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Where Do We Stand in Targeted Therapy Against BRCA1/2 Deficient Cancers?

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Abstract

Introduction: BRCA1 and BRCA2 are tumour suppressor genes that, when mutated, majorly increase the risk of cancer, particularly breast and ovarian cancers. Cancer patients with BRCA mutations are more likely to have aggressive forms of cancer. Targeted therapy is a key component of treatment for BRCA-deficient cancers. An important focus for targeted therapy is synthetic lethality. Synthetic lethality is the loss of viability from the disruption of two genes, but not from the disruption of either gene alone. The most established targeted therapy for BRCA-deficient cancers is poly (ADP-ribose) polymerase inhibitors (PARPi). This paper aims to summarize advancements in targeted therapy against BRCA-deficient cancers and provide future directions.

Methods: Relevant articles were found using the search engines PubMed and Google Scholar. Search terms for relevant articles included "BRCA1", "BRCA2", "targeted therapies", "BRCA-deficient cancer", and "synthetic lethality".

Results: PARPi is widely used in clinical settings and is the only targeted therapy approved by the FDA for clinical use. PARPi exploits synthetic lethality of the HR pathway in BRCA-deficient cells by trapping PARP at sites of DNA damage, obstructing replication machinery, and generating an accumulation of DSBs, leading to cell death. In addition to PARPi, there has been further research into the use of other synthetic lethal interactors and targeted therapy approaches to target BRCA-deficient cancers, such as RAD52 inhibitors, FANCD2 inhibitors, immunotherapy, FEN1 inhibitors, APE2 inhibitors, PLK1 inhibitors, DNA Damage Response Kinase inhibitors, and RNF168 inhibitors.

Discussion and Conclusion: One major limitation of the use of PARPi in clinical settings is the rapid development of resistance. Future steps must be taken to overcome PARPi resistance and improve sensitivity by finding therapies to use alone and with PARPi to create synergistic therapy. In sum, ongoing advancements in BRCA-targeted therapies are occurring, and future steps to improve the efficacy of targeted therapies will improve patient outcomes and quality of life.

Keywords: BRCA1; BRCA2; synthetic lethality; BRCA-deficient cancers; targeted therapy; PARP; PARP inhibitor; polymerase theta inhibitor; RAD52 inhibitor

Introduction

First discovered in the 1990s, *BRCA1* and *BRCA2* are tumour suppressor genes whose mutations are associated with an increased risk of breast and ovarian cancer [1, 2]. The lifetime risk of developing breast cancer for carriers of *BRCA1* and *BRCA2* mutations is 45-80%, and BRCA mutation holders are 10 to 30 times more likely to develop ovarian cancer [3,4]. About 70% of breast cancer diagnoses are considered sporadic, while 30% are considered familial breast cancer, having an inherited genetic component [5]. *BRCA1* accounts for most cases of inherited early-onset breast cancer and ovarian cancer and 45% of inherited breast cancer cases [6]. Therefore, a strong association has been established between *BRCA1* and *BRCA2* mutations and inherited breast and ovarian cancer.

BRCA proteins play important roles in repairing DNA double-strand breaks (DSBs), which are cytotoxic lesions that can lead to cell death [1]. The two key pathways of DSB repair are homologous recombination (HR) and non-homologous end joining (NHEJ). HR occurs in the S and G2 stages of the cell cycle and uses sister or homologous chromatids as a repair template [7]. Consequently, HR is considered less error-prone [8]. NHEJ occurs throughout the cell cycle and involves the slight processing of DSB ends and blunt end ligation [8]. NHEJ fuses the broken ends of DNA without using homologous DNA sequences, and processing of the DSB ends can result in a more error-prone mechanism of repair with insertions or deletions at repair sites [8]. *BRCA* is involved in steps in the HR pathway, therefore mutations in *BRCA* lead to HR deficiency.

The most common *BRCA* mutations are single-nucleotide or frameshift mutations caused by short deletions or insertions of nucleotides [9]. *BRCA* mutation patients are more likely to have aggressive forms of cancer [10]. For example, *BRCA1*

mutations are associated with a higher risk of triple-negative breast cancer (TNBC), which is characterized by a lack of estrogen receptors, progesterone receptors, and human epidermal growth factor receptor 2 [11]. TNBC accounts for 15% of clinical diagnoses of invasive breast cancer [12]. TNBC are often unresponsive to first-line cancer therapies, shifting importance to targeted therapy approaches [11].

Targeted cancer therapy begins with the identification of a genetic mutation and the resultant abnormal protein mutations, allowing for the target of the therapy to only affect cells harboring the abnormal proteins and not healthy cells [13]. In the context of *BRCA* deficient cancers, one promising targeted therapy approach is synthetic lethality. Synthetic lethality has become an important principle in targeted therapy against BRCA deficient cancers, as it can be used to target HR deficient vulnerability of cancer cells, while sparing normal, healthy cells. One of the most widely used synthetic lethal interactions used in clinic is Poly ADP-Ribose Polymerase inhibitors (PARPi). PARP enzymes are in the Poly-ADP Ribose Polymerase (PARP) protein family [15]. PARP1 and PARP2 are the primary enzymes that catalyze the addition of ADP-ribose, which is added post-translationally to other proteins and to PARP proteins [16, 17]. The addition of multiple ADP-ribose monomers to form long chains (PARylation) is important in the regulation of cellular processes such as DNA repair and transcription [15, 17]. PARP1 and PARP2 catalyze PARylation in response to DSBs and single-strand DNA breaks (SSBs), and interact with DNA to act as a regulator for DNA damage [14, 15, 17, 18].

This review will provide an overview of current targeted therapies used in clinical settings to target *BRCA*-deficient cancer as well as new therapeutic approaches that exploit synthetic lethality and genetic vulnerabilities in these aggressive cancers.

Methods

A literature search was conducted on the databases Medline and Pubmed. Search terms included “Homologous Recombination”, “PARP”, PARP inhibitors”, “BRCA1”, BRCA2”, “BRCA-deficient cancer”, “triple-negative breast cancer”, “poly ADP ribose polymerase”, “synthetic lethality”, “triple-negative breast cancer”, “polymerase theta”, “polymerase theta inhibitor”, “Olaparib”, “Rucaparib”, “Niraparib”, “ Talazoparib”, “PARP inhibitor resistance”, “RAD52 inhibitor”, “Immune therapy”, “FEN1 inhibitor”, “APE2 inhibitors”, “PLK1 inhibitors”, “RNF168 inhibitors”, “DNA Damage Response Kinase inhibitors”, “CRISPR-Cas9”, and “PARP trapping”. Selection criteria were as follows: (1) English language, (2) primary research article or review, (3) published between 1990-2024.

Results

The first synthetic lethal interaction with *BRCA* and PARP was described in two papers in 2005 [19, 20]. The initial studies found that *BRCA* mutated cells were more than 1000 times more sensitive to PARPi than *BRCA* wild type cells [8, 20]. These studies proposed that PARPi caused persistent SSBs, which would collapse DNA replication forks, potentially creating DSBs [8, 19, 20]. These initial studies led to models of PARP trapping as the mechanism of action of PARPi [8]. Since autoPARylation is a key step in releasing PARP from DNA, when PARP is bound by PARPi, PARylation is inhibited, and PARP is trapped onto DNA [8]. The trapped PARP at SSBs creates DSBs that interfere with DNA replication machinery [8, 16]. Since *BRCA*-deficient cells lack the less error-prone HR pathway, these DSBs result in persistent breaks that are repaired using more error-prone pathways which lead to chromosome aberrations and genome instability [16]. On the other hand, normal cells can correctly repair DSBs using HR and do not exhibit compromised viability from PARPi [21, 22]. However, the initial theory of PARP and synthetic lethality has since been modified based of the mechanism of action from the PARPi clinical trials of current PARPi’s in clinical practice [23]. There have been other proposed mechanisms of action involving PARPi, making this an active area of ongoing research [24, 25, 26].

There are currently four PARPi’s approved in the USA for clinical use, which include Olaparib, Rucaparib, Niraparib, Talazoparib [27]. Different PARPi’s are used for different severities and types of *BRCA*-deficient cancers [28]. The USA Food and Drug Administration (FDA), approved Olaparib and Talazoparib to treat advanced or metastatic HER2-negative breast cancers with deleterious germ line *BRCA* mutations [28]. There have been numerous advancements in the approved indications of PARPi, which are summarized in Table 1.

Table 1. Summary of PARPi's and approved indications

PARPi	Brand Name	Approved Indication
Olaparib	Lynparza	Approved by the USA FDA and European Medicines Agency (EMA) in 2014 for women with recurrent ovarian cancer with germline *BRCA* mutation, and have received at least 3 different chemotherapies [22, 29]. In 2017, Olaparib was approved to treat advanced ovarian, fallopian tube, and primary peritoneal cancer who are responsive to platinum-based chemotherapies [29]. In 2018, the FDA approved Olaparib for treatment of germline *BRCA* mutated Her2-negative metastatic breast cancer [22].
Rucaparib	Rubraca	In 2016, Rucaparib was approved for germline or somatic *BRCA* mutation advanced ovarian cancer [30]. In 2020, the FDA approved Rucaparib for *BRCA*-deficient associated metastatic castrate-resistant prostate cancer patients that have been treated with androgen receptor-directed therapy and a taxane [31].
Niraparib	Zejula	In 2017, Niraparib obtained approval from the FDA as the first PARPi for maintenance and not contingent on *BRCA*-deficiency for platinum-sensitive recurrent epithelium ovarian, fallopian tube, or primary peritoneal cancer [32, 33, 34].
Talazoparib	Talzenna	In 2018, Talazoparib was approved by the FDA for advanced HER2-negative germline BRCA-deficient cancers [35].

PARPi Acquired Resistance

Acquired resistance to PARPi is an increasing threat for cancer patients on PARPi therapy, and numerous mechanisms have been linked to acquired PARPi resistance [8]. Over 40% of *BRCA*-deficient cancer patients do not respond to PARPi because of acquired resistance [21]. Furthermore, there is the potential of patients obtaining acquired resistance to PARPi after prolonged oral administration [21].

The most established theories of PARPi resistance are through re-establishment of HR pathway [21, 36]. There are numerous methods of reactivating HR causing PARPi resistance, such as revision mutations, that restore *BRCA1* activity and consequently restore functional HR [9, 37]. Additionally, the protein p53-binding protein 1 (53BP1) promotes NHEJ by limiting DNA end resection at DSBs [38]. Loss or mutations of 53BP1 is linked to HR activation by promoting DSB end resection, steering DSB repair to HR [38,39]. Loss or mutations of RIF1 and REV7 proteins, which like 53BP1 are associated with promoting NHEJ, are also linked to acquired resistance through the activation of HR [9,23,40]. Recent studies examining *BRCA1*-mutated tumors, found that 20% of resistant PARPi tumours in clinical settings have a loss of 53BP1 or REV7 [9].

Further mechanisms of PARPi resistance which have been discovered are not linked to HR, specifically in treatments of PARP in cancer patients [28]. Poly ADP-ribose glycohydrolase (PARG) is an enzyme responsible for the degradation of poly ADP-ribose [28]. The loss of PARG in cancer patients has been linked to PARPi resistance as the loss causes a stabilization of the PARylation process, promoting PARPi resistance in *BRCA*-deficient cancers [28]. The numerous resistance mechanism are a prevalent issue leading to the frequency of resistance in clinics. The frequency of resistance mechanisms causes difficulty and limitations for treatment of *BRCA* deficient cancers, which can cause cancer progression. The prevalence of resistance emphasizes the need for new targeted therapy approaches that can be used for PARPi resistant cancers.

CRISPR-Cas9

CRISPR-Cas9 is a gene-editing technology used by researchers to induce DSBs, allowing for the editing of a genome [41]. CRISPR-Cas9 is the current technology for discovering new synthetic lethal interactions for anticancer drugs or identifying targets of PARPi resistance [42]. In a study done using CRISPR screens on prostate *BRCA* deficient cancers, it was discovered that *MMS22L* is lost in 14% of patients and results in the hypersensitivity to PARPi [43]. Furthermore, the study identified loss of *CHEK2* causes resistance to PARPi [43]. Another study using CRISPR-Cas9 to discover alterations in *BRCA2* deficient cancers, found that Cyclin C is a synthetic activation target that when activated restores the replication fork contributing to PARPi resistance [44]. CRISPR-Cas9 can be used in the future to find mechanisms of PARPi resistance and new synthetic lethal interactions for *BRCA*-deficient targeted therapy.

Polymerase Theta

Polymerase theta (polθ) is encoded by the *POLQ*, which is highly conversed among eukaryotes [45]. A major function of polθ is defense against DNA DSBs [45]. Polθ is a critical component of alternative end-joining (Alt-EJ) mechanism, a mutagenic pathway for DNA repair [14]. As with HR, alt-EJ

requires resection of the DSB ends, creating 3' resected ends [45]. In alt-EJ, polθ grasps a 3' terminus through its active site, allowing the joining of 3' DNA ends [45]. The result is the production of micro-homologies bound by polθ, which fills in the missing nucleotides, and the DNA ends are annealed by ligase I or III [14, 45].

Although the alt-EJ pathway is error-prone, polθ plays a role in maintaining chromosomal integrity by preventing more deleterious processes that can result in genomic aberrations [45]. In HR-deficient subtypes of breast cancer, polθ is upregulated because it acts as an alternative repair pathway for DSBs, compensating for the HR loss [46]. Upregulation of polθ in breast cancer patients was associated with worsened clinical outcomes [47]. The suppression of the *POLQ* gene has been linked to sensitivity of cancer cells to DSBs-inducing drugs, making it a target in therapies [45].

The depletion of *POLQ* in *BRCA*-deficient cancers has displayed promising synthetic lethal interactions with HR factors [46, 48]. Polθ contains a N-terminal conserved superfamily, 2 helicase domains, and a C-terminal DNA polymerase domain [48]. The helicase domains contain cavities, which can be druggable sites; however, there is also the availability of crystal structures in the polymerase domain, meaning both domains can be a target for polθ inhibition [48, 49]. The first publication that described polθ inhibitors was from Temple University in 2017 [50]. There have been fundamental findings about polθ since, and currently approximately two clinical trials for polθ inhibitors.

Novobiocin is currently in clinical trials and is a non-competitive inhibitor of ATP hydrolysis [51]. Novobiocin is originally an antibiotic, and it is theorized that it binds to enzymes allosteric sites, preventing the binding of polθ to DNA [51]. Novobiocin causes DSBs end resection, an accumulation of SSBs intermediates and the loading of non-functional RAD51 [51]. ART4215 was the first small molecule polθ inhibitor to undergo clinical trials in combination with Talazoparib in August 2022 [50]. There has been research to develop a polθ inhibitor drug that can be used in clinical treatment, and this is a growing field of research.

RAD52 Inhibitors

RAD52 is a DNA-binding protein that binds ssDNA and is involved in single-strand annealing (SSA) and HR of DSBs in DNA [14]. There are at least two different sub-pathways that HR can undergo, which include the *BRCA1/2*-dependent canonical pathway and the RAD52-dependent repair pathway [14]. The RAD52-dependent repair pathway uses RAD52 to load RAD51 onto ssDNA coated with replication protein A (RPA), in which RAD52 binds and promotes ssDNA annealing [14, 52]. In a healthy cell, *BRCA2* is involved with loading RAD52 on ssDNA, but in *BRCA*-deficient cells, RAD52 can compensate acting as a sub-pathway [14, 53]. RAD52 is not an essential protein in healthy tissues; however, its role in DNA repair in *BRCA*-deficient cancers makes it a potential target for synthetic lethality [14].

The proposed mechanism of RAD52 inhibition (RAD52i) synthetic lethality is from activity of the endonuclease/exonuclease/phosphatase family domain containing protein 1 (EEPD1) [54]. In *BRCA*-deficient cells stalled replication forks EEPD1 cleavage produces toxic intermediates that require *BRCA* or RAD52-dependent HR subpathways to repair [54]. However, without *BRCA* or RAD52, there is an accumulation of DSBs causing cell death [14, 54]. There have been several small-molecule RAD52i discovered, which include D-I03, 6-hydroxy-DL-dopa, epigallocatechin, and F779-0434; however, no RAD52i that have made it to clinical trials [14, 55]. RAD52i is a growing field of research and a possible targeted therapy for *BRCA*-deficient cancers.

Table 2. Summary of targeted therapies for *BRCA*-deficient cancers and their clinical trial status

Targeted therapy	Target	Mechanism	Clinical Trial Status
PARPi	PARP	Synthetic lethality	There are currently 4 PARPi that have obtained FDA approval.
Polθ inhibitors	*POLQ*	Synthetic lethality	There are clinical trials of ART4215 in combination with Talazoparib [50, 56] There are clinical trials for polθ inhibitor Novobiocin [51, 57].
RAD52 Inhibitors	RAD52 [54]	Synthetic lethality [54]	A limited number of RAD52 inhibitors have been identified, and for selectivity and toxicity reasons, none have entered preclinical or clinical trials [55].
FANCD2 inhibitor	FANCD2 [58]	Synthetic lethality [58]	Recently, the small molecule FANCD2 of the FA pathway has been proposed as a targeted therapy [59]. There have yet to be FANCD2 inhibitors to reach clinical trials [59].
Immunotherapy	Immune checkpoints [60]	Immune checkpoint inhibition [60]	Although there have been some clinical trials using immunotherapy combined with chemotherapy for *BRCA*-deficient cancers, the trials have had limited

Targeted therapy	Target	Mechanism	Clinical Trial Status
			success and the effect of immunotherapy and *BRCA*-deficient cancers is not well characterized [60, 61, 62]. Studies have identified mutations of *BRCA2* having a better response to blockade immunotherapies, as *BRCA2* mutations are associated with high expression of immune checkpoint receptors PD-L1, PD-L2, PD1, and CTLA4 which are potential targets for immunotherapies [63].
Flap-structure-specific endonuclease 1 (FEN1) inhibitor	FEN1 [14]	Synthetic lethality [14]	There is a need for further research in this field, but it shows promise for being a targeted therapy alone, and in combination with current treatments [14, 64].
Apurinic/apyrimidinic endodeoxyribonuclease 2 (APE2) inhibitor	APE2 [65]	Synthetic lethality [65]	APE2 role in MMEJ is poorly understood [65]. APE2 has a strong endonuclease activity in base-excision repair (BER) and interacts with HR proteins [14]. APE2 nuclease has been identified to unblock endogenous DNA 3' blocking lesions. Studies have identified that accumulation of 3'-blocked DNA lesions can cause cell death in *BRCA*-deficient cells because of the HR loss [66]. Further research is needed before APE2 inhibitors, as there are no current clinical trials.
Polo-like kinase 1 (PLK1) inhibitor	PLK1 [67]	Synthetic lethality [67]	There are currently no clinical trials testing PLK1 inhibitors in *BRCA*-deficient cancers. Pre-clinical studies have shown PLK1 to be potentially synthetic lethal in *BRCA1*-deficient cancers [14, 67].
Ring finger protein 168 (RNF168) inhibitor	RNF168 [14]	Synthetic lethality [14]	There are currently no clinical trials testing RNF168 inhibitors. RNF168 genomic stability in *BRCA*-deficient cells and loss of RNF168 leads to cell death in *BRCA*-deficient settings [14, 68].
DNA Damage Response (DDR) Kinase inhibitors	ATM, ATR and DNAPK [69]	Synthetic lethality	There are multiple ongoing clinical trials for ATR, ATM and DNAPK inhibitors [70]. Recently, the ATR inhibitor Camonsertib has shown promising results in a Phase I clinical trial for *BRCA*-deficient cancers [71]. The ATM inhibitor AZD0156 has shown promising preclinical results when combined with the PARPi Olaparib and is in Phase I clinical trial [72, 73]. AZD7648 is a DNAPK inhibitor that is currently in a Phase I/II clinical trial for combination therapy with Olaparib [74].

Discussion

BRCA-deficient cancers are more likely to be aggressive. Targeted therapies can be a way to address *BRCA*-deficient cancers, improving patient survival rates. The nature of BRCA-deficient cancers acts as a great target for synthetic lethality because these cancers are HR-deficient, which is a vulnerability that can be targeted. PARPi is the only targeted therapy used currently in the clinical treatment of *BRCA*-deficient cancers. PARPi exploits synthetic lethality of the HR pathway in *BRCA*-deficient cells by trapping PARP at SSBs, obstructing replication machinery, and generating an accumulation of DSBs, leading to cell death. Polθ is another major synthetic lethal target for *BRCA*-deficient cancers because when it is inhibited, the alt-EJ pathway is impaired and there is an accumulation of DSBs. Overall, there are many promising candidates for targeted therapies, such as RAD52i, FANCD2 inhibitors, immunotherapy, FEN1 inhibitors, APE2 inhibitors, PLK1 inhibitors, DNA Damage Response Kinase

inhibitors and RNF168 inhibitors, which are summarized in Table 2.

Although there are promising outcomes and research in the field of targeted therapy for *BRCA*-deficient cancer, there are multiple limitations. Acquired resistance is a major challenge, especially with the use of PARPi in clinical settings, where 40-70% of patients are likely to develop PARPi resistance [22]. There are numerous mechanisms that can cause acquired resistance when targeting *BRCA*-deficient cancers, which include alterations in HR-restoration pathways and DNA repair proteins. Given the genomic instability of these cancers, *BRCA*-deficient tumors may have acquired resistance and never respond to the targeted therapy or are more likely to develop acquired resistance at early stages.

Targeted therapy is a novel and growing field of therapy for *BRCA*-deficient cancers. New technical approaches, such as synthetic lethal screens using CRISPR-Cas9 technology and advanced drug screening approaches, have enabled the discovery of novel synthetic lethal interactors and inhibitors in recent years [42]. Future research should focus on novel targets for targeted therapies that can help overcome acquired resistance through new inhibitors and novel combination therapy approaches. Research is improving our understanding of the causes of PARPi resistance, which can be used as biomarkers for PARPi therapy response. Predictive tools of PARP-acquired resistance can be used in the future, such as molecular profiles that test tumour samples and use gene expression for predictive purposes [75, 76]. Furthermore, the use of PARPi in cancer types other than *BRCA*-deficient cancers that are also HR-deficient and can benefit from targeted therapy. There is currently literature on the possibility of the use of PARPi in lung cancer, renal cell carcinoma, head and neck squamous cell carcinoma, and cancers with underlying defects in DNA repair [77, 78, 79]. Targeted therapies for BRCA-deficient cancers are an exciting and growing field of research that demonstrates how understanding cellular mechanisms at the basic science level can be translated to the clinic to improve patient outcomes.

Conclusion

BRCA-deficient cancers lack the expression of BRCA1 or BRCA2 genes, which are deficient in HR. Although BRCA-deficient cancers tend to be aggressive and resistance to first- line therapies, there have been major advancements in BRCA-deficient targeted therapies exploiting synthetic lethality with BRCA-deficiency and HR. The most revolutionary and widely used targeted therapy in clinical settings for BRCA-deficient cancers is PARPi. Although effective, PARPi therapy has a high risk of acquired resistance. Consequently, there is a need for new advancements in targeted therapy to address the ever-growing issue of acquired resistance. There is a large amount of research investigating new targeted therapies and how to use therapies in combination with PARPi to decrease acquired resistance and improve patient outcomes. For example, inhibitors of Polθ and RAD52 have reached clinical trials, and many more targets have been identified utilizing synthetic lethality to exploit HR deficiency resulting in loss of BRCA1 or BRCA2.
Future advancements in the field will reveal novel targeted therapy approaches that can help patients facing aggressive BRCA-deficient cancers.

List of Abbreviations Used

Alt-EJ: alternative end-joining
APE2: apurinic/apyrimidinic endodeoxyribonuclease 2
BER: base excision repair
DSBs: double-strand DNA breaks
EEPD1: endonuclease/exonuclease/phosphatase family domain containing protein 1
EMA: european medicines agency
FANCD2: fanconi anemia complementation group D2
FDA: food and drug administration
FEN1: flap structure-specific endonuclease 1
FEN1: flap-structure-specific endonuclease 1
HR: homologous recombination
MMEJ: microhomology-mediated end joining
NHEJ: non-homologous end joining
PARG: poly ADP-Ribose glycohydrolase
PARP: poly ADP-Ribose polymerase
PARPi: poly ADP-Ribose polymerase inhibitors
RAD52: radiation sensitive 52
RAD52i: radiation sensitive 52 inhibitor
RPA: replication protein A
SSA: single strand annealing
SSBs: single-strand breaks
TNBC: triple-negative breast cancer

Conflicts of Interest

The author declares that she has no conflicts of interest.

Ethics Approval and/or Participant Consent

This study did not require ethics approval and/or participant consent as no experiment were preformed and no participants were recruited for the literature review.

Authors' Contributions

ZM: Designed the study, draft the manuscript, critically appraised, and revised the manuscript and gave approval for the final version to be published.

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