MicroRNA-mediated approaches in ovarian cancer therapy: A comprehensive systematic review

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Abstract. Ovarian cancer (OC) poses a significant health risk to women worldwide, with late diagnoses and chemotherapy resistance leading to high mortality rates. Despite several histological subtypes, the primary challenge remains the subtle nature of its symptoms, resulting in advanced-stage diagnosis and reduced treatment success rates. With platinum-based therapies showing relative efficacy but limited survival enhancements, the emergence of chemotherapy resistance during recurrence remains a critical obstacle. Precision medicine development has aimed to address these challenges in the context of the molecular diversity of OC. The present review explored the landscape of microRNA (miRNA)-mediated approaches in OC treatment. miRNAs have emerged as regulators of gene expression, serving as both oncogenes and tumor suppressors in OC. Dysregulated miRNAs are associated with disease progression and chemotherapy resistance, underscoring their significance in diagnosis and tailored treatment strategies. The present review extracted 295 publications from the PUBMED database. Out of the 73 eligible studies, 55 miRNAs were assessed. A total of three of these miRNAs were not associated with any disease or cancer, whilst eight were associated with OC, albeit also associated with other diseases. The present review encompassed three dimensions: i) The role of miRNAs in treatment efficacy; ii) the use of miRNAs to enhance therapy outcomes; and iii) adjunctive strategies for improved treatment results. Furthermore, it offered insights into potential avenues for improving OC treatment using miRNA-based approaches.

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Introduction

Ovarian cancer (OC) is a complex and challenging disease that affects women worldwide. As the fifth most common cancer in women (1), it poses several significant health risks, ranging from late diagnosis to chemoresistance, and contributes to ~150,000 global deaths per year, mental health problems and a financial burden for patients (2). OC is not a singular entity; it comprises several histological subtypes, each with distinct characteristics. Epithelial (E)OC is the most common type, accounting for 85-90% of OCs (3,4). It arises from the cells that cover the outer surface of the ovary. EOC includes subtypes such as serous, mucinous, endometrioid and clear cell carcinoma. Hereditary factors also serve a role, with family histories of ovarian or breast cancer increasing the risk. The association between OC and mutations in the BRCA genes, particularly BRCA1 and BRCA2, highlights the genetic contribution to the etiology of the disease. Individuals with familial histories of breast or OC carrying BRCA1/2 mutations have elevated risks, emphasizing the importance of genetic testing and precision medicine approaches for targeted risk assessment and management (5-7). This risk increases with age, as the median age of diagnosis is ~63 years (8).

The primary challenge in OCs pertains to its diagnosis, which is characterized by an absence of efficient early detection methods as the symptoms of OC are notoriously subtle and are often referred to as 'stealthy assailant' (4). This leads to patients being diagnosed in advanced stages (9), rendering surgical intervention more complex due to widespread metastasis. If effective early-stage detection is achievable, the survival rate can potentially increase to 70%. However, with an estimated early-stage detection rate of only 20%, late-stage detection with advanced cancer notably lowers the survival rate to 35% for most patients (10).

The current standard treatment for OC includes surgery and chemotherapy, alongside emerging therapies like

anti-angiogenic agents, poly(ADP-ribose) polymerase inhibitors and immunotherapeutic approaches. To mitigate morbidity rates, a strategy involving pre-sensitization of cancer cells with standard therapy has been investigated, particularly effective with platinum-based agents due to its heightened response in relapsed cases, addressing drug resistance. Second-line chemotherapy selection depends on tumor sensitivity to platinum derivatives, often incorporating carboplatin or cisplatin in combination with other drug therapy (such as paclitaxel and gemcitabine) (11). However, the emergence of chemotherapy resistance, especially during disease recurrence, remains a critical challenge. Given the inherent heterogeneity of OC, a precision medicine approach aims to identify specific mutations and customize treatment strategies accordingly. This tailored approach aims to address the challenges of resistance and enhance treatment efficacy in the context of the molecular diversity of OC (12).

Within the last decades, several biomolecular studies focused on trying to address the aforementioned challenges. Following their first discovery in 1993 (13), microRNAs (miRNAs/miRs) have been studied in many diseases, including OC, to understand biological mechanisms of diseases as well as improving the diagnosis and treatment of patients. miRNAs are small RNA molecules that regulate gene expression and can act as oncogenes (promoting cancer) or tumor suppressors (inhibiting cancer) in OC. Research on miRNAs has reported that deregulation of miRNAs is one of the pathogenesis processes found in several types of OC. Furthermore, dysregulation of specific miRNAs has been associated with OC development, progression and chemoresistance (12).

miRNAs have dual roles in OC management: i) The miRNA expression profile can be used for diagnostic and prognostic purposes, forming the basis of a personalized medicine approach. By identifying specific miRNA signatures, clinicians can tailor treatment plans to improve outcomes and minimize exposure to ineffective therapies (12,14); and ii) miRNAs themselves are being explored as therapeutic agents. Synthetic miRNAs, such as miRNA mimics and inhibitors, have shown promise in preclinical studies. These synthetic miRNAs can restore normal gene expression patterns, inhibit tumor growth and enhance the sensitivity of cancer cells to chemotherapeutic agents like cisplatin. Studies have concluded that targeting miRNAs can be a viable therapeutic strategy in OC. By modulating miRNA activity, researchers aim to correct the aberrant gene expression that drives cancer progression and resistance. Therefore, the miRNA profile not only aids in selecting effective therapies but also forms the basis for developing miRNA-targeted treatments. This dual approach shows the potential of miRNA research to revolutionize OC therapy, leading to better patient outcomes (12).

The present review aimed to assess the current research landscape concerning OC treatment within the past decades, and the outcomes of the review are categorized into the following distinct dimensions: i) Understanding the role of miRNAs in influencing treatment outcomes; ii) harnessing miRNAs to improve therapy outcomes; and iii) miRNA-enhanced adjunctive strategies for therapy outcomes. In the former dimension, the review identified the underlying mechanisms of miRNAs that have been elucidated to contribute to therapy, addressing both their impacts on treatment efficacy and the development of resistance. In the two latter dimensions, a review of previously published studies that centered around miRNAs and OC revealed potential avenues for enhancing the current treatment strategies in the clinical practice.

Materials and methods

A systematic search was performed by first searching with keywords that were built around two key terms, namely: 'Ovarian cancer' and 'miR'. More detailed terminology was elaborated on for each term, which further combined to construct comprehensive search keywords, allowing for a broader background while maintaining the study's emphasis (Table SI). To guarantee optimal studies that might suit the aims of the current investigation, high false-positive search results were tolerated, in which 'therapy'-related terms were not included in the search keywords. The keywords were then used in the PubMed database (https://punmed.ncbi.nlm.nih.gov/), using the PubMed Advanced Search Builder tool. Subsequently, the titles and abstracts of the eligible studies were retrieved from the database.

The systematic review process was as follows: First, two independent reviewers scanned titles and abstracts by applying the following inclusion criteria: i) A focus on human OC; ii) use of and a focus on miRNAs; and iii) a focus on chemotherapy. Subsequently, the full report of all studies that passed the first screening were reviewed. The inclusion criteria for the second screening were as follows: i) Use of synthetic miRNAs; and ii) an available full text in the English language. All discrepancies between two reviewers were resolved by discussions to reach an agreement. The reasons for the exclusion of studies is summarized in Table SII. Finally, the following information was extracted from all the studies that passed the second screening: Year of publication, country of first author, key findings, tissues/cell lines, therapy type and miR of interest (including its regulatory functions). The reporting and workflow of the present systematic review study followed the Preferred Reporting Items for Systematic Reviews and Meta-Analysis reporting guidelines (15).

Results and Discussion

Systematic search results. As of July 2023, the keyword search resulted in 295 publications from the PubMed repository. The two-step screening process resulted in 73 eligible publications for information extraction (Fig. 1). All eligible studies exclusively used tissue samples and/or cell lines. However, this outcome was not predetermined; namely, sample types were not specifically defined during the search process as one of selection criteria. Notably, there was a relatively low annual publication count on the topic of interest, in particular the association of miRNAs with ovarian cancer chemotherapy (Fig. S1), averaging only two publications per year. The countries of the first authors were also mostly centralized to China and the United States (Fig. S2). Furthermore, 36% of the eligible studies focused on cisplatin therapy (Fig. 2). Cisplatin is a potent chemotherapy drug used in the treatment of several cancers, including OC. It is part of a class of drugs known as platinum-containing compounds and it exerts its anticancer

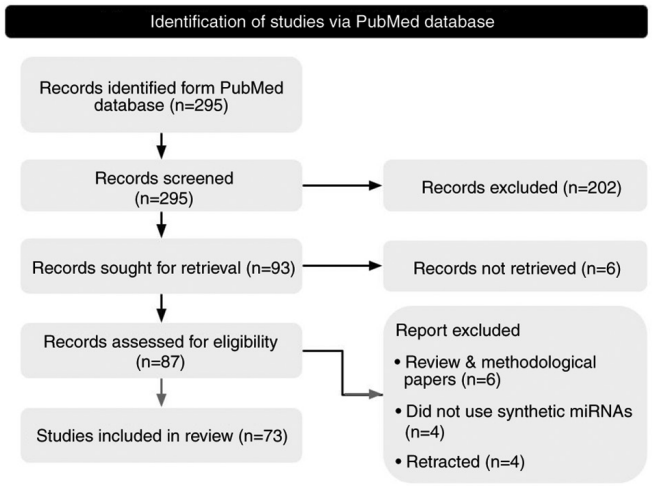

Figure 1. Workflow of the present systematic review. Each box represents a step in the systematic review process, along with the number of studies corresponding to that step. miRNA, microRNA.

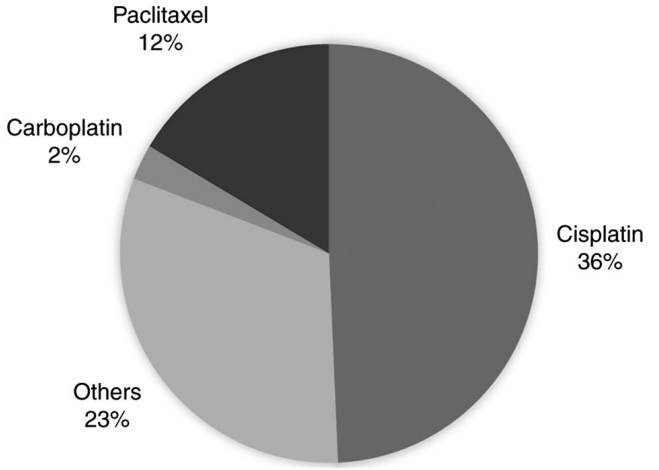

Figure 2. Therapies used in the eligible studies. The distribution of therapies may also reflect the popularity of the therapy in practice. 'Others' include the following: Olaparib, Oleuropein, Chitosan and Berberin.

effects by binding to and damaging the DNA in cancer cells. This damage interferes with the ability of the cells to divide and grow, ultimately leading to cell death (16).

There was a notable proportion of studies amongst the eligible studies that focused on understanding the role of miRNAs in influencing treatment outcomes (79.45%; Fig. 3), indicating substantial unknown aspects regarding treatment outcomes in OC from the perspective of miRNAs. This hypothesis was strengthened by the wide variety of miRNAs studied in the eligible studies, in which there were cumulatively 66 miRNAs investigated. A total of nine of those miRNAs were identified by the Human Gene Database (17), which were associated with OC, although they were not specific to the disease. Moreover, four miRNAs were not reported to be associated with any diseases (Table SIII).

Understanding the role of miRNAs in influencing treatment outcome. OC is known for its high mortality rate, often due to chemoresistance. This resistance significantly limits the effectiveness of treatment and often leads to the recurrence of the disease and poor patient outcomes (10,18). Table SIV presents the eligible studies that evaluated the association between miRNAs and therapy outcomes in OC, with a focus on studies that used miRNAs to assess why specific therapeutic interventions yielded suboptimal results.

miR-21 is a well-known miR that is associated with therapy resistance in OC. It is known as oncomiR in several other cancers, including cervical, colorectal and breast cancer (19). Abnormally highly expressed miR-21 may regulate drug resistance via augmented apoptotic pathways (20). As such, whether through natural compounds like icariin or by modulating c-MYB expression, targeting miR-21 may hold promise for enhancing the efficacy of therapies, particularly against drug resistance in OC. Icariin was assessed by Li *et al* (21) as a potential alternative therapy for OC. Icariin, the primary bioactive compound present in epimedium, a traditional Chinese medicinal herb, demonstrates diverse pharmacological properties including bolstered immune function, anticancer potential, cardiovascular enhancement and modulation of endocrine activity (21). Moreover, icariin has been reported to suppress miR-21 expression in OC cells, although the precise mechanisms underlying modulation of miR-21 expression by icariin remains unknown (21). Another study on cisplatin-resistant therapy indicated that miR-21 serves a crucial role in c-MYB-induced cisplatin resistance (22). c-MYB is a transcription factor protein encoded by the MYB gene and dysregulation of c-MYB has been implicated in several cancers, including OC, where it contributes to tumor progression and chemotherapy resistance (22). Silencing c-MYB has been reported to lead to reduced miR-21 levels, decreased epithelial-mesenchymal transmission (EMT), lowered cisplatin resistance and increased β-catenin phosphorylation (22).

Cisplatin stands as the prominent platinum-based therapy entwined with miR regulation, based on the results of the present systematic review, which revealed that 36% of the total eligible studies focused on cisplatin therapy. The emergence of cisplatin resistance poses a formidable challenge to effective treatment. The following miRNAs were mentioned due to their pivotal roles in orchestrating this resistance phenomenon: i) A high expression of miR-93 has been reported to be associated with cisplatin resistance and it can target genes that regulate apoptosis. L-tetrahydropalmatine (L-THP; an anticancer compound obtained mainly from genera *Stephania* and *Corydalis*) has been reported to suppress miR-93 expression whilst increasing PTEN levels, a pivotal tumor suppressor in OC (23). Furthermore, PTEN small interfering (si)RNA-treated cells increased survival, which was reversed by the AKT inhibitor Triciribine. L-THP enhanced OC cell sensitivity to cisplatin by modulating the miR-93/PTEN/AKT pathway (23); ii) in cisplatin-resistant OC cells, miR-1271 is often overexpressed. It can target tumor suppressors and cell cycle regulators like p53 and cyclin B1, promoting cell survival and reducing apoptosis. This, in turn, makes cancer cells more resistant to the cytotoxic effects of cisplatin (24); iii) miR-302 is known to influence cisplatin resistance through multiple mechanisms. It can affect drug transporters and drug-metabolizing enzymes. In certain cases,

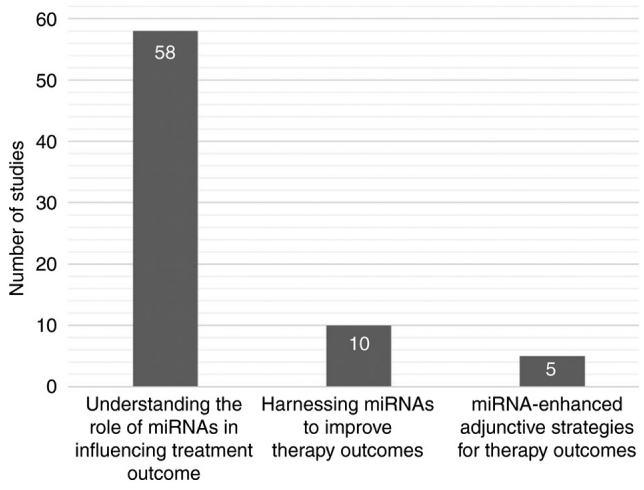

Figure 3. Main research topics of the eligible studies. A total of 80% of the eligible studies fall into the category of 'Understanding the role of miRNAs in influencing treatment outcome', indicating numerous unknowns regarding the role of miRNAs in influencing treatment outcomes, especially concerning popular platinum-based therapy. miRNA, microRNA.

miR-302 can downregulate copper transporters such as solute carrier family 31 member 1, leading to decreased intracellular cisplatin accumulation. This limits the access of the drug to its target DNA (25); iv) miR-138-5p appears to influence cisplatin resistance through its ability to regulate cellular senescence and stemness. The miR was reported to be downregulated in cisplatin resistance cell-lines. Increasing miR-138-5p levels (either by inducing HOX transcript antisense RNA siRNA or by its mimics) improved chemosensitivity and reduced enhancer of zeste 2 polycomb repressive complex 2 subunit and sirtuin 1 expression, which are key players in cisplatin resistance (26); and v) high expression of miR-149-3p in OC tissues has been reported in cisplatin-resistant OC cells. Knockdown of miR-149-3p inhibited cisplatin resistance and malignant traits in OC cells. Mechanistically, miR-149-3p targeted cyclin dependent kinase inhibitor 1A and TIMP metallopeptidase inhibitor 2 to promote cisplatin resistance and EMT in OC (27). Fig. 4 summarizes key insights on cisplatin resistance from the eligible studies presented in this sub-section.

Notably, there appears to be potential associations between the aforementioned miRNAs, indicating overlapping molecular pathways or biological processes affected in OC. Table I provides a comparative analysis of the effectiveness of those miRNAs: miR-21 and miR-93 are associated with cisplatin resistance by regulating apoptosis pathways in several types of cancer; miR-1271 and miR-149-3p are also associated with cisplatin resistance in ovarian cancer cells by modulating multiple pathways involved; and miR-302 and miR-138-5p are associated with drug transport in cancer cells through the stem pathway and several other pathways. However, the aforementioned miRNAs require further experimental validation to ensure their significance and clinical implications, which further may offer promise for optimizing therapy outcomes in OC management.

Harnessing miRNAs to improve therapy outcomes. The present review explored studies in which miRs were used to improve standard treatment outcomes via the transfection of anti-miRs or mimic-miRs. This pursuit aimed to both enhance treatment effectiveness and gain more insights into alternative instances where therapeutic interventions failed to achieve the intended outcomes, by either reinstating miR expression in tumor suppressor genes or by inhibiting the activity of oncogenic miRNAs, referred to as 'mimic-miRs' and 'anti-miRs', respectively. By assessing the scientific evidence, the present review aimed to present how miRNA-based interventions offer their potential for optimizing therapeutic strategies. The present review identified 10 studies that reported that mimic- and/or anti-miRs could help improve therapy outcomes, and cumulatively ten miRNAs of interest were discussed (Table II). Notably, none of the studies were registered in a clinical trials database. Moreover, cisplatin and paclitaxel were the most common type of therapies used in the experimental studies (Fig. 2).

Jin and Wei (28) indicated that when miR-23a inhibition was coupled with cisplatin treatment in OC cells, there was a significant increase in the effectiveness of cisplatin in limiting cell proliferation. miR-23a had been previously reported to be upregulated in a chemotherapy-resistant OC cell and this led to a marked increase in the rate of apoptosis in cancer cells. However, this effect was not observed when cells were treated with cisplatin alone, emphasizing the role of miR-23a in suppressing cell death and promoting drug resistance (29). Another study reported how the downregulated miR let-7d-3p could improve therapy outcomes (30). let-7d-3p is a miR associated with tumor progression and chemotherapy resistance in OC, where it is reported to be upregulated. let-7d-3p is the passenger strand and used to be considered 'non-functional' (30). Moreover, it is part of the let-7 family, which is comprised of 13 members that are highly conserved across species. let-7 is a key regulator of differentiation, pluripotency and apoptosis in eukaryotic cells, and has a role in cell cycle deregulation, cell division, proliferation, angiogenesis and apoptosis (31). Thus, let-7 can be used as a molecular tool and marker in cancer therapy (31-34). Previous studies have reported that miR-let-7d-3p can be used as a diagnostic biomarker for non-invasive screening of ovarian cancer and its precursors (31-34). To observe the potential of the miR to enhance treatment outcomes, García-Vázquez *et al* (30) used a two-fold strategy: i) let-7d-3p was inhibited using an antagomiR, an antagonist designed to suppress the activity of miRNAs. This inhibition led to a marked decrease in cell proliferation and the activation of apoptosis. These outcomes suggest that inhibiting let-7d-3p with the antagomiR sensitizes OC cells to therapy and increases their susceptibility to cell death; and ii) carboplatin was introduced. let-7d-3p affects the Ras pathway, which is associated with therapy resistance; therefore, targeting let-7d-3p with an antagomiR may modulate key cellular processes and signaling pathways, including ErbB and hypoxia-inducible factor-1, which are implicated in tumor progression and drug resistance (30). As such, the antagomiR for let-7d-3p inhibited the activity of carboplatin, leading to reduced cell proliferation and increased apoptosis. Suppressing let-7d-3p using an antagomiR sensitized the OC cells to carboplatin and enhanced the effectiveness of the treatment by promoting apoptosis. This two-pronged approach, using an antagomiR and chemotherapy, offers a promising strategy to

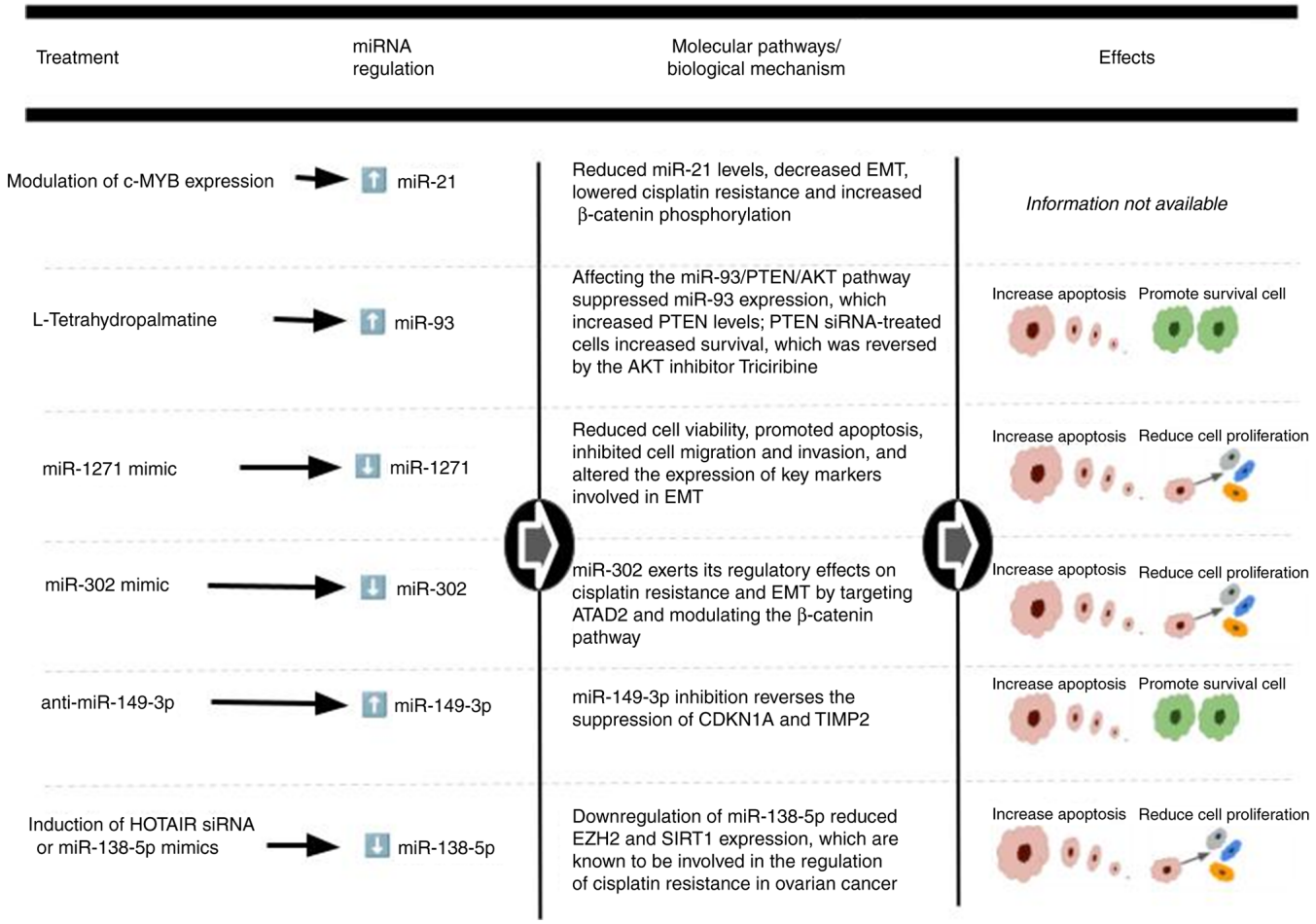

Figure 4. Key insights on cisplatin resistance from the eligible studies. Treatments include interventions aimed at enhancing cisplatin sensitivity, potentially influencing the regulatory function of known miRNAs implicated in cisplatin resistance. miR regulation indicates the regulatory role of miRNAs known to influence cisplatin resistance. Molecular pathways/biological mechanisms provides detail on the biological mechanisms triggered by the treatment, which may subsequently enhance cisplatin sensitivity. Effects illustrates the ensuing effects resulting from the treatment that could impact cisplatin sensitivity. miR/miRNA, microRNA; siRNA, small interfering RNA; EMT, epithelial-mesenchymal transition. HOTAIR, HOX transcript antisense intergenic RNA; TIMP2, tissue inhibitor of metalloproteinases 2; EZH2, enhancer of zeste homolog 2; SIRT1, sirtuin 1.

improve therapy outcomes and combat the challenges of drug resistance in OC (30-34).

The present review also investigated studies that focused on reinstating the expression of miRNAs which are associated as tumor suppressor genes, indicating that the injection of mimic-miR to OC cells (possibly in combination with another treatment) may yield an improved therapy outcome (35). miR-873 mimics were introduced into OC cells and the results revealed that the overexpression of miR-873 led to a marked increase in the sensitivity of the cells to cisplatin and paclitaxel. In another study, researchers aimed to enhance therapy outcomes for OC by using miR-424-3p mimics. This miR-based approach targeted the expression of galectin-3, an anti-apoptotic protein that is often overexpressed in OC and associated with resistance to chemotherapy, especially cisplatin (28). miR-424-3p mimics were transfected into OC cells to assess its impact on the expression of galectin-3. The results demonstrated that miR-424-3p mimics notably suppressed the expression of galectin-3 at the protein level. This downregulation of galectin-3 is critical as this protein is associated with inhibiting apoptosis, a process that serves a central role in the response of the cell to chemotherapy. Following that, the cell viability and proliferation rates decreased, indicating a reduced capacity for the cells to grow and divide. Moreover, apoptosis was enhanced, with the cells treated with miR-424-3p mimics and cisplatin demonstrating a marked increase in apoptosis compared with the control group. Another similar study that assessed the enhancement of platinum-based-therapy through mimic-miRs, reported similar results, although they used miR-186 as their main object of observation (33).

miRNA-enhanced adjunctive strategies for therapy outcomes. Finally, the present study investigated adjunctive substances that have the potential to enhance therapy outcomes in OC, with a focus on their interactions with anti- and mimic miRs. The aim was to provide insights into emerging strategies that leverage miRNAs in conjunction with other compounds to optimize the effectiveness of OC treatments. For example, nanoparticles have been used for targeted miR therapy as drug delivery systems for miRNA-based cancer therapy (36-38) (Table III). These nanoparticles were engineered to efficiently deliver anti-miR or miR-mimics payloads to OC cells, specifically either targeting overexpressed oncogenic miRNAs or reinstating miR expression in tumor suppressor genes. The

Table I. Summary of potential associations and comparative analysis of the effectiveness of certain microRNAs in enhancing therapy outcomes.

miR	Potential association	Comparative analysis
miR-21 and miR-93	Associated with cisplatin resistance by regulating apoptotic pathways	Targeting miR-21 may offer broader applicability in enhancing therapy outcomes due to its involvement in multiple cancer types
miR-1271 and miR-149-3p	Associated with cisplatin resistance in ovarian cancer cells	Targeting miR-149-3p may offer broader implications for overcoming cisplatin resistance and malignant traits in ovarian cancer cells due to its modulation of multiple pathways involved in drug resistance and epithelial-mesenchymal transition
miR-302 and miR-138-5p	Influenced cisplatin resistance, albeit through distinct mechanisms; whilst miR-302 affects drug transporters, miR-138-5p regulates cellular senescence and stemness	Targeting miR-138-5p may offer potential advantages in overcoming cisplatin resistance by modulating stemness-related pathways, thereby sensitizing cancer cells to chemotherapy-induced apoptosis. However, combination strategies targeting both miRNAs may provide synergistic effects in combating cisplatin resistance by simultaneously modulating multiple pathways involved in drug resistance

miRNA/miR, microRNA.

Table II. List of observed miRNAs from studies focused on improving therapy outcomes through miRNAs and other substances.

A, Downregulated miR can improve therapy sensitivity

First author/s, year	miRNA of interest	anti-miR	mimic-miR	Type of therapy	(Refs.)
Jin and Wei, 2015	miR-23a	AntagomiR-23a	x	Cisplatin	(28)
Rupaimoole *et al*, 2016	miR-630	Anti-miR 630[a]	miR-630 mimics	Anti-vascular endothelial growth factor antibody and anti-miR-630	(43)
García-Vázquez *et al*, 2018	let-7d-3p	let-7d-3p inhibitor and let-7d-3p antagomiR	x	Carboplatin and paclitaxel	(30)
Ye *et al*, 2011	miR-376c	anti miR-376c	x	Cisplatin	(44)
Echevarría-Vargas *et al*, 2014	miR-21	miR-21 inhibitors	x	Cisplatin	(45)
Vandghanooni *et al*, 2018		anti miR-21	x	Cisplatin	(46)
Suardi *et al*, 2020	miR-324-5p	Antagonist miR-324-5p[a]	x	Chitosan	(47)

B, Upregulated miR can improve therapy sensitivity

First author/s, year	miRNA of interest	anti-miR	mimic-miR	Type of therapy	(Refs.)
Wu *et al*, 2016	miR-873	anti-miR-873	miR-630 mimics	Cisplatin and paclitaxel	(35)
Bieg *et al*, 2019	miR-424-3p	x	miR-424-3p mimics	Cisplatin	(36)
Sun *et al*, 2015	miR-186	anti-miR-186	x	Cisplatin and paclitaxel	(37)
Suardi *et al*, 2020	miR-155-5p	x	miR-155-5p mimics	Chitosan	(47)

[a]Synthetic miRs may improve therapy sensitivity, based on the corresponding study. miR/miRNA, microRNA; x, not employed.

Table III. Observed miRNAs from studies which focused on improving therapy outcomes through microRNAs and other substances.

First author/s, year	miRNA of interest	anti-/mimic-miRs	Substance	(Refs.)
Bertucci *et al*, 2019	miR-21	anti-miR-21	CGKRK-pSiNP	(38)
Javanmardi *et al*, 2020			PEG2k-CMPEI-ss	(39)
Vandghanooni *et al*, 2020	miR-214	anti-miR-214	Ap-CIS-PCL NPs	(40)
Gandham *et al*, 2022	miR-let-7b	miR-let-7b mimics	Hyaluronic acid-based nanoparticle	(41)
Zhao *et al*, 2022	miR-484	miR-484 mimics	RGD-modified exosomes	(42)

miR/miRNA, microRNA; CGKRK-pSiNP, intravesically-administered cell-penetrating peptide (Cys-Gly-Lys-Arg-Lys)-porous silicon nanoparticles; PEG2k-CMPEI-ss, PEGylation 2000-subsequent carboxymethylation reaction; Ap-CIS-PCL NPs, Ap-functionalized polyethylene gylated-polycaprolactone encapsulating cisplatin nanoparticles.

five studies presented in Table III demonstrated innovative approaches to OC therapy by emphasizing the use of nanotechnology and miRNA-based strategies to target oncogenic miRNAs, sensitize drug-resistant cells, and enhance the precision and effectiveness of treatment.

miR-21 serves a role in therapy resistance in OCs, indicating its potential to regulate drug resistance via apoptosis. Furthermore, it serves an important role in the oncogenic process as indicated by its association with the high proliferation, low apoptosis, high invasion and metastatic potential of cancer cells. Whilst evaluating the potential of anti-miR-21 as a therapeutic strategy for countering the oncogenic effects of miR-21 in OC, studies have concurrently explored the enhancement of treatment outcomes through the efficient nanoparticle-based delivery of anti-miR-21 to cancer cells whilst minimizing off-target effects. Biodegradable porous silicon nanoparticles were engineered to encapsulate an anti-miR-21 locked nucleic acid payload (38). Additionally, these nanoparticles displayed a tumor-homing peptide that enabled targeted distribution. This targeting peptide, CGKRK, ensured that the nanoparticles accumulated primarily in the tumor environment. CGKRK is a tumor-tracking peptide discovered by phage display techniques and it shows high selective binding affinity to neovascular endothelial cells and tumor tissue, but not to non-tumorigenic cells (39). Another nanoparticle, redox-sensitive, Polyethylene (PEG)-shielded carboxymethyl polyethylenimine (PEI) nanogels were used as a delivery system for anti-miR-21 (39). These nanogels were designed to efficiently deliver the anti-miR-21 to the OC cells by modifying branched PEI, which involved PEGylation (PEG2k-PEI) for steric shielding, redox-sensitive crosslinking for nanogel synthesis (PEG2k-PEI-ss nanogels) and carboxymethylation (PEG2k-CMPEI-ss) to modulate the properties of the polymer. Another study aimed to develop a novel polymeric drug delivery system (DDS) using star-shaped glucose-core polycaprolactone-polyethylene glycol (Glu-PCL-PEG) block copolymer nanoparticles. This system was used to deliver cisplatin and locked nucleic acid anti-miR-214 to OC cells. The study confirmed that nucleolin-mediated endocytosis of the targeted polymeric DDS containing both cisplatin and anti-miR-214 A2780 R cells led to enhanced apoptosis (40).

Other studies with a specific focus on addressing relapse and multidrug resistance issues have assessed let-7b (41) and miR-484 (42). Both studies recognized tumor suppressors with the capacity to target a range of oncogenes and chemoresistance-related genes. let-7b has an important role in growth and proliferation and induces apoptosis of cancer cells by inhibiting cell cycle progression through pathways such as CYP2J2 regulation and Wnt/B-catenin pathway. Downregulation of let-7b levels in clinical OC has been linked to chemotherapy resistance, heightened proliferation, invasion and relapse in EOCs. The restoration of let-7b expression was pivotal as it can significantly heighten sensitivity to chemotherapy whilst inhibiting oncogenic pathways and thwarting chemoresistance mechanisms (41). To ensure effective delivery of let-7b to tumor cells, innovative nanoparticle systems (namely, hyaluronic acid-based nanoparticles and Glu-PCL-PEG nanoparticles) were used to act as versatile delivery vehicles adept at transporting nucleic acids like miRNA. The delivery of let-7b to tumor cells involved using HA-PEI as a delivery vehicle, which is a versatile system known for efficient nucleic acid delivery, including miR (41). The strategic combination of let-7b with these nanoparticles represents a multifaceted approach aimed at reprogramming the miR profile within tumor cells.

Another study that also assessed a tumor suppressor miRNA, provided mechanistic insights into how the delivery of miR-484 via exosomes impacted the tumor vasculature and chemotherapy sensitization (42). It revealed that miR-484 may serve a role in vessel normalization, which enhances the response of cancer cells to chemotherapy-induced apoptosis. Mechanistically, miR-484 may achieve this effect by simultaneously inhibiting the expression of VEGF-A in cancer cells and its corresponding receptors in endothelial cells. The research demonstrates how miR-484 and exosomal delivery contributed to vascular normalization and chemotherapy sensitization in OC.

Limitations. Despite the comprehensive nature of this systematic review, several limitations may affect the generalizability and applicability of the findings. First, this study was limited to the PubMed database, potentially excluding relevant studies indexed in other databases, such as Scopus, Web of Science or Embase. Second, the included studies varied widely in their methodologies, miRNAs investigated and therapeutic interventions used. This heterogeneity makes it challenging to draw definitive conclusions and compare results across

studies. Finally, while the review highlighted associations between miRNAs and treatment outcomes, detailed mechanistic insights were often lacking. Understanding the precise molecular mechanisms is crucial for the development of effective therapeutic strategies.

Conclusion. The present systematic review highlights the role of miRNAs in enhancing OC treatment outcomes. Half of the selected studies, which focused on understanding the impact of miRNAs on treatment outcomes, highlighted the presence of numerous unanswered questions, indicating significant unknowns about OC therapy from the perspective of miRNAs and the need for more comprehensive and ongoing research in this area. The present analysis reveals potential associations between miRNAs that may imply those miRNAs affect similar molecular pathways or biological processes in OC. However, further research is needed to confirm their significance and clinical implications. Furthermore, the innovative use of nanotechnology for targeted miR delivery represents a significant advancement in treatment precision. The findings of the present review demonstrate the intricate relationship between miRNAs and therapy outcomes, providing valuable insights for future research directions and the development of miRNA-based therapeutic interventions in OC management.

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Availability of data and materials

The data generated in the present study may be requested from the corresponding author.

Authors' contributions

HMARP designed the study, formulated the strategy for the literature search, performed the review and information extraction, confirmed the authenticity of the data, wrote and reviewed the article. PWN performed a systematic search, reviews and information extraction, confirmed the authenticity of the data, drafted and wrote the article. HP and SMH analyzed the data, drafted and reviewed the article. All authors have read and approved the final manuscript.

Ethics approval and consent to participate

Not applicable.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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