Active Targeted Nanoparticles

Subjects: Oncology

Contributor: Sadanand Pandey

PARP inhibitors were introduced as tools to protect from inflammatory diseases. Later, these selective inhibitors were evaluated as nanotherapeutic agents in clinical trials as targeted treatment strategies against solid tumors derived from ovarian, prostate, breast, colorectal, and uterine tissues. Although previous reports have established that PARP inhibitors effectively treat BRCA1-deficient cancers and increase patients' progression-free survival (PFS), new studies have suggested that HR-deficient cells may also be vulnerable to PARP inhibition.

nanotechnology nanomaterials DNA repair Poly(ADP-ribose) polymerases PARP inhibitors targeted treatment drug resistance mechanism toxicity

1. Introduction

Over the past few years, there have been tremendous efforts to develop novel new carriers for various cancer treatments [1][2][3][4][5][6][7][8][9][10]. The advent of nanotechnology and machine learning have helped to design novel alternative targeting strategies to circumvent MDR [11][12][13][14]. As an innovative field with immense potential, nanomedicine allowed biocompatible materials to be developed for various theranostic applications [15][16][17]. Having ushered in multiple established drug delivery platforms, nanostructures such as niosomes [18], liposomes [19], nanomicelles [20], polymeric micelles [21], and nanoparticles (NPs) [22][23][24][25] were broadly used in clinics to enhance the efficacy of anticancer agents for single and combinatorial treatments. Due to their specific design, structural variety, pH-sensitivity, excellent stability, biocompatibility, high drug loading, and simple elaboration, these nano-sized materials have attracted much attention as a new reversal MDR tool in cancer therapy [26][27].

Small-molecule inhibitors have revolutionized the treatment of cancer [28], and autoimmune [29], infectious [30], and metabolic [31][32] diseases. These selective inhibitors can effectively target a wide range of signaling pathways in cancerous cells, such as protein tyrosine kinases (PTKs) and protein tyrosine phosphatases (PTPs) [33], mitogen-activated protein kinase (MAPK) pathway [34], vascular endothelial growth factor (VEGF), epidermal growth factor (EGF) and their receptors (VEGFR and EGFR) [35][36], hedgehog signaling pathway [37], the activator of transcription-3 (Stat3) signaling pathway [38], phosphoinositide 3-kinase (PI3K)/Akt and the mammalian target of Rapamycin signaling network [39][40], Wnt/beta-catenin signaling [41], transforming growth factor β (TGFB) signaling [42], insulinlike growth factor I receptor signaling [43], and DNA repair pathways [44][45][46][47].

The targeting of DNA repair pathways is among the different strategies to combat MDR [48]. In this context, the Poly(ADP-ribose) polymerase (PARP) family members are known to engage in various biological and cellular

processes, such as DNA repair, gene transcription, signaling cascades, regulation of the cell cycle, cell division, and intracellular antioxidant response [49][50]. PARP inhibitors account for one of the most remarkable novel strategies for targeted therapy against cancer cells [51]. These synthetic small-molecules act through synthetic lethality in cancer cells having mutations in DNA repair genes [52]. Some of the PARP inhibitors have already been approved to treat cancers with germline mutations in the BRCA1 and BRCA2 genes [53]. At the same time, druggable genomic changes are varied and include a minority of patients with a specific cancer type, limiting the examination of the efficacy of these inhibitors in clinical trials [54].

Drug resistance and unwanted side effects are two significant drawbacks to using PARP inhibitors for cancer therapy [45][51]. Therefore, new formulations containing these selective inhibitors were subsequently designed to overcome MDR. Through this review, we hope to cast light on the most innovative progress made in applying PARP inhibitors for therapeutic purposes.

2. PARP Inhibitors

There PARP family is comprised of 17 members out of which the primary nuclear PARPs are of Poly(ADP-ribose) polymerase-1 (PARP-1), Poly(ADP-ribose) polymerase-2 (PARP-2) , Poly(ADP-ribose) polymerase-3 (PARP-3), PARP-5a, PARP5b, and tankyrase 1 and 2 [49]. The small-molecules including olaparib (AZD-2281, TOPARP-A), veliparib (ABT-888), talazoparib (BMN-673), rucaparib (AG014699, PF-01367338, CO338), niraparib (MK4827), BMN 763, AZD2461 (NCT01247168), E7016 (NCT01127178), INO-1001 (NCT00272415), EP9722 (NCT00920595) are potent submicromolar competitive nicotinamide adenine dinucleotide (NAD+) inhibitors of PARP-1 and PARP-2 enzymes [55][56]. Inhibition of PARP enzymes blocks PARylation reaction, through which ADP-ribose residues transfer to target substrates via ADP-ribosyl transferase using NAD+ [57]. It has been established that PARP trapping is responsible for the anticancer potency of PARP inhibitors [58]. Among all the PARP inhibitors in clinical development, talazoparib is the most potent PARP inhibitor, whereas veliparib demonstrated the lowest PARP trapping potency [56]. With less inhibitory effect than against PARP-1 and PARP-2, olaparib and rucaparib can also inhibit PARP-3 in BRCA-mutated advanced cancers [57].

Endogenous and exogenous DNA damaging agents cause cellular stresses that result in DNA damage [59]. These damages pose a threat to the genome and are routinely repaired by different mechanisms, such as base excision repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), ataxia-telangiectasia mutated/ataxia-telangiectasia, and Rad3-related (ATM/ATR)-mediated DNA damage response, nonhomologous end-joining repair (NHEJ) and more importantly, homologous recombination (HR) pathways [60][61]. On the other hand, PARP enzymes contribute to these mechanisms by acting as proteins that share enzymatic and scaffolding activities and have broad roles in overall DNA repair mechanisms [49].

PARP1 consists of three domains that are involved in auto-modification, PARylation (catalysis) and DNA-binding. In case of single-strand break (SSB) or double-strand break (DSB) in DNA, PARP1 recruits to the damaged site and forms branched poly (ADP-ribose) (PAR) chains. Other PARPs, including PARP2, PARP5a, and PARP5b, create long branching PAR chains of up to 200 units in length [62]. The formed chain would protect DNA from nuclease

enzymes and facilitates the recruitment of DNA repair proteins involved in BER, HR, and NHEJ pathways [49][63]. Later, the poly (ADP-ribose) glycohydrolase (PARG) enzyme effectively hydrolyses poly ADP-ribose units [64]. PARP inhibitors entrap PARP enzymes and destabilize replication forks at the damaged site of DNA [65]. This results in inducing apoptotic cell death via replication-stress mitotic catastrophe, and therefore suppresses tumor growth via suppressing the DNA damage repair pathway [66][67]. In addition to PARP inhibitors, PARG inhibitors can exacerbate replication deficiencies and be considered promising therapeutic modalities against cancer types with genomic instability [65].

NPs serve as a unique platform of drug delivery and therefore they have been extensively investigated for their potential use in anticancer drug delivery. NPs can be fabricated in a variety of ways to increase the drug encapsulation capacity at the inner core, and they can be also equipped with multiple functions on the outer core to improve the drug activity in the target environment [68]. Besides, they have the potential to deliver poorly water-soluble drugs and provide a sustained releasing profile to prolong the blood circulation time. Thus, NPs offer far superior pharmacokinetics compared to small molecule drugs [69]. Many promising drugs fail to pass clinical trials due to their short half-life and high toxicity in vivo. Besides, orally administered drugs undergo extensive degradation in the liver resulting in decreased optimum concentration of the drugs before reaching the target site. However, if the drugs could be loaded in specially designed NPs for delivery, the drugs would circulate for longer times in the blood, enabling sustained interaction with the tumor and leading to increased tumor accumulation. NPs also serve as a sheath that would shield the body from off-target toxicities of drugs, alter the cellular uptake of the drugs and lessen the probability of the emergence of drug resistance. At present, many NPs are being studied in clinical trials for a wide variety of medical treatments, and a few of them have been clinically approved for chemotherapies [70]. For example, conventional oral delivery of PARP inhibitors is hindered by limited bioavailability and off-target toxicities [71]. On the other hand, due to complementary activity of PARP inhibitors, the use of them during radiotherapy (RT) has yielded promising results. Unfortunately, this approach is often hindered by toxicity and poor in vivo stability of the PARP inhibitors [72]. Additionally, the preclinical PARP inhibitors are limited by their rapid washout kinetics and consequently modest pharmacological performances [73]. In several cases, these could be improved by loading the PARP into nanoparticulates, improving blood half-life, in vivo uptake and overall pharmacodynamics [73][74]. For instance, olaparib has advanced the treatment of ovarian cancer by providing patients with an effective and molecularly targeted maintenance therapy. However, olaparib must undergo first-pass metabolism. A nanoparticle delivery system has the advantage of administering olaparib directly into the peritoneal cavity for local treatment [75].

3. Nanoformulations for Delivery of PARP Inhibitors to Cancer Cells

Radiotherapy has been investigated for many years for the treatment of cancer. Recently, PARP inhibitors have been used in combination with radiotherapy to enhance DNA damage in the tumor cells. Lipid formulation was developed using olaparib (NanoOlaparib) to measure their efficacy in the prostate cancer cell lines. The activity of the NanoOlaparib was investigated along with the focused beam of X-ray radiation in the Pten/Trp53-deficient

mouse model. The therapy elevated the DNA damage in the radiation-resistant cells. After 13 weeks of therapy with NanoOlaparib and radiation, the mice's survival was prolonged. Additionally, the NanoOlaparib accumulated in the cancer cells up to 19 folds. Altogether, NanoOlaparib was found to be the optimistic delivery vehicle for improving the radiosensitivity in prostate cancer [76]. Nanoformulation containing olaparib (NanoOlaparib) and the nanoformulation with olaparib along with platinum conjugation (NnaoOlaparibPt) were formulated and the activity was demonstrated against the ovarian cancer cell line. The nanoformulations improved the pharmacokinetic and bioavailability profile. The cytotoxicity as studied on the ovarian cancer cell line revealed that nanoformulations were able to suppress cell proliferation. NanoOlaparib improved the therapeutic activity by reducing tumor proliferation. An elevated response was shown by using NanoOlaparib and NanoOlaparibPt on the MDR cell line SKOV-3. Additionally, the use of olaparib and cisplatin in the nanoformulation was developed and found to significantly affect cancer cell death [77].

Plectin is a protein that is mislocalized on the surface of ovarian cancer cells. Hence, it can be considered as a therapeutic target for active drug delivery in cancer. A study demonstrated this idea by developing the plectin-targeted peptide anchored to the NPs and loaded with an AZ7379 PARP inhibitor. The plectin-targeted peptide conjugated liposomes significantly decreased cell proliferation in the mice bearing OVCAR8 (epithelial ovarian cancer). The findings affirmed the advantage of nanotechnology and active targeting in improving cancer therapeutics [78].

Nanomaterials comprised of polymers have high stability, biodegradation, and biocompatibility. The composition of the NPs can modulate the drug release and enhance the targeting of the cancer cells.

Another novel molecule, fluorescent PARP inhibitor (PARPi-FL), a fluorescently labeled sensor of olaparib was studied to target the cancer cells. Nanoformulation was developed, which encapsulated the PARPi-FL. The encapsulation not only improved the delivery of the agent to the cancer cells but also helped in the imaging [79]. The nanoemulsion was stabilized with lipids and cholesterol. The nanoemulsion improved permeation followed by subsequent uptake by the PARP1-expressing small cell lung cancer (SCLC). The PARPi-FL nanoemulsion was tested in the xenograft mouse models of SCLC and exhibited good circulation. This nanoemulsion presented good imaging and targeting possibilities [73].

4. Conclusions and Outlook

PARP inhibition has opened windows of opportunity to treat many diseases, specifically solid tumors. Yet, drug resistance and unwanted side effects are two significant drawbacks to using them for therapeutic purposes. These selective inhibitors have been widely explored by formulating nanomedicine to reduce off-site toxicity or drug resistance. The NPs loaded with PARP inhibitors have shown significant improvement in cancer therapeutics. In addition, PARP inhibitors can be explored as diagnostic therapy along with targeted delivery in cancers. There is still a gap between the laboratory findings and clinical translation of these developed nanoformulations. Further investigations on the tumor microenvironment and MDR mechanisms are needed to minimize or eliminate the

limitations of using these inhibitors. An extensive effort needs to be put into exploring nanoformulations in terms of their safety, non-specific accumulation, tissue targeting, and efficacy.

References

1. Aferni, A.E.; Guettari, M.; Tajouri, T.; Rahdar, A. The confinement of PVP in AOT microemulsions: Effect of water content and PVP concentration regime on electrical percolation phenomenon. J. Mol. Liq. 2020, 318, 114012.
2. Arshad, R.; Pal, K.; Sabir, F.; Rahdar, A.; Bilal, M.; Shahnaz, G.; Kyzas, G.Z. A review of the nanomaterials use for the diagnosis and therapy of salmonella typhi. J. Mol. Struct. 2021, 1230, 129928.
3. Hakami, T.M.; Davarpanah, A.; Rahdar, A.; Barrett, S. Structural and magnetic study and cytotoxicity evaluation of tetra-metallic nanoparticles of Co0. 5Ni0. 5CrxFe2-xO4 prepared by co-precipitation. J. Mol. Struct. 2018, 1165, 344–348.
4. Hasanein, P.; Rahdar, A.; Bahabadi, S.E.; Kumar, A.; Kyzas, G.Z. Manganese/cerium nanoferrites: Synthesis and toxicological effects by intraperitoneal administration in rats. Inorg. Chem. Commun. 2021, 125, 108433.
5. Heydari, M.; Yousefi, A.R.; Rahdar, A.; Nikfarjam, N.; Jamshidi, K.; Bilal, M.; Taboada, P. Microemulsions of tribenuron-methyl using Pluronic F127: Physico-chemical characterization and efficiency on wheat weed. J. Mol. Liq. 2021, 326, 115263.
6. Mohammadi, L.; Pal, K.; Bilal, M.; Rahdar, A.; Fytianos, G.; Kyzas, G.Z. Green nanoparticles to treat patients from Malaria disease: An overview. J. Mol. Struct. 2021, 129857.
7. Nikazar, S.; Sivasankarapillai, V.S.; Rahdar, A.; Gasmi, S.; Anumol, P.; Shanavas, M.S. Revisiting the cytotoxicity of quantum dots: An in-depth overview. Biophys. Rev. 2020, 12, 703–718.
8. Rahdar, A.; Aliahmad, M.; Samani, M.; HeidariMajd, M.; Susan, M.A.B.H. Synthesis and characterization of highly efficacious Fe-doped ceria nanoparticles for cytotoxic and antifungal activity. Ceramics Int. 2019, 45, 7950–7955.
9. Zou, Q.; Xing, P.; Wei, L.; Liu, B. Gene2vec: Gene subsequence embedding for prediction of mammalian N6-methyladenosine sites from mRNA. RNA 2019, 25, 205–218.
10. Yang, Y.; Liu, J.; Zhou, X. A CRISPR-based and Post-amplification Coupled SARS-CoV-2 Detection with a Portable Evanescent Wave Biosensor. Biosens. Bioelectron. 2021, 190, 113418.
11. Gao, Z.; Zhang, L.; Sun, Y. Nanotechnology applied to overcome tumor drug resistance. J. Control. Release 2012, 162, 45–55.

12. Wang, X.-F.; Gao, P.; Liu, Y.-F.; Li, H.-F.; Lu, F. Predicting thermophilic proteins by machine learning. Curr. Bioinform. 2020, 15, 493–502.
13. Niu, M.; Lin, Y.; Zou, Q. sgRNACNN: Identifying sgRNA on-target activity in four crops using ensembles of convolutional neural networks. Plant Mol. Biol. 2021, 105, 483–495.
14. Sun, S.; Xu, L.; Zou, Q.; Wang, G. BP4RNAseq: A babysitter package for retrospective and newly generated RNA-seq data analyses using both alignment-based and alignment-free quantification method. Bioinform. 2021, 37, 1319–1321.
15. Pucci, C.; Martinelli, C.; Ciofani, G. Innovative approaches for cancer treatment: Current perspectives and new challenges. Ecancermedicalscience 2019, 13, 961.
16. Sheervalilou, R.; Shirvaliloo, M.; Sargazi, S.; Ghaznavi, H. Recent advances in iron oxide nanoparticles for brain cancer theranostics: From in vitro to clinical applications. Exp. Opin. Drug Deliv. 2021, 1–29.
17. Shirvalilou, S.; Khoei, S.; Esfahani, A.J.; Kamali, M.; Shirvaliloo, M.; Sheervalilou, R.; Mirzaghavami, P. Magnetic Hyperthermia as an adjuvant cancer therapy in combination with radiotherapy versus radiotherapy alone for recurrent/progressive glioblastoma: A systematic review. J. Neurooncol. 2021, 1–10.
18. Tila, D.; Yazdani-Arazi, S.N.; Ghanbarzadeh, S.; Arami, S.; Pourmoazzen, Z. pH-sensitive, polymer modified, plasma stable niosomes: Promising carriers for anti-cancer drugs. EXCLI J. 2015, 14, 21.
19. Chang, D.-K.; Chiu, C.-Y.; Kuo, S.-Y.; Lin, W.-C.; Lo, A.; Wang, Y.-P.; Li, P.-C.; Wu, H.-C. Antiangiogenic targeting liposomes increase therapeutic efficacy for solid tumors. J. Biol. Chem. 2009, 284, 12905–12916.
20. Raveendran, R.; Bhuvaneshwar, G.; Sharma, C.P. Hemocompatible curcumin–dextran micelles as pH sensitive pro-drugs for enhanced therapeutic efficacy in cancer cells. Carbohydr. Polym. 2016, 137, 497–507.
21. Biswas, S.; Kumari, P.; Lakhani, P.M.; Ghosh, B. Recent advances in polymeric micelles for anti-cancer drug delivery. European J. Pharm. Sci. 2016, 83, 184–202.
22. Cong, Y.; Wang, L.; Wang, Z.; He, S.; Zhou, D.; Jing, X.; Huang, Y. Enhancing therapeutic efficacy of cisplatin by blocking DNA damage repair. ACS Med. Chem. Lett. 2016, 7, 924–928.
23. Hosseinikhah, S.M.; Barani, M.; Rahdar, A.; Madry, H.; Arshad, R.; Mohammadzadeh, V.; Cucchiarini, M. Nanomaterials for the Diagnosis and Treatment of Inflammatory Arthritis. Int. J. Mol. Sci. 2021, 22, 3092.
24. Miri, A.; Sarani, M.; Khatami, M. Nickel-doped cerium oxide nanoparticles: Biosynthesis, cytotoxicity and UV protection studies. RSC Adv. 2020, 10, 3967–3977.

25. Nazaripour, E.; Mousazadeh, F.; Moghadam, M.D.; Najafi, K.; Borhani, F.; Sarani, M.; Ghasemi, M.; Rahdar, A.; Iravani, S.; Khatami, M. Biosynthesis of lead oxide and cerium oxide nanoparticles and their cytotoxic activities against colon cancer cell line. Inorg. Chem. Commun. 2021, 131, 108800.
26. Farooq, M.A.; Aquib, M.; Farooq, A.; Haleem Khan, D.; Joelle Maviah, M.B.; Sied Filli, M.; Kesse, S.; Boakye-Yiadom, K.O.; Mavlyanova, R.; Parveen, A. Recent progress in nanotechnology-based novel drug delivery systems in designing of cisplatin for cancer therapy: An overview. Artif. Cells Nanomed. Biotechnol. 2019, 47, 1674–1692.
27. Panzarini, E.; Dini, L. Nanomaterial-induced autophagy: A new reversal MDR tool in cancer therapy? Mol. Pharm. 2014, 11, 2527–2538.
28. Wang, M.; Liu, Y.; Cheng, Y.; Wei, Y.; Wei, X. Immune checkpoint blockade and its combination therapy with small-molecule inhibitors for cancer treatment. Biochim. Biophys. Acta Rev. Cancer 2019, 1871, 199–224.
29. Prieto-Peña, D.; Dasgupta, B. Biologic agents and small-molecule inhibitors in systemic autoimmune conditions: An update. Pol. Arch. Intern. Med. 2020, 131, 171–181.
30. Smithgall, T.E.; Thomas, G. Small molecule inhibitors of the HIV-1 virulence factor, Nef. Drug Disc. Today Technol. 2013, 10, e523–e529.
31. Watanabe, M.; Uesugi, M. Small-molecule inhibitors of SREBP activation–potential for new treatment of metabolic disorders. MedChemComm 2013, 4, 1422–1433.
32. Kannt, A.; Rajagopal, S.; Kadnur, S.V.; Suresh, J.; Bhamidipati, R.K.; Swaminathan, S.; Hallur, M.S.; Kristam, R.; Elvert, R.; Czech, J. A small molecule inhibitor of Nicotinamide N-methyltransferase for the treatment of metabolic disorders. Sci. Rep. 2018, 8, 1–15.
33. Jiang, Z.-X.; Zhang, Z.-Y. Targeting PTPs with small molecule inhibitors in cancer treatment. Cancer Metastasis Rev. 2008, 27, 263–272.
34. Yap, J.L.; Worlikar, S.; MacKerell, A.D., Jr.; Shapiro, P.; Fletcher, S. Small Molecule Inhibitors of the ERK Signalling Pathway: Towards Novel Anti-Cancer Therapeutics. ChemMedChem 2011, 6, 38.
35. Ivy, S.P.; Wick, J.Y.; Kaufman, B.M. An overview of small-molecule inhibitors of VEGFR signaling. Nat. Rev. Clin. Oncol. 2009, 6, 569–579.
36. Zhong, H.; Phillip Bowen, J. Recent advances in small molecule inhibitors of VEGFR and EGFR signaling pathways. Curr. Top. Med. Chem. 2011, 11, 1571–1590.
37. Peukert, S.; Miller-Moslin, K. Small-molecule inhibitors of the hedgehog signaling pathway as cancer therapeutics. ChemMedChem: Chem. Enabling Drug Discov. 2010, 5, 500–512.

38. Deng, J.; Grande, F.; Neamati, N. Small molecule inhibitors of Stat3 signaling pathway. Curr. Cancer Drug Targ. 2007, 7, 91–107.
39. McNamara, C.R.; Degterev, A. Small-molecule inhibitors of the PI3K signaling network. Future Med. Chem. 2011, 3, 549–565.
40. Segerström, L.; Baryawno, N.; Sveinbjörnsson, B.; Wickström, M.; Elfman, L.; Kogner, P.; Johnsen, J.I. Effects of small molecule inhibitors of PI3K/Akt/mTOR signaling on neuroblastoma growth in vitro and in vivo. Int. J. Cancer 2011, 129, 2958–2965.
41. Voronkov, A.; Krauss, S. Wnt/beta-catenin signaling and small molecule inhibitors. Curr. Pharm. Des. 2013, 19, 634–664.
42. Akhurst, R.J. Large-and small-molecule inhibitors of transforming growth factor-ß signaling. Curr. Opin. Investig. Drugs 2006, 7, 513–521.
43. Gable, K.L.; Maddux, B.A.; Penaranda, C.; Zavodovskaya, M.; Campbell, M.J.; Lobo, M.; Robinson, L.; Schow, S.; Kerner, J.A.; Goldfine, I.D. Diarylureas are small-molecule inhibitors of insulin-like growth factor I receptor signaling and breast cancer cell growth. Mol. Cancer Ther. 2006, 5, 1079–1086.
44. Srinivasan, A.; Gold, B. Small-molecule inhibitors of DNA damage-repair pathways: An approach to overcome tumor resistance to alkylating anticancer drugs. Future Med. Chem. 2012, 4, 1093–1111.
45. Steffen, J.D.; Brody, J.R.; Armen, R.S.; Pascal, J.M. Structural implications for selective targeting of PARPs. Front. Oncol. 2013, 3, 301.
46. Xue, C.; You, J.; Zhang, H.; Xiong, S.; Yin, T.; Huang, Q. Capacity of myofibrillar protein to adsorb characteristic fishy-odor compounds: Effects of concentration, temperature, ionic strength, pH and yeast glucan addition. Food Chem. 2021, 130304.
47. Xu, L.; Jiang, S.; Wu, J.; Zou, Q. An in silico approach to identification, categorization and prediction of nucleic acid binding proteins. Briefings Bioinform. 2021, 22, bbaa171.
48. Sadeghi, M.B.; Nakhaee, A.; Saravani, R.; Sargazi, S. Significant association of LXRβ (NR1H2) polymorphisms (rs28514894, rs2303044) with type 2 diabetes mellitus and laboratory characteristics. J. Diabetes Metab. Disord. 2021, 20, 1–10.
49. Anwar, M.; Aslam, H.M.; Anwar, S. PARP inhibitors. Hered. Cancer Clin. Pract. 2015, 13, 1–4.
50. Martínez-Romero, R.; Martínez-Lara, E.; Aguilar-Quesada, R.; Peralta, A.; Oliver, F.J.; Siles, E. PARP-1 modulates deferoxamine-induced HIF-1α accumulation through the regulation of nitric oxide and oxidative stress. J. Cell. Biochem. 2008, 104, 2248–2260.
51. Patel, M.; Nowsheen, S.; Maraboyina, S.; Xia, F. The role of poly (ADP-ribose) polymerase inhibitors in the treatment of cancer and methods to overcome resistance: A review. Cell Biosci.

2020, 10, 1–12.

52. Dedes, K.J.; Wilkerson, P.M.; Wetterskog, D.; Weigelt, B.; Ashworth, A.; Reis-Filho, J.S. Synthetic lethality of PARP inhibition in cancers lacking BRCA1 and BRCA2 mutations. Cell Cycle 2011, 10, 1192–1199.
53. Azim, H.A.; Kassem, L.; Azim, H., Jr. Integrating PARP inhibitors into the management of breast cancer: Where are we? Chin. Clin. Oncol. 2020.
54. Zugazagoitia, J.; Guedes, C.; Ponce, S.; Ferrer, I.; Molina-Pinelo, S.; Paz-Ares, L. Current challenges in cancer treatment. Clin. Ther. 2016, 38, 1551–1566.
55. Bogliolo, S.; Cassani, C.; Dominoni, M.; Musacchi, V.; Venturini, P.L.; Spinillo, A.; Ferrero, S.; Gardella, B. Veliparib for the treatment of ovarian cancer. Expert Opin. Investig. Drugs 2016, 25, 367–374.
56. Murai, J.; Pommier, Y. Classification of PARP inhibitors based on PARP trapping and catalytic inhibition, and rationale for combinations with topoisomerase I inhibitors and alkylating agents. In PARP Inhibitors for Cancer Therapy; Springer: Berlin, Germany, 2015; pp. 261–274.
57. Min, A.; Im, S.-A. PARP inhibitors as therapeutics: Beyond modulation of PARylation. Cancers 2020, 12, 394.
58. Hopkins, T.A.; Shi, Y.; Rodriguez, L.E.; Solomon, L.R.; Donawho, C.K.; DiGiammarino, E.L.; Panchal, S.C.; Wilsbacher, J.L.; Gao, W.; Olson, A.M. Mechanistic dissection of PARP1 trapping and the impact on in vivo tolerability and efficacy of PARP inhibitors. Mol. Cancer Res. 2015, 13, 1465–1477.
59. Mehta, I.S.; Kulashreshtha, M.; Chakraborty, S.; Kolthur-Seetharam, U.; Rao, B.J. Chromosome territories reposition during DNA damage-repair response. Genome Biol. 2013, 14, 1–15.
60. Yan, S.; Sorrell, M.; Berman, Z. Functional interplay between ATM/ATR-mediated DNA damage response and DNA repair pathways in oxidative stress. Cell. Mol. Life Sci. 2014, 71, 3951–3967.
61. Guo, H.; Liu, H.; Wu, H.; Cui, H.; Fang, J.; Zuo, Z.; Deng, J.; Li, Y.; Wang, X.; Zhao, L. Nickel carcinogenesis mechanism: DNA damage. Int. J. Mol. Sci. 2019, 20, 4690.
62. Qi, H.; Price, B.D.; Day, T.A. Multiple roles for mono-and poly (ADP-ribose) in regulating stress responses. Trends Genet. 2019, 35, 159–172.
63. Wei, H.; Yu, X. Functions of PARylation in DNA damage repair pathways. Genom. Proteom. Bioinform. 2016, 14, 131–139.
64. Houl, J.H.; Ye, Z.; Brosey, C.A.; Balapiti-Modarage, L.P.; Namjoshi, S.; Bacolla, A.; Laverty, D.; Walker, B.L.; Pourfarjam, Y.; Warden, L.S. Selective small molecule PARG inhibitor causes replication fork stalling and cancer cell death. Nat. Commun. 2019, 10, 1–15.

65. Slade, D. PARP and PARG inhibitors in cancer treatment. Genes Dev. 2020, 34, 360–394.
66. Virág, L.; Szabó, C. The therapeutic potential of poly (ADP-ribose) polymerase inhibitors. Pharmacol. Rev. 2002, 54, 375–429.
67. Farmer, H.; McCabe, N.; Lord, C.J.; Tutt, A.N.; Johnson, D.A.; Richardson, T.B.; Santarosa, M.; Dillon, K.J.; Hickson, I.; Knights, C. Targeting the DNA repair defect in BRCA mutant cells as a therapeutic strategy. Nature 2005, 434, 917–921.
68. Amreddy, N.; Babu, A.; Muralidharan, R.; Panneerselvam, J.; Srivastava, A.; Ahmed, R.; Mehta, M.; Munshi, A.; Ramesh, R. Recent advances in nanoparticle-based cancer drug and gene delivery. Adv. Cancer Res. 2018, 137, 115–170.
69. Amreddy, N.; Babu, A.; Muralidharan, R.; Munshi, A.; Ramesh, R. Polymeric nanoparticle-mediated gene delivery for lung cancer treatment. Polym. Gene Delivery Syst. 2017, 233–255.
70. Ventola, C. LProgress in Nanomedicine: Approved and Investigational Nanodrugs. Pharm. Ther. 2017, 42, 742.
71. Di Zhang, P.B.; Leal, A.S.; Carapellucci, S.; Sridhar, S.; Liby, K.T. A nano-liposome formulation of the PARP inhibitor Talazoparib enhances treatment efficacy and modulates immune cell populations in mammary tumors of BRCA-deficient mice. Theranostics 2019, 9, 6224.
72. Neufeld, M.J.; DuRoss, A.N.; Landry, M.R.; Winter, H.; Goforth, A.M.; Sun, C. Co-delivery of PARP and PI3K inhibitors by nanoscale metal–organic frameworks for enhanced tumor chemoradiation. Nano Res. 2019, 12, 3003–3017.
73. Gonzales, J.; Kossatz, S.; Roberts, S.; Pirovano, G.; Brand, C.; Pérez-Medina, C.; Donabedian, P.; de la Cruz, M.J.; Mulder, W.J.; Reiner, T. Nanoemulsion-based delivery of fluorescent PARP inhibitors in mouse models of small cell lung cancer. Bioconjug. Chem. 2018, 29, 3776–3782.
74. Singh, B.; Yang, S.; Krishna, A.; Sridhar, S. Nanoparticle formulations of poly (ADP-ribose) polymerase inhibitors for cancer therapy. Front. Chem. 2020, 8, 1129.
75. Baldwin, P.; Ohman, A.W.; Tangutoori, S.; Dinulescu, D.M.; Sridhar, S. Intraperitoneal delivery of NanoOlaparib for disseminated late-stage cancer treatment. Int. J. Nanomed. 2018, 13, 8063.
76. van de Ven, A.L.; Tangutoori, S.; Baldwin, P.; Qiao, J.; Gharagouzloo, C.; Seitzer, N.; Clohessy, J.G.; Makrigiorgos, G.M.; Cormack, R.; Pandolfi, P.P. Nanoformulation of olaparib amplifies PARP inhibition and sensitizes PTEN/TP53-deficient prostate cancer to radiation. Mol. Cancer Ther. 2017, 16, 1279–1289.
77. Baldwin, P.; Tangutoori, S.; Sridhar, S. In vitro analysis of PARP inhibitor nanoformulations. Int. J. Nanomed. 2018, 13, 59.
78. Dasa, S.S.K.; Diakova, G.; Suzuki, R.; Mills, A.M.; Gutknecht, M.F.; Klibanov, A.L.; Slack-Davis, J.K.; Kelly, K.A. Plectin-targeted liposomes enhance the therapeutic efficacy of a PARP inhibitor in

the treatment of ovarian cancer. Theranostics 2018, 8, 2782.

79. Jing, X.; Wang, H.; Huang, X.; Chen, Z.; Zhu, J.; Wang, X. Digital image colorimetry detection of carbaryl in food samples based on liquid phase microextraction coupled with a microfluidic thread-based analytical device. Food Chem. 2021, 337, 127971.