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Mini Review

microRNAs as Therapeutic Targets in Diagnosis, Prognosis, and Treatment of Pancreatic Cancer: A Mini Review

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Abstract

MicroRNAs (miRNA) are potent targets for cancer therapy. Altered miRNA expression is commonly associated with cancer stem cells and EMT (epithelial-to-mesenchymal transition) phenotypes which are hallmarks of tumor initiation, progression, and metastasis. These non-coding RNAs bind to the 3′ UTR of target mRNAs and degrade them or inhibit their translation; they are potent diagnostic, prognostic, and therapeutic molecules. Although some miRNAs can prevent tumor growth, some others can promote cancer. For cancer treatment, tumor suppressor miRNAs should be up-regulated whereas oncomirs should be down-regulated. Furthermore, studies show that nature-derived components such as oridonin, curcumin, isoflavone, I3C, DIM, EGCG, and resveratrol can target several miRNAs simultaneously and inhibit cancer growth, induce apoptosis, reverse EMT to MET phenotypes, and eliminate CSCs or EMT phenotypic cells (which cause tumor recurrence and resistance to different conventional therapies). This mini review will discuss the list of nature-derived components which improve the overall survival of cancer patients.

INTRODUCTION

Due to its poor prognosis, inadequate detection, and treatment, pancreatic cancer is one of the tumor types with a high fatality rate [1]. There are numerous therapeutic strategies against this cancer, with chemotherapy being the most popular treatment. However, chemotherapy is ineffective against pancreatic cancer because of the unique tumor microenvironment, which leads to reduced drug efficacy. Another popular therapeutic method is radiotherapy, which has benefits for local tumors but does not work for incurable pancreatic malignancies [2]. Surgery is another option for some malignancies, but because 80–85% of patients are ineligible, it does not achieve the desired outcome for this malignancy [3,4]. Precise knowledge about some of the crucial intracellular processes in cancer cells can help us to find more effective treatments.

One of the most significant intracellular agents is the microRNA family. Endogenous non-coding single-strand RNAs with an average length of 19 to 23 ribonucleotides are referred to as microRNAs (miRNAs) [5]. Their mode of action involves complementarity aligning with the target messenger RNA (mRNA) sequences to reduce their RNA expression levels, which in turn prevents them from being translated or causes the mRNAs to be degraded. Most coding genes are regulated by miRNAs. As a result, they are useful targets for researchers and can aid medical professionals in prognosis, diagnosis, and therapy.

CHARACTERISTICS OF MIRNAS

One of the mystifying characteristics of miRNA is that a single miRNA can target many mRNAs and the same mRNA can be the target of multiple miRNAs. For instance, miR-145 controls a variety of mRNAs, including mucin 13, the TGF-â receptor, SMAD2, and NEDD9 (neural precursor cell expressed developmentally down-regulated 9), to reduce the growth and metastasis of pancreatic cancer and to increase the chemosensitivity to gemcitabine (a chemotherapy drug) [6-8]. A candidate target, slug mRNA, may also be suppressed by miR-34 and miR-203a-3p [9]. So, miRNAs contribute to a puzzling and huge network with mRNAs and their targeting is not straightforward. This limits their clinical application. miRNAs are implicated in chemotherapy and drug resistance and understanding their involvement can help clinicians and patients experience better therapeutic outcomes [10].

TARGETING MIRNAS IN PANCREATIC CANCER AS A THERAPEUTIC OPTION

Concerning the roles of miRNAs in cancer, they are categorized into two main groups: tumor suppressors and oncogenic miRNAs oncomirs. The role of miRNAs tightly depends on the function of their target sequences. When the natural balance between these two fundamental groups breaks, the onset of different conditions occurs [11]. It is postulated that several anticancer actions, such as proliferation, invasion inhibition and increased apoptosis and chemosensitivity can be generated in cancer cells by decreasing the oncomir levels and activating tumor suppressor miRNAs.

TUMOR SUPPRESSOR MIRNAS IN PANCREATIC CANCER

The tumor suppressor miRNA group can degrade target mRNAs to prevent the progression of pancreatic cancer. Therefore, a medical application of these miRNAs is to overexpress them. These miRNAs are associated with up-regulating apoptosis, controlling cell cycle mediators, inhibiting oncogenic transcription factors, inhibiting angiogenesis, and increasing chemosensitivity. For instance, miR-455-3p suppresses pancreatic cancer progression by blocking the Wnt/catenin signaling pathway and promoting these cells' death by up-regulating the expression of Bcl-2 and Bax proteins, which play a key role in the activation of caspases and apoptosis [5,12]. Other tumor suppressors like miR-373-3p and miR708 increase chemosensitivity. miR-373-3p decreases Cyclin D2 expression, enhances gemcitabine sensitivity (a chemotherapeutic agent), and prevents the growth of gemcitabine-resistant pancreatic cancer cells [13]. miR708 works as a proliferation and chemoresistance inhibitor that suppresses surviving expression [14]. miRNA-145, prevents cancer growth and angiogenesis by angiopoietin-2 (Ang-2) down-regulation while Let-7 prevents the progression of this cancer by up-regulation of cytokine signaling 3 (SOCS3) suppressors to block the phosphorylation of STAT3.

Tumor suppressor miRNAs can also work by controlling other signaling pathways. For instance, miR-34a promotes apoptosis and inhibits metastasis by blocking the expression of Snail1 and Notch 1. However, miR-34a is up-regulated when Notch 1 is down-regulated, creating a feedback loop between the two [15]. Additionally, miR-34 can improve the chemosensitivity of pancreatic tumor cells to gemcitabine gemcitabine as a chemotherapy drug against different types of cancer and induce apoptosis by down-regulating Slug [9,16]. It contributes to pancreatic CSCs' capacity for self-renewal despite their resistance to a variety of conventional treatments [17]. miR-203a-3p also suppresses Slug and inhibits the proliferation of pancreatic cancer cells and the epithelial to mesenchymal transition (EMT) [9]. EMT is crucial in cancer metastasis. In this regard, focusing on the up-regulation of miRNA candidates involved with suppressing EMT is crucial to stopping the metastasis of cancer. Another tumor suppressor miRNA is MiR-16-1, located on the 13q14.3 locus, and its deletion is reported in B-cells in 65% of chronic lymphocytic leukemia patients [18]. Any decrease in miR-15/16 leads to deficiency of DROSHA processor and elevated activity of histone deacetylases. It leads to the epigenetic silencing of several tumor suppressor genes. Expression of miR-16-1 blocks cell proliferation and promotes apoptosis [19]. In NB4 cells transduced with lentiviral miR-16-1, the proliferation and general activity of NB4 cells decreased significantly. But the expression of two important apoptosis-associated genes, Bax and Bcl-2 was like non-treated NB4 cells. Also, miR-16-1 arrests treated NB4 cells in the G1 phase and elevate caspase-3 activity significantly, which can lead to apoptosis. Based on this data, miR-16-1 has medical effects on leukemia [19]. Another study showed that miRNA-20a is overexpressed in various malignancies, including pancreatic, lung, and B-cell lymphomas, and it negatively regulates the E2F TF1 (E2F1), Stat3, and cyclin D1 genes, it can also be regarded as an oncogene [17,20].

ONCOGENIC MIRNAS

Oncogenic miRNAs act in the reverse direction of tumor suppressor miRNAs and promote the progression of cancer, metastasis, and drug-resistance. For example, the miR-21 gene is over-expressed in a variety of human malignancies like pancreatic, lung, liver, and esophageal cancers. It promotes tumor growth, invasion, and migration through targeting some tumor suppressors such as PDCD4, and PTEN (tumor-suppressing phosphatase and tensin homolog), which regulate intracellular signaling pathways, and modulate the cell microenvironment [21,22]. Over-expressed miR-21 in cancer-associated fibroblasts (CAF) can promote metastasis and gemcitabine chemo-resistance by enhancing, level of platelet-derived growth factor (PDGF) as well as matrix metalloproteinases such as MMP-3 and MMP-9 [22]. A significant level of miR-21 also increases 5-fluorouracil (5-FU, a chemotherapeutic agent) resistance [23].

Additionally, in pancreatic cancers, a positive feedback loop has been seen between miR-21 and the epidermal growth factor (EGF) pathway [24]. EGF causes miR-21 to be overexpressed, whereas miR-21 enhances EGF function by inhibiting EGF inhibitors. The activation of additional intracellular cascades, such as the MAPK/ERK and PI3K/AKT signaling pathways, as well as the suppression of apoptosis via Sprouty2 inhibition, are additional ways that miR-21 can promote cell proliferation. One of miR-21's roles is to reverse the relationship with the Von Hippel-Lindau tumor suppressor [25]. Like a lot of molecules, miR-21 plays two different intracellular roles as it can work as a tumor suppressor miRNA too. For example, it inhibits pancreatic cancer cell proliferation by blocking the HIF1a/VEGF pathway and the expression of some kinds of matrix metalloproteinases such as MMP-2 and MMP-9[12]. In general, overexpression of miR-21 is associated with worse remission rates, progression-free survival, more metastatic lymph-nodes and less differentiated tumors [17,26]. Based on some research, it can be considered an appropriate prognostic indicator for chemotherapy classification and a target in the treatment of pancreatic cancer [26]. miR-155 is another oncomir that is introduced as a major molecule in pancreatic cancer progression by Foxo3a down-regulation which leads to Reactive Oxygen Species (ROS) induction [27]. Furthermore, miR-155 decreases the level of cytokine signaling 1 and SOCS3 suppressing molecules which leads to STAT3 activation and subsequently induces pancreatic cancer cells proliferation and metastasis [28,29]. Based on these studies, as its role is solely oncogenic, it is promising as a medical target.

Based on some studies, the miR-200 family plays a key role in tumor initiation, metastasis, and the prognosis of pancreatic cancer [30]. In EMT, the expression of the mir-200 family is down-regulated or absent. After pancreatic duct cell carcinoma surgery, the EMT is linked to a lower survival rate. Additionally, mir-200 and let-7 are down-regulated in pancreatic cancer patients, which is related to their resistance to gemcitabine. ZEB1 and vimentin, which are EMT inducers, are down-regulated by the mir-200 family whereas cadherin 1 is up-regulated. Targeting EMTs or CSCs with miRNA can be a medicinal strategy because they promote tumor recurrence and metastasis [17]. miR-320a significantly is up-regulated in pancreatic cancer and leads to the proliferation, intravasation, extravasation, metastasis, and EMT. It binds to the 3'UTR of programmed cell death protein 4 (PDCD4) mRNA, and its down-regulation leads to 5-FU resistance. When the PDCD4 expression increases, the function of miR-320a is attenuated in a negative feedback loop [11]. mir-301 is another oncogenic miRNA known as an invasion and metastasis-related oncogene that is highly expressed only in pancreatic cancer parallel with cox-2 and MMP-2 proteins which can be a specific pancreatic cancer marker [34]. mir-301 has the potential to be a new target for the prognosis, early diagnosis, and treatment of pancreatic cancer [34]. The cancer was diagnosed in the later phases however, miRNAs can open new windows to a better future [17].

In general, targeting oncogenic miRNAs is a goal of medical strategies. miRNA antagonists are introduced as single-stranded antisense oligodeoxynucleotides (ASO) that target the oncogenic miRNAs, show the anti-cancer effect, and can protect miRNAs from nucleases with high stability and affinity. They can decrease tumor dissemination by inhibiting the function of the oncogenic miRNAs. Thus, providing the basis for integrating miRNAs into pancreatic cancer therapy [11].

REGULATION OF MIRNAS BY NATURE-DERIVED COMPONENTS IN PANCREATIC CANCER THERAPY

Concerning resistance or non-eligibility of pancreatic cancer for various common cancer treatments, like surgery, radiotherapy, and chemotherapy, some researchers instead focused on nature-derived remedies. Natural agents were introduced as promising medical candidates because they do not have any toxic effect on humans. They normalize the level of miRNA in patients, [31] and reduce cancer stem cell resistance

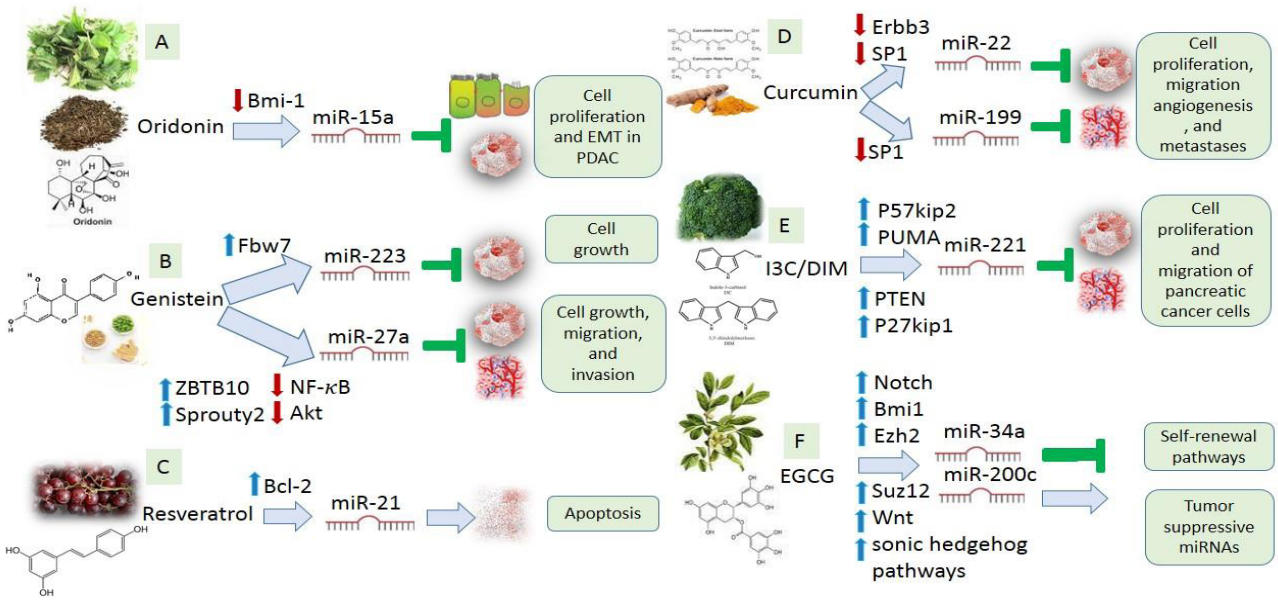

Figure 1 Mechanism of action of A) Oridonin targeted miR-15a by down-regulation of Bmi-1 which inhibit cell proliferation and epithelial to mesenchymal transition in pancreatic ductal adenocarcinoma [39].

B) Genistein targeted miR-223 by up-regulation of F-box and WD-40 domain protein 7 (Fbw7) which suppresses cell growth and induces apoptosis. Genistein targeted miR-27a by up-regulation of ZBTB10 and Sprouty2, blocks NF-κB and Akt signaling pathways which suppresses cell growth, migration, and invasion, and induces apoptosis [60,61].

C) Resveratrol targeted miR-21 by up-regulation of Bcl-2 which increases apoptosis [66].

D) Curcumin targeted miR-22 and miR-199 by down-regulation of Erbb3 and decreases SP1 proteins to inhibit cell proliferation, migration angiogenesis, and metastases [43,59].

E) I3C/DIM targeted miR-221 by up-regulation of PTEN, p27kip1, p57kip2, and PUMA which suppresses cell proliferation and migration of MiaPaCa-2 and Panc-1 pancreatic cancer cells [63]. DIM targeted miR-146 and miR-200 by down-regulates EGFR, IRAK-1, NF-kB, and MTA2 which inhibits cell invasion [64]. DIM targeted miR-200 by down-regulation of ZEB1, slug, vimentin, and E-cadherin which reversal of mesenchymal to epithelial morphology [47].

F) EGCG targeted miR-34a by inhibition of Notch, Bmi1, Ezh2, Suz12, Wnt and sonic hedgehog pathways which selectively blocks self-renewal pathways. EGCG targeted miR-200c by up-regulates the key tumor suppressive miRNAs on pancreatic cancer [65].

to traditional agents. Numerous analyses confirm that consuming natural agents regulate miRNA expression [32]. Figure 1 presents the targets, mechanism of action, and consequence of several effective nature-derived components such as oridonin, curcumin, isoflavone, I3C, DIM, EGCG, and resveratrol against pancreatic cancer.

One of the natural agents is oridonin, which is a natural terpenoid in traditional Chinese herbal medicine [33]. It has some antitumor effects, such as, the promotion of apoptosis, as well as cell growth and invasion inhibition [34]. According to a microarray profile analysis in BxPC-3 human pancreatic cancer cells, one hundred and five miRNAs are differentially expressed following oridonin treatment, confirming the potential of oridonin as a candidate in future research on tumor treatments [35,36]. The effect of oridonin has not been evaluated in any cancers in clinical trials. For filling this information gap, conducting a clinical trial to gain evidence of the oridonin effect on cancer treatment is highly recommended.

Curcumin (diferuloylmethane) is another natural agent derived from turmeric. It boosts with antioxidant, anti-proliferative, pro-apoptotic, anti-inflammatory, and tumor inhibitory properties and control of the cell cycle by regulating signaling pathways such as NF-κB, and the expression of their target genes [37,38]. For example, in human pancreatic cells, curcumin up-regulates miR-22, the tumor suppressor gene while it down-regulates the miR-199a, an oncogene [39]; Despite its promising mechanism of action, its administration is limited because of its weak bioavailability [31].

Soy Isoflavones like genistein, daidzein, and glycitein are other natural agents that are derived from soybean. Genistein inhibits tumor progression, cancer cell proliferation, invasion, and metastasis through oncomir degradation [40-43]. The miR-200 and let-7 families are down-regulated in gemcitabine-resistant pancreatic cancer cells with EMT conditions which lead to pancreatic cancer aggressiveness [43]. Isoflavones increase miR-200 expression and subsequently, decrease vimentin expression which reverses the EMT phenotype. As a result, it also up-regulates let-7 and inhibits cancer cell growth.

Dimer diindolylmethane (DIM) and Indole-3-carbinol (I3C) are driven by glucosinolates that are in the Cruciferae plant family. In fact, *in vivo,* I3C dimerizes with DIM. They restrict cancer cell proliferation and metastasis by EMT-related miRNA gene regulation. They affect both tumor suppressors and oncogenic miRNAs. It has been observed that in lung cancer, I3C normalizes miRNA abnormalities [5]. For example, it down-regulates miR-21, miR-31, miR-130a, miR-146b, and miR-377. Moreover, I3C inhibits PTEN, PDCD4, and RECK as miR-21 target genes while in pancreatic cancer, DIM is EMT reversing. DIM also up-regulates miR-200 and let-7 families in gemcitabine resistant cells. These miRNAs usually have been lost in many cancers including pancreatic cancer. Conversely, DIM down-regulates vimentin and slug in mesenchymal to an epithelial phenotype. Therefore, it is a potent nature-derived therapeutic component against pancreatic cancer [6].

Additionally, it has been shown that DIM elevated the level of miR-34a in prostate cancer via epigenetic regulation. The miR-34a re-expression resulted in the androgen receptor's (AR) down-regulation [44]. These findings demonstrate the positive impacts of DIM on the activation of tumor-suppressive miRNAs. It suggests a potential therapeutic strategy for the treatment of human prostate cancer. More research on other malignancies, including pancreatic cancer, will shed light on the therapeutic agent's significance in preventing cancer.

EGCG (Epigallocatechin-3-gallate) is a polyphenol derived from natural green tea with anticancer characteristics through effects on miRNAs [45-47]. EGCG down-regulates 48 miRNAs and up-regulates 13 miRNAs such as miR-16 in HepG2 human hepatic cancer cells. The latter leads to apoptosis through a decrease of Bcl-2 in this cell line [47]. Based on such data, EGCG can inhibit cancer growth through miRNA regulation.

Resveratrol is a natural phytoalexin that can be found in some plants such as mulberries, grapes, and peanuts. It has anti-cancer effects by miRNAs regulation that leads to cancer cells growth inhibition and apoptosis induction [48, 49]. CAY10512 is a synthetic analog of resveratrol that can affect miR-146a expression [50]. Based on this research, resveratrol plays a role in changing physiological characteristics of cells by miRNA expression regulation and their subsequent signal transduction [35]. Therefore, this nature-derived compound as a controller of cell proliferation, resveratrol can be considered for wider anti-cancer investigations.

THE SELECTED NATURE-DERIVED COMPONENTS IN THE CLINICAL TRIALS

This study focused on pancreatic cancer in clinical trials, including a thorough literature assessment on the chosen nature-derived components against malignancies (Table 1). The findings of this investigation revealed that while other cellular processes like signal transduction have been taken into consideration, the effects of oridonin and curcumin on miRNA levels have not been explored in any clinical trials with respect to malignancies. For example, in the Phase 2 clinical trial (NCT00094445), 21 pancreatic cancer patients received curcumin orally to assess its biological effects. The authors reported no toxicities nor side effects, and a down-regulation of NF-κB, cyclooxygenase-2, and phosphorylated STAT3 in mononuclear immune cells of peripheral blood obtained from patients [51]. Most of the patient baseline levels of NF-κB, cyclooxygenase-2, and phosphorylated STAT3 were significantly higher than their counterparts in healthy controls [51]. In another investigation, the curcumin effect was evaluated in cancer patients who were treated with gemcitabine. This study is in phase 2 clinical trial (NCT00192842). In another trial which is a recruiting phase III (NCT00486460), the effect of three drugs combination of gemcitabine, curcumin and Celebrex have been evaluated in patients suffering from advanced or inoperable pancreatic cancers. There are no released results from this study, but in theory, curcumin can be considered a successful candidate alone or in combination with conventional drugs.

Since resveratrol inhibits miR-21 and acts as an anti-apoptotic agent of BCL-2. Specifically, it could potentially reduce the growth of cancerous cells in the pancreas and bladder. The effectiveness of resveratrol as an anti-cancer drug has been assessed in numerous clinical trials on a wide range of cancer

Table 1: Clinical trials evaluating the effects of curcumin, isoflavone, I3C, DIM, EGCG, and resveratrol on various human cancers.

Natural component	Cancer type	Trial identifier	Phase
Curcumin	Breast	NCT01042938	2
	Pancreatic	NCT00094445	2
	Pancreatic	NCT00192842	2
	Colorectal	NCT01333917	1
	Colorectal	NCT00027495	1
	Uterine cervical	NCT01035580	1
	Multiple myeloma	NCT00113841	N.A
	Breast	NCT01975363	N.A
	Colorectal	NCT01859858	1
	Rectal	NCT00745134	2
	Colon	NCT01294072	1
	Prostate	NCT01917890	N.A
	Head and neck	NCT01160302	0
	Colon	NCT01490996	1/2
	Prostate	NCT02095717	2
	Endometrial	NCT02017353	2
	Prostate	NCT02064673	2
	Familial adenomatous Polyposis	NCT00641147	N.A
	Familial adenomatous Polyposis	NCT00927485	N.A
	Colorectal	NCT01948661	2
Resveratrol	Colon	NCT00256334	1
	Colorectal	NCT00433576	1
	Solid tumors	NCT00098969	1
	Neuroendocrine	NCT01476592	N.A
Genistein	Breast	NCT00244933	2
	Bladder	NCT00118040	2
	Breast	NCT00099008	1
	Prostate	NCT00584532	2/3
	Pancreatic	NCT00376948	2
	Prostate	NCT00269555	N.A
	Prostate	NCT00499408	2
	Prostate	NCT00078923	2
	Colon cancer, rectal cancer, and colorectal cancer	NCT01985763	1/2
	Prostate Adenocarcinoma	NCT01325311	2
	Adenocarcinoma of the prostate and recurrent prostate cancer	NCT01126879	2
	Non-small cell lung cancer	NCT01628471	1/2
	Kidney Cancer and Melanoma (Skin)	NCT00276835	1
	Pancreatic	NCT01182246	1/2
EGCG	Adenocarcinoma of the prostate	NCT00459407	1
	Barrett esophagus	NCT00233935	1
	Lung cancer and tobacco use disorder	NCT00573885	2
	Cervical cancer, cervical intraepithelial neoplasia grade 1, and human papilloma virus infection	NCT00303823	2
	Prostate	NCT01105338	2/3
	Estrogen receptor-negative breast cancer and progesterone receptor-negative breast cancer	NCT00516243	1

	Multiple myeloma, plasma cell neoplasm, and precancerous condition	NCT00942422	2
	Prostatic hyperplasia	NCT00596011	2
	Adenocarcinoma of the colon	NCT01606124	2
	Precancerous condition prostate cancer	NCT00253643	N.A
	Breast	NCT00917735	2
	Colorectal	NCT01360320	2
	Breast	NCT00949923	N.A
I3C	Prostate	NCT00607932	N.A
	Breast	NCT00033345	1
	Unspecified adult solid tumor	NCT00100958	1
DIM	Prostate	NCT00450229	1
	Prostate	NCT00305747	1
	Cervical cancer and precancerous condition	NCT00462813	3
	Prostate	NCT00888654	2
	Breast	NCT01391689	2/3

and malignancies including colon cancer prevention by blocking the Wnt pathway (an important signaling pathway in vitro and in animal colon cancer). Currently, 18 studies have assessed colon cancer, liver cancer, neuroendocrine tumors, neoplasms, colorectal adenocarcinoma, unspecified adult solid tumor, breast cancer, multiple myeloma, lymphangioleiomyomatosis, but no trial has studied the effect of resveratrol on miRNAs in pancreatic cancer or other cancers. We thus highly-recommend designing a trial in this area.

No studies have been found for the evaluation of soy isoflavones' effects on pancreatic cancer, but a couple of studies on other cancers may prove useful. For example, the effects of soy isoflavone on prostate-specific antigen (PSA), hormone levels, gene expression, and apoptosis were evaluated in men suffering from localized prostate cancer in a clinical trial (NCT00255125). The gene expression data showed twelve genes related to the control of the cell cycle and nine genes related to apoptosis being down-regulated in the treatment group compared to the placebo control group [52]. Designing a novel study for the assessment of isoflavone's effect on pancreatic cancer patients can be useful.

Similarly, there are no studies for assessing the effects of BioResponse 3,3′-diindolylmethane (BR-DIM) in pancreatic cancer. However, 52 studies were found evaluating this natural component's effects on different cancers. For example, in the phase II clinical trial (NCT00888654), the effect of DIM treatment on castration-resistant prostate cancer (CRPC) was assessed. The result showed BR-DIM down-regulated the wild-type AR *in vitro* and *in vivo*. AR can induce epithelial-to-mesenchymal transition (MET) phenotypes and maintain stem cell characteristics; both phenotypes lead to enzalutamide resistance. The enzalutamide resistance occurs partly because the AR, Lin28B, and EZH2 are dysregulated via the re-expression of miR-34a, miR-320, miR-27b, and let-7 in human prostate cancer (PCa). The final analysis proved that BR-DIM was well-tolerated in these clinical trials, and in 93% of patients, prostatic DIM levels were detectable. The blocking effects of BR-DIM on the AR, its target genes, and PSA were detectable, and a modest efficacy was observed. As a result, BR-DIM is a potential medical candidate to delay or prevent cancer development [53] and more studies on the evaluation of its effects on pancreatic cancer in trials is necessary.

The effect of EGCG on miRNAs in cancers has not been evaluated in any trial and only one study has evaluated the effect of EGCG in pancreatic adenocarcinoma and unresectable pancreatic carcinoma. The status of this phase I clinical trial (NCT02336087) is active, not recruiting and no data has been released yet. Forty-one studies were found for the evaluation of EGCG in other cancers. As obesity has an important role in cancer progression, the control of obesity is effective in cancer treatment. For example, in a trial (NCT00596011), the effect of EGCG was assessed on obese men suffering from prostate cancer. The results demonstrated that EGCG was not effective in reducing body mass index and subsequently it was not effective in cancer treatment [54]. This trial failed to meet the endpoints but more studies in this area are needed.

As there are no trials concerning the effect of resveratrol on miRNAs in pancreatic or any other cancers, we present an analysis of its effects on other intracellular compounds. In a phase I pilot study on eight patients suffering from colon cancer (NCT00256334), the efficacy of low dose resveratrol and resveratrol in the form of freeze-dried grape powder (GP) was evaluated on Wnt signal transduction in the colon. The result of this trial shows GP in combination with various bioactive components inhibits the Wnt pathway in the normal colonic mucosa, but not cancerous ones. More studies on supplements containing whole grapes or GP as a potent colon cancer drug are warranted [55].

CONCLUSIONS

According to our earlier studies and the literature analysis, miRNAs are effective cancer therapy targets because when one of them is altered, a network of genes is subsequently affected. Due to CSCs as well as EMT phenotypes, the modified pattern of miRNA expression is associated with tumor initiation, progression, invasion, and metastasis. The deregulation of miRNA expression modifies the biological activity of the processes. miRNAs are effective diagnostic, prognostic, and therapeutic agents due to

their sequence specificity on the target mRNA and their ability to prevent mRNAs translation in the first place.

Natural substances provide new possibilities for therapies since they simultaneously target several miRNAs, which in turn regulate multiple targets. Curcumin, isoflavones, I3C, DIM, EGCG, and resveratrol are examples of natural substances that modulate miRNAs to prevent the development of cancer cells, trigger apoptosis, and turn EMT into MET phenotypes. They can therefore be used as chemo-preventive drugs in lieu of traditional treatments. The natural substances remove CSCs or EMT phenotypic cells, which are responsible for tumor recurrence and resistance to several conventional treatments. As a result, natural remedies increase the overall survival of cancer patients [31]. Few clinical studies have been conducted to evaluate natural therapeutic agents for pancreatic cancer; therefore, new clinical trials should be planned.

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