low encapsulation efficacy in case of highly hydrophobic or highly hydrophilic drugs (Gaillard et al., 2014). Another important property of PBCA NPs is that their biodegradation is rapid, which may be beneficial in minimizing toxicity due to CNS accumulation of the carrier polymer (Wong et al., 2012) (Figure 2D).

While there is a considerable amount of papers on the polymeric NP-mediated treatment of various pathological brain conditions, such as glioma (Mahmoud, Alamri, & McConville, 2020) and Alzheimer’s disease (Wong et al., 2019), CNS delivery of intoxication antidotes by polymer nanocarriers has not been thoroughly researched yet. In this review, our goal is to emphasize the potential of polymer NPs for the delivery of antidote molecules via the blood-brain barrier by presenting various examples, including heavy metal and OP compound intoxications.

3 | DELIVERY OF ANTIDOTES BY POLYMERIC NANOPARTICLES

3.1 | Arsenic poisoning

Chronic arsenic toxicity affects more than 150 000 people in 70 countries worldwide mainly through the consumption of contaminated drinking water (Liu et al., 2014; Paul et al., 2013). Long-term intake of arsenic contributes to a wide variety of reactive oxygen species-mediated diseases including cancer, skin lesions and cardiovascular problems (Chattopadhyay et al., 2002; Paul et al., 2013). Arsenic can also cross the BBB and accumulate in the brain, disturbing the concentration and distribution of neurotransmitters (Rodríguez, Jiménez-Capdeville, & Giordano, 2003; Tripathi et al., 1997).

A promising candidate to fight arsenic-induced oxidative stress is quercetin, a polyphenolic compound that exhibited antioxidant effect against several diseases (Lee, Lee, Shin, Yoon, & Moon, 2003; Peres et al., 2000; Tokyol, Yilmaz, Kahraman, Çakar, & Polat, 2006). However, clinical application of free quercetin is hindered by its water-insoluble nature. To overcome this limitation and to improve BBB penetration of the antioxidant, Ghosh et al. encapsulated quercetin into PLGA NPs with the average diameter of 270 nm. The therapeutic potential of the nanoformulated quercetin (NPQC) to treat arsenic-induced oxidative damage was examined in brain cells in a rat model (Ghosh et al., 2009). Rats were exposed to a single injection (subcutaneous) of sodium arsenite (13 mg/kg body weight), which resulted in significant depletion of components of the neuronal antioxidant defense system. The neuroprotective effect of NPQC compared with its native form was evaluated by orally pretreating rats with both the nanoformulated and the free form of the drug before arsenic injection. It was found that NPQC completely prevented antioxidant depletion of brain cells, while native quercetin had no significant protective effect. Arsenic exposure also contributed to the deposition of inorganic arsenic in neuronal cells at the level of 110 ± 12.8 ng/g mitochondrial protein as well as decreased the mitochondrial membrane microviscosity in the brain. NPQC proved superior in these aspects as well, maximally reducing elevated arsenic levels to the extent that no detectable amount of arsenic was found in the mitochondrial fraction of rat brain tissue. Pretreatment with NPQC also completely conserved the integrity of the mitochondrial membrane, while the non-formulated quercetin did not have such an effect. While the authors did not conduct experiments to determine the exact transport mechanism of NPQC via the BBB, they suggested that it is probably an endocytotic uptake by the brain capillary endothelial cells, which is followed by either quercetin release within the capillary endothelial cells and subsequent diffusion to the brain or by transcytosis.

Another high potential antidote of metal poisonings, including arsenic, is curcumin (CUR), which has strong antioxidant, radical-scavenging and metal-chelating properties (Ak & Gülçin, 2008; Shukla, Khanna, Khan, & Srimal, 2003; Yadav et al., 2009). However, CUR is practically water-insoluble and poorly absorbed by the intestines, as well as having a high clearance rate (Wahlstrom & Blennow, 1978). As a result, CUR exhibits a very low bioavailability, which greatly hinders its therapeutic potential. Moreover, in case of CNS disorders, the applicability of CUR is further limited by its poor permeability via the blood-brain barrier (Belkacemi, Doggul, Dao, & Ramassamy, 2011; Mathew et al., 2012). To enhance its water solubility and BBB penetration, as well as to reduce its required dosage and its instability in physiological media, encapsulation of CUR into NPs was suggested in several studies (Bisht et al., 2007; Rabanel et al., 2015; Tiyabonochai, Tungpradit, & Plianbangchang, 2007). Yadav and coworkers loaded CUR in chitosan (MW 400 kDa) NPs crosslinked with glutaraldehyde (Yadav et al., 2012). The NPs had the average diameter of 20-50 nm, spherical morphology and >90% entrapment efficacy. The antitodal effect of nano-CUR was evaluated by orally co-administering arsenic (2 mg/kg) with chitosan-CUR NPs at a low (1.5 mg/kg) and at a high (15 mg/kg) dose to male Wistar rats. It was demonstrated that CUR NPs at 1.5 mg/kg dose were as effective in recovering brain oxidative stress and lipid peroxidation markers, as well as brain biogenic amine (neurotransmitter) levels as the free CUR at 15 mg/kg dose. Another important finding was that while free CUR was not able to chelate arsenic in the brain at the applied 15 mg/kg concentration, the polymer encapsulated CUR removed a significant amount of the accumulated metal from the brain at the same dose. The authors concluded that the enhanced antioxidant and chelating potential of CUR NPs resulted from their capacity to evade reticuloendothelial system (RES) uptake and thus spend a longer time circulating in the blood, as well as from their ability to cross the BBB.

Sankar et al. attempted to improve the therapeutic efficacy of CUR by incorporation into PLGA nanocarriers (Sankar et al., 2016). The NPs were significantly larger (139 nm) than the chitosan-CUR NPs developed by Yadav et al. (2012), but showed a similarly high encapsulation efficacy (86%). The performance of the PLGA-CUR nanodrug (at 100 mg CUR/kg body weight dose) was assessed on an arsenic-generated (25 ppm sodium arsenite through drinking water for 42 days) neuronal oxidative stress model in male Wistar rats.
Compared with free CUR, the nano-encapsulated form was superior in reducing arsenic-induced depletion of both enzymatic and non-enzymatic antioxidants. Elevated lipid peroxidase levels in brain were reduced only by 52% in case of free CUR, while nano-CUR achieved a 73% reduction. Depleted glutathione peroxidase activity was also restored to a much higher extent by PLGA-CUR NPs (78%) than by the unformulated drug (30%). It was also found that in case of certain antioxidant parameters, free CUR only improved enzymatic activities in the kidney, but not in the brain of rats. For example, depleted glutathione content in brain was not significantly restored by free CUR, but nano-CUR treatment increased it by 66%. Similarly, native CUR could not improve the reduced glutathione reductase concentration in brain, while the nano-CUR increased glutathione reductase activity in the brain by 77%. Aside the disturbance of the antioxidant system, arsenic-exposed rats also showed engorgement of capillaries, of pyknotic neurons in dendritic gyrus and of eosinophilic neurons in the cerebral cortex. The mean score of these histopathological changes was also more efficiently reduced by the nano-CUR (74% reduction) than by the free CUR (40% reduction). Similarly to Yadav et al. (2012), Sankar et al. also suggested that the observed increase in the reduction of arsenic-induced oxidative stress can be attributed to the longer time circulating in the blood and thus to the enhanced bioavailability of the nanodrug compared with free CUR. However, the finding that the arsenic ameliorating effect of PLGA-CUR NP was significantly higher in the brain than in the kidney, also implies that the polymeric NPs were able to enhance the transport of CUR to the CNS selectively.

The ability of CUR NPs to cross the BBB and to enhance the accumulation of CUR in CNS tissues compared with free CUR was explicitly proved by Tsai et al. (2011). In their studies, CUR was encapsulated in PLGA (MW 5000-15 000) NPs stabilized with PVA (MW 9000-10 000). The nanocarriers were characterized by an average diameter of 163 nm, 47% entrapment efficacy, and spherical or ellipsoidal shape. The pharmacokinetics, tissue distribution and blood-brain barrier penetration of PLGA-CUR NPs was examined on male Sprague-Dawley rats treated with 25 mg/kg nano-CUR intravenously. The first important finding of Tsai et al. was that after an initial burst discharge, nano-encapsulation enabled the gradual release of CUR sustained over 6 days. The other major conclusion was that, according to high-performance liquid chromatography analysis of brain tissue of rats, PLGA-CUR NPs passed the BBB and significantly enhanced (by 33%) the mean residence time of CUR in the brain compared with free CUR. The authors suggested that this prolonged retention time of CUR in brain is probably attributed to the sustained, diffusion-controlled release of the antidote from the PLGA NPs. It is very important to note, that the concentration of nano-CUR greatly varied between the different brain regions 30 minutes after administration. Nano-encapsulation particularly increased the half-life of CUR in the cerebral cortex (8.6-fold increase) and in the hippocampus (2.2-fold increase). Accordingly, the retention time of CUR was also significantly enhanced in the cerebral cortex (2.0-fold increase) and in the hippocampus (1.8-fold increase). The observations reveal that even in the case of the same nanocarrier, the different transport properties of the particular brain cells will determine the accumulation of drugs in the different regions of the brain.

In summary, the above-described pharmacokinetic studies proved that polymer NPs are able to deliver CUR to the brain as well as maintain its brain concentration for longer times, and thus show a greater therapeutic potential in the treatment of CNS conditions than the conventional form of the antioxidant.

According to epidemiological studies, arsenic also shows a diabetogenic effect, which necessitates large-scale and high-dose administration of insulin in arsenical contaminated areas (Liu et al., 2014; Samadder et al., 2013). As chronic high-dose use of insulin is costly, requires constant monitoring and carries the risk of sudden hypoglycemia, novel formulations are needed that provide the required antihyperglycemic effect at a reduced insulin dose (Samadder et al., 2013). Samadder and coworkers suggested that the encapsulation of insulin into polymeric NPs is a high potential alternative approach for the dose-reduced treatment of arsenic-induced hyperglycemia (Samadder et al., 2013). In their studies, they prepared spherical insulin-PLGA NPs (NIn) with smooth surface and an average diameter of 94 nm. NIn exhibited several beneficial properties, such as high encapsulation efficacy (90.2%), high stability (both at storage and at treatment conditions) and constant release of insulin from 0 to 30 minutes post-administration. It was found that NIn exhibited the same efficacy in modulating diabetes markers (mean blood glucose level, glycosylated hemoglobin, total cholesterol, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglycerides) in chronically arsenic-fed (20 mg/kg body weight) hypoglycemic mice even at a 10-fold decreased dose compared with free insulin. Furthermore, nano-encapsulation seemed to protect insulin from the denaturing effect of arsenic, which could disturb the secondary structure of insulin within the NPs to a much lesser extent then in case of the free insulin. To assess the ability of NIn to cross the BBB, mice were administered the nanodrug at two concentrations (0.5 and 1 mIU/g body weight) intraperitoneally. After 3 days, injections were repeated one more time. The presence of insulin NPs in the brain was confirmed in transmission electron microscopy images, where the NIn appeared as black dot-like structures in a dose-dependent manner. At low dose, nano-insulin only entered the cytoplasm of brain cells; however, at high dose it appeared in both the cytoplasm and the nucleus. This finding is of great significance, as the hypothalamus has been proposed to be the glucose-sensor region in the body, having a crucial role in initiating the counter regulatory response to glucose homeostasis.

### 3.2 | Mercury poisoning

Mercury is a neurotoxic metal, which both occurs naturally and is emitted via various industrial activities (Fernandes Azevedo et al., 2012; Martinez-Finley & Aschner, 2014). Mercury poisoning is usually treated with chelating agents; however, traditional antidotes such as selenomethionine exhibit low bioavailability (Thomas & Janz, 2011) and limited detoxification capacity (Risher & Amler, 2005).
Alternatively, nucleic acid aptamers have the potential to be used as mercury (Hg) detoxification agents as they show high affinity and high selectivity towards Hg$^{2+}$ (Abu-Ali, Nabok, & Smith, 2019), as well as being nonimmunogenic (Keefe, Pai, & Ellington, 2010). The disadvantage of unmodified aptamers is that they are highly susceptible to serum degradation (Keefe et al., 2010); however, it was reported that biocompatible NPs are able to keep them stable in blood (Phillips, Gran, & Peppas, 2010). To determine the therapeutic potential of polymer-aptamer NPs to reduce neurotoxic effects of Hg on the CNS in vivo, Hu et al. stabilized a thiamin-rich aptamer on PLGA and PEG (MW 3400) copolymer NPs with an average diameter of 120 nm (Hu, Tulsieram, Zhou, Mu, & Wen, 2012). Efficacy of the nano-antidote was studied on male Wistar rats that were fed with Hg-containing rice, which resulted in the accumulation of $84 \pm 8.2$ ng/g methylmercury (MeHg) and $43 \pm 82.5$ ng/g inorganic Hg (IHg) in their brain tissue, as well as significant motor deficits and impaired exploratory behaviors. The polymer encapsulated aptamer clearly proved superior, showing $7 \times$ and $2.7 \times$ higher detoxifying capacity in the brain than the unformulated drug towards MeHg and IHg, respectively. Unlike the free aptamer, which had no significant ameliorating effect, the nano-antidote also greatly reduced impairment and normalized the previously diminished locomotor and exploratory activities in water maze tests. On the biochemical level, polymeric NP-aptamer was able to restore normal thiolredoxin reductase and lipid peroxidation activities. Aside from demonstrating the greater CNS delivery potential of the polymeric NPs, the authors also found that the nanocarriers were nonimmunogenic, noninflammatory, enabled pH-controlled antidote release as well as increased aptamer stability at 37°C in plasma by 11.35 times compared with its free form.

### 3.3 | Lead poisoning

Lead is a widespread environmental pollutant, heavy metal, which is used in more than 900 industries (Hou et al., 2013; Karrari, Mehrpour, & Abdollahi, 2012). Lead negatively affects almost all organ systems by disturbing several vital enzymatic reactions via the generation of reactive oxygen species (Flora, Gupta, & Tiwari, 2013). Lead can also cross the BBB and accumulate in the CNS-inducing neurodegenerative processes, which is particularly dangerous to children whose nervous system is still under development (Flora et al., 2013; Hou et al., 2013; Karrari et al., 2012). As shown in the section that discusses arsenic intoxication (see Section 3.1), CUR has the high potential to treat metal poisonings, and thus is suggested as an antidote for lead-induced oxidative stress (Ak & Gülçin, 2008; Shukla et al., 2003). As we also remarked earlier, low systemic bioavailability of CUR greatly hinders its clinical applicability (Maiti, Mukherjee, Gantait, Saha, & Mukherjee, 2007). This problem is often addressed by loading the antioxidant into polymeric NPs (Bisht et al., 2007; Rabanel et al., 2015; Tiyaboonchai et al., 2007), such as chitosan (Yadav et al., 2012). However, it is very important to note that nanocapsulation of antioxidants does not always enhance therapeutic efficacy compared with the free drug, and even in case of the same antidote-polymeric combination, results may vary greatly. A relevant example of this phenomenon is the experiments from Flora et al., who attempted to treat lead-induced oxidative stress in Swiss albino mice with CUR-loaded chitosan (MW 400 kDa) NPs after intraperitoneal administration of lead acetate (25 mg/kg). Arsenic exposure caused elevated levels of thiobarbituric acid-reactive substances and glutathione dissulfide, as well as depletion of glutathione in the brain of mice, but the authors found that nano-CUR administered orally (15 mg/kg) 1 hour after lead exposure successfully recovered normal concentrations of all three markers. Despite these promising results, further analysis of the study, as well as comparison with similar experiments reveal that in the case of lead poisoning, encapsulation of CUR in chitosan NPs did not enhance its protective effect on the brain. Even though chitosan-CUR NPs were able to enter the CNS, Flora and coworkers concluded that the nano-CUR did not have a significantly higher ameliorating effect than free CUR in the brain (Flora et al., 2013). In contrast to these findings, the experiments of Yadav et al. (2012) demonstrated that the incorporation of CUR in chitosan NPs enhanced its antioxidant and chelating capacity by at least 10-fold in case of against arsenic intoxication.

### 3.4 | Organophosphorus exposure

OP have been widely used as pesticides around the world since the 1950s (Masson & Nachon, 2017). According to WHO, accidental and self-poisoning with organophosphates cause over 3 million intoxications and 200 000 deaths worldwide each year (Gunnell, Eddleston, Phillips, & Konradsen, 2007). Furthermore, organophosphonates are also used as chemical warfare nerve agents (such as sarin, tabun and soman) during military activities and terrorist attacks (Herkert et al., 2011; Nagao et al., 1997).

The acute toxicity of OP (organophosphates and organophosphonates) is due to inhibition of the enzyme acetylcholinesterase (AChE), which metabolizes the neurotransmitter acetylcholine (ACh). The inhibition of esterases results from phosphorylation (i.e., either phosphorylation or phosphonylation) of the hydroxyl group of serine in the active center of the enzyme and translates into an "endogenous acetylcholine poisoning" (Chigumira et al., 2015; Masson & Nachon, 2017; Petroianu, 2005, 2006). The accumulation of ACh drives an initial sympathomimetic response due to stimulation of nicotinic receptors in the adrenal medulla followed by a longer-lasting parasympathomimetic response due to stimulation of muscarinic receptors. Both responses can, and must, be controlled by appropriate medications. In addition, organophosphates and organophosphonates cause an ACh overflow at neuromuscular synapses with ensuing depolarizing block, requiring artificial ventilation. Furthermore, activation of central cholinergic receptors results clinically in seizure activity (Petroianu, Toomes, Petroianu, Bergler, & Rüfer, 1998). Although, the mechanism of action of oximes is relatively well characterized in theory, their practical value remains uncertain and oximes have disappointed clinically (Eddleston, 2002). Owing to the presence of a positively charged nitrogen atom, oxime
molecules are polar, have a negative logP and are hydrophilic. Oximes rarely enter the brain (Lorke et al., 2007). The peak brain concentration \( (C_{\text{max}}) \) of the monopyridinium aldoxime pralidoxime is only about 10% of its blood \( C_{\text{max}} \) and penetration of bis-pyridinium aldoximes is significantly lower (Lorke et al., 2007; Lorke & Petroianu, 2019; Petroianu et al., 2007). The major challenge in the treatment of OP intoxications is that the currently available antidote formulations can only protect the peripheral nervous system, while OP compounds can rapidly penetrate the CNS due to their lipophilic nature (Zorbaz et al., 2018). Thus, even though antidotes can improve survival, incapacitation still occurs due to irreversible brain damage (Masson & Nachon, 2017).

Butyrylcholinesterase (BChE) is a promising OP poisoning antidote, because it is able to act as a bioscavenger of OP compounds even before they reach their synaptic targets. However, exogenous BChE does not provide protection to the CNS, as it cannot cross the BBB when administered intravenously, intramuscularly, subcutaneously or intraperitoneally (Gaydess et al., 2010). As block ionomer complexes were earlier reported to deliver larger molecules via the BBB effectively, Gaydess and coworkers encapsulated huBChE enzyme in cross-linked cationic PLL-g-PEG NPs (Gaydess et al., 2010). PLL-g-PEG was synthesized from poly(L-lysine) hydrobromide (MW 15-30 kDa) and mPEG-succinimidy propionate (MW 5 kDa). The resulting nanocarriers were spherical, 15 nm in diameter and consisted of a protein-polycon junction, showed elevated prophylaxis time compared with its free AChE activity. For instance, in contrast to the performance of the antidote too. For instance, in contrast to the biphasic release profile of conventional Hup A, the encapsulated antidote exerted an AChE inhibiting effect in a sustained manner, and in vivo on male BALB/C mice treated with sublethal doses of either PO or DFP. It was found that the co-administering either of the nano-encapsulated enzymes with the AChE reactivator pralidoxime (2-PAM) restored AChE activity to a significantly higher extent both in the case of PO and DFP intoxication than treating the poisonings only with 2-PAM alone. As the enzymes are able to scavenge OP compounds from the body, the authors concluded that directly injecting OP acid anhydrolase-DP or OP hydrolase-DP NPs may provide greater protection against OP agents than the currently used antidotal regimen, i.e., the combination of 2-PAM and atropine, which only treats the symptoms of OP poisoning and does not protect AChE from subsequent inhibition by OPs persistent in the body.

Another high potential OP poisoning antidote is alkaloidal huperzine A (Hup A), which is a reversible and selective inhibitor of AChE (Liang & Tang, 2004). Hup A is able to cross the BBB (Albuquerque et al., 2006), and is already used in clinical practice for the treatment of Alzheimer’s disease (Yang, Wang, Tian, & Liu, 2013). Hup A is proved particularly useful in the treatment of Soman poisoning, where it can prevent Soman-induced seizures and other neuro-pathological processes (Lallement et al., 1997). However, at effective doses, Hup A exhibits toxicity and causes unwanted side effects such as tremors and respiratory distress (Albuquerque et al., 2006). With the aim of reducing the toxicity of Hup A, while keeping its efficacy and its ability to cross the BBB, Zhang et al. incorporated the antidote in PLGA (MW 20 000) NPs (Zhang et al., 2015). The resulting Hup A NPs had the mean diameter of 209 nm and exhibited a smooth surface without pores. The drug loading was 2.86% ± 0.6%, which was sufficient for animal studies according to the authors. Protective effect of Hup A-PLGA NPs (0.5 mg/kg, intravenously) against 1.0 × LD_{50} Soman toxicity (143.0 µg/kg) in the brain of ICR mice was evaluated by measuring AChE activity using Elmann’s spectrophotometrical method. The experiments demonstrated that the nanocarriers were not just able to enter the brain, but significantly improved therapeutic performance of the antidote too. For instance, in contrast to the biphasic release profile of conventional Hup A, the encapsulated antidote exerted an AChE inhibiting effect in a sustained manner, and in conjunction, showed elevated prophylaxis time compared with its free form. It was also found that by encapsulating the antidote in PLGA NPs, its toxicity could be decreased approximately by 3.5 times: LD_{50} values of free Hup A and Hup A-PLGA NP were 1.40 and 4.85 mg/kg,
TABLE 1
Overview of polymeric nanocarriers developed for the central nervous system delivery of antidotes for various poisonings

| Poisoning         | Antidote          | Composition of polymeric carrier | Diameter of antidote NP (nm) | Reference                  |
|-------------------|-------------------|---------------------------------|------------------------------|---------------------------|
| Arsenic           | Quercetin         | PLGA                            | 270                          | Ghosh et al., 2009        |
|                   | Curcumin          | Chitosan                        | 20-50                        | Tsai et al., 2011         |
|                   | Curcumin          | PLGA                            | 139                          | Sankar et al., 2013       |
|                   | Curcumin          | PLGA-PVA                        | 163                          | Tsai et al., 2012         |
|                   | Insulin           | PLGA                            | 94                           | Samadder et al., 2013     |
| Mercury           | Thiamin-rich aptamer | PLGA-PEG                      | 120                          | Hu et al., 2012           |
| Lead              | Curcumin          | Chitosan                        | Not specified                | Flora et al., 2013        |
| Organophosphorus compounds | Butyrylcholinesterase | PLL-g-PEG                     | 15                           | Gaydess et al., 2010      |
|                   | Huperzine A       | PLGA                            | 209                          | Zhang et al., 2015        |

4 | DISCUSSION

Polymer NP-mediated transport of poisoning antidotes via the BBB is a relatively new research area, which has the high potential to overcome limitations of the current delivery methods and thus provide protection for both the peripheral and the CNS after exposure to toxic agents. However, more than a decade of investigation in the field resulted only in a dozen of articles, which mainly focus on intoxications caused by heavy metals (including arsenic, Hg and lead) and organophosphates (Table 1). In all of these studies with one exception (Tripathi et al., 1997), polymeric NPs proved to be superior to conventional formulations in accumulating antidote molecules in the CNS, regardless of the composition of the polymeric matrix. Aside from bettering BBB transport, in most experiments nanocapsulation also contributed to an array of other improvements, such as increased half-life (Sankar et al., 2016; Tsai et al., 2011) and brain retention (Tsai et al., 2011), enhanced antioxidant capacity (Ghosh et al., 2009; Gaydess et al., 2010; Hu et al., 2012; Sankar et al., 2016; Yadav et al., 2012) and chelating potential (Ghosh et al., 2009; Yadav et al., 2012), as well as higher stability (Hu et al., 2012; Samadder et al., 2013). In certain cases, polymeric delivery systems also enabled sustained drug release (Hu et al., 2012; Samadder et al., 2013; Tsai et al., 2011) and/or reduction of the effective dose (Gaydess et al., 2010; Samadder et al., 2013; Yadav et al., 2012; Zhang et al., 2015) and in conjunction, contributed to lower toxicity (Zhang et al., 2015). While these currently available research data clearly demonstrate that polymeric nanocarriers are able to improve CNS distribution and pharmacokinetics of poisoning antidotes, to design clinically-applicable antidote nanoformulations, the relationships between composition, physicochemical properties and therapeutic performance have to be considered in a more comprehensive manner.

Particle size is one of the critical factors that determines the biological fate of nanocarriers after administration. In general, smaller particles are preferred, as increasing the particle size above 200 nm greatly rises the risk of being removed by the spleen and RES. However, decreasing the particle size under 10 nm can also be disadvantageous, as it leads to extensive extravasation and renal clearance (Tosi, Costantino, Ruozzi, Forni, & Vandelli, 2008). For that reason, the ideal size of CNS-targeting NPs is between 10 and 200 nm. In most studies reviewed in this article, the size of polymer-antidote NPs fell into this Goldilocks (optimal) interval. It is also crucial that the nanocarriers do not have a high tendency to aggregation, as it would hinder their cellular uptake due to the larger size of aggregates compared with individual NPs (Chigumira et al., 2015). In this section, we highlight that while size reduction is beneficial in enhancing therapeutic efficacy, it can also fundamentally alter the toxicological parameters of drug delivery systems. Therefore, it is not sufficient to estimate the toxicity of polymeric nanocarriers based on the bulk toxicity of their component polymers, and thus the toxicological profile of each antidote nanoformulation have to be explored individually before administration. The zeta potential of drug NPs is also an important aspect worth considering. Low zeta potential values are associated with poor stability against aggregation, due to the low electrostatic repulsive forces between individual particles (Honary & Zahir, 2013). Consequently, negatively charged NPs quickly aggregate and the resulting increase in particle size contributes to a higher clearance rate from the blood by RES macrophages (Khan et al., 2005). Likewise, highly surface charged particles are also more effectively phagocytized than those with small charge (He, Hu, Yin, Tang, & Yin, 2010). In addition, it was shown that NPs with a high positive charge have immediate toxic effects on the blood-brain barrier (Lockman, Koziara, Mumper, & Allen, 2004). Therefore, the pharmacokinetically ideal polymeric nanocarrier exhibits a small, positively charged zeta potential value, which maximizes its circulation time in the blood (Chigumira et al., 2015; He et al., 2010).

Structure is also a pivotal, yet not well-studied basic property of nanocarriers. In most of the reviewed articles, structural properties of
nanocarriers were not considered and the relationship between the architecture of polymeric building blocks and the final NP structure is typically not well understood. There is also a general lack of systematic studies that examine the correlation between the structure of the polymeric nanocarrier and its performance, such as encapsulation capacity, drug release profile or therapeutic efficacy (Manek, Tombácz, Geissler, & László, 2017). An exception to this phenomenon is the work of Rabanel et al., where it was demonstrated that the efficacy of CUR to reduce the effects of oxidative stress on neuronal cells strongly depended on the architecture of the polymeric building blocks, as well as on the structure of the nanocarriers (Rabanel et al., 2015).

Another important factor that can determine the delivery efficacy of polymer NP-based antidote carriers is surface modification. On the one hand, it was suggested that NPs can avoid being recognized and taken up by the RES due to their small size (Stolnik, Illum, & Davis, 2012). On the other hand, it was also observed that bare NPs are still subject to quick opsonization and elimination by the components RES, such as liver Kupffer cells and spleen macrophages (Barbu et al., 2009; Rabanel et al., 2015). To decrease the uptake of nano-antidotes by the RES, surface modification with hydrophilic moieties can be applied (Stolnik et al., 2012), such as conjugation with polyethylene oxide containing amphiphilic polymers, such as poloxamers and polyoxyamines (Calvo et al., 2001; Storm, Belliot, Daemen, & Lasic, 1995). For instance, it is widely accepted that PEGylation increases circulation time of NPs in blood, which provides enough time for transport mechanisms to take place and thus enhances the accumulation of nanocarriers in the brain at therapeutically efficient concentrations (Rabanel et al., 2015). It was also shown that attaching certain polymers, such as Poloxamers®, polysorbates and PEG, to the external parts of nanocarriers can contribute to the adsorption of serum apolipoprotein (ApoE) on their surface (Kreuter, Alyautdin, Kharkевич, & Ivanov, 1995). The ApoE then can serve as a targeting ligand, which enables the translocation of NPs through the BBB via the ApoE receptor of the endothelial cells (Zensi et al., 2009). Aside ApoE, several other ligands have also been suggested to improve the brain targeting ability of polymeric NPs, such as folate, lactoferrin, glutathione and polysorbate 80 (Wohlhart, Gelperina, & Kreuter, 2012).

However, optimal surface density and arrangement of the conjugating agents is not established yet (Rabanel et al., 2015). It is also not well-explored how ligands may affect the pharmacologically important properties of nanocarriers, such as charge, stability, toxicity and immunogenicity. Therefore, to predict the impact of surface modification on the therapeutic performance of polymer-antidote NPs precisely, additional research is required.

Furthermore, host-guest interactions between the polymeric matrix and the carried antidote have to be explored thoroughly. On the one hand, host-guest interactions greatly influence the physicochemical properties (e.g., size, structure, stability) of antidote NPs, which, as we noted earlier largely determine the pharmacokinetic performance of the formulation (Chigumira et al., 2015; Manek, Domján, Madároz, & László, 2015). On the other hand, it is of high importance that polymer-drug interactions do not hinder free release of the antidote, which would restrict its bioavailability (Manek, Domján, Menyhárd, & László, 2015). If dissolution of the antidote from its carrier is not hindered by specific interactions, most polymer-based NPs can enable sustained drug release (Liang & Tang, 2004; Tsai et al., 2011), which is highly beneficial in decreasing toxicity and increasing prophylaxis time. Typically, polymeric carriers show the biphasic drug release profile. The initial step is a burst release, where drug molecules associated with the surface and pores of the nanocarrier are discharged to the surrounding medium by diffusion. Then, a lag phase and a zero order phase follow due to the erosion of the polymeric matrix (Zolnik & Burgess, 2007). It was also found that in the case of certain polymeric carriers, such as low MW PLGA, a diffusion controlled release profile can be obtained too (Zolnik, Leary, & Burgess, 2006). If the possibility for controlled antidote release is the objective, sensitivity of the carrier system to certain physiological conditions such as various pH and temperature values should also be specified proportional to the parameters of the targeted CNS tissue (Parvaz, Taheri-Ledari, Esmaili, Rabbani, & Maleki, 2020).

Lastly, for clinical applicability, interactions of polymer-antidote NPs with target tissues in the brain need to be investigated meticulously. As it was demonstrated by Tsai et al. (2011), the distribution of antidote molecules between various brain regions after polymeric NP-mediated BBB transport varies greatly. Nanocarrier-mediated accumulation of drugs to the CNS is largely determined by the efficacy of intra- and paracellular transport; however, these processes are not fully understood yet. Moreover, the capacity to detect and quantify NPs, particularly in highly complex biological systems such as the brain is very limited (Barbu et al., 2009). Therefore, parallel to designing novel antidote nanoformulations, the development of diagnostic and imaging techniques is also essential to enable direct visualization of the transport of antidote NPs via the BBB, as well as to explore their fate in their target brain tissues.

CONFLICT OF INTEREST
The authors have no conflict of interest to report.

ORCID
Georg A. Petroianu https://orcid.org/0000-0001-9110-4750

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