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Review

microRNAs associated to anthracycline-induced cardiotoxicity in women with breast cancer: A systematic review and pathway analysis

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ABSTRACT

Background: Cardiotoxicity is a common and serious adverse effect of anthracycline therapy in breast cancer patients. The current criteria for cardiotoxicity are based on imaging and cardiac biomarkers. However, there is a need for new biomarkers to help with early diagnosis. MicroRNAs (miRNAs) are small non-coding RNA molecules that play an important role in the regulation of gene expression. Several miRNAs have been associated with cardiovascular diseases and are biomarkers under investigation for cancer treatment-related cardiotoxicity.
Methods: We performed a systematic literature search of Medline/PubMed, Cochrane Central Register of Controlled Trials, Scopus, Lilacs, Web of Science and Embase, until April 2020. Cohort studies that reported miRNA biomarkers in breast cancer patients with anthracycline-induced cardiotoxicity and non-cardiotoxicity patients were included. Moreover, we searched the miRTarBase for experimentally validated miRNA-target interactions.
Results: Among the 209 studies retrieved, five fulfilled the inclusion criteria. Let-7f, miR-1, miR-20a, miR-126 and miR-210 were validated in two population-based cohorts. The pro-angiogenic miRNAs let-7f, miR-20a, miR-126 and miR-210 were significantly down-regulated in epirubicin-cardiotoxicity when compared to the non-cardiotoxicity group. miR-1 has been shown to provide diagnostic and prognostic information in the setting of myocardial infarction, but changes in its levels are controversial in doxorubicin-treated breast cancer patients with cardiotoxicity. Reactome pathways relevant to cardiotoxicity were found from the target genes for let-7f, miR-1, miR-20a, miR-126 and miR-210 at miRTarBase.
Conclusion: The data suggest that let-7f, miR-1, miR-20a, miR-126 and miR-210 are associated with anthracycline-based cardiotoxicity during chemotherapy in breast cancer patients.

1. Introduction

Breast cancer is the most common female cancer and is the leading cause of cancer-related deaths [1]. The World Health Organization has estimated that 627,000 women died of breast cancer in 2018, which represents 15 % of all female cancer deaths [2]. Anthracyclines, such as doxorubicin and epirubicin, are commonly used in the treatment of breast cancer and have significantly improved the disease-specific survival [3]. However, this chemotherapy regimen has been associated with adverse cardiovascular effects and increased cardiovascular mortality, especially in older women. In this sense, appropriate risk factor stratification is essential for early diagnosis and the prevention of cardiovascular disease [4].

The recommendations outlined in recent studies for identify early myocardial injury in cancer patients treated with anthracyclines and/or anti-HER2 (human epithelial growth factor receptor 2) therapy are based on cardiac imaging and cardiac biomarkers [5,6]. A decrease in left ventricular ejection fraction (LVEF) is the most widely recognized echocardiographic profile to cardiotoxicity evaluation. However, LVEF sensitivity is limited for the detection of subtle myocardial dysfunction [7]. Troponins and brain natriuretic peptides, circulating markers of cardiac disease onset, have progressively emerged as useful biomarkers

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to identify patients who are more prone to developing myocardial dysfunction and may be helpful in detecting subclinical cardiotoxicity during patient follow-up [8,9]. However, circulating levels of these biomarkers increase only after tissue damage has occurred.

Both *in vitro* and *in vivo* models have been focused on the association of microRNAs (miRNAs) in anthracyclines-induced toxicity [10]. miRNAs are a class of small noncoding RNAs (21–25 nucleotides), which regulate posttranscriptional gene expression by either inhibiting messenger RNA (mRNA) translation or promoting its degradation [11]. They are involved in many important biological processes such as cellular development and cellular signaling, cell proliferation, cell-to-cell communication, and apoptosis. Importantly, abnormal miRNA expression has been associated with the initiation and progression of pathological conditions, including cardiac diseases [12].

Doxorubicin-treated rats showed significant increase in plasma levels of miR-1, miR-133a, and miR-208 [13,14]. Specifically, miR-133a levels rapidly increased during acute myocardial infarction and were found to be more sensitive than cardiac troponin T [15]. Moreover, higher plasma levels of miR-34a and miR-122 were found in 25 breast cancer patients receiving anthracycline-based chemotherapy after treatment [16]. Although these previous studies have shown that miRNAs represent potential biomarkers for cardiac diseases, further research is needed to investigate the possible involvement of miRNAs in anthracycline-induced cardiotoxicity [17]. Despite the clinical importance, many of the studies have focused on the use of preclinical animal models, which have limitations as predictors of human biology [18].

In the present study, the aim was to perform a systematic review to assess the differential expression levels of circulating miRNAs in breast cancer patients, in order to relate them to anthracycline-induced cardiotoxicity. We also aimed to carry out pathway analysis to investigate molecular pathways related to these miRNAs.

2. Materials and methods

This systematic review was designed and conducted in accordance with the Cochrane Handbook recommendations [19]. Results were reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement [20]. Supplementary material 1 shows the PRISMA checklist. The protocol of the current study was registered in the International Prospective Register of Systematic Reviews (PROSPERO) (http://www.crd.york.ac.uk/ PROSPERO, number CRD42020177833).

2.1. Search strategy

The search strategy was defined based on the PECO question: P (participants) = women with breast cancer treated with anthracyclines; E (exposure) = cardiotoxicity; C (control) = women with breast cancer treated with anthracyclines without cardiotoxicity; and O (outcome) = microRNA expression levels. A literature search was performed in the medical electronic databases Medline via PubMed (Medical Literature Analysis and Retrieve System Online), the Cochrane Central Register of Controlled Trials (CENTRAL), CINAHL EBSCO (Cumulative Index to Nursing and Allied Health Literature), Scopus, LILACS via Virtual Health Library (VHL) (Latin American and Caribbean Health Sciences), Scientific Electronic Library Online (Scielo), ISI Web of Science: Core Collection and Embase until April 2020 to find studies that investigated the differential expression of miRNAs in breast cancer patients. The search included the Mesh terms 'breast neoplasms', 'cardiotoxicity', 'microRNA' and the entry terms. Supplementary material 2 describes the search strategy used for the PubMed database.

The same terms were used to search for clinical studies in Google Scholar, www.scholar.google.com/ and OpenGrey, www.opengrey.eu/. Searches were performed on the following dissertation/thesis databases: ProQUEST Dissertations & Theses Global, Federal University of Minas Gerais (https://repositorio.ufmg.br/), University of São Paulo (https://www.teses.usp.br/), Oswaldo Cruz Foundation - Fiocruz (https://portal.fiocruz.br/repositorio-institucional-arca), University of Brasilia (https://repositorio.unb.br/) and Federal University of Bahia (https://repositorio.ufba.br/ri/). All possibly relevant reports were considered for review, irrespective of language and date of publication. Reference lists of included articles were also checked to identify additional relevant citations.

2.2. Inclusion and exclusion criteria

Two authors working independently (J.D.P. and M.T.A.) performed the review of the titles and abstracts of all articles retrieved to evaluate eligibility for inclusion in this study. In cases of disagreement, a third investigator (K.B.G. or J.A.G.T.) contributed to the final decision.

Eligible studies were considered when they evaluated the differential expression of miRNA in breast cancer patients over 18 years old who received cancer therapy with anthracycline with or without cardiotoxicity. We excluded studies that did not present a proper non-cardiotoxicity group, or which were conducted on animal models/cell lines, or did not report the outcomes of interest. Therefore, we excluded reviews and meta-analyses.

2.3. Study selection and data extraction

The studies were retrieved from each electronic database and included on a single electronic library, and duplicates were removed using the EndNote® software. Two reviewers (J.D.P. and M.T.A.) independently collected the results using a standardized form. When consensus could not be achieved, a third reviewer (K.B.G. or J.A.G.T.) resolved the differences in data extraction. The extraction of data comprised: 1) characteristics of studies, such as author and year of publication; 2) the sample type (plasma, serum or tissue) that was evaluated; 3) miRNAs measured; 4) method of miRNA detection; and 5) the expression of miRNAs in each study group. Data from the exposure and control group were also collected.

2.4. Quality assessment of bias for each study

The risk of bias and methodological quality of the included studies was independently assessed by two reviewers (J.D.P. and M.T.A.) following the Newcastle-Ottawa quality assessment scale (http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp). This scale contains eight items, including representativeness of the sample in the exposed cohort, selection of the unexposed cohort, exposure by the type of measure used (e.g., secure records or structured interviews), how the outcome of interest was assessed, whether the follow-up of the study was long enough for the hypothesis of the results to occur, and if there was adequate follow-up of the cohorts. Stars are assigned to each completed item, with the highest possible score being nine. A score above six means that the study has high methodological quality. Importantly, we considered a p-value <0.05 to indicate a statistically significant difference in the expression of miRNAs when the cardiotoxicity and non-cardiotoxicity groups were compared, in at least two population-based cohorts.

2.5. Target gene search and pathway analysis

We searched the miRTarBase to find target genes for each of the five miRNAs identified in this systematic review, and considered their different names or aliases, as follows: let-7f (hsa-let-7a-5p), miR-1 (hsa-miR-1-3p), miR-20a (hsa-miR-20a-3p and hsa-miR-20a-5p), miR-126 (hsa-miR-126-3p and hsa-miR-126-5p), and miR-210 (hsa-miR-210-3p). miRTarBase was developed to provide comprehensive information on experimentally validated miRNA-target interactions [21]. For the pathway analysis, we considered only target genes that were experimentally validated by at least one of the validation methods that provide

strong evidence according to miRTarBase, namely reporter assay, western blot, and qPCR [21]. We manually retrieved the target genes for each miRNA (Table 3) and interrogated them for significant well-curated signaling pathways obtained from Reactome 2016 Human Pathway [22] sorted by p-value ranking <0.5 using Enrichr [23].

3. Results

3.1. Study selection

The flowchart of the strategy used to select studies for inclusion in this systematic review is shown in Fig. 1. The initial search identified 209 studies, of which 53 were excluded as they were duplicates or did not meet the eligibility criteria. Exclusion criteria were: studies that did not evaluate breast cancer therapy with anthracycline, experimental studies, review papers and meta-analyses. The remaining 156 articles were evaluated based on titles and abstracts. In this phase, the Kappa coefficient of agreement between the two investigators (J.D.P and M.T. A) was 0.862.

After reading the titles and abstracts, 133 studies were excluded for not fulfilling the inclusion criteria, and 23 potentially eligible articles were selected. Reasons for excluding studies were: participants aged <18 years old, patients who were not treated with chemotherapy with anthracyclines, studies conducted on animal models or cell lines, studies which did not evaluate microRNA levels, those which did not present a proper non-cardiotoxicity group, review papers and meta-analyses. Eligible studies evaluated miRNA expressions in breast cancer patients aged ≥18 years old and anthracycline-cardiotoxicity (cases) and breast cancer patients without this condition (control groups). However, following full text analysis, 18 studies were excluded due to the following reasons: did not evaluate cancer therapy with anthracycline (n = 4), did not present a non-cardiotoxicity group (n = 4), were conducted on animal models/cell lines (n = 5), or were not a primary study (n = 5). Finally, five articles that fulfilled the eligibility criteria were included in this systematic review [24–28].

3.2. Study characteristics and quality assessment

Among the five included studies, one was performed in a population from Italy [24], two from China [25,28], one from Brazil [26] and one from the United States of America [27]. One study [24] was included as two independent reports because the findings were described by the use of different anthracyclines (doxorubicin and epirubicin). The main characteristics of these articles are shown in Table 1.

The studies were designed as cohorts and evaluated the miRNA expression between anthracycline-induced cardiotoxicity and non-cardiotoxicity groups in plasma samples during the follow-up. In particular, Rigaud et al. [26] used data from the CECCY trial (NCT01724450) and Gioffre et al. [24] assessed results from the ICOS-ONE clinical trial (NCT01968200), to investigate miRNA expression as possible circulating markers of cardiotoxicity. One of the studies evaluated only triple negative breast cancer [28] and one excluded HER-2 positive breast cancer patients [26]. In four studies, the cardiac impairment was evaluated in one-year follow-up compared to the baseline, and also included evaluations during the treatment. Only one study [27] was considered as a short follow-up (after first infusion).

The most common parameter used to define cardiotoxicity was LVEF (assessed by echocardiography), which was considered in four studies. Only one study [24] evaluated the occurrence of cardiotoxicity by cardiac troponin (troponin I or T). Sample sizes ranged from 32 to 363 in the included studies. Collectively, these studies investigated a total of 708 subjects (cardiotoxicity, n = 76; non-cardiotoxicity, n = 632) and

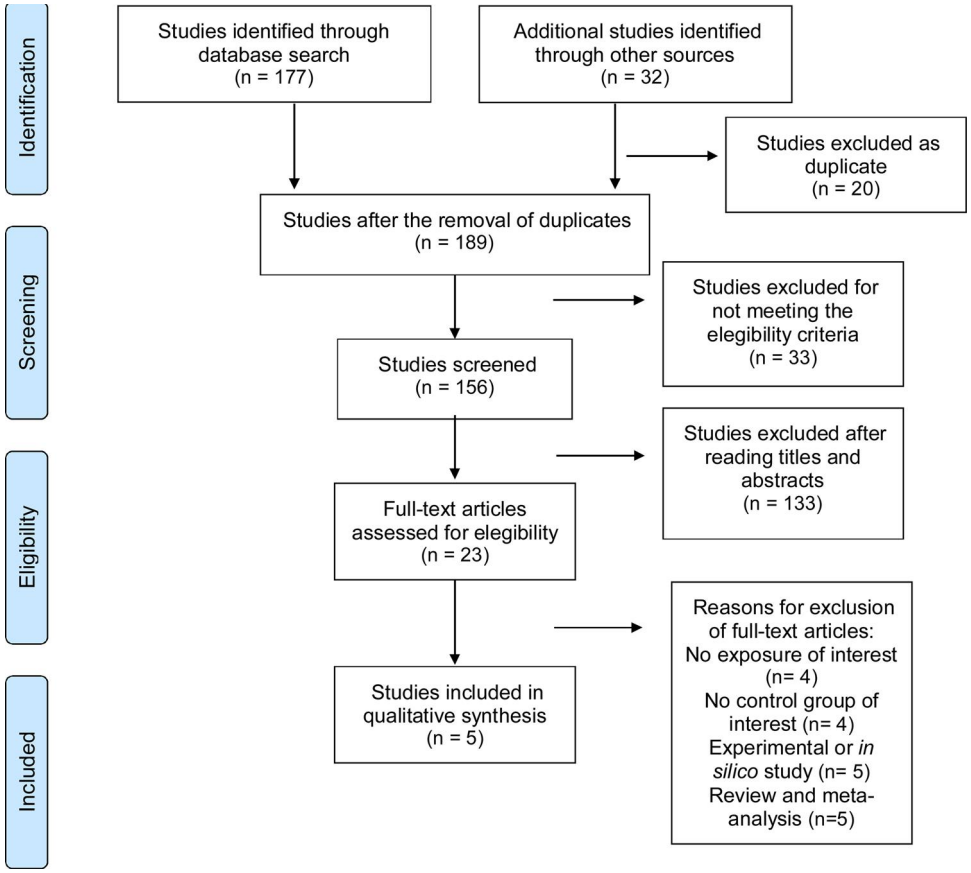

Fig. 1. Flowchart of the literature search and the study selection process.

the age ranged from 45.38 to 49.9 years old.

Among the included studies, anthracycline was used in combination with other cytotoxic agents. Todorova et al. [27] used doxorubicin (60 mg/m^2) with cyclophosphamide (600 mg/m^2), and Rigaud et al. [26] combined doxorubicin (cumulative dose of 240 mg/m^2) and cyclophosphamide (600 mg/m^2) followed by paclitaxel (80 mg/m^2 or docetaxel 75 mg/m^2). Only Rigaud et al. [26] excluded patients who used cardio-protective drugs, including ACE inhibitors, angiotensin II receptor blockers, or β-blockers. In another study, neoadjuvant chemotherapy included epirubicin (100 mg/m^2) and cyclophosphamide (600 mg/m^2), followed by docetaxel (75–100 mg/m^2) [28]. The same neoadjuvant chemotherapy regimen was employed in the study developed by Qin et al. [25], which also included HER2 positive patients who received trastuzumab treatment on demand (6 mg/kg, after docetaxel treatment). As mentioned above, one study evaluated the effects of both anthracyclines [24]. According to the clinical trial, epirubicin and doxorubicin have a median cumulative dose of 360 [270–360] and 240 [240–240] mg/m^2, respectively. During the trial, 63 % of the patients with breast cancer were treated with taxanes and 22.5 % with trastuzumab; 2 (0.8 %) patients were treated with a tyrosine-kinase inhibitor, imatinib [29].

Two studies used miRNA PCR arrays to assess the plasma miRNA profiles of patients with anthracycline-based therapy [24,27]. Only Gioffre et al. [24] selected miRNA candidates to validate the miRNA array results through single qPCR analysis. Two studies [25,26] selected miRNAs based on a literature search and performed RT-qPCR of these selected miRNAs, while another study did not report the candidate miRNA selection process [28].

Quality assessment of the included studies by using NOS for cohort studies is shown in Supplementary material 3. The median score of NOS was 8. All studies presented a high quality (low risk of bias) score ≥6.

3.3. *Differentially expressed miRNAs in breast cancer patients with anthracycline-induced cardiotoxicity and non-cardiotoxicity*

In two studies, the expression of miRNAs was only assessed at baseline [25,28]. However, one study assessed the expression of miRNAs at baseline and after the first dose of the drug [27], and the other studies performed the analysis at baseline and at least twice during the treatment [24,26].

The number of differentially expressed miRNAs found when comparing cardiotoxicity and non-cardiotoxicity patients varied in the studies from 3 [24] to 32 miRNAs [27]. Considering the five studies, we identified 40 differentially expressed miRNAs ($p < 0.05$) (Table 2). Among them, four miRNAs (let-7f, miR-20a, miR-126 and miR-210) showed concordant results in two studies [25,28], both being down-regulated in the cardiotoxicity group compared to the non-cardiotoxicity group. Only miR-1 showed discordant results, since it was reported as being down-regulated in cardiotoxicity patients in one study [27], and up-regulated in another [26].

Notably, one study found 26 miRNAs to be up-regulated in cardiotoxicity group when compared to non-cardiotoxicity subjects [27]. Also, three miRNAs have shown increased expression levels in cardiotoxicity patients in another study [24]. Moreover, two, three and one miRNAs were found to be down-regulated in anthracycline-treated breast cancer patients with cardiotoxicity in different studies [25,27] and [28], respectively.

The levels of 11 miRNAs (let-7b, miR-17-3p, miR-18a, miR-19b-1, miR-130a, miR-146a, miR-148a-3p, miR-208a, miR-208b, miR-296, miR-423-5p) were not different between the cardiotoxicity and non-cardiotoxicity groups ($p > 0.05$, data not show).

3.4. *Pathway analysis of target genes for the five differentially expressed miRNAs*

We used an approach focused on the target genes identified in the miRTarBase for the five miRNAs (let-7f, miR-1, miR-20a, miR-126 and miR-210) or their aliases. Notably, the number of target genes varied from 46 to 80 for the let-7f and miR-1, respectively (Table 3). We then performed pathway analysis using the target genes for each miRNA in order to search for molecular pathways which may be related to anthracycline-induced cardiotoxicity. Reactome pathways for each of the five miRNAs are shown in Fig. 2. Notably, some pathways are shared among the miRNAs, such as "Signal transduction R-HAS-162582" (let-7f, miR-1, miR-20a, and miR-126) and "Cellular responses to stress R-HAS-2262752" (let-7f, miR-20a, and miR-210) (Fig. 2).

4. Discussion

The search for novel biomarkers for the early detection of cardiotoxicity is clinically relevant to the detection of initial cardiac injury before the established dysfunction [17]. In this field, several studies have suggested that miRNAs are key mediators in modulating anthracycline-induced cardiac injury [13–16]. Circulating miRNAs can be potentially non-invasive biomarkers because they are stable in the circulation, resistant to degradation by nucleases, and can be detected before the onset of clinical symptoms [30].

However, studies have shown discordant results regarding miRNA expression profiles, which make the identification of the best miRNA candidates for cardiotoxicity assessment difficult [31]. Furthermore, significant heterogeneity was also observed in different studies related to cardiotoxicity criteria, the number of patients included and the number of miRNAs investigated [32]. Given the importance of miRNAs as diagnostic biomarkers in anthracycline-induced cardiotoxicity in breast cancer patients, we performed this systematic review of all studies that evaluated the differential expression of miRNAs in breast cancer patients. Notably, we found five miRNAs (let-7f, miR-1, miR-20a, miR-126 and miR-210) which were significantly deregulated in two cohorts of breast cancer patients with anthracycline-induced cardiotoxicity.

Let-7f is a pro-angiogenic miRNA, belonging to the let-7 family [27]. This molecule has angiogenic and endothelial function and influences the clinical prognosis for ischemic stroke in young subjects [13]. Let-7f facilitates the vascular network, acting directly on the transformed growth factors (TGF)-β and vascular endothelial growth factor (VEGF) [27]. It was also reported that low levels of let-7f expression were related to LVEF in dilated cardiomyopathy [27]. Thus, let-7f can reduce the risk of cardiac dysfunction and protect patients being treated with anthracyclines against cardiotoxicity [27]. Two Chinese studies included in this systematic review reported that breast cancer patients with anthracycline-induced cardiotoxicity had lower levels of let-7f compared to non-cardiotoxicity patients [25,28]. Both studies selected 14 miRNAs to be evaluated by RT-qPCR, based on their previously proposed pro-angiogenic role. Although miRNA candidates were selected from the literature or based on prior evidences, the validation of miRNAs on an independent cohort of subjects contributed to reinforce the use of miRNAs as minimally invasive screening and triage tools for subsequent diagnostic evaluation. Additionally, the authors enrolled patients undergoing chemotherapy with epirubicin (dose of 100 mg/m^2) and considered a follow-up period of 12 months. Cardiotoxicity was defined as a decrease in LVEF by 10 % from baseline to a final value less than 53 % in both studies. The similarity in the study design and miRNA detection method allows the reliable comparison of results. In addition, in these two studies, let-7f was found in plasma miRNA expression profiles from women with breast cancer in China, which limits the extension of the findings to other population groups. Importantly, replication in samples collected from other population groups is important to validate these findings.

Regarding the pathway analysis, LIN28A (Lin-28 Homolog A) was found among the target genes for let-7a-5p. Notably, Lin28a was recently shown to play a pivotal role in pathological cardiac hypertrophy in a mouse model [33]. Through the inhibition of microRNA let-7 maturation or directly binding to mRNAs to regulate their abundance

Table 2
Differentially expressed microRNAs in cardiotoxicity compared to non-cardiotoxicity patients in all studies included in the systematic review.

miRNA	Study [reference]	Change of expression in cardiotoxicity group	P-value	Time of miRNA evaluation	Potential role [Reference]
let-7f	Qin et al., 2018 [25]	Down	<0.001*	Baseline	Pro-angiogenic [59]
	Zhu et al., 2018 [28]	Down	0.001*	Baseline	
	Rigaud et al., 2017 [26]	Up	<0,05*	At cycle 2, 3 and 4	
miR-1	Todorova et al., 2017 [27]	Down	0.003*	After first dose	Arrhythmia, myocardial infarction, cardiac hypertrophy and heart failure [60]
	Gioffre et al., 2020 [24]a,b	Unreported	>0.05	Baseline	
miR-15a-5p	Todorova et al., 2017 [27]	Up	0.015*	After first dose	Diffuse myocardial fibrosis [61]
miR-15b-5p	Todorova et al., 2017 [27]	Up	0.029*	After first dose	Arteriogenesis and angiogenesis [62]
miR-16-2-3p	Todorova et al., 2017 [27]	Up	0.008*	After first dose	Sympathetic denervation and PPARγ activation [63]
miR-16-5p	Todorova et al., 2017 [27]	Up	0.016*	After first dose	Cardiac insufficiency [64]
miR-17-5p	Qin et al., 2018 [25]	Down	0.003*	Baseline	Pro-angiogenic, acute myocardial infarction) [65] [66]
	Zhu et al., 2018 [28]	Down	0.332	Baseline	
miR-19a	Qin et al., 2018 [25]	Down	0.126	Baseline	Pro-angiogenic, acute myocardial infarction) [65] [66]
	Zhu et al., 2018 [28]	Down	0.023*	Baseline	
miR-20a	Qin et al., 2018 [25]	Down	<0.001*	Baseline	Pro-angiogenic [67]
	Zhu et al., 2018 [28]	Down	0.040*	Baseline	
miR-23b-3p	Todorova et al., 2017 [27]	Up	0.041*	After first dose	Cardiac insufficiency [64]
miR-25-3p	Todorova et al., 2017 [27]	Up	0.006*	After first dose	Myocardial Infarction [68]
miR-28-3p	Todorova et al., 2017 [27]	Up	0.008*	After first dose	Type 2 diabetes mellitus [69]
miR-30d-5p	Todorova et al., 2017 [27]	Up	0.034*	After first dose	Myocardial infarction [70]
miR-34a-5p	Todorova et al., 2017 [27]	Up	0.002*	After first dose	Cardiotoxicity and apoptosis with the use of anthracyclines [71]
	Gioffre et al., 2020 [24]a,b	Unreported	>0.05	Baseline	
miR-92a	Qin et al., 2018 [25]	Down	0.882	Baseline	Pro-angiogenic [72]
	Zhu et al., 2018 [28]	Down	0.160	Baseline	
miR-122-5p	Todorova et al., 2017 [27]	Up	0.019*	After first dose	Acute coronary syndrome, severity of coronary diseases [73,74]
	Gioffre et al., 2020 [24]a	Up	0.007*	Baseline	
	Gioffre et al., 2020 [24]b	Up	0.50	Baseline	
miR-126	Qin et al., 2018 [25]	Down	<0.001*	Baseline	Pro-angiogenic [75]
	Zhu et al., 2018 [28]	Down	0.020*	Baseline	
miR-133a-3p	Todorova et al., 2017 [27]	Down	0.010*	After first dose	Proliferation, differentiation, survival, hypertrophic growth [76,77]
miR-133b	Rigaud et al., 2017 [26]	Up	>0,05	At baseline, cycle 2, 3 and 4	Proliferation, differentiation, survival, hypertrophic growth [76,77]
	Todorova et al., 2017 [27]	Down	0.004*	After first dose	
miR-140-3p	Todorova et al., 2017 [27]	Up	0.014*	After first dose	Myocardial infarction [78]
miR-142-5p	Todorova et al., 2017 [27]	Up	0.024*	After first dose	Inflammation, oxidative stress and apoptosis [79]
miR-144-5p	Todorova et al., 2017 [27]	Up	0.007*	After first dose	Proliferation, migration, invasion and apoptosis of human umbilical vein endothelial cells [80]; identified in heart and colon mouse tissue [81]
miR-145-5p	Todorova et al., 2017 [27]	Up	0.006*	After first dose	Inflammatory response, apoptosis in cardiomyocytes [82]
miR-205-5p	Todorova et al., 2017 [27]	Up	0.034*	After first dose	Differentiation, capture and proliferation of breast cancer [83]

(*continued on next page*)

Table 2 (*continued*)

miRNA	Study [reference]	Change of expression in cardiotoxicity group	P-value	Time of miRNA evaluation	Potential role [Reference]
miR-210	Qin et al., 2018 [25]	Down	0.021*	Baseline	Pro-angiogenic [84]
	Zhu et al., 2018 [28]	Down	0.032*	Baseline	
miR-324-5p	Todorova et al., 2017 [27]	Up	0.025*	After first dose	Mitochondrial fission, apoptosis and myocardial infarction [85]
miR-331-3p	Todorova et al., 2017 [27]	Up	0.023*	After first dose	Tumor suppression [86]
miR-363-3p	Todorova et al., 2017 [27]	Up	0.023*	After first dose	Tumor suppression [87]
miR-376a-3p	Todorova et al., 2017 [27]	Down	0.028*	After first dose	Tumor suppression [87]
miR-378	Qin et al., 2018 [25]	Down	0.002*	Baseline	Pro-angiogenic [88]
	Zhu et al., 2018 [28]	Down	0.104	Baseline	
miR-421	Todorova et al., 2017 [27]	Up	0.015*	After first dose	Cardiomyocyte apoptosis, myocardial infarction [89]
miR-486-5p	Todorova et al., 2017 [27]	Up	0.006*	After first dose	Protection against cardiomyocyte apoptosis [90]
miR-499a-5p	Gioffre et al., 2020 [24]a	Up	0.029*	Baseline	Acute myocardial infarction [91]
	Gioffre et al., 2020 [24]b	Up	0.75	Baseline	
miR-501-3p	Todorova et al., 2017 [27]	Up	0.013*	After first dose	Alzheimer's disease, metastasis [92] and hepatocellular carcinoma [93]
miR-502-3p	Todorova et al., 2017 [27]	Up	0.010*	After first dose	Triple negative breast cancer [94]
miR-532-3p	Todorova et al., 2017 [27]	Up	0.040*	After first dose	Mitochondrial fission, apoptosis in the presence of doxorubicin [95]
miR-532-5p	Todorova et al., 2017 [27]	Up	0.002*	After first dose	Acute myocardial infarction, apoptotic [96]
miR-660-5p	Todorova et al., 2017 [27]	Up	0.005*	After first dose	Platelets, thrombotic events and acute myocardial infarction [97]
miR-885-5p	Gioffre et al., 2020 [24]a	Up	0.035*	Baseline	Liver toxicity [98]
	Gioffre et al., 2020 [24]b	Up	0.14	Baseline	
miR-1260a	Todorova et al., 2017 [27]	Up	0.027*	After first dose	Metastatic melanoma [99]

* $P < 0.05$. Baseline: before treatment.

and translation, the evolutionarily conserved RNA-binding protein Lin28a and its paralog Lin28b play critical roles in pluripotency, organismal growth, tissue repair, and oncogenesis [34,35].

miR-20a is a member of the miR-17 family, which in turn belongs to the miR-17/92 cluster, a gene family with an oncogenic role that is differentially expressed in breast cancer, mainly in tumors negative for estrogen receptors [36]. Notably, the miR-17/92 cluster was deregulated in cardiovascular, immune and neurodegenerative diseases [37]. miR-20a was shown to control angiogenesis in breast cancer and induces abnormalities in the vascular development of the mesh [38]. Moreover, a decreased plasma levels of miR-20a was found when compared cardiotoxicity-affected and non-cardiotoxic patients, which suggest that miR-20a is a potential circulating marker of cancer treatment-related cardiotoxicity [25,28].

miR-126 is involved in angiogenic and inflammatory processes, therefore playing an important role in cancers and autoimmune diseases [39]. miR-126 was shown to be decreased in tumors, because it is able to inhibit the growth, adaptation, migration and invasion of the cancer cell of origin. Notably, miR-126 levels are used as a prognostic pattern for the survival of neoplastic patients [40]. In addition, miR-126 was also shown to play a role in improving myocardial damage after acute myocardial infarction events. Two studies found decreased levels of miR-126 in breast cancer patients when comparing the cardiotoxicity and non-cardiotoxicity groups [25,28], suggesting that miR-126 is a possible marker of cardiotoxicity risk. Conversely, miR-126 was found to be significantly up-regulated after neoadjuvant chemotherapy (cyclophosphamide or fluorouracil and epirubicin followed by docetaxel or paclitaxel) in 25 breast cancer patients before and after chemotherapy [16]. Importantly, this study did not evaluate whether there was a correlation between miR-126 levels and biomarkers of cardiotoxicity [16]. Therefore, these discordant results may be due to the lower level or absence of cardiac toxicity. Moreover, the mechanisms of miR-126 underlying cardiotoxicity is still unclear.

miR-210 modulates endothelial cells response to hypoxia and has a robust anti-hypoxia ability. miR-210 was shown to enhance the formation of capillary networks and the migration and differentiation of endothelial cells [41]. *In vitro* experiments showed that miR-210, when overexpressed, could mitigate hypoxia-induced injury [42]. In addition, the positive regulation of miR-210 was reported in cardiac stem cells under conditions of hypoxia, which prevented apoptosis and promoted cell migration [43]. In cells of breast cancer lineage, when in a hypoxic environment, miR-210 promoted metastasis, proliferation and self-renewal [44]. Importantly, a correlation between miR-210 levels and the decrease in LVEF was observed in a cohort of 97 breast cancer patients under anthracycline treatment; twelve had cardiotoxicity with a reduction in basal LVEF [45]. Decreased levels of miR-126 were also shown in patients affected by cardiotoxicity compared to unaffected subjects [25,28]. Taken together, these data suggest that the differential regulation of miR-126 may modulate cardiotoxicity.

The miR-1 is encoded by *miR-1-1* and *miR1-2,* which are located in two distinct loci on chromosomes 20 and 18, respectively. The two precursors, after being exported to the cytoplasm by the Exportin 5

Table 3
Target genes identified in the miRTarBase for the differentially expressed miRNAs (or their aliases) identified in the systematic review.

miRNA	Target genes identified in miRTarBase
let-7f	EWSR1, PARP1, NF2, UHRF2, E2F2, HMGA2, KRAS, CCR7, RAB40C, ITGB3, IL6, UHRF1, NKIRAS2, HRAS, CCND2, AGO1, RRM2, HMGA1, PKM, PRDM1, PAK1,
hsa-let-7a-5p (46 target genes)	EZH2, ARG2, MAP4K4, AURKB, WNT1, RAVER2, TNFAIP3, CDK6, CASP3, NRAS, DICER1, LIN28A, TNFRSF10B, MYC, TGFBR3, CDC34, STAT3, IGF2BP1, TRIM71, EGFR, IGF2, HAS2, AGO4, CDKN1A, LIN28B
miR-1	EDN1, PTBP1, IGF1, API5, TAGLN2, MPL, CDK4, FZD7, PIM1, MET, GJA1, SNAI2, FOXP1, PIK3CA, VEGFA, LASP1, G6PD, XPO6, HCN2, KRAS, CCL2, FRS2, FN1, CCND1, PAX3, RARB, HCN4, PNP, KCNJ2, PTMA, HDAC4, FABP3, NOTCH3, KCNE1, TWF1, ETS1, NAIP, PPP2R5A,
hsa-miR-1-3p (80 target genes)	SPRED1, SLC8A1, PGD, TKT, TNKS2, HAND2, MEF2A, ABCB1, TWIST1, BAG4, YWHAZ, CXCL12, FASN, ANXA2, SOX9, ADAR, ND1, SOX6, CNN3, PRKCE, COX1, HSPD1, PGM2, CEBPA, HSPA4, SERP1, CALM3, GATA4, AGO1, BDNF, SRXN1, LARP4, TMSB4X, KIF2A, NETO2, ATP6V1B2, ASPH, TH, POGK, SP1, CAND1, IL11
miR-20a hsa-miR-20a-3p	SMO, PTEN, BID, NR4A3, EGR2, HIF1A, TCEAL1, CCND1, E2F1, BMPR2, CDKN1A, TGFBR2, PTEN, APP, RUNX1, SMAD4, IRF2, KIT, UBE2C, STAT3, LIMK1, GJA1, DUSP2, SMAD7, MAP3K5, MCL1, TP53INP1, EGR2, ABL2, ATG16L1, PRKG1, ETV1, FBXO31, RUNX3, NFKBIB, KIF26B, DAPK3, EGLN3, REST, ITGB8, ZFYVE9, RGS5,
hsa-miR-20a-5p (74 target genes)	TGFBR1, ITGB8, MYC, BNIP2, MAP3K12, BCL2, MEF2D, VEGFA, CCND2, E2F3, RB1, RBL1, RBL2, WEE1, PPARG, BAMBI, CRIM1, MAP2K3, PURA, ARHGAP12, TSG101, SIRPA, PHLPP2, ANKH, EPAS1, DNMT1, PKD1, PKNOX1, RB1CC1, TIMP2, PTPRO, PPP2R2A, NRAS, THBS1, MUC17
miR-126 hsa-miR-126-3p	PITPNC1, IGFBP2, KRAS, SPRED1, PLK2, EGFL7, RGS3, TOM1, HOXA9, MERTK, CRK, VEGFA, PIK3R2, IRS1, SOX2, TWF1, TWF2, PTPN7, DNMT1, SLC7A5, PIK3CG, TEK, ADAM9, CRKL, FOXO3, BCL2, CXCR4, RHOU, LRP6,
hsa-miR-126-5p (48 target genes)	SIRT1, NFKBIA, CADM1, EZH2, ROCK1, SLC45A3, VCAM1, PGR, ADGRE5, AKT1, CCNE2, MMP7, CXCL12, TCF4, ADM, E2F1, SPRED1, PTPN7, HOTAIR, CRK, CYLD, SLC45A3, MYC, ADAM9, MMP7, CXCL12, VEGFA
miR-210	FGFRL1, RAD52, EFNA3, PTPN1, BDNF, ISCU, E2F3, MNT, AIFM3, NDUFA4, SDHD, ALDH5A1, FOXN3, MCM3, IGFBP3, COL4A2, INPP5A, EHD2, SH3BGRL, PTPN2, FOXP3, HIF3A, BNIP3, ATG7, THSD7A, VMP1, BTK, NPTX1, XIST, CPEB2, GPD1L, NCAM1, DDAH1, TFRC,
hsa-miR-210-3p (75 target genes)	HSD17B1, STMN1, DIMT1, LDHA, LDHB, P4HB, PTBP3, HIF1A, HOXA9, TP53I11, PIM1, HOXA1, CASP8AP2, KCMF1, PLK1, TWIST1, MRE11A, XPA, SMCHD1, TNPO1, CBX1, ABCB9, CDK10, DENND6A, HOXA3, MYORG, MDGA1, MID1IP1, SEH1L, UBQLN1, SERTAD2, ACVR1B, APC, ATP11C, CHD9, CLASP2, ELK3, PTAR1, NIPBL, MIB1, HECTD1

molecule, are processed in mature identical forms of miR-1. It has been seen that miR-1 is related to several types of cancer, including breast cancer [46]. miR-1 has been reported to be elevated in cardiac muscle, but not in other tissues [47]. Patients who have suffered from acute myocardial infarction had higher plasma levels of miR-1 compared to healthy patients. As miR-1 is abundantly expressed in skeletal muscle, it was suggested that miR-1 is released by necrotic cardiac myocytes [48]. While increased levels of miR-1 were found in the plasma of breast cancer patients who had to be treated with doxorubicin and suffered from cardiac dysfunction after cycles 2, 3 and 4 [26], miR-1 was also found to be down-regulated after the first dose of doxorubicin [27]. Although both studies have investigated patients treated with doxorubicin, they have adopted different combined regimes and dosages [26,27]. Considering that cardiotoxicity is related to both the peak plasma concentration and cumulative dose of anticancer drugs [49], their findings may differ because of the chemotherapy cycles (dosage, time and periodicity) and drug combinations. Moreover, their findings probably differed due to different molecular subtypes of breast cancer, which could have distinct clinical outcomes. Importantly, different sample size and detection methods were employed. In particular, Rigaud et al. [26] selected 6 candidate miRNAs, based on the literature, to be evaluated in plasma of 56 breast cancer patients with abnormal cardiac function by qRT-PCR. On the other hand, Todorova et al. [27] performed plasma profiling, using a miRNome PCR panel, in sample of 20 breast cancer patients with cardiotoxicity. Different commercial kits and protocols may lead to different conclusions and make the comparison of results very difficult. Finally, Gioffre et al. [24] did not find any significant differences in miR-1 levels in 88 breast cancer patients treated with doxorubicin or epirubicin. Moreover, this study evaluated the effects of anthracycline by cTnT and cTnI levels, because of the lack of a decrease in LVEF [24]. Conversely, two other studies assessed cardiotoxicity using LVEF [26,27]. Using an OpenArray screening, miR-1 was not found to be differentially expressed at baseline, during treatment and at follow-up, probably because few patients presented cardiac toxicity [24]. Importantly, only this study confirmed the expression of miRNAs by a second RT-qPCR technique using TaqMan assays on the same plasma samples for results validation.

In order to search for pathways that are relevant to anthracycline-induced cardiotoxicity, we searched the miRTarBase for target genes for the five miRNAs (Table 3) and found relevant Reactome pathways (Fig. 2). Notably, the "Cellular responses to stress R-HAS-2262752" pathway was found from the target genes for the miRNAs let-7f, miR-20a, and miR-210. Accordingly, redox cycling and oxidative stress are among the well-known molecular pathways related to doxorubicin-induced cardiotoxicity [50–53]. Notably, recent studies indicate the role of non-coding RNAs, including miRNAs and long non-coding RNAs, in the pathogenic process of oxidative stress and the response of cells to oxidative stress [54,55]. However, recent evidence suggested that doxorubicin cardiotoxicity is not solely due to redox cycling. Novel explanations include anthracycline-dependent regulation of major signaling pathways controlling DNA damage response, cardiomyocyte survival, cardiac inflammation, energetic stress and gene expression modulation [56]. Interestingly, the "Signal transduction R-HAS-162582" pathway was found from the target genes for the miRNAs let-7f, miR-1, miR-20a, and miR-126. Indeed, the review of molecular advances regarding anthracycline-associated cardiomyopathy have uncovered the complex balance between cardiomyocytes and endothelial homeostasis through reactive oxidative stress, interference in apoptosis/growth/metabolism, and angiogenic imbalance [52].

The reliable prediction of who will develop cardiomyopathy and heart failure upon anthracycline exposure have proven elusive [52]. Predictive genomic biomarkers of functional relevance for doxorubicin-induced cardiotoxicity and heart failure were previously identified using human Induced Pluripotent Stem Cells-derived cardiomyocytes [57]. Doxorubicin exposure for more than two days was shown to deregulate genes participating in apoptosis, DNA damage, and the oxidative stress response. Several clusters of genes were found to be down-regulated (sarcomere, myofibril, contractile fiber, and regulation of heart contraction genes) or up-regulated (stress response, p53 signaling pathway, and apoptosis genes) after two and six days of treatment with 156 nM doxorubicin, again becoming up-regulated or down-regulated toward control levels after washing out of the drug [57,58].

The major strength of this systematic review and pathway analysis was the novelty of the study. To the best of our knowledge, this was the first systematic review focusing on the predictive role of miRNAs in anthracycline-induced cardiotoxicity in the prognosis of breast cancer patient. Moreover, we showed two shared pathways among the miRNAs including "Signal transduction R-HAS-162582" and "Cellular responses to stress R-HAS-2262752".

Although the literature search was conducted in accordance with

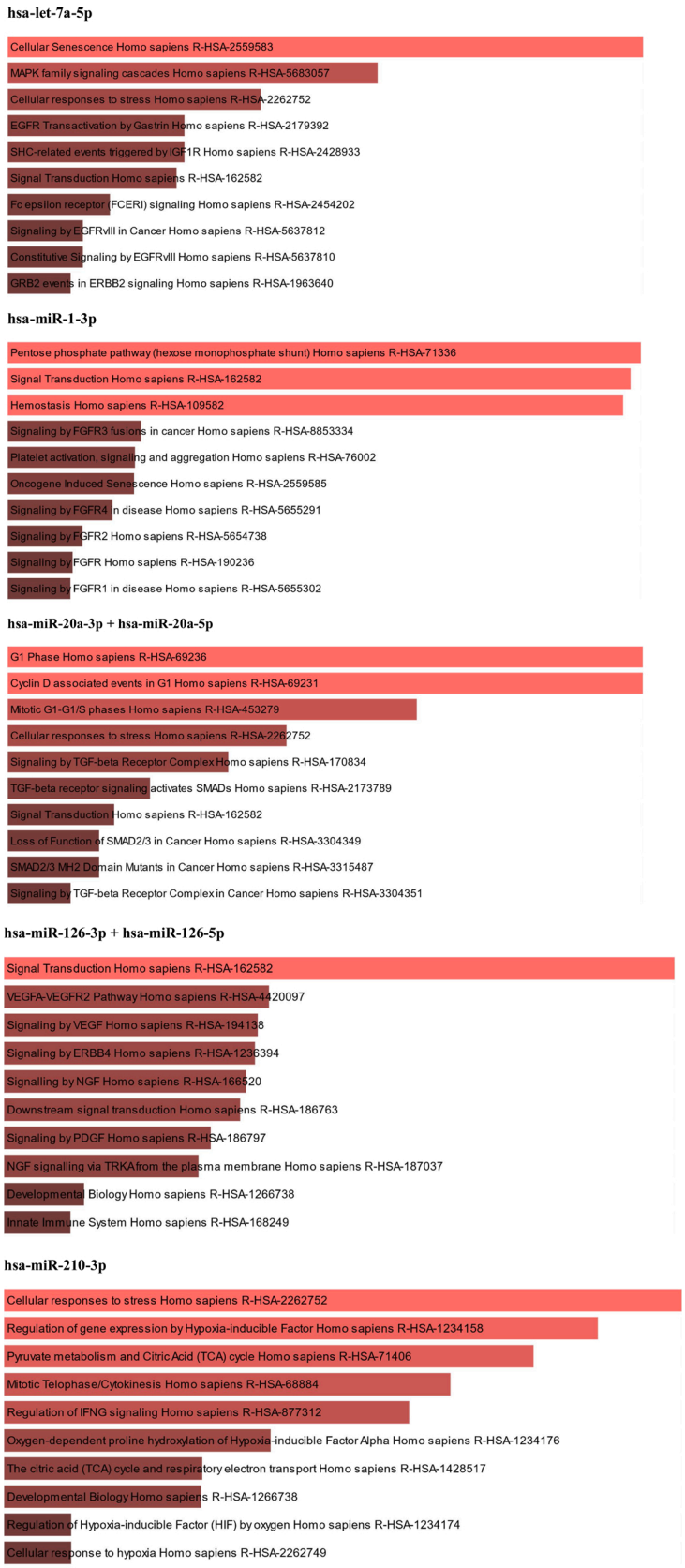

Fig. 2. Reactome pathways obtained from the target genes identified in the miRTarBase for the five differentially expressed miRNAs (or their aliases) identified in this systematic review.

Table 1
Characteristics of the studies included in the systematic review.

First author, year, country, reference	Type of breast cancer	Study duration	Cardiotoxicity diagnosis	Number of patients; mean age ± SD or median (interquartile range) in years			Chemotherapy regimens; dose (mg/m^2) ± SD			miRNA detection method	miRNA studied
				Entire cohort	Cardiotoxicity	Non-cardiotoxicity	Entire cohort	Cardiotoxicity	Non-cardiotoxicity		
Gioffre et al., 2020; Italy [24] a	unreported	12 months	cTn I and cTnT	32 unreported	18 53.3 ± 11.3	14 53.9 ± 10.8	Doxorubicin Median cumulative dose of 240 [240-240] mg/m^2	Doxorubicin 226.2 ± 38.7 (cumulative dose)	Doxorubicin 240.0 ± 0 (cumulative dose)	Open Array screening and RT-qPCR	miR-1-3p miR-34a-5p miR-99b-5p miR-122-5p miR-125b-5p miR-499a-5p miR-532-5p miR-885-5p
Gioffre et al., 2020; Italy [24] b	unreported	12 months	cTn I and cTnT	56 unreported	12 52.2 ± 6.3	44 49.3 ± 11.4	Epirubicin Median cumulative dose of 360 [270-360] mg/m^2	Epirubicin 239.1 ± 45.3 (Cumulative epirubicin dose converting in terms of doxorubicin equivalents)	Epirubicin 223.3 ± 42.5 (Cumulative epirubicin dose converting in terms of doxorubicin equivalents)	Open Array screening and RT-qPCR	miR-1-3p miR-34a-5p miR-122-5p miR-128-3p miR-181b-5p miR-181c-5p miR-361-3p miR-499a-5p miR-885-5p
Rigaud et al., 2017; Brazil [26]	Adenocarcinom; HER-2 positive was excluded	12 months	Reduction in LVEF ≥10% and/or LVEF <50%	46 56 49.9±3.3	10 48.6 ± 3.2	49.9 ± 1.2	Doxorubicin Cumulative dose of 240 mg/m^2) and cyclophosphamide (600 mg/m^2) followed by paclitaxel (80 mg/m^2 or docetaxel 75 mg/m^2)	Doxorubicin 408.4 ± 1.4 (Total dose)	Doxorubicin 410.6 ± 11.4 (Total dose)	RT-qPCR	miR-1 miR-133b miR-146a miR-208a miR-208b miR-423-5p
Qin et al., 2018; China [25]	unreported	12 months	LVEF declined by 10% from baseline to below 53%	363 45.38 ± 6.05	19 ≥45 years: 11 (5.5) <45 years: 8 (4.8)	346 ≥45 years: 189(94.5) <45 years: 157(95.2)	Epirubicin 100 mg/m^2, (treatment regimen), cyclophosphamide (600 mg/m^2), then followed by docetaxel (75-100 mg/m^2), trastuzumab treatment on demand (6 mg/kg, after docetaxel treatment)	Epirubicin unreported	Epirubicin unreported	RT-qPCR	let-7b let-7f miR-17-3p miR-17-5p miR-18a miR-19a miR-19b-1 miR-20a

(*continued on next page*)

Table 1 (*continued*)

First author, year, country, reference	Type of breast cancer	Study duration	Cardiotoxicity diagnosis	Number of patients; mean age ± SD or median (interquartile range) in years			Chemotherapy regimens; dose (mg/m^2) ± SD			miRNA detection method	miRNA studied
				Entire cohort	Cardiotoxicity	Non-cardiotoxicity	Entire cohort	Cardiotoxicity	Non-cardiotoxicity		
											miR-92a miR-126 miR-130a miR-210 miR-296 miR-378
Todorova et al., 2017; United States [27]	Invasive ductal carcinoma	After one dose of chemotherapy	Decline of LVEF below by >10% or below 50%	20 unreported	8 unreported	12 unreported	Doxorubicin 60 mg/m^2 (treatment regimen) cyclophosphamide (600 mg/m^2)	Doxorubici unreported	Doxorubicin unreported	RT-qPCR using a miRNome PCR panel	Unreported
Zhu et al., 2018; China [28]	Triple negative	12 months	LVEF declined by 10% from baseline to below 53%	179 45.9 ± 6.1	9 unreported	170 unreported	Epirubicin 100 mg/m^2(treatment regimen), cyclophosphamide (600 mg/m^2), then followed by docetaxel (75-100 mg/m^2)	Epirubicin unreported	Epirubicin unreported	 RT-qPCR	let-7b let-7f miR-17-5p miR-17-3p miR-18a miR-19a miR-19b-1 miR-20a miR-92a miR-126 miR-130a miR-210 miR-296 miR-378

Abbreviations: cTnI: troponin I; cTnT: troponin T; HER-2: epithelial growth factor receptor 2; LVEF: left ventricular ejection fraction; RT-qPCR: reverse transcriptase quantitative polymerase chain reaction; SD: standard deviation.

standardized guidelines, the current study has some limitations. There were only five eligible studies in this systematic review. While we identified five miRNAs that are associated with the anthracycline-based cardiotoxicity, it was difficult to accurately evaluate their potential use for monitoring of early cardiotoxicity from chemotherapy because they have been reported in a few studies. Importantly, some studies lack a clear and detailed description of the studied population (e.g., histological classification of breast cancer type, number of patients, age), treatment (e.g., total or cumulative anthracycline dose) and different assessment of cardiotoxicity, including image evaluation (e.g., echography) or by the dosage of circulating markers (e.g., troponins). Notably, in almost studies, patients using cardioprotective drugs were not excluded and their beneficial effects on the cardiovascular system were not considered. Importantly, the presence of comorbidities is a factor that can accelerate cardiotoxicity, although the authors did not discuss these confounding factors or adjust the confounders for the analysis. Another limitation was the inclusion of studies that selected only miRNAs reported in the literature (e.g., miR-1). Indeed, the studies showed high variability in breast cancer treatment – including the use of other concomitant agents known to have cardiotoxic effects – and different follow-up periods. Therefore, in this systematic review, the limited number of studies with the same differentially expressed miRNA makes it impossible to perform a quantitative analysis of the data (meta-analysis). In addition, most studies did not report the raw or normalized miRNA expression data, only if the miRNA was significantly up- or down-regulated. Large prospective studies are needed to confirm the involvement of the five miRNAs identified in the current systematic review in breast cancer patients with anthracycline-induced cardiotoxicity. Moreover, it is important to conduct studies using screening methods like microarrays and/or RNAseq techniques in order to investigate additional miRNAs, related to other pathways in cardiotoxic process.

5. Conclusion

In conclusion, our systematic review showed five miRNAs (let-7f, miR-1, miR-20a, miR-126 and miR-210) with the potential to predict anthracycline-induced cardiotoxicity in breast cancer patients. These miRNAs and their targets participate in pathways of known relevance for cardiotoxicity pathogenesis, such as pro-angiogenesis and myocardial infarction. Moreover, analysis of the target genes found for the five miRNAs suggests that cellular responses to stress and signal transduction pathways may contribute to anthracycline-induced cardiotoxicity. To the best of our knowledge, this is the first systematic review investigating the differential expression of circulating miRNAs in breast cancer patients affected by anthracycline cardiotoxicity, considering their clinical potential as early prediction tools and prognostic markers.

Declaration of Competing Interest

The authors report no declarations of interest.

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Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.biopha.2020.110709.

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