

**Review**

## **MicroRNA-mediated regulation of BCL-2 in breast cancer**

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**Abstract:** Breast cancer, a prominent form of cancer in women, arises from the inner lining of mammary glands, ducts, and lobules. With an approximate prevalence rate of 1 in 8 women, the standard treatment methods for this condition include the surgical excision of afflicted tissues, chemotherapy, radiation, and hormone therapy. The BCL-2 gene, also known as the B cell lymphoma gene, prevents apoptosis in eukaryotic cells. It is commonly found to be excessively active in many types of malignancies, such as leukemia, carcinomas, and breast cancer. The excessive expression of this gene has a role in the advancement of cancer by inhibiting apoptosis. Recent research emphasizes the function of microRNAs (miRs) in regulating the expression of BCL-2. These miRs can either decrease or increase the activity of specific genes involved in programmed cell death, thus making them potential targets for therapeutic interventions. This review explicitly examines the regulatory impacts of several miRs on BCL-2, thereby investigating their ability to trigger apoptosis and function as targeted treatments for breast cancer. By comprehending the complex interplay between miRs and BCL-2, it is possible to devise novel therapeutic approaches that can augment the efficacy of breast cancer treatments, thus eventually enhancing patient outcomes.

**Keywords:** oncology; miR; BCL-2 gene; breast cancer; targeted therapy

## 1. Introduction

Breast cancer (BC) is a complex and diverse condition marked by notable differences among those affected, thus posing a considerable obstacle in the development of successful therapies [1,2]. Notwithstanding the intricacy involved, improvements in diagnostic technologies have decreased the mortality rates related to BC [3,4]. Further advancements in the timely identification, assessment, and mitigation of BC are essential to enhance the survival rates [5–7]. BC is mainly caused by unregulated cell growth in the inner lining of mammary glands and ducts [8]. The uncontrolled growth of cells is frequently aided by the suppression of apoptosis, which is a biological process controlled by the BCL-2 protein family [9]. Conventional BC therapies include hormone therapy, surgical procedures, chemotherapy, and radiation therapy [10]. Although these treatments can yield positive results, they frequently come with notable adverse effects such as post-operative infections, sensory impairments, toxicities, and drug resistance [11]. The intricate origin of BC encompasses various phases, including tumor initiation, development, metastasis, invasion, angiogenesis, and recurrence [12]. Disturbances in cellular and molecular signaling networks mark each stage. These characteristics emphasize the necessity for more focused and less harmful therapeutic approaches [13].

Among the several genetic variables implicated in BC, the BCL-2 gene emerges as a pivotal controller of programmed cell death (apoptosis) [14]. BCL-2, a proto-oncogene, acts as an inhibitor of cell death and is a member of a protein family with essential responsibilities in regulating programmed cell death [15]. The change in a chromosomal location, t(14;18), which is found in certain types of cancer of the lymphatic system, such as non-Hodgkin's lymphoma, results in the over-production of the BCL-2 protein that aids cancer growth [16]. Additionally, this upregulation has been detected in many solid malignancies, including BC [17]. In addition to its involvement in cancer, the BCL-2 family of proteins regulates apoptosis, tissue formation, and immunological responses to pathogens [18]. Mammals possess more than twelve fundamental proteins in the BCL-2 family, which exhibit structural resemblances to BCL-2 and play several crucial functions in biological processes, such as controlling programmed cell death [19].

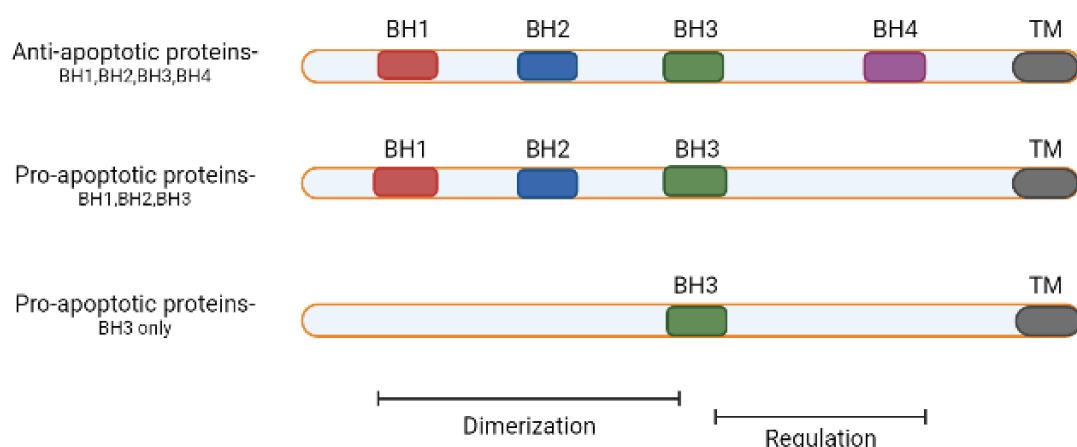
Recent studies have emphasized the substantial influence of microRNAs (miRs) in the control of BC [20–22]. miRs are tiny, single-stranded RNA molecules that indirectly affect physiological activities and directly regulate gene transcription [23]. miRs can either enhance or inhibit gene expression depending on their biological roles, thereby functioning as either tumor suppressor miRNAs (tsmiRs) or oncogenic miRNAs (oncomiRs) [24]. The dysregulated expression of miRs has been detected at several phases of BC, ranging from the early stages of tumor development to cell death [25]. By influencing critical processes such as cell proliferation, apoptosis, and cancer cell metastasis, TsmiRs and oncomiRs are essential in BC control [26].

Recent research suggests that miRs have a role in regulating the expression of BCL-2, thus indicating that manipulating miRs could potentially increase apoptosis in BC cells [27,28]. This offers a hopeful treatment approach, as miRs that decrease the expression of BCL-2 can counteract one of the main ways BC cells avoid programmed cell death [29]. By prioritizing the regulatory correlation between miRs and BCL-2, it is possible to devise novel therapeutic approaches that are more specific and potentially less harmful than conventional treatments [30]. Implementing these measures can greatly enhance the treatment outcomes for patients with BC. This review emphasizes the possibility of miR-based therapeutics as a new and successful to treat BC by studying the different miRs that control BCL-2 expression and their ability to trigger apoptosis. By gaining a

more profound comprehension of the miR-BCL-2 regulatory axis, we can devise inventive therapeutic approaches that augment the effectiveness of BC treatments and eventually boost the patient outcomes.

## 2. BCL-2 family proteins in apoptosis

The BCL-2 protein family is crucial in controlling apoptosis, which involves maintaining a careful balance between cell survival and programmed cell death (PCD) [31]. This family includes substances that prevent and promote apoptosis, thus demonstrating its essential role in maintaining cellular balance [32]. BCL-2 proteins, which vary in size from 20 to 37 kDa, have substantial similarities in their amino acid sequences [33]. They are categorized into three primary classifications, depending on their functions in apoptosis. Antiapoptotic proteins can prevent apoptosis and have BCL-2 homology domains BH-1, BH-2, BH-3, and BH-4 [34]; notable members of this class include BCL-2, BCL-W, MCL1, BCL-XL, BCL-2A1, and BCL-B. Pro-apoptotic proteins promote apoptosis and typically possess three BH domains [35]; the proteins BAX, BAK, and BOK are noteworthy members of this category. The pro-apoptotic class of proteins is characterized by its diversity and consists solely of proteins with the BH-3 domain (i.e., BH3-only proteins) (Figure 1); some examples of proteins in this class include BIK, BID, BAD, BIM, BMF, NOXA, HRK, and PUMA [36,37]. These proteins can attach to and control antiapoptotic BCL-2 proteins, resulting in the initiation of apoptosis.



**Figure 1.** Sequence homology of BCL-2 protein.

BCL-2 proteins primarily function on the outer membranes of the mitochondria and the endoplasmic reticulum [38]. Their location and activity are facilitated by a hydrophobic anchor located near the C-terminal of the BCL-2 homologous region. BCL-2 proteins typically adopt a structural conformation characterized by  $\alpha$ -helical hairpins and tend to form heterodimers [39]. Heterodimerization occurs when the BH3 region of a pro-apoptotic protein binds to the hydrophobic groove of an antiapoptotic protein, which contains BH1, BH2, and BH3 domains. The BH3 domain plays a crucial role in promoting apoptosis, whereas antiapoptotic proteins need numerous BH domains to successfully carry out their action [40]. Mitochondrial Outer Membrane Permeabilization

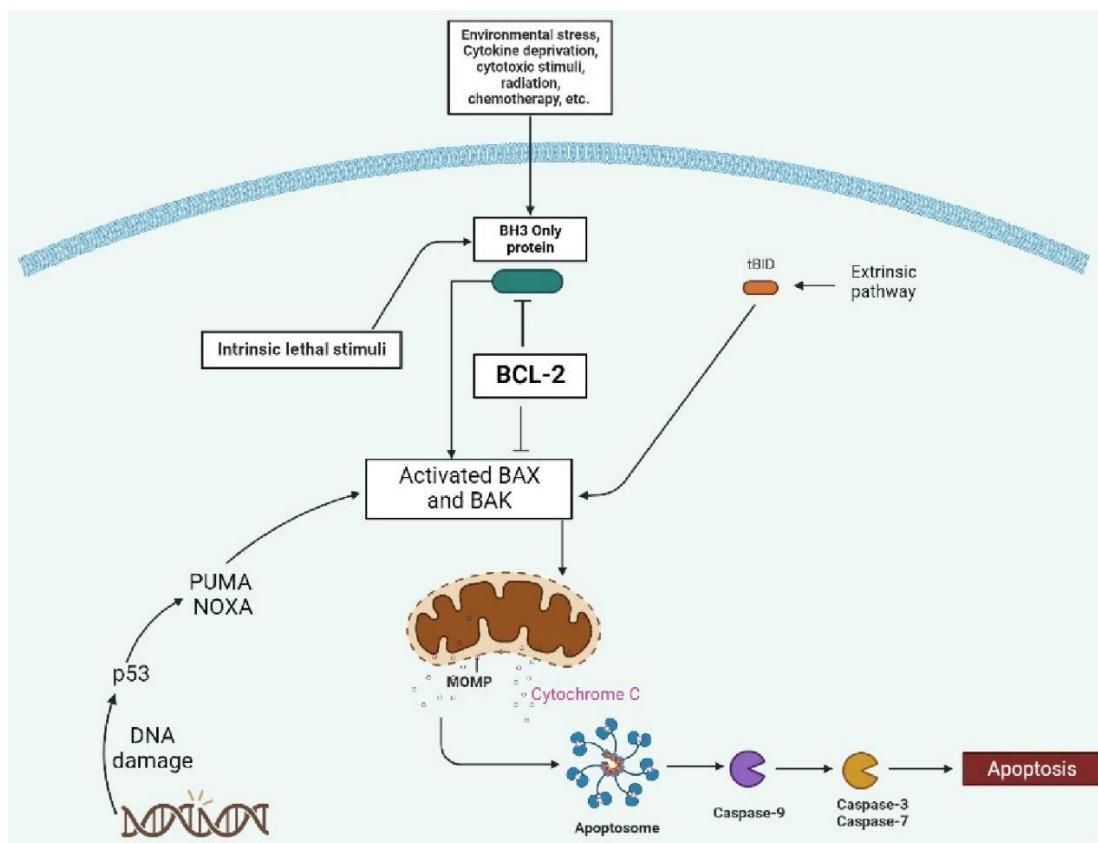
(MOMP) is a crucial mechanism that regulates apoptosis by BCL-2 proteins [41]. MOMP causes the liberation of apoptotic components, including cytochrome c and Apoptosis Promoting Factor (APF), from the mitochondria into the cytoplasm [42]. The caspase cascade, which causes cells to die, starts with this occurrence. Antiapoptotic proteins are promoted by pro-apoptotic proteins, such as BAX and BAK [43]. In addition to inhibiting antiapoptotic proteins, BH3-only proteins can enhance the activation of BAX and BAK. This dual action ultimately leads to the promotion of apoptosis [44].

### 3. miRs regulating BCL-2

miRs are small RNA molecules which naturally occur within an organism and have a single strand [23]. miRs are synthesized from double-stranded DNA by RNA polymerases II and III, thus forming primary miRNAs (pri-miRs) [45]. The enzyme Drosha, which belongs to the RNA POL III family, processes these pri-miRs that produce precursor miRNAs (pre-miRs) in the nucleus [46]. Pre-miRs are subsequently transported to the cytoplasm by Exportin-5, which is a protein that relies on GTP for its function [47]. Within the cytoplasm, the enzyme Dicer, which belongs to the RNA POL III family, trims pre-miRs to produce mature miRs [48]. These miRs are generally around 20–22 nucleotides long. The mature miRs are integrated into the RNA-induced silencing complex (RISC), which aids in breaking target miRs, thus suppressing gene expression [49]. When miRs attach to the 3' untranslated region and 5' untranslated region of target miRs, it leads to the inhibition of translation, which effectively inhibits gene expression. miRs participate in diverse biological processes, such as cell proliferation, cellular specialization, morphogenesis, and apoptosis [50]. Figure 2 demonstrates that miRs selectively cut target-specific mRNAs to prevent non-specific binding and control these biological processes. Significantly, a solitary miR can control numerous genes, while a solitary gene can be subjected to the influence of multiple miRs.

Recent research has extensively concentrated on identifying certain miRs linked to cancer apoptosis and their corresponding target genes [51]. Tumor suppressor miRs, frequently downregulated in cancer, are crucial in impeding tumor growth by negatively influencing oncogenes or genes that control cell differentiation and apoptosis [52]. Tumor-suppressing miRs can be downregulated due to deletions, epigenetic silencing, or a lower expression of transcription factors. Due to their crucial involvement in multiple biological processes, changes in miR expression are associated with a wide range of human illnesses, including cancer [53]. Research has demonstrated that malignant tumors and tumor cell lines display extensive and abnormal miR expression compared to normal tissues [54]. During carcinogenesis, miRs play a crucial role in regulating apoptosis. Cancer cells can modify miRs to govern cell survival during cancer development [55].

The intrinsic pathway is a well-researched mechanism of apoptosis [56]. In this process, cytochrome c is released from the mitochondria and moves into the cytoplasm. Once in the cytoplasm, it triggers the activation of caspases by interacting with the apoptotic peptidase activating factor-1 [57]. Hence, miRNAs that govern these molecules can profoundly impact the efficacy of anticancer medications [58]. A comprehensive understanding of these regulatory systems is crucial to identify and develop effective treatment targets for BC [59].



**Figure 2.** The intrinsic route initiates with either post-translational activation or BH3-only protein induction, which inactivates several BCL-2 family members. As a result, BAX and BAK activation are no longer inhibited, which encourages apoptosis. It's possible that specific BH3-only proteins, such as PUMA and BIM, can also activate BAX and/or BAK (as shown by the dotted line). Once activated, BAX and BAK encourage the release of cytochrome c and mitochondrial fission, which causes APAF1 to become an apoptosome and triggers caspase-9 to trigger caspase-3. The cell is destroyed by caspase, which cleaves several substrates and activates DNases. By passing the mitochondrial step, the extrinsic route can immediately activate caspase-8, which causes caspase-3 to activate and destroy cells.

Many researchers have aimed to find miRs linked to cancer apoptosis and their corresponding target genes [60]. Table 1 provides a comprehensive list of several miRs that control the BCL-2 family, emphasizing their potential as targets for therapeutic interventions in BC. By manipulating the expression and function of these miRs, it would be feasible to augment the efficacy of BC treatments, enhance the patient outcomes, and devise novel therapeutic approaches. The comprehensive comprehension of miR control of BCL-2 and its family members offers vital clues that underlie BC and presents new possibilities for targeted therapies [44].

**Table 1.** Different miRNAs up or downregulating BCL-2, particularly in BC.

Target gene	miR	Regulation	Reference
BCL-2	miR-7	Inhibits target BCL-2 gene directly	[61]
BCL-2	miR-15a/16	Inhibits target BCL-2 gene directly	[62]
BCL-2	miR-21	Activates target BCL-2 gene directly	[63]
BCL-2	miR-24-2	Inhibits target BCL-2 gene directly	[64]
BIM	miR-24-3p	Inhibits target BIM gene directly	[65]
BCL-2	miR-31	Inhibits target BCL-2 gene directly	[66]
BCL-2	miR-34a	Inhibits target BCL-2 gene directly	[67]
BCL-2	miR-93	Inhibits target BCL-2 gene directly	[68]
BAX		Inhibits target BAX gene directly	
BCL-2	miR-106	Activates target BCL-2 gene directly	[69]
BCL-2	miR-122-5p	Inhibits target BCL-2 gene directly	[70]
BCL-2	miR-125b	Inhibits target BCL-2 gene directly	[71,72]
BAK1		Inhibits target BAK1 gene directly	
BCL-2	miR-134	Inhibits target BCL-2 gene directly	[73]
BAX	miR-149-5p	Inhibits target BAX gene directly	[74]
BIM	miR-181b	Inhibits target BIM gene directly	[75]
BAD	miR-192-5b	Inhibits target BAD gene directly	[76]
		Inhibits target BCL-2 gene indirectly	
BCL-2	miR-195	Inhibits target BCL-2 gene directly	[77]
BCL-XL	miR-203a-3p	Inhibits target BCL-XL gene directly	[78]
	miR-203b-3p	Inhibits target BCL-XL gene directly	
BIM BAX BAK	miR-221	Inhibits target BIM gene directly	[79]
BIM	miR-222	Inhibits target BIM gene directly	[80]
BCL-2	miR-451	Inhibits target BCL-2 gene directly	[81]
BCL-2	miR-489	Inhibits target BCL-2 gene directly	[82]
BAX*	miR-663b	Activates target BCL-2 gene directly	[83]

The table provides a concise overview of different miRs that control the expression of BCL-2 and other genes involved in programmed cell death in BC. Several miRs, including miR-7, miR-15a/16, miR-24-2, miR-31, miR-34a, miR-93, miR-122-5p, miR-125b, miR-134, miR-195, miR-451, and miR-489, directly hinder the expression of the BCL-2 gene, which is known to facilitate programmed cell death, and hence function as tumor suppressors. Additional miRNAs, such as miR-21 and miR-106, stimulate the activation of BCL-2, which hinders programmed cell death and potentially enhances the ability of cancer cells to survive. In addition, miRs such as miR-93, miR-125b, and miR-192-5b can target both pro-apoptotic genes BAX and BAK1, thus suggesting the existence of an intricate regulatory network. miR-149-5p, miR-181b, miR-221, and miR-222 precisely target genes such as BIM and BAD, thereby exerting an additional influence on the pathways that regulate cell death (apoptosis). Remarkably, miR-663b stimulates the activation of BCL-2, which contrasts with its typical suppression by other miRs. The varied regulatory impacts of these miRs on BCL-2 and the associated genes emphasize their potential as therapeutic targets to manipulate apoptosis in breast cancer, thus providing opportunities to enhance cancer cell death and overcome resistance to traditional treatments.

Numerous studies have shown that miRs significantly affect the upregulation or downregulation of BCL-2 family proteins, which is pivotal in regulating apoptosis in breast cancer. Several principal miR species have been identified that interact with BCL-2 to influence tumor cell viability directly. For example, miR-34a is a recognized tumor suppressor often downregulated in breast cancer and has been shown to post-translationally control BCL-2 by binding to its 3' UTR [84]. This interaction facilitates the degradation of BCL-2, thereby initiating apoptotic pathways that result in the death of tumor cells. Similarly, miR-15a/16, which is often deleted or downregulated in several neoplasms, including breast cancer, diminishes BCL-2 levels and promotes apoptosis [85]. Conversely, some miRs, such as miR-21, have been identified to elevate BCL-2 levels, thus enhancing chemoresistance by facilitating the survival of cancer cells [86]. The pro-survival effect is particularly significant in breast cancer, where miR-21 is overexpressed and linked to an unfavorable prognosis. Furthermore, it has been shown that miR-125b directly interacts with BCL-2, thereby altering the apoptotic threshold to promote cancer cell survival [72]. These miRs target BCL-2 within a complex signaling network that, in addition to influencing the mitochondrial integrity, also governs essential apoptotic events, including the release of cytochrome c and the activation of caspases. The deregulation of these miRs in breast cancer may indicate their potential as biomarkers for early diagnoses and therapeutic approaches [87]. Clarifying the complex mechanisms via which miRs regulate BCL-2 and its associated family members is crucial to develop novel miRNA-based therapeutic approaches aimed at inducing tumor cell apoptosis and surmounting resistance to standard treatments.

The fundamental characteristics of miR activities suggest a complex interaction with upstream regulators, co-activators, co-repressors, and post-transcriptional regulators that influence miRNA synthesis, stability, and functionality. G protein-coupled receptors may promote and inhibit miR transcription, as other transcription factors such as p53 and MYC are implicated in the transcriptional activation or repression of apoptosis-related pathways and gene networks [88]. An interesting research showed that other epigenetic changes, including DNA methyltransferases and histone-modifying enzymes, might influence the promoter of miRNA genes, therefore either silencing or activating specific miRs [89,90]. Moreover, RNA-binding proteins, including Argonaute (AGO) proteins, are essential to form the RNA-induced silencing complex, which is necessary for target recognition with miR and facilitates either mRNA destruction or translational repression [91]. Furthermore, crosstalking ceRNAs, such as lncRNA and circRNA, function as miRNA sponges, hence modulating the availability of miR to its target mRNAs, which are reviewed in the literature [92]. The several levels of control illustrate the intricacy of miRNA-mediated gene silencing and emphasize the need to explore upstream regulators and co-factors to effectively harness miRNAs as therapeutic targets in breast cancer.

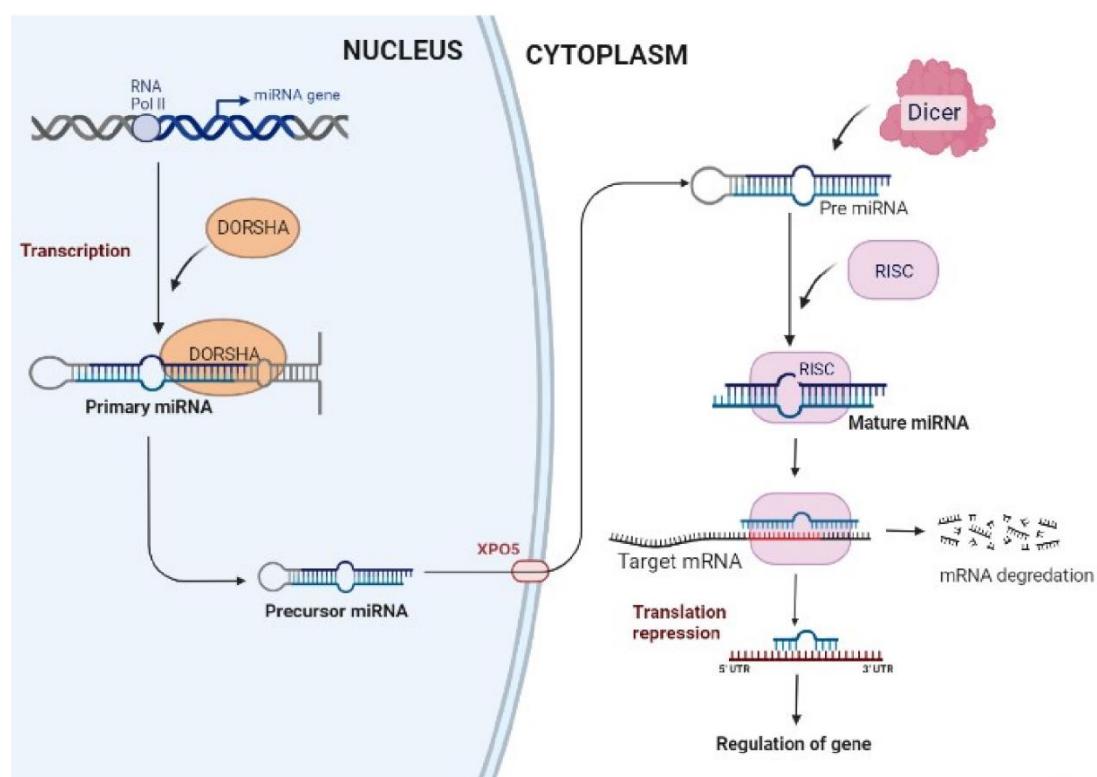
#### 4. BCL-2 as a BC target

Apoptosis is essential for the development and upkeep of multicellular creatures, as it eliminates cells that are damaged, aged, or affected by autoimmune conditions [93]. The last stages of apoptosis entail initiating cell death proteases, which trigger a series of protein breakdown processes, including effector caspases (Figure 3). Cancer cells can avoid apoptosis, which allows them to survive in challenging conditions, unlike healthy cells. They accomplish this through several means, such as modifying the balance between apoptotic molecules. Significantly, the balance is linked to the

proliferation of tumors and their capacity to withstand the effects of drugs such as cisplatin (DDP) and paclitaxel [94].

Cancer cells can adjust the equilibrium between pro-apoptotic and antiapoptotic factors to avoid undergoing apoptosis [95]. Research has demonstrated that the BCL-2 protein is frequently expressed at higher levels in the cytoplasm of fully developed BC cells. At the same time, its expression is lower in less specialized cancer cells [96]. These findings indicate that the modulation of BCL-2 is vital in controlling apoptosis and suppressing tumor growth, thus impacting the destiny of BC cells [97]. Undifferentiated BC cells are more susceptible to apoptosis compared to well-differentiated cells [98].

The BCL-2 and BCL-XL families have attracted interest as targets for therapy because of their essential functions in controlling cell death. Scientists have investigated different approaches to regulate apoptosis, such as retroviral systems, alterations to the localization machinery, antibodies that impede action, RNA interference (RNAi), and miRNAs [99]. Nevertheless, BH3-mimetic drugs have been demonstrated to be the most efficacious strategy to specifically target the BCL-2 family. Comprehending the molecules implicated in apoptosis is essential advance novel or enhanced chemotherapies [100].



**Figure 3.** miRNA biogenesis and functions. RNA polymerase II synthesizes primary miRNAs (Pri-miRNAs) from miRNA transcripts. Drosha and Pasha work together in the nucleus to trim Pri-miRNAs into precursors miRNA (Pre-miRNAs). Exportin 5 transports pre-miRNAs from the nucleus to the cytoplasm, where Dicer processes them into mature miRNAs. After maturation, these miRs become part of the RNA-induced silencing complex (RISC), which may be used to silence genes encoding proteins by interacting with their 3'-UTRs or their messenger RNAs (mRNAs).

miRs' swift post-transcriptional impacts and capacity to control numerous target genes, including transcription factors, may present superior therapeutic possibilities to address neurological illnesses compared to medications that focus on a solitary gene. Nevertheless, the specific cells and the physiological or pathological circumstances in which the miR family affects the BCL-2 family proteins still need to be better understood. Although pretreatment with miRs has shown efficacy in animal models' cerebral ischemia, conducting tests on these treatments is still essential as a vital part of developing a therapy for neurological illnesses. Several miRs are being tested in clinical trials for liver illnesses, thereby indicating that creating and administering miR therapeutics for new disease situations or targets will be possible. However, delivering miR treatments to the central nervous system (CNS) presents substantial difficulties and remains a crucial barrier to therapeutic use. However, specific challenges about miR-based therapeutics remain pertinent and must be addressed to enable their practical implementation in clinical settings: miRs exhibit instability in bodily fluids due to degradation by nucleases; thus, developing ways to enhance their stability is necessary. Several chemical changes, including 2'-O-methylation, phosphorothioate backbones, and locked nucleic acids (LNAs), have been shown to improve the stability of miR while preserving its biological activity. Thus, encapsulation in lipid nanoparticles, polymeric carriers, or exosomes offers enhanced protections against degradation while facilitating targeted administration [101,102]. The ultimate problem pertains to off-target effects that arise from the ability of miRs to bind to several mRs since they just use a segment of their sequence for this interaction, potentially leading to gene silence in unintended targets. Recent advancements in computational target prediction and experimental validation enhance the sequence selectivity and minimize off-target effects. Moreover, alterations in the seed area of miR mimics and antagomiRs have improved the targeting efficacy [103]. A further issue in delivering miRs to the CNS is that the blood-brain barrier impedes this distribution. Recent techniques using nanoparticles, liposomes, and Adeno-Associated Viruses have shown enhanced CNS uptake by receptor-mediated transcytosis and direct stereotaxic injection [104]. Despite the positive outcomes demonstrated in preclinical investigations, additional advancements in the delivery methods, dose regulation, and safety concerns remain important. Addressing these difficulties will be essential to realize the full potential of miR therapies in neurological and other illnesses.

## 5. Future research directions

Notwithstanding these advancements, several challenges and inquiries remain unresolved, thus continuing to stimulate researchers' interest. A comprehensive knowledge of the context-dependent regulation of miRs and the influence of various cellular and physiological conditions on their targets, including the BCL-2 family, is essential. Comprehending miR's biology and regulation may reveal novel gene expression regulatory mechanisms and potential therapeutic targets. Nonetheless, the precise delivery mechanisms for miR-based therapeutics remain in the developing phase, particularly for targeting the CNS due to obstacles such as the blood-brain barrier. Cancer-targeted nanoparticles, exosome-based drug delivery systems, and ligand-conjugated carriers have promise; nevertheless, more research is necessary to improve the targeting efficacy and minimize adverse effects. Comprehensive clinical trials are required to evaluate miR therapeutics' long-term safety profiles and potential immune responses. Concurrently, creating novel miR bioinformatics resources to predict and experimentally validate the targets of these therapeutics is essential to reduce the off-target

effects. From a translational perspective, using miRs with conventional chemotherapy, radiation, and immunotherapy may provide synergistic benefits and reduce resistance in certain aggressive malignancies. Moreover, discovering miR expression patterns in patients may facilitate the establishment of biomarkers for diagnosis, prognosis, and therapy response monitoring, thus representing a crucial advancement toward personalized treatment strategies. The observed gaps provide avenues for future research, thus expanding the therapeutic uses of miRs and presenting novel strategies for conventional challenges in treating cancer and neurological illnesses. This review emphasizes the innovative role of miRNA regulation and its intricate involvement in apoptosis, thus offering guidance for future research to leverage these insights for therapeutic advancements.

## 6. Conclusions

The primary objective of BC research has been to comprehend the etiology and mechanisms underlying the neoplastic alterations that impact the epithelial tissue of the mammary gland. While post-transcriptional mechanisms are important, recent research has demonstrated that miRs are crucial in regulating BC. Lately, the significance of BCL-2 in BC has been acknowledged, as miRs can either suppress or stimulate cancer development. Studies suggest that cancer cells display varying levels of miRs, which can either increase or decrease the expression of the BCL-2 protein family. This control has a significant effect on the prediction of the course of a disease and assists in ensuring consistent levels of gene expression in various types of cancers. Scientists have discovered that monitoring the level of BCL-2 expression can be utilized to monitor a patients' progress and identify the most optimal therapy approaches. While numerous miRs have been found that can selectively target and influence specific genes differently, further investigation is required to establish definitive findings and comprehensively comprehend the function of miRs in controlling the BCL-2 family proteins in treating BC.

## Author contributions

TA and KMS designed the study; KM performed data collection and literature analysis; SV prepared figures and tables; TA and KMS prepared initial draft; KMS contributed to review and editing. All authors approved the final version of the manuscript.

## Use of AI tools declaration

The authors declare they have not used Artificial Intelligence (AI) tools in the creation of this article.

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The institutional ethics committee of the Bharath Institute of Higher Education and Research approved all the research protocols.

## Conflict of interest

The authors declare no conflicts of interest.

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