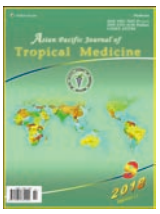

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Role of dietary phytochemicals in modulation of miRNA expression: Natural swords combating breast cancer

Banzeer Ahsan Abbasi[1], Javed Iqbal[1✉], Tariq Mahmood[1✉], Ali Talha Khalil[2,3,4], Barkat Ali[1], Sobia Kanwal[5], Sayed Afzal Shah[1], Riaz Ahmad[6]

[1]*Department of Plant Sciences, Quaid–i–Azam University, Islamabad 45320, Pakistan*
[2]*Nanosciences African Network (NANOAFNET), iThemba LABS–National Research Foundation Somerset West, Western Cape 7129, South Africa*
[3]*Department of Zoology, University of Gujrat, Sub Campus Rawalpindi 46000, Pakistan*
[4]*Department of Eastern Medicine and Surgery, Qarshi University, Lahore 56000, Pakistan*
[5]*UNESCO UNISA Africa Chair in Nanoscience and Nanotechnology, College of Graduate Studies, University of South Africa, Pretoria 0002, South Africa*
[6]*College of Life Sciences, Shaanxi Normal University, Xi'an 710119, China*

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ABSTRACT

The National Cancer Institute had projected breast cancer (BC) as one of the topmost prevalent malignancies around the globe. In many cases, BC becomes resistant to chemotherapy, radiation and hormonal therapies. Traditional BC therapies are associated with adverse side effects, drug resistance and recurrence. Extensive research work has shown that these dietary phytochemicals (DPs) may exert therapeutic effects by regulating the miRNA expression. A large number of DPs have been researched as miRNA regulatory agents against BC and some other DPs have not yet been tested against BC. We have discussed the effects of curcumin, diallyl disulphide, 3,3′ diindolylmethane, ellagic acid, genistein, indole-3-carbinol, quercetin, resveratrol, and sulforaphane on regulation of expression of BC miRNAs in a wide range of *in vitro* and *in vivo* models. We have also shown some of the possible DPs (Oleanolic acid, capsaicin, benzyl isothiocyanate, epigallocatechin gallate, phenethyl isothiocyanate and ursolic acid) that have shown miRNA regulatory activities and have not yet been tested against BC miRNAs. Finally, current limitations, challenges, future perspectives of DPs and BC research are also critically discussed.

1. Introduction

Breast cancer (BC) is a serious global health concern in both developed and developing countries. It is one of the major causes of cancer associated death among women across the world accounting for 25% of all new cancer cases and 15% of all new cancer deaths[1,2]. BC is not only restricted to women, it also affects men[3], transgender individuals and people from all racial and ethnic backgrounds[4]. At present, large number of treatment methods are available for BC including surgical treatment, adjuvant chemotherapy, radiotherapy, hormonal therapy, targeted therapies together with immunotherapy, monoclonal antibody therapy and surgery [lumpectomy (breast-conserving surgical treatment) or mastectomy (surgical removal of breast tissues)][5]. But, the development of drug resistance and their side effects has weakened the potentials of these treatment strategies on cancer cells[6]. As a result, development of novel and potent drugs with no/less side effects is crucial to control the incidence of BC.

Recently, dietary phytochemicals (DPs) have appeared as chemo-preventive and chemotherapeutic agents for BC because they have no/less side effects and low toxicity compared to synthetic drugs.

First author: Banzeer Ahsan Abbasi, Department of Plant Sciences, Quaid-i-Azam University, Islamabad 45320, Pakistan.
E-mail: benazirahsanabbasi786@gmail.com
✉Corresponding author: Javed Iqbal, Department of Plant Sciences, Quaid-i-Azam University, Islamabad 45320, Pakistan.
Phone: +92-3028886505
E-mail: javed89qau@gmail.com
Tariq Mahmood, Department of Plant Sciences, Quaid-i-Azam University, Islamabad 45320, Pakistan.
E-mail: tmahmood.qau@gmail.com

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Additionally, they are inexpensive and readily available. Growing evidences indicates that these phytochemicals could be used as a chemo-preventive and chemo-therapeutic agent in wide range of cancer including BC[7,8]. Emerging evidences suggested that miRNAs have played important role in the initiation, promotion and progression of various types of cancers including BC. They control the expression level of different genes and proteins related to cell growth, metastasis, proliferation and apoptosis[9,10]. Due to their significant roles in cancer initiation and proliferation, targeting miRNAs has been considered as an effective treatment option for cancer. Recent evidences indicate that DPs may inhibit BC progression through the modulation of miRNA expression[11,12].

A large number of DPs such as sulforaphane, ellagic acid (EA), genistein, curcumin, indole-3-carbinol (I3C), resveratrol (RV), diallyl disulphide (DADS), 3,3'-diindolylmethane (DIM), and quercetin have been tested as potent agents for regulating miRNAs against BC and a large number of DPs are still under clinical trials for their potential role against miRNAs regulation in BC. This review article focuses on some potential DPs which has shown promising results while targeting miRNAs in BC.

2. miRNAs involved in BC regulation

miRNAs are playing a vital role in regulating BC, and it is clear from large number of evidences that disturbance in the regulation of these miRNAs are mainly involved in the initiation promotion and progression of BC. An extensive research work has been carried out to identify large number of these dysregulated miRNAs in BC. These dysregulated miRNAs play a significant role in the regulation of a wide range of different molecular processes such as invasion, proliferation, metastasis, caspase mediated cell death, self-renewal, and epithelial to mesenchymal transition. miRNAs can perform dual functions as oncogenes (biological accelerators) and tumor suppressor genes (biological breaks). Onco-miRNAs expression is up-regulated (Figure 1); whereas, tumor-suppressor miRNAs expression (Figure 2) is downregulated in BC. Some important miRNAs along with their molecular mechanism of actions are given in Table 1 and 2.

Table 1

Different kinds of onco-miRNAs along with their molecular mechanism of actions involved in initiation, promotion and progression of breast cancer.

Onco-miRNAs	Mechanism of action	Literature cited
miR-181a	It promotes metastasis by targeting BIM protein	[13]
miR-9	Promoted angiogenesis and metastasis by targeting E-cadherin transmembrane proteins	[14]
miR-155	It regulates cell survival, growth, epithelialmesenchymal transition by targeting *Foxo3a*, E-cadherin signaling pathways	[15]
miR-373, miR-520c	These miRNA promote metastasis and invasion by targeting CD44 protein	[16]
miR-10b	Promoted metastasis, invasion and self-renew by targeting HOXD10, *PTEN*, *Akt* signaling pathways	[17,18]
miR-632	Promoted invasion, metastasis by targeting *DNAJB6* gene	[19]
miR-214	Promoted cell growth by upregulating PTEN-PI3K/*Akt* signaling pathway	[20]
miR-21	Promotes metastasis by targeting different proteins such as PTEN, TIMP1, TIMP3, and PDCD4	[21,22]
miR-449a	Promoted cancer progression by targeting CRIP2 protein	[23]
miR-548j	Promoted metastasis and invasion targeting Tensin1 and CDC42	[24]
miR-182	Promotes invasion, metastasis by targeting RECK protein	[25]
miR-375	Promoted proliferation of BC by targeting RASD1 protein	[26]
miR-375	Promotes invasion, metastasis by targeting MIM protein	[27]
miR-22	Modulate metastasis, stemness by targeting TET protein	[28]
miR-498	Promotes cell growth by targeting *BRCA1* gene	[29]
miR-374a	These miRNA promotes metastasis by targeting Wnt/b-catenin signaling pathway	[30]
miR-27a	Induced angiogenesis, proliferation by targeting Myt-1 and ZBTB10 protein	[31,32]

Table 2

Different kinds of tumor suppressor miRNAs along with their molecular mechanism of actions involved in suppression of breast cancer.

Tumor suppressor-miRNAs	Mechanism of action	Literature cited
miR-335	Suppressed metastasis by targeting SOX4, TNC transcriptional factors	[33]
miR-146a	Inhibited cell proliferation by targeting *EGFR* receptor protein	[34]
miR-290	Induced apoptosis by targeting ARID4B protein	[35]
miR-124	Suppressed angiogenesis and tumor growth by *Akt2* protein kinase	[36]
miR-17/20	Inhibited invasion, metastasis by targeting Cyclin D1 protein	[37]
miR-200 family	Suppressed epithelial-mesenchymal transition, inhibits cancer stem-like cells growth by targeting ZEB1, SIP1, and BMI1 proteins	[38,39]
let-7	Inhibited self-renewal capacity by targeting H-RAS and HMGA2	[40]
miR-320a	Suppressed metastasis by targeting *MTDH* gene and its product	[41]
miR-206	Suppressed epithelial-mesenchymal transition by targeting TGF- β , NRP1, and Smad2 factors	[42]
miR-342	Induced apoptosis by targeting BIRC6 protein	[9]
miR-30	Inhibited self-renewal capacity, induces apoptosis by targeting *Ubc9* and *ITGB3* gene and its product	[43]
miR-489	Inhibited cell proliferation by targeting HER2 protein	[44]
miR-224	Inhibits invasion, metastasis by targeting CDC42 and CXCR4 proteins	[45,35]
miR-340	Inhibited cell proliferation, invasion by targeting ZEB1 protein	[10]
miR-34a/c	Inhibited invasion, metastasis by targeting Fra-1 transcriptional factor	[46]
miR-148a	Suppressed metastasis by targeting Wnt1 and NRP1 signaling pathway	[47]

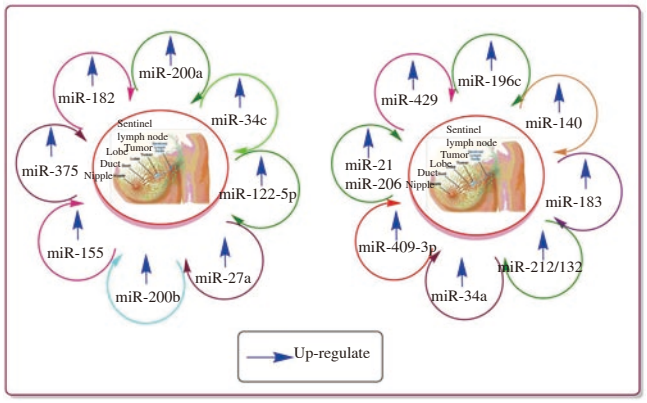

Figure 1. Effect of some dietary phytochemicals against breast cancer while up-regulating expression of large number of miRNAs in order to inhibit breast cancer.

Blue arrow indicates that the mentioned dietary phytochemicals up-regulate the expression of different miRNAs involved in breast cancer control.

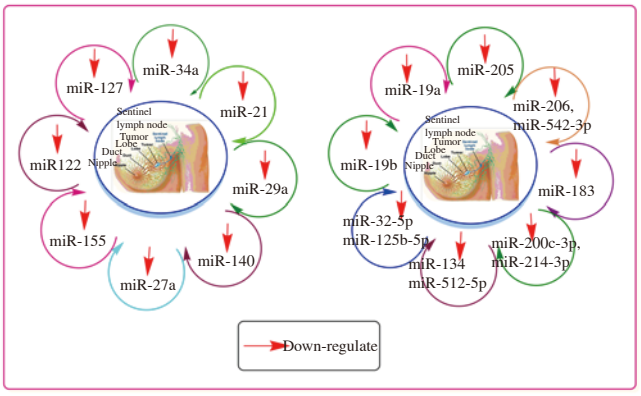

Figure 2. Effect of some dietary phytochemicals against breast cancer while down-regulating expression of large number of miRNAs in order to cope up with breast cancer.

Red arrow indicates that the mentioned dietary phytochemicals down-regulate the expression of different miRNAs involved in breast cancer control.

Table 3

In vitro and *in vivo* effects of dietary phytochemicals against breast cancer while up-regulating and down-regulating the expression of different miRNAs.

Bioactive compound	Cell line/animal model used	Type of study	miRNA regulation	Mechanism of actions	Literature cited
Indole-3-carbinol (I3C)	MCF-7	*In vitro*	Downregulate the expression level of miR-34a	Induced cell growth inhibition and apoptosis by upregulating *p53*, *p53ser15* and *p21* expression	[48]
Sulforaphane	MCF10DCIS/nude mice	*In vitro*, *In vivo*	Downregulate miR-21 and miR-29a and upregulate miR-140	Inhibited cancer stem-like cell growth by altering *ALDH1* expression	[49]
Sulforaphane	MCF10DCIS/ female nude mice	*In vitro*, *In vivo*	Upregulate the expression of miR-140	Inhibited cancer stem-like cell growth by altering *SOX9* and *ALDH1* expression	[50]
Pomegranate polyphenols	BT-474, MDA-MB-231/ female BALB/c athymic nude mice	*In vitro*, *In vivo*	Downregulate the expression of miR-27a and miR-155	Inhibited cell survival and inflammation by modulating *SHIP-1*, *Sp*, *PI3K*, *Akt*, *VEGF*, and *ZBTB10* expression	[51]
Ellagic acid	Female ACI Rats	*In vivo*	Upregulate the expression of miR-34c, miR-182, miR-183, miR-196c, miR-375, miR-429 and downregulate the expression of miR122, miR-127, miR-205, miR-206 and miR-335	Exhibited antitumor effect by modulating *ERa*, *cyclin D1*, *RASD1*, *FoxO3a*, *FoxO1*, *cyclin G1*, *Bcl-w*, and *Bcl-2* expression	[52]
3,3′-Diindolylmethane (DIM)	T47D, MDA-MB-231/ female BALB/c athymic nude mice	*In vitro*, *In vivo*	Upregulate the expression of miR-212/132	Suppressed metastasis by downregulating *SOX4* expression	[11]
3,3′-Diindolylmethane (DIM)	SKBR-3, MDA-MB-468	*In vitro*	Upregulate the expression of miR-200a and miR-200b	Inhibited cell growth by downregulating *FoxM1* and *pAkt* expression	[53]
Curcumin	MCF-7	*In vitro*	Downregulate the expression of miR-19a and miR-19b	Inhibited cell proliferation by modulating *PTEN*, *PCNA*, *pAkt*, *p-MDM2*, and *p53* expression	[54]
Resveratrol	MCF-7, MDA-MB-231	*In vitro*	Downregulate the expression of miR-32-5p, miR-125b-5p, miR-134, miR-200c-3p, miR-214-3p, miR-512-5p, miR-542-3p and upregulate the expression of miR-122-5p and miR-409-3p	Induced apoptosis by altering *Bcl-2*, *XIAP*, *CDK2*, *CDK4*, *CDK6*, *caspase-8*, and *caspase-9* expression	[12]
Curcumin (alone or in combination with emodin)	MDA-MB-231, MDA-MB-435	*In vitro*	Upregulate the expression of miR-34a	Inhibited cell proliferation and invasion by downregulating *Bcl-2* and *BMI-1* expression	[55]
Genistein	MDA-MB-435, Hs578t	*In vitro*	Downregulate the expression of miR-155	Inhibited cell survival and proliferation, and induced apoptosis by regulating *FoxO3*, *PTEN*, *CKIa*, β *-catenin*, and *p27* expression	[56]
Diallyl disulphide (DADS)	MDA-MB-231/male Balb/c nude mice	*In vitro*, *In vivo*	Upregulated the expression of miR-34a	Inhibited cell proliferation and invasion by suppressing *SRC/Ras/ERK* expression	[57]

3. Dietary phytochemicals as potential miRNA regulatory agents

DPs are found in large number of dietary supplements such as vegetables, fruits, grains, beans, and other plants. Some DPs have been tested against BC miRNAs (Table 3). Here we discussed the effects of some DPs on BC miRNAs expression. They are chemically diverse and can regulate the miRNA expression through different strategies (Figure 3).

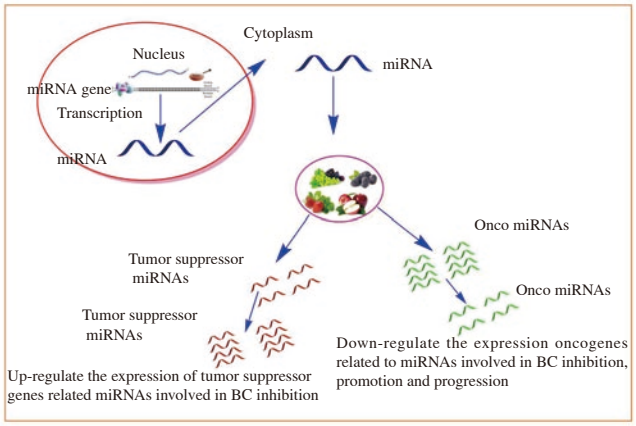

Figure 3. Effects of dietary phytochemicals on miRNA processing and expression.

These dietary phytochemicals are involved in regulating the expression of different miRNAs genes: some are up-regulated while others are down-regulated.

3.1. I3C

I3C are strong phytochemicals widely distributed in the cruciferous vegetables such as kohlrabi, cauliflower (*Brassica oleracea* var. botrytis), broccoli (*Brassica oleracea* var. *italica*), horseradish (*Armoracia rusticana*), cabbage (*Brassica oleracea* var. *capitata*), collard greens (*Brassica oleracea* var. *acephala*), mustard (*Brassica* spp.), brussels sprouts (*Brassica oleracea* var. *gemmifera*), kale (*Brassica oleracea* var. *acephala*), rutabaga (*Brassica napobrassica*), turnips (*Brassica rapa* var. *rapa*), bok choy (*Brassica rapa* var. *chinensis*), wasabi (*Wasabia japonica*), Chinese cabbage (*Brassica rapa* var. *chinensis*), arugula (*Eruca sativa*), radish (*Raphanus sativus*) and watercress (*Nasturtium officinale*)[58-60].

I3C has been shown to modulate miRNA expression in BC cells. I3C up-regulate miR-34a expression level in MCF-7 BC cells as a result of miR-34a expression, and I3C treatment increases the expression of *p21*, *p53*, and *p53ser15* genes, eventually inducing apoptosis and inhibiting cell growth[48]. Hence, I3C may inhibit BC progression by modulating miRNA expression. These I3C may need further research and investigations to unfold their biological potentials.

3.2. EA

EA is an anti-BC flavonoid polyphenol present in grapes (*Vitis vinifera*), cloudberry (*Rubus chamaemorus*), wolfberry (*Lycium barbarum*), pomegranates (*Punica granatum*), strawberries (*Fragaria* spp.), raspberries (*Rubus* spp.), blackberries (*Rubus* spp.), pecans (*Carya* spp.) and walnuts (*Juglans* spp.)[61].

Female ACI rats were treated with estrogen to induce mammary tumorigenesis and the efficacy of EA on the miRNAs expression was observed. EA treatment up-regulated the synthesis of miR-182, miR-375, miR-183, miR-34c, miR-196c, and miR-429, and down-regulated the expression of miR122, miR-127, miR-335, miR-205, and miR-206 in tumors cells. EA also reduced the expression of their targets *ERa* (miR-206), *cyclin D1* (miR-206), *cyclin G1* (miR-182, -122), *Bcl-w* (miR-122), *Bcl-2* (miR-122), and increased the expression of their targets *RASD1* (miR-182), *FoxO3a* (miR-182), *FoxO1* (miR-182, -183), and thereby caused the inhibition of tumor growth[52]. This finding indicates that EA has the capability of inhibiting BC progression by regulating miRNA expression; thereby, this phytochemical can be a potent anti-BC agent and needs further studies.

3.3. Pomegranate polyphenols

Pomegranate (*Punica granatum* L.) has been consumed for different medicinal purposes and is defined as "nature's power fruit". Pomegranate extract has been shown to inhibit cell survival and inflammation by modulating the expression of miRNA in BT-474 and MDA-MB-231 BC cells. It decreased miR-155 expression, contributing to inhibition of *pAkt*, pPI3K, and *Akt* expression, and eventually caused the induction of phosphatidylinositol-3,4,5-trisphosphate 5-phosphatase 1 (*SHIP-1*) expression in BT-474 and MDA-MB-231 cells. Moreover, it was also noticed that pomegranate extract down-regulated miR-27a expression, resulting in transcriptional repressor *ZBTB10* upregulation, and subsequently caused the downregulation of Sp (specificity protein)-1, -3, -4, VEGF, VEGF receptor-1, survivin, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-jB) p65 expression in cancer cells. Thus, pomegranate extract inhibited cell survival and inflammation[51]. Furthermore, pomegranate extract also regulated miRNA expression in BT-474 xenografts *in vivo* study. Pomegranate extract reduced miR-155 expression, induced *SHIP-1* expression, and inhibited *pAkt* and pPI3K expression. Moreover, it decreased miR-27a expression, increased *ZBTB10* expression, and decreased Sp1, Sp3, Sp4 expression as well as VEGF, survivin, and *NFκB* p65 expression[51]. Therefore, the potential impact of pomegranate extract against BC miRNAs may be warranted for future exploration.

3.4. Sulforaphane

Sulforaphane, an isothiocyanate, is found in higher concentration in cauliflower (*Brassica oleracea* var. *botrytis*), Chinese cabbage (*Brassica rapa* var. *chinensis*), brussels sprouts (*Brassica oleracea* var. *gemmifera*), arugula (*Eruca sativa*), radish (*Raphanus sativus*), broccoli (*Brassica oleracea* var. *italica*), kohlrabi (*Brassica oleracea* Gongylodes Group), turnips (*Brassica rapa* var. *rapa*), bok choy

(*Brassica rapa* var. *chinensis*), horseradish (*Armoracia rusticana*), mustard (*Brassica* spp.), rutabaga (*Brassica napobrassica*), collard greens (*Brassica oleracea* var. *acephala*) and watercress (*Nasturtium officinale*)[61]. Sulforaphane has been researched to regulate miRNA expression in BC cells. Sulforaphane treatment was found to increase the expression level of exosomal miR-140 and decrease the expression of exosomal miR-29a and miR-21 in CD49f+/CD24 and ALDH1+MCF10DCIS stem-like cells. Moreover, sulforaphane decreased cancer stem cell marker *ALDH1* expression and mammosphere formation in these cells. These results indicated that sulforaphane may inhibit cancer stem-like cells by regulating the expression level of miRNA[50]. Furthermore, researchers found that sulforaphane treatment up-regulated miR-140 expression in MCF10DCIS cells *in vitro*. Moreover, sulforaphane treatment also increased the expression of miR-140 and decreased *ALDH1* and *SOX9* expression in CD44+/CD24 and ALDH1+ MCF10DCIS cells *in vivo*. These results suggested that sulforaphane targets *SOX9* and *ALDH1* by regulating the expression of miR-140 and eventually suppress BC stem-like cells[50]. These findings would gain further attention for the investigations of sulforaphane as a chemo-prevention and chemo-therapeutic agent for BC.

3.5. DADS

DADS is an organosulphur compound present in garlic[7,62]. It has been researched that DADS has shown to modulate miRNA expression in BC cells. Investigators reported that DADS treatment up-regulated the expression level of miR-34a in MDA-MB-231 cells. By up-regulating miR-34a expression, DADS treatment down-regulated sarcoma (*SRC*, a proto-oncogene) protein levels, and caused the suppression of Ras-GTP, leading to inhibition of extracellular signal-regulated kinase1/2 (ERK1/2) phosphorylation. These effects indicate that DADS inhibits BC cell proliferation and invasion via miR-34a mediated *SRC/Ras/ERK* inhibition[57]. DADS plus miR-34a treatment reduced tumor volume (as compare to control) in rats implanted with MDA-MB-231 BC cells, indicating miR-34a increases antitumor effect of DADS[57]. Hence, DADS could be a promising anticancer phytochemical against BC by targeting miRNAs and needs further research work in future.

3.6. DIM

DIM is widely distributed in cruciferous vegetables including brussels sprouts (*Brassica oleracea* var. *gemmifera*), cauliflower (*Brassica oleracea* var. *botrytis*), kale, broccoli (*Brassica oleracea* var. *italica*), kohlrabi (*Brassica oleracea* Gongylodes Group), watercress (*Nasturtium officinale*), cabbage (*Brassica rapa* var. *chinensis*), arugula (*Eruca sativa*), daikon (*Raphanus sativus*), bok choy (*Brassica rapa* var. *chinensis*), turnips (*Brassica rapa* var. *rapa*), collard greens (*Brassica oleracea* var. *acephala*), mustard greens (*Brassica juncea*) and radishes (*Raphanus sativus*)[63,58].

DIM has been shown to regulate miRNA expression. It has been researched that DIM increased the expression level of miR-212/132 cluster and down-regulated the expression of *SOX4* in T47D and MDA-MB-231 BC cells *in vitro* and *in vivo* in an aryl hydrocarbon receptor-dependent fashion. This study indicates that DIM inhibits BC metastasis via miR-212/132 mediated *SOX4* downregulation[11]. Study also reported that treatment of BC SKBR-3 and MDA-MB-468 cells with DIM up-regulated miR-200a and miR-200b expression and down-regulated oncogenic forkhead box M1 (*FoxM1*) and *pAkt* expression. This in turn resulted in the arrest of cell growth[53]. These results indicated that DIM can be a potent BC miRNA regulatory agent and need further research studies.

3.7. Curcumin

Curcumin is a natural polyphenolic compound with potent anti-BC potential. And high concentration of curcumin was found in the rhizomes of turmeric[64]. It has been proven from different scientific evidences that curcumin can regulate BC miRNAs expression. Curcumin has been shown to alter bisphenolA-induced upregulation of miR-19a and miR-19b and dysregulation of tumor suppressor-*PTEN*, phospho serine/threonine-specific protein kinase (*p-Akt*), *p-MDM2*, *p53*, and proliferating cell nuclear antigen (*PCNA*) in BC MCF-7 cells, which lead to suppression of cell proliferation[54]. It has also been researched that curcumin inhibit metastasis in BC MDA-MB-231 cells. This effect was related with down-regulation of pro-inflammatory c-x-c motif chemokine ligand (CXCL)-1 and -2 cytokines expression through up-regulation of miR-181b expression[65]. Curcumin alone or in combination with emodin up-regulated miR-34a expression in MDA-MB-231 and MDA-MB-435 BC cells *via* downregulating the expression of anti-apoptotic gene B-cell lymphoma 2 (*Bcl-2*) and oncogene *BMI-1*, which finally suppressed cell proliferation and invasion in the surrounding cells[55]. Curcumin also increased the expression of miR-15a and miR-16, translated into a decrease expression of *Bcl-2* and finally induced caspase mediated cell death in MCF-7 cells[66]. These scientific studies have shown that curcumin has the potential to inhibit BC progression via modulating miRNA expression; therefore, curcumin can be a potential anti-BC agent and needs further research.

3.8. Genistein

Genistein is an isoflavone widely distributed in lupine (*Lupinus* sp.), kudzu (*Pueraria* sp.), fava beans (*Vicia faba*), soybeans (*Glycine max*) and psoralea (*Psoralea corylifolia*)[67]. It has also been researched and proven that genistein regulated miRNA expression in BC cells. Genistein down-regulated miR-155 expression and altered miR-155 targets *Foxo3*, *PTEN*, and casein kinase 1a (*CK1a*), b-catenin and *p27* expression in MDA MB-435 and Hs578t cells. As a consequence, genistein inhibited cancer cell survival and proliferation, and induced caspase mediated cell death[56]. This study indicates that genistein can be useful for targeting BC miRNAs. Further investigations are needed.

3.9. Quercetin

Quercetin is a flavonoid found in onions (*Allium* spp.), apples

(*Malus* spp.), red wine, tea (*Camellia sinensis*), lemon (*Citrus* spp.), tomato (*Solanum lycopersicum*), honey, broccoli (*Brassica oleracea* var. *italica*), kale, and beans[68,69]. Quercetin exhibited effect on BC cell growth by regulating miRNA expression. Quercetin increased the expression level of pro-apoptotic-*Bax* (*Bcl-2* associated X), caspase-3, and decreased oncogenic-*EGFR* expression in MCF-7 and MDA-MB-231 cells via increasing the expression level of miR-146a expression. Quercetin induced apoptosis through *Bax* and caspase-3 activation by up-regulating miR-146a expression and inhibited invasion through *EGFR* downregulation[70]. Quercetin also up-regulated the expression of miR-146a in xenografted cells and reduced tumor volume in mice[70]. Based on this study, quercetin could be a promising anti-BC agent and needs further investigations.

3.10. RV

RV is a polyphenol found in grapes (*Vitis vinifera*), berries, tomato (*Solanum lycopersicum*), peanuts (*Arachis* spp.), and red wine[61]. RV down-regulated the expression of different miRNAs such as, miR-125b-5p, miR-214-3p, miR-512-5p and miR-542-3p in MCF-7 BC cells and induces apoptosis. Moreover, it also down-regulated the expression of miRNAs as for example miR-32-5p, miR-134, miR-200c-3p and miR-542-3p in MDA-MB-231 BC cells resulting in BC arrest. Furthermore, RV also increased the expression of apoptosis-related miR-409-3p and miR-122-5p in MCF-7 and MDA-MB-231BC cell lines respectively[12]. Moreover, RV down-regulated the expression of 18 miRNAs including miR-125b-1-3p and miR-93-5p in MCF-7 cells as well as 9 miRNAs such as miR-20a-5p and 125b-1-3p in MDA-MB-231 cells. In both cell lines, RV decreased *Bcl-2*, X-linked inhibitor of apoptosis protein (*XIAP*), cyclin-dependent kinase (*CDK*)-2, 4 and 6 protein expression and up-regulated caspase-8 and 9 protein expression. These results indicated RV induces apoptosis in BC cells *via* regulating miRNA expression[12]. According to a research study performed by Qin *et al*., RV also increased the expression of miR-21, miR-129, miR-204, and miR-489 and down-regulated the expression of DNA methyltransferase 3b (*DNMT3b*) in *in vivo* rat tumors[71]. Additionally, RV increased the expression of miR-663 and miR-744 by down-regulating eukaryotic translation elongation factor 1A2 (*eEEF1A2*) expression in MCF-7 cells resulting in the inhibition of invasion and cell proliferation[72]. Study revealed that RV treatment increases tumor suppressive miR-16, miR-141, miR-143 and miR-200c expression in MDAMB-231-luc-D3H2LN, MCF-7, and MCF-7-ADR cells. In addition, miR-26a, miR-34a, miR-125a-3p, miR-126, miR-128, miR-185, miR-193b, miR-195, miR-196a, miR-335, miR-340, and miR-497 expression and argonaute2 (*Ago2*) expression were also up-regulated in RV treated MDA-MB-231-luc-D3H2LN cells. This study indicates that RV increases *Ago2* activity by upregulating tumor suppressive miRNAs, leading to suppression of tumor growth[73]. RV also suppressed tumor formation in mice injected with MB-231-luc-D3H2LN cells[73]. Clearly, RV has the potential to inhibit BC progression by regulating miRNA expression. All these studies suggested that RV needs further research to develop more anti-BC treatment agents.

4. Current challenges and emerging alternatives

Although DPs have been recognized as BC miRNA regulatory weapons, in this literature review much more attention is given to cope up with the following limitations.

(1)Low bioavailability and poor potency of DPs are some of the limitations associated with their *in vivo* use. However, these problems can be resolved by developing semi-synthetic analogs of them. For example, synthetic curcumin analog 5-bis (4-hydroxy-3-methoxybenzyli dene)-N-methyl-4-piperidone has shown higher bioavailability than curcumin in mice[74] and RV analog 4,4′-dihydroxy-trans-stilbene inhibited BC cell proliferation and invasion with higher efficiency than RV[75].

The development of nanoparticle encapsulated phytochemical formulations is another solution for these bioavailability and potency limitations[2]. For example, nano-encapsulated curcumin and quercetin have shown higher bioavailability than free compounds in rats and nano-encapsulated quercetin has improved *in vivo* anti-BC effects compared to the free forms[61].

Another study found that nanoparticles encapsulated with both quercetin and doxorubicin significantly suppressed doxorubicin-resistant MCF-7 cells *in vivo*[76]. Combinations of two or more DPs may also be beneficial for bioavailability and greater potency. For example, combination of genistein and capsaicin exhibited higher anti-inflammatory and anticarcinogenic effects in MCF-7 and tissue-type plasminogen activator-induced rat mammary tumor cells than either agent alone[77].

(2)Regulation of different signaling pathways by DPs may result in some undesirable changes. For instance, the antiangiogenic characteristic of RV is not only associated with pathological angiogenesis but it also disturbs the physiological angiogenesis inside the cells[78].

(3)It is largely unknown whether advantageous effects of DPs will be seen in humans since many DP potentials have been examined only in pre-clinical trials. Based on the above evidences, it is crystal clear that a much better understanding of the efficacy of DPs in BC prevention is needed. Future research work should emphasis on: (a) Perfect characterization of these DPs, (b) Better elucidation and explanation of the molecular mechanisms actions of these DPs, (c) Confirmation of their efficacy by *in vivo* studies using proper animal models of BC, (d) Demonstration of their effectiveness in clinical trials and (e) Demonstration of their safety.

5. Concluding remarks

BC is a serious concern and miRNAs are dysregulated in BC playing critical roles in regulating different stages of carcinogenesis such as tumor initiation, promotion, progression and chemoresistance. Therefore, miRNAs are gaining more attraction and are novel targets for BC treatment. Different research studies have suggested that DPs can potentially modulate the expression level of different miRNAs involved in cancer. In the present review,

we have discussed some DPs that have shown promising role for targeting BC miRNAs and we have also suggested some potential DPs that can be tested against BC miRNAs for possible molecular mechanism of actions. RV, sulforaphane, genistein, curcumin, DADS, DIM, EA, I3C and quercetin exhibit promising anti-BC results inhibiting BC progression through regulating miRNA expression and it has shown efficacy to regulate miRNAs in both *in vitro* and *in vivo* studies. Among these different DPs, RV has been tested against more miRNAs than the rest of the phytochemicals. Besides, there are some other DPs (benzyl isothiocyanate, capsaicin, EGCG, oleanolic acid, phenethyl isothiocyanate, ursolic acid, *etc*.,) which have anti-BC potentials but yet they have not been tested and researched against miRNAs involved in BC. Importantly, further studies of these potential bioactive compounds might lead to development of strategies for BC control. Recently, different miRNAs along with their molecular targets have been identified in BC and have been recognized as therapeutic targets as well. To the best of our knowledge and after careful literature survey, DPs have been tested against only a limited number of BC miRNAs and a large number of miRNAs still need extensive research work in order to unfold their molecular mechanism of action.

Conflict of interest statement

The authors declare that they have no conflicts of interest.

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