Jiang et al. targeted the KB cells (with high expression of folate receptor) by FA-conjugated magnetic Fe_3O_4 nanoparticles (as MRI contrast enhancer) for hyperthermia and MRI aims [54].

Theranostics applications of InP/ZnS quantum dots conjugated with FA, D-glucosamine, or both of them have also been investigated [55]. It has also been observed that the presence of FA in the carboxymethyl chitosan nanoparticles loaded with the anticancer drug doxorubicin resulted in specific uptake by HeLa and B16F1 cells, thereby enhancing the therapeutic efficacy of the synthesized nanoparticles [56]. Evaluation of the ability of FA as a targeting factor on curcumin-containing Fe_3O_4 magnetic nanoparticles in tumor-bearing mice indicates that FA-conjugated nanoparticles have better therapeutic efficacy than non-FA-targeting particles [57]. Nosrati et al. synthesized FA-conjugated, and curcumin-loaded Bi_2S_3@BSA nanoparticles (Bi_2S_3@ BSA-FA-CUR) and investigated the therapeutic efficacy of the established nanocomplex both in vitro and in vivo conditions. In this study bismuth-based nanoparticles have been used as an enhancer for X-Ray therapeutic efficacy as well as curcumin carrier due to their high ability to increase X-Ray sensitivity. It was observed that approximately 3 weeks after the injection of Bi_2S_3@ BSA-FA-CUR complex into tumor-bearing mice, the tumor was completely removed, indicating the high therapeutic efficacy of the synthesized nanocomplex and the accumulation of particles in the tumor (Fig. 7) [58].

2.4. Aptamer

Aptamers are small fragments of peptide or oligonucleotide sequences that are capable of specific binding to the target molecule by creating three-dimensional structures such as antibodies [59, 60]. Generally, aptamers can be divided into two classes: (1) oligonucleotide aptamers (RNA, DNA, or XNA) consisting of short oligonucleotide strands; (2) peptide aptamers are synthetic proteins that consist of one or more peptide domains. Peptide aptamers bind to cellular protein targets and perform biological functions in vivo. Peptide aptamers can also identify and bind to specific targets in vitro. A number of aptamers exist naturally and some are produced for a specific purpose [61]. Because of their small size and unique properties, aptamers have superiorities over antibodies, including (1) aptamers show faster and more efficient penetration into the tissues because of their low molecular weight (8–25 kDa); (2) since aptamers are oligonucleotides, they are therefore not recognized by the immune system and do not result in the immune response; (3) aptamers are stable at higher temperatures due to their oligonucleotide property; and (4) low cost of producing aptamers compared with antibodies. In general, aptamers can identify and bind to a wide range of targets such as proteins, viruses, cells, and drugs [61–64].

Tetrahedral DNA nanostructures (TDNs) are programmable and controllable structures that are used in a variety of fields including drug delivery. These DNA nanostructures have been considered promising carriers in drug delivery because of their properties (biocompatibility, biodegradability, penetrable the cell membrane, and capable of functionalizing with different groups). To increase the efficiency and capability of these DNA nanostructures for drug delivery, the AS1411 aptamer was attached to TDNs, and the efficiency of the developed system was compared with TDNs for drug delivery in different cells. AS1411 has the ability to bind specifically to nucleolin, which is highly expressed on tumor cells. It has been found that AS1411 containing TDN is more efficient in tumor cells targeting for drug delivery than free TDN and also capable of inhibiting tumor cells growth (Fig. 8) [65].

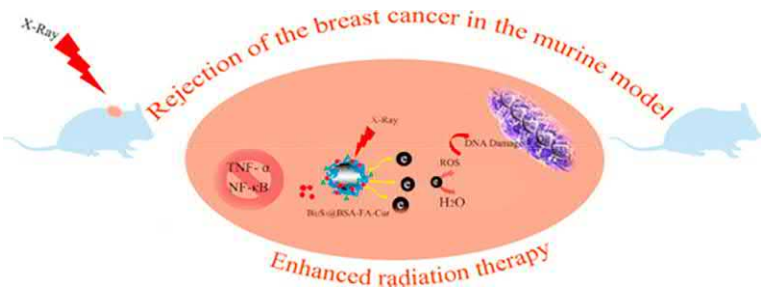

FIG. 7 Schematic illustration of Bi_2S_3@ BSA-FA-CUR nanocomplex therapeutic mechanism. (Reprinted from H. Nosrati, et al., Tumor targeted albumin coated bismuth sulfide nanoparticles (Bi_2S_3) as radiosensitizers and carriers of curcumin for enhanced chemoradiation therapy, ACS Biomater. Sci. Eng. 5 (9) (2019) 4416–4424 with permission from American Chemical Society.)