3. PASSIVE TARGETING

In the passive targeting method, drug-containing nanoparticles (drug formulation) accumulate in the tumor environment by EPR phenomenon due to different characteristics around the tumor tissue compared with normal cells and tissues [70]. Actually, this targeting method is used when the target tissue has different properties than other cells and tissues [70]. The EPR effect occurred mainly due to (1) high vascular permeability of malignant tumor tissues and (2) lack of lymphatic drainage within tumors. The enhanced permeability of the tumor vasculature allows macromolecules, lipids, and nanoparticles circulating in the blood to extravasate through the leaky tumor blood vessel, then enter the tumor interstitial space. Therefore by binding the drug to a suitable carrier, the drug accumulation in the target area can be increased up to 100-fold [4, 71]. The delivery of the nanoparticles and drug to the target region is related to factors such as tumor microvasculature, size, shape, and surface charge of the nanoparticles [70]. One of the most important issues in the passive targeting method that guarantees success in drug delivery and therapeutic efficacy is the long-term circulation of the drug. Nanoparticles are usually eliminated in the bloodstream by the RES, and therefore, modification of the nanoparticle surface is essential for the long-term circulation of the drug-containing nanoparticles [72]. This is possible by coating the nanoparticles with substances such as PEG that could decrease hydrophobicity of the nanoparticles surface. The hydrophobic surface of the nanoparticles forms a hydrogen bond between the oxygen molecules of the PEG coating with the water molecules, which creates a hydration film around the nanoparticles that prevents the drug-containing nanoparticles from being removed by the phagocytic system. One example of PEG coating using to prolong the circulation of drug-containing nanoparticles was doxorubicin liposomal PEGylation, which lasted from minutes to hours. Other materials have also been used for coating nanoparticles, including polaxamer, polyvinyl alcohol, poly (amino acid) s and polysaccharides [73–76].

Albumin nanoparticles are an attractive and efficient drug carrier for delivery of hydrophobic drugs to inflamed joints. In this regard, the targeting and antiinflammatory properties of tacrolimus-loaded albumin nanoparticles (TAC) were studied by Thao et al. Evaluation of the therapeutic effects of established nanocomplex on splenocytes extracted from the spleen of inflammatory model mice showed the antiproliferative effect of this nanocomplex on activated T cells. It was also observed that the established nanocomplex showed a significant antiinflammatory effect, indicating the efficient targeting of the inflamed region by the albumin nanoparticles as well as the accumulation of the nanocomplex in the target region (Fig. 10) [77].

The multifunctional nanosystem based on magnetic iron oxide nanoclusters containing polymer polypyrrole (PPy) and functionalized with PEG as carrier of doxorubicin was investigated for synergistic cancer treatment under NIR light. This nanosystem enjoyed from iron oxide for controlling drug delivery through the magnetic field as well as contrast imaging agent for T_2-weighted MRI. PPy also has a strong photothermal effect due to its high NIR absorption, which showed high efficacy in killing cancer cells (Fig. 11) [78].

The properties of the nanoparticles can be modified by attaching polysaccharides to the particles surface. For example, by binding positively charged chitosan to the nanoparticle surface, it gives positive charge to the nanoparticles, which through electrostatic interactions can bind to negatively charged cargoes such as DNA sequences. Actually, one of the important uses of polysaccharides in giving new features to nanoparticles is to prevent the rapid clearance of the nanoparticles by the mononuclear phagocyte system (MPS) [79–82]. It was shown that lipochitosan-modified lipid nanocapsules showed more uptake by HEK293 cells. These lipid nanocapsules attached to lipochitosan and lipochitosan polysaccharides look promising for targeting ligands such as peptides or proteins as well as molecules such as siRNA [83].

Betulinic acid conjugated *N*-(2-hydroxypropyl) methacrylamide (HPMA) polymer was studied for tumor targeting and controlled release of betulinic acid derivatives in tumor cells [84]. In another attempt, to enhance the EPR effect, nitric oxide (NO) producing nanoparticles were developed for specific delivery of NO. In addition, doxorubicin was loaded onto the synthesized nanoparticles, and the therapeutic effect of the drug-containing nanoparticles was observed with the significant accumulation of doxorubicin in the tumor, indicating the remarkable ability of these nanoparticles to enhance the EPR effect [85]. Denis et al. developed a pH-sensitive delivery system for the specific release of Vorinostat in mesothelioma tumors as well as histone reacetylation [86]. Hoffmann et al. synthesized dual-fluorescent HPMA copolymers for passive targeting of tumor and drug release [87]. THCPSi nanoparticles encapsulated in solid lipids (SLN) were examined for passive tumor targeting and drug delivery [88]. Im et al. also showed that re-injection of nanocomplex composed of reduced graphene oxide and iron oxide nanoparticles, then coated with PEG leads to the phenomenon of accelerated blood clearance (ABC), which