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REVIEW

A Review on DNA Repair Inhibition by PARP Inhibitors in Cancer Therapy

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The DNA repair process protects the cells from DNA damaging agent by multiple pathways. Majority of the cancer therapy cause DNA damage which leads to apoptosis. The cell has natural ability to repair this damage which ultimately leads to development of resistance of drugs. The key enzymes involved in DNA repair process are poly(ADP-ribose) (PAR) and poly(ADP-ribose) polymerases (PARP). Tumor cells repair their defective gene via defective homologues recombination (HR) in the presence of enzyme PARP. PARP inhibitors inhibit the enzyme poly(ADP-ribose) polymerases (PARPs) which lead to apoptosis of cancer cells. Current clinical data shows the role of PARP inhibitors is not restricted to BRCA mutations but also effective in HR dysfunctions related tumors. Therefore, investigation in this area could be very helpful for future therapy of cancer. This review gives detail information on the role of PARP in DNA damage repair, the role of PARP inhibitors and chemistry of currently available PARP inhibitors.

INTRODUCTION

Cancer is one of the major human health problems worldwide. The discovery of new target based therapy has opened a new window in the treatment of cancer. One major problem in current cancer chemotherapy is resistance development and severe toxic effects. Resistance may occur through several different cell mechanisms. Therefore, the challenge is to identify new less toxic drugs and to improve the existing cancer therapy. There is active research going on to identify targets whose expression or activation increases cancer growth. The cell DNA repair mechanism may provide important information on the above stated problem.[1] PARP is the enzyme which is involved in the DNA damage repair process. Inhibition of PARP may induce apoptosis **(Fig. 1)**. PARP enzymes are important for many cellular functions[2] which includes inflammatory gene[3] in smooth muscles to response tumor necrosis factor (TNF).[4]

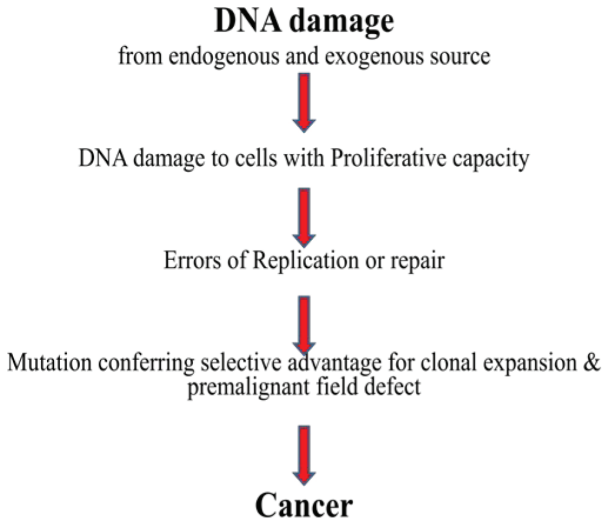

Figure 1. Link between DNA damage repair and cancer.

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PARP inhibitors inhibit the enzyme poly(ADP-ribose) polymerases (PARP). The most important role of PARP inhibitors is in treatment of cancer.[1] Some types of cancers (ovarian and breast) depend on PARP inhibition.[5-7] PARP inhibitors can also be useful in other diseases like stroke, myocardial infarction and long term neurodegenerative diseases.[8]

This review gives detailed information of the link between DNA damage repair and cancer, the role of PARP in DNA damage repair, the medicinal importance of PARP inhibitors and its role in the treatment of different cancers.

PARP STRUCTURE

PARP structure is made up of four different units.
1. DNA binding domain: it contains two zinc finger motifs. In case of DNA damage, this domain binds with DNA and induces conformational shift.
2. Auto-modification domain: it releases protein from DNA.
3. Caspase cleaved domain: this cleavage inhibition induces cell death program.
4. Catalytic domain.

Fig. 2 shows the catalytic activity of PARP. The cleavage of NAD+ moiety liberates ADP ribose monomer (blue) and nicotinamide moiety (red) in presence of PARP. This chain supplies DNA repair proteins.[9,10]

ROLE OF PARP IN DNA REPAIR

PARP is located in the cell nucleus. The main function of PARP is to detect and signal single strand DNA breaks (SSB) and give message to the machinery section which is involved in the repair of SSB. Several factors like metabolic, chemical or radiation undergo SSB which activates the PARP.

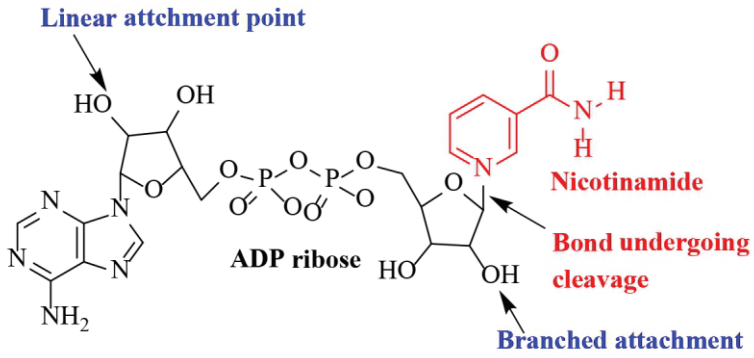

Figure 2. Catalytic activity of PARP.

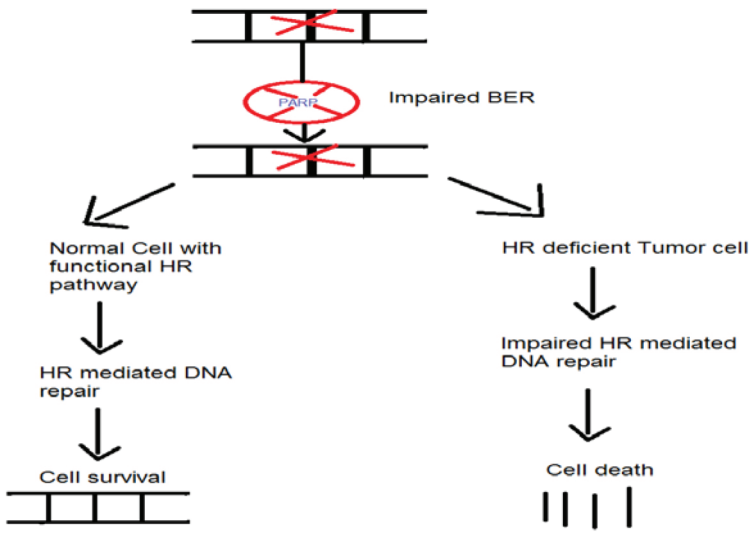

Figure 3. Mechanisms of PARP inhibitors to produce cell death without affecting normal cells.

After detection of SSB, PARP binds with DNA, does structural modification and starts the synthesis of poly(ADP-ribose) chain (PAR) to provide signal to DNA repairing enzymes like DNA ligase III (LigIII), DNA polymerase beta (polβ), and scaffolding proteins such as X-ray cross-complementing gene 1 (XRCC1). Once repair is done PAR chains is degraded by the enzyme glycohydrolase.[11] NAD^+ is required to generate ADP-ribose monomers. It has been found that overactivation of PARP leads to disturbance in glycolysis due to the reduction of cellular NAD^+ and ATP. PARP is inhibited by DNA caspase-III cleavage which produces cell death.

DNA REPAIR MECHANISMS AND ROLE OF PARP INHIBITION

DNA is unstable, alterations of DNA mechanism occur through different factors like environmental or by-products of normal cellular metabolism or disruption of chemical bond in DNA.[12] This activity causes single strand breaks (SSBs), double strand breaks (DSBs) and intra- or inter-strand cross-links.

This DNA damage is repaired by four different DNA repair mechanisms: base-excision repair (BER), nucleotide-excision repair (NER), mismatch repair (MMR), homologous recombination (HR) and non-homologous end-joining (NHEJ). SSBs are repaired by BER, NER, and MMR while DSBs are repaired by HR and NHEJ. Some DNA can be repaired directly.

NORMAL DNA REPAIR MECHANISMS AND ROLE OF PARP IN SSBS AND DSBS REPAIR

Modification of single DNA strand including SSBs is the most common deviation. Repairing by BER, NER, and MMR provides remaining uninjured strand as complementary which act as a template.[12] Approximately 10,000 spontaneous SSBs occur every day in each cell.[13] The BER pathway generates PARP enzyme which is involved in repair mechanism.[12] For the first time PARP was described in 1963 which involves 17 members and amongst them PARP-1 is the most important.[14] The PARP function is to bind to SSBs in BER pathway.[15-17] PARP can also get involved in the NER pathway.[18] Thus, PARP plays an important role in DNA damage repair and stabilization.

DSBS REPAIR

SSBs convert to DSBs via replication. DSBs damage can be induced by X-rays, chemical or other factors and repaired by HR pathway which is an error free repair. Due to unavailability of complementary DNA strand, it is potentially more problematic than SSBs. If it is repaired by NHEJ, it causes error and leads to change in DNA sequence at break site.[12]

ABNORMAL SSBS AND DSBS REPAIR AND PARP DEFICIENCY

DNA damage leads to activation of PARP-1 and PARP-2. PARP-1 deficiency doesn't create any problem in non-malignant cells though PARP-1 have an important role in SSBs repair.[16,19,20] The loss of PARP-1 guides DNA damage repair with different pathways. Unrepaired SSBs convert into DSBs which is repaired by HR in the presence of BRCA1 and BRCA2 is an error free pathway.[19,21-23] PARP inhibition blocks the conversion of SSBs to DSBs. PARP-1 inhibition blocks the repair of SSBs but the repair of DSBs proceeds further.[22,23]

Deficiency of BRCA functions forces cells to repair DSBs via NHEJ or single strand annealing sub pathway of HR but both mechanisms produce errors. BRCA deficient cell either dies or produces DNA mutations if it survives. Clinically, it has been observed that BRCA deficiency increases the risk of some cancers such as breast cancer and ovarian cancer.[24,25] It was also reported that the clinical role of PARP inhibitors is not restricted to BRCA deficient cancer but also in tumors occur due to dysfunction of HR pathway with less toxicity.[24] **(Fig. 3)**

ONGOING RESEARCH IN PARP INHIBITORS

The first identified PARP-1 inhibitor was based on a composition of NAD^+ moiety. They were designed structurally similar to the nicotinamide moiety. 5-methyl nicotinamide derivatives were developed as competitive inhibitor of PARP. Similarly benzamide derivatives were also synthesized but they show weak inhibition.[1] With the help of X-ray crystallography, the crystal structure of catalytic domain of PARP with inhibitor is established.[26] After this new PARP inhibitors developed which have more selectivity and potency towards PARP-1.[27,28] The structure activity relationship of various PARP inhibitors is illustrated in **Fig. 4.**

Penning et al.[29] have reported of a novel series of cyclic amine-substituted benzimidazole analogs[1] and developed SAR. They have found that introduction of amine group at the second position in benzimidazole improves potency. These compounds

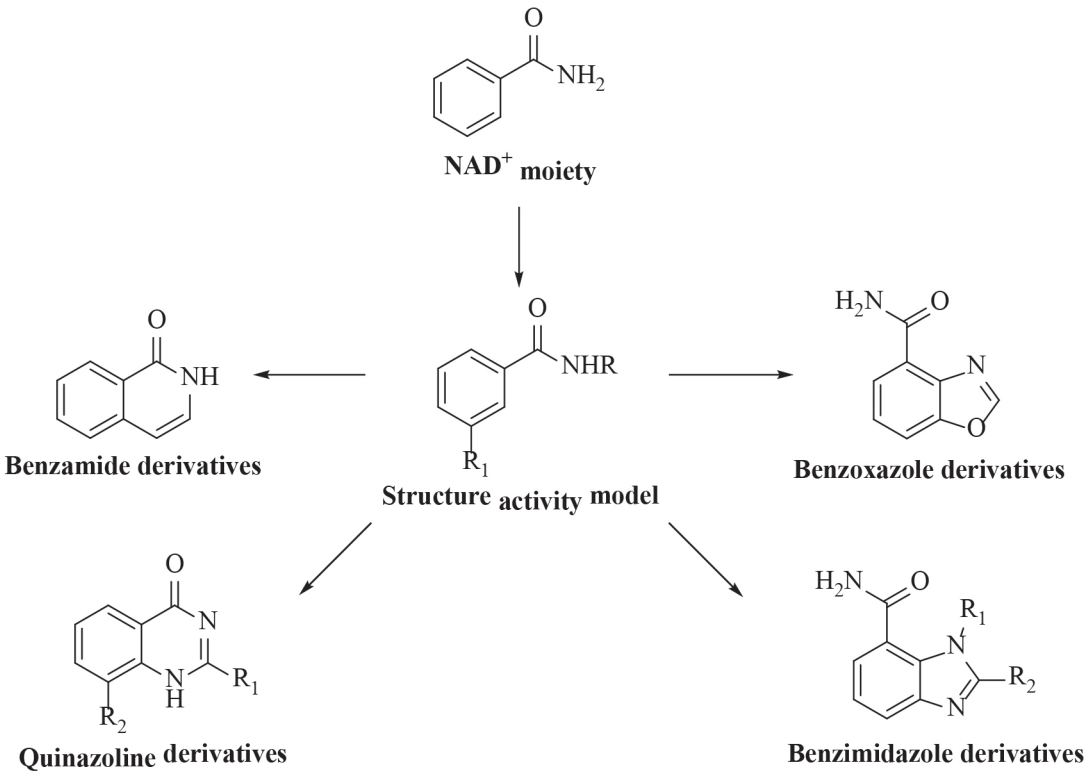

Figure 4. Structure activity model of PARP-1 inhibitors derived from the nicotinamide core structure.

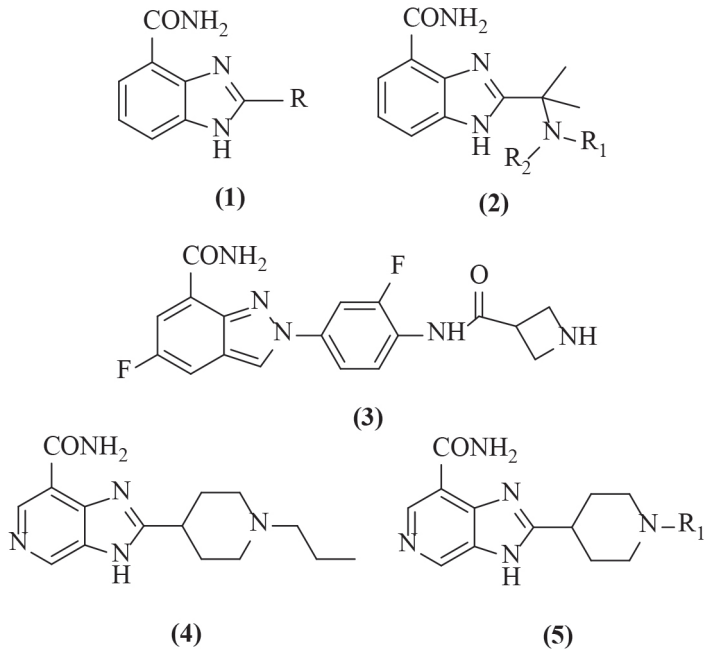

Figure 5. Examples of PARP inhibitors reported with good inhibitory activity.

help to potentiate the efficacy of radiation therapy and several cytotoxic agents like temozolomide (TMZ) and cisplatin.

Zhu et al.[30] reported novel quaternary methylene-amino substituent at C-2 position of benzimidazole moiety.[2] They found that introduction of quaternary methylene-amino substituent at C-2 position improves aqueous solubility as well as potency.

A potent series of substituted 2-phenyl-2H-indazole-7-carboxamides were evaluated as PARP inhibitors. After an extensive study of SAR on indazole scaffold and the pendant phenyl ring compound[3] was identified as potent PARP inhibitor with IC_{50}= 4nM (nano molar).[31]

Zhu et al.[32] reported series of novel cyclic amine-substituted imidazo[4,5-*c*]pyridine carboxamide analogs as potent PARP-1 inhibitors. They found that combination of compound[4] with cisplatin is effective at well tolerated doses when administered orally.

Abdullah et al.[33] reported novel benzimidazole derivatives as PARP-1 and dihydroorotate dehydrogenase (DHODH) inhibitor. Amongst them some derivatives had shown good potencies[5] (**Fig. 5)**.

CURRENT PARP INHIBITORS IN CLINICAL TRIALS

The structures of various PARP inhibitors are shown in **Fig. 6**. Details of some PARP inhibitors in clinical trials and their toxicity profiles are given in **Tables 1** and **2,** respectively.

CONCLUSION

PARP is an emerging target for cancer therapy. PARP inhibitors have shown promising results in some cancer related to BRCA mutations as well as mutations related to HR dysfunctions. Moreover current clinical studies of PARP inhibitors show common adverse effects and toxicity profile is nearly similar to current chemotherapeutic agents. However, clinical efficacy of PARP inhibitors need to be check for long-term therapy before making it a part of clinical practice. New strategies are being developed to expand application of PARP inhibitors which show more selectivity towards PARP with more potency and lower toxicity.

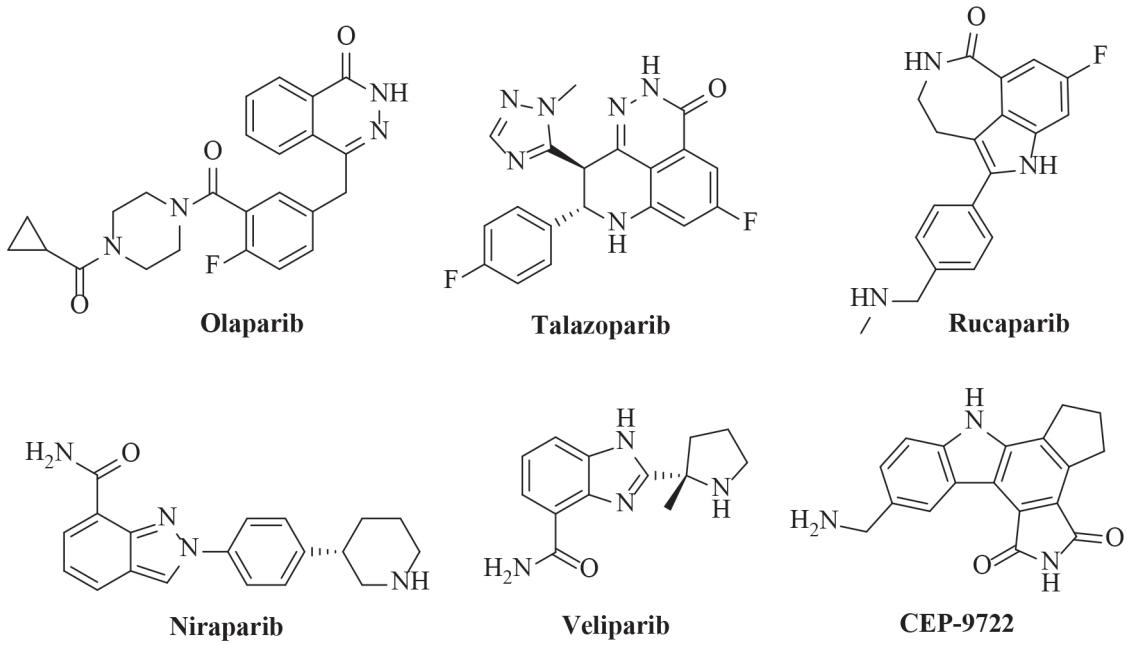

Figure 6. Structures of PARP inhibitors in clinical trials.

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Table 1. Some PARP inhibitors in clinical trials

Drug name	Pharmaceutical company	Clinical phase	Current clinical phase
Olaparib (AZD2281)[34]	AstraZeneca	3	BRCA mutated breast cancer
Veliparib (ABT-888)[35]	Abbvie	3	Combination therapy in triple-negative breast cancer
		2	BRCA mutated breast cancer
Niraparib (formerly MK-4827)[36]	Tesaro	3	BRCA mutated breast cancer
Talazoparib (BMN-673)[37]	BioMarin Pharmaceuticals	3	Germline BRCA mutated breast cancer
		2	advanced and neoadjuvant settings in BRCA mutated breast cancer and BRCA intact breast cancer
Rucaparib (formerly AG-14699)[38]	Clovis Oncology	2	germline BRCA mutated solid tumors and triple-negative breast cancer
CEP-9722[37]	Teva Pharmaceutical Industries	2	Solid tumors
BSI-201[39]	BiPar/Sanofi-Aventis	1	Solid tumors
		2	Triple-negative breast cancers
INO-1001[40]	Inotek/Genentech	1	Melanoma, glioblastoma multiform

Table 2. Toxicity profile of PARP inhibitors currently in clinical trials

Drug	Toxicity related to breast cancer	Toxicity related to ovarian cancer
Olaparib	Nausea, vomiting, fatigue, anorexia, headache, diarrhea[41-43]	GI symptoms, fatigue, anemia[44, 45]
Veliparib	Dizziness, nausea, dysgeusia[35]	Nausea, fatigue, lymphopenia[46]
Talazoparib	Fatigue, nausea, alopecia, anemia, neutropenia, thrombocytopenia [47]	Fatigue, alopecia, GI symptoms, anemia, neutropenia, thrombocytopenia[48]
Niraparib	Anemia, nausea, thrombocytopenia, vomiting, insomnia, constipation, fatigue, anorexia[49]	Anemia, thrombocytopenia, neutropenia, GI symptoms, fatigue[49]
Rucaparib	Fatigue, nausea, diarrhea, vomiting, dizziness, anorexia[50]	GI symptoms, fatigue, anaemia[50]

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Обзор ингибирования ДНК репарации с использованием PARP ингибиторов при раковой терапии

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Процесс репарации ДНК предостерегает клетки от воздействия ДНК разрушающего агента разными способами. Большинство способов терапии против рака вызывают повреждения ДНК, которые приводят к апоптозу. Клетка обладает естественной способностью восстанавливать повреждения, которая приводит к развитию резистентности к лекарственным средствам. Ключевыми ферментами в процессе репарации ДНК являются поли (АДФ-рибоза) (ПАР) и поли (АДФ-рибоза) полимеразы (ПАРП/ PARP). Опухолевые клетки восстанавливают свой дефектный ген в результате дефектной гомологичной рекомбинации (ГР) при наличии ПАРП фермента. ПАРП ингибиторы подавляют ферментные поли (АДФ рибоза) полимеразы (ПАРП), что в свою очередь приводит к апаптозу опухолевых клеток. Текущие клинические показатели дают основание считать что , что роль ПАРП ингибиторов не ограничивается в рамках BRCA мутаций, а они являются достаточно эффективными при опухолях, связанных с XP дисфункцией. В связи с этим можно утверждать, что исследование в данной области является исключительно перспективным для будущего лечения рака. Настоящий обзор рассматривает в деталях информацию о роли ПАРП при репарации повреждений ДНК, о роли ПАРП ингибиторов и о химии наличных ПАРП ингибиторов.