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Plant bioactive compounds driven microRNAs (miRNAs): A potential source and novel strategy targeting gene and cancer therapeutics

Sahreen Sumaira [a], Soundararajan Vijayarathna [a], Manisekaran Hemagirri [a], Mohd Adnan [b], Md Imtaiyaz Hassan [c], Mitesh Patel [d], Reena Gupta [e], Shanmugapriya [a], Yeng Chen [f], Subash C. B. Gopinath [g], Jagat R. Kanwar [h], Sreenivasan Sasidharan [a,*]

[a] Institute for Research in Molecular Medicine (INFORMM), Universiti Sains Malaysia, USM, 11800, Pulau Pinang, Malaysia
[b] Department of Biology, College of Science, University of Hail, Hail, P.O. Box 2440, Saudi Arabia
[c] Centre for Interdisciplinary Research in Basic Sciences, Jamia Millia Islamia, Jamia Nagar, New Delhi, 110025, India
[d] Research and Development Cell and Department of Biotechnology, Parul Institute of Applied Sciences, Parul University, Vadodara, 391760, Gujarat, India
[e] Institute of Pharmaceutical Research, Department. Pharmaceutical Research, GLA University, Mathura, India
[f] Department of Oral & Craniofacial Sciences, Faculty of Dentistry, University of Malaya, 50603, Kuala Lumpur, Malaysia
[g] Faculty of Chemical Engineering Technology, Universiti Malaysia Perlis, Perlis, Malaysia
[h] Department of Biochemistry, All India Institute of Medical Sciences (AIIMS), 174001, Bilaspur, Himachal Pradesh, India

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ABSTRACT

Irrespective of medical technology improvements, cancer ranks among the leading causes of mortality worldwide. Although numerous cures and treatments exist, creating alternative cancer therapies with fewer adverse side effects is vital. Since ancient times, plant bioactive compounds have already been used as a remedy to heal cancer. These plant bioactive compounds and their anticancer activity can also deregulate the microRNAs (miRNAs) in the cancerous cells. Therefore, the deregulation of miRNAs in cancer cells by plant bioactive compounds and the usage of the related miRNA could be a promising approach for cancer cure, mainly to prevent cancer and overcome chemotherapeutic side effect problems. Hence, this review highlights the function of plant bioactive compounds as an anticancer agent through the underlying mechanism that alters the miRNA expression in cancer cells, ultimately leading to apoptosis. Moreover, this review provides insight into using plant bioactive compounds -driven miRNAs as an anticancer agent to develop miRNA-based cancer gene therapy. They can be the potential resource for gene therapy and novel strategies targeting cancer therapeutics.

1. Introduction

Cancer, as a multifactorial health situation involving abnormal cell division and genetic mutation, is a deadly disease with a large percentage of recurrence and resistance that affects men, women and even children all over the world [1]. A recent analysis claims that the prevalence of cancer has significantly increased, that in 2020 new reported cancer cases were 19.3 million, with a subsequent 10 million demises. If this rate persists, then by 2040, there will be more than 30 million cases per year, and we can face the cancer epidemic [2]. In normal cells, symmetric and asymmetric cell divisions are proliferation and differentiation processes, respectively, while uncontrolled cell division is considered a primary reason to cause different types of cancer. Comprehensively, uncontrolled proliferation produces genetic instabilities and alterations, transforming malignant cells from normal cells. Mutations in oncogenes, DNA repair genes, tumour suppressor genes, and genes involved in cell growth metabolism trigger these genetic instabilities. Besides, internal factors like body immune and genetic mutations and external factors like smoking, pollutants, radiation, chemicals, and infectious agents are also causes of cancer [3]. Humans can develop 36 different types of cancer, with thyroid, cervical, colorectal, breast, and lung cancer being the majority of cases in women and

* Corresponding author. Institute for Research in Molecular Medicine, Universiti Sains Malaysia, 11800, USM, Pulau Pinang, Malaysia.
E-mail addresses: sumairasahreen@gmail.com (S. Sumaira), vijaya_r_1984@yahoo.com (S. Vijayarathna), hemagirri97@gmail.com (M. Hemagirri), drmohdadnan@gmail.com (M. Adnan), mihassan@jmi.ac.in (M.I. Hassan), patelmeet15@gmail.com (M. Patel), reena.gupta@gla.ac.in (R. Gupta), shan_priya1125@yahoo.com (Shanmugapriya), chenyeng@um.edu.my (Y. Chen), subash@unimap.edu.my (S.C.B. Gopinath), jagat_rocky@hotmail.com (J.R. Kanwar), srisasidharan@yahoo.com (S. Sasidharan).

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stomach, liver, lung, and prostate cancer in men [4]. Malignant cells are, by definition, localised, but they can nonetheless spread throughout the body by a process known as metastasis, which entails the cancerous cells becoming mobile and detachable, causing them to adhere to endothelial cells and subsequently grow in particular areas [5]. Resistance to apoptosis-induced metastasis is one of the leading causes of cancer-related death [1].

It is also noticed that present chemotherapy drugs are ineffective in killing only cancer cells, as they destroy healthy cells/tissues. Additionally, it has been observed that typical chemical medications also have adverse side effects on healthy cells, including nausea, alopecia, and bone marrow tissue dysfunction [6], thus impairing patients' quality of life. Increased mortality rates with poor prognosis and diagnosis support the curiosity to investigate novel therapeutic targets. So, it is rational to discover new alternative cancer therapies to control the cell cycle machinery [7]. One such important alternative for cancer therapies is the usage of non-toxic plant bioactive compounds that target the cancerous cells' miRNAs and modulate the cancerous cells' metabolism, leading to apoptosis. Plant bioactive compounds could regulate the miRNA expression in cancer cells and play an essential role in the post-transcriptional level to control various proteins related to cell growth and apoptosis induction. Greenwell et al. [8] reported that altering miRNAs expression levels in cancer cells by plant bioactive compounds regulates several biological processes necessary for cancer development, including cell proliferation, cell cycle regulation, metabolism, and apoptosis. The function of plant bioactive compounds as an anticancer agent is thus summarized in this review through the underlying mechanism that altered miRNA expression in cancer cells, finally leading to apoptosis. Interestingly, miRNAs are proven to be used as cancer therapeutic with the ability to regulate entire biological pathways, so this review may shed light on the development of miRNA-based cancer gene therapy as well as to understand the role of the plant bioactive compounds that control miRNA as an anticancer treatment (Fig. 1). Since single miRNA targets multiple pathways and gene products, so possesses more therapeutic potential for cancer diagnosis, prognosis and treatments.

2. The usage of plant bioactive compounds driven by the miRNAs as a novel strategy in cancer therapy

Chemotherapy, radiotherapy, and chemically derived medications are only a few of the numerous therapies available for cancer treatment and management. However, these treatments result in negative side effects and other health issues for the patients. Therefore, there is a pressing need to discover alternative therapies with fewer downsides. Due to their non-toxic nature and absence of/minimal side effects, medicinal plant bioactive compounds are receiving much attention for their potential application as cancer treatment agents [7,8]. Our world is rich with a wide variety of important medicinal plants with a range of therapeutic properties to cure diseases that affect the world population. Even since ancient times, plants and plant bioactive compounds are already used as remedy to heal numerous illnesses and as functional food by human beings. Along with a wide range of therapeutic properties, these plant bioactive compounds can also deregulate the miRNAs of the organism (Fig. 1). Therefore, utilizing associated miRNAs and deregulating miRNAs in cancer cells could be a potential strategy for treating the disease, especially to eliminate cancer progression and proliferation, inhibit metastasis, and avoid problems with chemotherapy side effects. Studying the anticancer effects of plant bioactive compounds and their miRNA regulation activity is crucial to identifying the oncogenic miRNAs and the tumor suppressor miRNAs, which will aid in developing plant bioactive compounds and miRNA-based cancer therapies. This is since regulation of the expression levels of many miRNAs results from the anticancer activity of plant bioactive compounds. For instance, novel miRNAs discovered through the abovementioned research will contribute to the emergence of miRNA-based cancer gene therapy or the discovery of novel miRNAs as biomarkers for cancer diagnosis or prediction.

Therefore, using plant bioactive compounds, which regulate miRNAs and related miRNAs in cancer cells as novel strategies and approaches to develop cancer therapy, can provide new insights owing to uncovering the novel miRNAs and mechanism of actions of bioactive compounds in medicinal plants. These multi-level strategies and approaches are breakthroughs for identifying plant-based bioactive compounds. Firstly, genomics resources, used in every aspect of life, showed significant

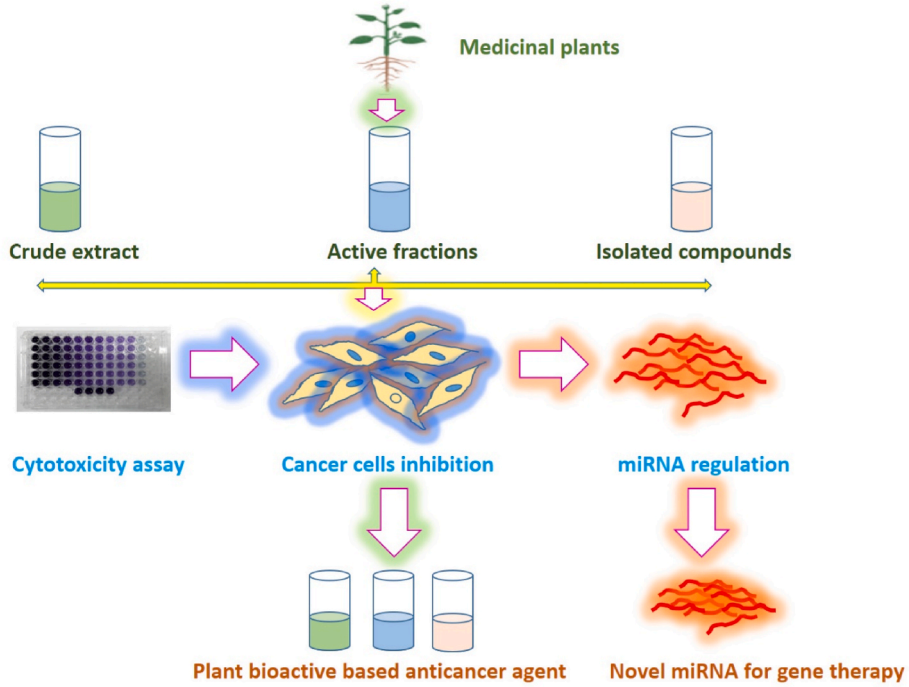

Fig. 1. Schematic diagram shows various form of plant bioactive compounds/miRNAs inhibit cancer progression.

progress regarding phytochemicals for developing anticancer drugs.

Plant-regulated miRNAs can be utilized to identify the desired miRNA on a genetic basis for cancer-related therapeutic potential via genetic engineering and genetic composition. Secondly, the transcriptomic approach is beneficial to uncover the curtains of genetic pathways responsible for miRNA to deliver therapeutic targets in carcinogenesis further. To achieve the goal, both transcriptomics and genomics approaches must be harmonized with metabolomics and proteomic technologies. Proteomics approaches involve pre- and post-transcriptional modifications and provide proteins' biological mechanisms and functions. Therapeutic properties of plant metabolites are engaged with their biosynthesis stages both genetically and environmentally. Metabolite profiling investigates the number of targeted metabolites in cancer drug discovery. Consequently, integrative multi-omics, transcriptomics and genomics approaches will fasten the discovery of novel cancer drugs and miRNAs driven by plant bioactive compounds.

Therefore, plant bioactive compounds driven miRNAs could be a novel strategy in cancer therapy by targeting various molecular and biochemical grounds. Firstly, the deregulation against the mRNAs, where a single miRNA can concurrently regulate multiple mRNAs, while a single mRNA can be aimed by several miRNAs [9], thus triggering either translational suppression and/or target mRNA degradation. For instance, it was reported that the MCF-7 cancer cells treated with resveratrol upregulated the expression of miR-663 and miR-774, which leads to the inhibitions of MCF-7 cell proliferation by translational suppression of elongation factor 1A2 (eEF1A2) at mRNA and protein levels [10]. Regardless of the development of new anticancer drugs, drug resistance issues to conventional chemotherapies often obstruct effective treatment, and many tumors are still noncompliant with an existing chemotherapy agent. However, using miRNAs could be a novel strategy in the drug resistance issues of cancer therapy, where the miRNA dysregulation in resistant cancer cells will help to overcome the drug resistance and make them susceptible to the drug. For example, research has shown that miRNA-219-2 and miRNA-199b expression levels were related to the treatment outcome of imatinib in patients with CML. Reducing miRNA-199b expression could reduce the CML patients resistant to imatinib [11]. Besides, the MiRNAs also can control drug resistance by modulating critical genes involved in cell proliferation, cell cycle, and apoptosis-related signaling pathways [12]. The phosphatase and tensin homolog (PTEN) can prevent the PI3K/Akt signaling pathway, thus preventing cell proliferation and promoting apoptosis, which is closely associated with a series of miRNAs that affect the response of cancer cells to various drugs by controlling the PTEN. For example, the upregulation of miRNA-21 in the stomach and breast cancer, which target the PTEN will encouraging cell resistance to various anticancer drugs. Meanwhile, the upregulation of miRNA-221/222 and miRNA-214, which targets the PTEN (the inhibitor of cyclin-dependent kinase (CDK)), could stimulate the expression of CDK to adjust the chemoresistance of cancer cells by using plant bioactive compounds treatments [12]. MiRNAs, namely miRNA-16, miRNA-29, and miRNA-107, are vital in regulating drug resistance by targeting essential cell cycle genes. The deregulation of these miRNAs [12] by plant bioactive compounds might help alter the cancer cells' chemoresistance.

Moreover, the natural 10′(Z),13′(E),15′(E)-heptadecatrienylhydroquinone [HQ17(3)] compound isolated from Rhus succedanea targets the transcriptional factors of miRNA gene, where research findings showed that HQ17(3) treatment caused downregulation of miR-17-92 cluster in leukemia cells by directly targeting the c-Myc regulatory protein for miRNA-17-92 gene [13]. In addition, the miRNAs also can affect epigenetic regulations, namely DNA methylation and histone modification. Plant bioactive compounds could affect the miRNA expression by demethylating its promoter. The natural compound curcumin was reported to mediate epigenetic modulation of the expression of miRNA. Research findings showed that curcumin treatment upregulated the expression miR-203 by activating hypomethylation of the miR-203 promoter, which led to the downregulation of miR-203 target genes Akt2 and Src that prevents the cell proliferation and promotes apoptotic bladder cancer cell death [14]. Further, plant bioactive compounds also can target miRNA biogenesis of over-expressed miRNAs linked with cancer. It was reported that natural compounds daunorubicin and doxorubicin directly affect the pre-miRNA target (hsa--mir-155) and obstruct Dicer-facilitated miRNA biogenesis [15].

Alternatively, plant bioactive compounds also could indirectly regulate the miRNA without being associated with the miRNA biogenesis or maturation by targeting Certain circular RNAs (circRNAs) and long noncoding RNAs (lncRNAs), which function as miRNA sponges. Sponge RNAs comprise matching binding sites to a miRNA of concern, making the target miRNA lose function in cell lines. For example, the lncRNA myocardial infarction-associated transcript (MIAT) encourages hepatocellular carcinoma (HCC) cell proliferation and invasion by sponging and inhibiting the action of miR-214, which helps to suppress the proliferation and invasion of HCC cells [16]. Moreover, the natural compound resveratrol was reported to modulate cancer cell activities by altering the expression of lncRNAs such as MALAT1 and NEAT1 [17], which play an essential role in a range of RNA binding proteins (RBPs) and globally affect cancer-related miRNAs processing [18]. Accordingly, it is predicted that NEAT1 and MALAT1 conceivably take part in the resveratrol-controlled miRNAs expression in cancer cells.

3. Medicinal plants as green anti-cancer agents

Medicinal plants are nature's gift to humanity, having effective, cheap, and less toxic therapies for human health. Since the prehistoric eras, phytochemicals and natural products have been considered excellent sources of alternative medicines. It is reported that there are 250,000 plant species on the planet, and 10 % have been discovered for medicinal value [19]. Around 60 % of clinically prescribed anti-cancer treatments are derived from plants, while 80 % of the global populace relies on traditional remedies [20]. As a result, the ongoing research for bioactive substances and anti-cancer medications made from botanicals has been crucial in identifying potential safe methods to enhance the quality of life for people with cancer by lessening the harmful effects of chemotherapy.

To extract bioactive compounds from various plant materials like roots, fruits, stems, leaves, and flowers, several extraction procedures are used, such as separation of the membrane, distillation, ultracentrifugation, extraction based on the enzyme, etc. Following extraction, bioactive compounds are subsequently kept in natural compound libraries for their use in compound synthesis and the search for new drugs to treat diseases or epidemics. However, quick initial steps like HPLC, GC-MS, and NMR are required to revitalize high throughput screening procedures and omics approaches to increase the probability of novel bioactive compounds from plant extracts or mixtures. About 100 of the nearly 200 novel chemical compounds approved as anti-cancer as anti-cancer medicines originate from naturally occurring chemicals [21]. Terpenes, flavonoids, alkaloids, lignans, saponins, vitamins, glycosides, anthocyanins, and other secondary metabolites are only a few of the phytochemicals that are essential for the selective suppression of proliferation and activation of malignant cell death [22]. In various medicinal plant regions, it has been found that several bioactive molecules with properties like anti-diabetic, antioxidant, antimicrobial, hepatoprotective, anti-inflammatory, antimalarial, immunomodulation, anti-hypertension, anti-tumor, and anti-cancer activities can treat human diseases [23,24]. Green anticancer agents are derived from renewable green sources such as natural products, including vegetables, fruits, and leaves. Natural green anticancer agents are an excellent source for producing anticancer remedies because they are affordable, easy to obtain, have high stability, have a simple protocol, are safer and are eco-friendly, which are available in abundance and regulate miRNAs to induce the anticancer activities.

4. Natural polyphenols as anti-cancer agents

Natural polyphenols are eminent for their pharmacological properties due to their structural diversity and improved clinical effectiveness for cancer patients. Foods and beverages with plant origins, such as fruits, vegetables, spices, soy, nuts, tea, and wine [25–27], include a substantial class of secondary metabolites with, at best, one aromatic ring with one or more hydroxyl functional groups attached and are called polyphenols [28]. Natural polyphenols have been identified in numerous laboratories during the past 20 years as prospective candidates for their anti-cancer capabilities. Based on their chemical makeup, polyphenols are categorized into five classes, including flavonoids, phenolic acids, lignans, stilbenes, and other polyphenols. Phenolics and flavonoids are major groups, accounting for 30 % and 60 % of all-natural polyphenols [29]. Natural polyphenols have been shown to have anti-cancer potential due to their potent antioxidant and anti-inflammatory properties, as well as their capacity to modify cell signaling pathways and molecular targets for the normal functioning of cells, such as cell proliferation, angiogenesis, migration, differentiation, hormonal balance, and enzyme detoxification [30,31].

Various research findings showed that specific natural polyphenols from medicinal plants provide a safe and effective novel mechanism for cancer therapies [32,33]. Polyphenols not only reduces the survival and multiplication ability of cancerous cells but also eliminate the free radicals by scavenging them to decrease the evolution of the disease and reduce tumor angiogenesis [32] and intricate mode of action, including transcription factors, membrane receptors, tumor-suppressor proteins, caspases and microRNAs in multiple biological signaling pathways [33]. Li et al. [34] summarize recent information on the current understanding of the bioactivities of natural polyphenols and their benefits to human health. Li et al. [34] reported that past 20 years, polyphenols have been extensively studied for their therapeutic ability in cancer, cardiovascular problems, inflammation, and microbial diseases, their antioxidant, free radical scavenger, and metal chelator properties, and their ability to inhibit different enzymes. They also suggested that the role of polyphenols in human health is still a productive area of investigation. Future research should concentrate on the mechanism in an animal model, the bioavailability of polyphenols, and the interaction between polyphenols [34]. For example, Kausar et al. [35] demonstrated for the first time that the combination of delphinidin and anthocyanidin synergistically inhibited the growth of two aggressive non-small-cell lung cancer cell lines by induction of apoptosis, suppression of cell-cycle, NSCLC cell invasion and migration, affecting the oncogenic Notch and WNT pathways and their downstream targets (β-catenin, c-myc, cyclin D1, cyclin B1, pERK, MMP9 and VEGF proteins), enhanced cleavage of the apoptotic mediators Bcl2 and PARP and inhibition of TNFα-induced NF-kappa B activation. Interestingly the *in vivo* antitumor study also showed that the mixture of anthocyanidins and delphinidin significantly inhibited the growth of H1299 xenografts in nude mice by ≈ 60 % [35]. Besides, Wang et al. [36] established that when A549 cells are treated with TGF-β1 and resveratrol, the latter inhibits the initiation of TGF-β1-induced EMT. Their finding showed that 20 μM resveratrol increases the expression of the epithelial phenotype marker E-cadherin, represses the expression of the mesenchymal phenotype markers, and inhibits the expression of EMT-inducing transcription factors Snail1 and Slug. However, the expression of the Twist1 transcription factor remained unchanged, eventually leading to the suppression of lung cancer invasion and metastasis *in vitro* through inhibiting TGF-β1-induced EMT [36].

In addition, Shi et al. [37] showed that the different concentrations of epigallocatechin-3-gallate (EGCG), a polyphenol in green tea extract, inhibited nicotine-induced migration and invasion in non-small cell lung cancer cells. They also reported that the EGCG reversed the upregulation of HIF-1α, vascular endothelial growth factor (VEGF), COX-2, p-Akt, p-ERK and vimentin protein levels and the downregulation of p53 and β-catenin protein levels mediated by nicotine in A549 cells and also inhibited HIF-1α-dependent angiogenesis induced by nicotine *in vitro* and *in vivo*, and suppressed HIF-1α and VEGF protein expression caused by nicotine in A549 xenografts of nude mice [37]. Furthermore, Rigalli et al. [38] reported that genistein (GNT) present in soybeans increased the protein level of ABCC1 and ABCG2 in MCF-7 and MDA-MB-231, respectively. The MCF-7 cells also showed a related increase in doxorubicin, mitoxantrone efflux, and resistance, dependent on ABCG2 activity. In addition, the ABCC1 stimulation by GNT in MDA-MB-231 cells was found to modify neither drug efflux nor chemoresistance due to simultaneous acute inhibition of the transporter activity by GNT. Interestingly, the miR-181a, which was reported to inhibit ABCG2 translation, was found down-regulated by GNT treatment, explaining translational induction [38]. Moreover, Carpi et al. [39] showed that one of the most abundant secoiridoid presents in Extra-virgin olive Oil (EVOO), Oleacein (OA), induced cell growth inhibition in 501Mel melanoma cells by inducing the G1/S phase cell cycle arrest, DNA fragmentation, and downregulation of genes encoding antiapoptotic (BCL2 and MCL1) and pro-proliferative (c-KIT, K-RAS, PIK3R3, mTOR) proteins, while increased transcription levels of the proapoptotic protein BAX. They also reported that the OA treatment also increased the levels of miR-193a-3p (targeting MCL1, c-KIT and K-RAS), miR-193a-5p (targeting PIK3R3 and mTOR), miR-34a-5p (targeting BCL2 and c-KIT) and miR-16-5p (miR-16-5p targeting BCL2, K-RAS and mTOR), while decreased miR-214-3p (targeting BAX). They also predicted that the abovementioned modulatory effects might contribute to the inhibition of 501Mel melanoma cell growth observed after treatment with an olive leaves-derived formulation rich in OA, with the potential application against *in situ* cutaneous melanoma [39]. Following are several notable instances of naturally occurring polyphenols that act as anti-cancer substances, including flavonoids as a primary group and phenolic acids, lignans, and stilbenes acquired from various dietary sources.

4.1. Flavonoids

The six subclasses of flavonoids, which comprise a vast group of polyphenols called flavonoids, are flavones, isoflavones, flavanones, flavonols, catechins, and anthocyanins. Flavonoids are well known for their wide range of biological activity and clinical applications [40].

4.2. Anthocyanins

The plant kingdom as a whole is covered in anthocyanins, which are responsible for the appealing brilliant red, blue, and purple hues of fruits and vegetables. The aglycone forms of this polyphenol are cyanidin, petunidin, peonidin, pelargonidin, delphinidin, and malvidin. In colorectal cancer cells, anthocyanins' antioxidant capability showed oxidative stress-based cytotoxicity [41], and chemopreventive action in colon cancer cells [42] decreased the activity of the matrix metalloproteinase by preventing lung cancer cell invasion and metastasis [43] and inhibited angiogenesis and invasion of breast cancer cells [44]. By inhibiting the NF-B pathway, the anthocyanin delphinidin, which has substantial anti-cancer properties, caused apoptosis and cell cycle arrest in malignant cells [45,46].

4.3. Flavanols

Various subclasses of flavones like epicatechin, epigallocatechin, epigallocatechin gallate (EGCG), and procyanidins are reported in food supplements. Apples, pears, beans, tea, chocolate, and wine are the most popular sources. The primary catechin in green tea (Camellia sinensis), epigallocatechin (EGCG), has anti-cancerous potential by regulating the production of reactive oxygen species (ROS), which promotes apoptosis, promoting alteration at the epigenetic level by regulating acetylation of histones and inhibiting DNA methyltransferase activity, and impeding the pathway linked to NF-B signaling. These actions also include the main inhibition of migration, invasion and angiogenesis [47–49]. An

accumulation of EGCG in cancer tissue and a reduction in the level of proliferation and apoptosis were seen in a randomized phase II pilot study of polyphenols in bladder cancer patients [50].

4.4. Flavanones

Flavanones like naringenin and hesperitin are the class of flavonoids abundant in citrus fruits to regulate multiple signaling pathways. Several studies report that naringenin inhibits the proliferation of malignant gastric cells by repressing the Akt signalling pathway [51] and mediate apoptosis by facilitating a p38-dependent pathway in colon cancer cells [52]. In hepatic carcinoma cells (HCC) upregulation of p53 and downregulation of NF B/ERK/JNK signalling pathways [53] via naringenin is induced to mediate mitochondrial apoptosis and cell cycle arrest [54]. Naringenin also regulates the estrogenic activity and overpower breast cancer cells' metastasis [55,56]. Similarly, hesperitin exhibit anti-proliferative activity in colon cancer cells [57] and induce ROS accumulation by stimulating ASK1/JNK pathways in breast cancer cells [58] and gastric cancer cells [59], and triggers apoptosis by impeding the NF-κB pathway in PC-3 prostate cancer cells [60] and cervical cancer cells [61].

4.5. Flavones

Celery, chamomile, and parsley are a few examples of various fruits and vegetables, including flavones, naturally occurring flavonoids found in apigenin (APG), chrysine, and luteolin. Mediating apoptosis in malignant gastric [62], and colorectal cells [63], targeting the Bax/Bcl-2 pathway in H460 lung cancer cells [64], interceding the PI3K/Akt signaling pathways in prostate cancer cells [65] are some of the characteristics of the low toxicity and non-mutagenic APG. It also involves in the expression of caspase-3 and caspase-8 that hinders the STAT3 signaling pathway and inhibiting the phosphorylation of JAK2 in MDA-MB-453 breast cancer cells [66] Chrysin [5,7-dihydroxyflavone] possess effective anti-cancer potential on various cancer cell lines [67,68] such as in colorectal cancer, apoptosis in SW480 is induced, G2/M phase cell cycle arrestment and MAPK and P38 proteins activation in the prostate cancer cells [69,70] and in breast cancer cells, PI3K/Akt signaling pathways are regulated [71]. In colon cancer, the cytotoxic effect is exhibited by luteolin via induction of apoptosis and G2 cell cycle arrest [72,73]. In contrast, it activates MCF-7 in breast cancer cells [74] and in lung cancer cells, the JNK and inhibition of NF-κB pathways are activated [75].

4.6. Flavonols

Flavonols are ubiquitously distributed flavonoids in foods, i.e., tea, grapefruit, broccoli, berries, apple, and beans, but in low concentration, having subclasses of kaempferol, quercetin, myricetin, isorhamnetin and galangin. Kaempferol, a natural anti-cancer drug, inhibits the activity of CDK enzymes to stop the cell cycle at the G1 and G2/M phases in a variety of cancer cell lines, including HT-29 colon cancer cells [76] and promotes the transcription of the p53 gene and the caspase-3 enzyme in colorectal cancer [77,78]. Additionally, in cancerous MCF-7 breast cells, apoptosis is induced via blocking the MAPK cascades [79,80], whereas in human liver cancer cells by regulation of the CDK/AMPK and AKT signaling pathways [81], an antiproliferative effect in gastric cancer cells [82].

Modulation of Bax and Bcl-2 in MCF-7 breast cancer [83], modulation of the AMPK signaling pathway in HCT116 colon cancer cells [84], ROS accumulation and G2/M cell cycle interruption in HeLa cervical cancer cells are some of the few ways quercetin induces apoptosis [85]. Meanwhile, the antiproliferative activity of myricetin is exhibited through a series of apoptosis and cell cycle arrest [86], such as in HCC cells, the apoptotic activity is induced [87], and Bax/Bcl-2-dependent pathways are regulated in HCT-15 human colon cancer cells [88].

4.7. Isoflavones

Isoflavones, also known as phytoestrogen (subclasses: genistein and daidzein), are identified in soybeans, lentils, beans, and chickpeas. The proapoptotic properties of genistein against colorectal cancer [89] can be seen by inhibiting NF-kb and topoisomerase II enzymes, regulating Bax and p21 protein expressions [90,91], ROS enzymes [92], suppressing metastasis, and preventing NF-B signaling pathways from being mediated by angiogenesis [93–95]. In MCF-7 breast cancer cells, on the other hand, apoptosis is induced via decreasing $CD44+CD24^{-}$cancer stem cells and down-regulating the Hedgehog-Gli1 signaling pathway [96].

4.8. Phenolic acids

Hydroxybenzoic acid and hydroxycinnamic acid are the two main types of phenolic acids; the former is found in food plants, including pomegranate, grapes, berries, walnuts, chocolate, wine, and green tea, while the latter is found in coffee and cereal grains. Gallic acid and ellagic acid are hydroxybenzoic acid subclasses, whereas ferulic acid and chlorogenic acid are hydroxycinnamic acid subclasses [97].

4.9. Gallic acid

Gallic acid is abundant in various foods, including berries, walnuts, chocolates, and green tea. Numerous research studies have shown that gallic acid has pharmacological potential with antibacterial, anti-inflammatory, and anticancer effects [98,99]. Gallic acid's antioxidant properties enabled it to trigger apoptosis in HCT-15 prostate and colon cancer cells [100,101]. Gallic acid exposure mediates the expression of NF-κB and AKT/GTPase signaling pathways, which inhibits cancer in gastric cells [102], through the mitochondria-mediated apoptotic mechanisms in liver cancer cells [103], the downregulation of MMP-9 and MMP-2 in PC-3 prostate cancer cells [104] as wells as the reduced proliferation of cell, invasion and angiogenesis in cervical cancer cells [105]. The antioxidant and antiproliferative properties of ellagic acid trigger PC3 prostate cancer cells to undergo caspase-dependent apoptosis [106], breast cancer cells' angiogenesis via VEGFR-2 signaling pathways [107] and anti-inflammation in liver cancer cells [108].

4.10. Ferulic acid

Cereals and grains are the primary dietary source of ferulic acid, having therapeutic potency against cancer, neurodegenerative and cardiovascular ailments. Ferulic acid's pro-oxidant properties aid in the buildup of ROS in cervical cancer cells [109]. The effects of ferulic acid on several cell types were discovered in a subsequent investigation of prostate cancer through cell cycle arrest and apoptosis [110].

4.11. Lignans

Secoisolariciresinol diglucoside (SDG) and sesamin, two subclasses of lignans that are typically found in flaxseed and sesame, have anti-cancer properties for hormone-based malignancies including breast, prostate, and colon. For instance, SDG enables the estrogen receptors of mammary glands to be modulated [111] and in cell cycle arrest and proliferation of MDA-MB-231 breast cancer cells [112]. Sesamin, a sesame oil-derived lignan that is lipid-soluble, triggers apoptosis in MCF-7 breast cancer cells via the down-regulation of the VEGF and MMP-9 pathways [113] as well as in HepG2 cells [114] and altered the PC3 prostate cancer cell's p38-MAPK and NF-B signaling pathways [115].

4.12. Stilbenes

Another critical group of natural polyphenols is stilbenes distributed in grapes and berries. Studies on natural stilbenes to treat cancers such as liver, colorectal, pancreatic, breast, prostate, and lung carcinoma have focused on resveratrol, an essential class member. Resveratrol works by downregulating MMPs, NFkB, AP-1, Bcl-2, cyclins, cyclin-dependent kinases, cytokines, and COX-2 proteins and upregulating p53 and Bcl-2 associated proteins [116,117]. Additionally, resveratrol suppressed angiogenesis, inhibited VEGF protein action, and reduced MAP kinase phosphorylation [118]. Bioactive compounds as secondary metabolites possess toxicological and pharmacological potential, leading to their utilization in food and pharmaceutical industries, verifying their diversification in application due to their novel properties. Current biomedical investigations have explored its clinical and practical applications against cancer and other ailments [119].

5. MicroRNAs biogenesis: potential usage for gene therapeutics

In all higher eukaryotes, the non-coding RNA molecule class known as microRNAs (miRNAs) negatively regulates the stability of genes or the activity of their target messenger RNA (mRNA) [120–123]. These tiny single strands, which are composed of nucleic acids with nucleotides that are typically 19 to 25 amino acids long, are essential for several physiological processes, including the maturation of the immune system [124], heterochrony, differentiation and proliferation of the cell, cell mortality, metabolic regulation, transposon silencing and antiviral protection in cells [125]. The genes encoding miRNAs are highly co-expressive and located within the genome either as single genes or clusters [126,127], transcribing under the control of the same promoter (polycistronic) [128,129]. Over the past 10 years, consequential results were obtained for miRNA targets, including deconstruction of their biogenesis reported through which they are regulated by miRNA-driven protein complex [130–132]. However, there are still abundant questions left unanswered on the grounds of how miRNA expression is regulated [133,134]. Investigation of mature miRNA levels has in fact disclosed that high miRNA expression is strictly controlled during biogenesis and uniformly across tissues [135,136]. Furthermore, abnormal expression of certain miRNAs was demonstrated to be linked with a vast number of pathogenesis [137–139]. Substantiate investigation has also revealed the impact of key transcription factors and signaling pathways on miRNA expression under various physiologic and pathophysiologic conditions [140–142]. Moreover, different miRNA was reported to control numerous genes at the post-transcriptional stages. Increasing proofs have specified that miRNAs are often deregulated in numerous cancers. Hence, understanding the miRNAs biogenesis in a cancer cell may recognize them as potent post-transcriptional gene therapeutic agents or targets of human cancers and highlight their great biomarker potential for early screening of cancers.

RNA polymerase II initiates the first stage of miRNA synthesis in the nucleus. (Fig. 2). The polymerase then transcribes a transcript with hundreds of kilobases in length known as primary microRNA (pri-miRNA) [143,144]. The synthesised pri-miRNA is linked together in such a way that at least one of its hairpin structures, each longer than 10 kilobases, is present [144]. Within this structure lies mature miRNA sequences in introns and exons regions that fold into imperfect hairpin structures [145]. A multiprotein complex called the microprocessor, which is made up of the RNA III enzyme Drosha and the cofactor DiGeorge Syndrome Critical Region Gene 8 (DGCR8)/Pasha, then recognizes and cleaves the pri-miRNA. The juncture between the single-stranded and double-stranded regions at the hairpin base, where the latter is said to cleave with (1 helical turn), is where Pasha identifies and directs Drosha to Ref. [146]. In this stage, distinct stem-loop miRNA precursors (pre-miRNAs) that are roughly 70 nucleotides long are

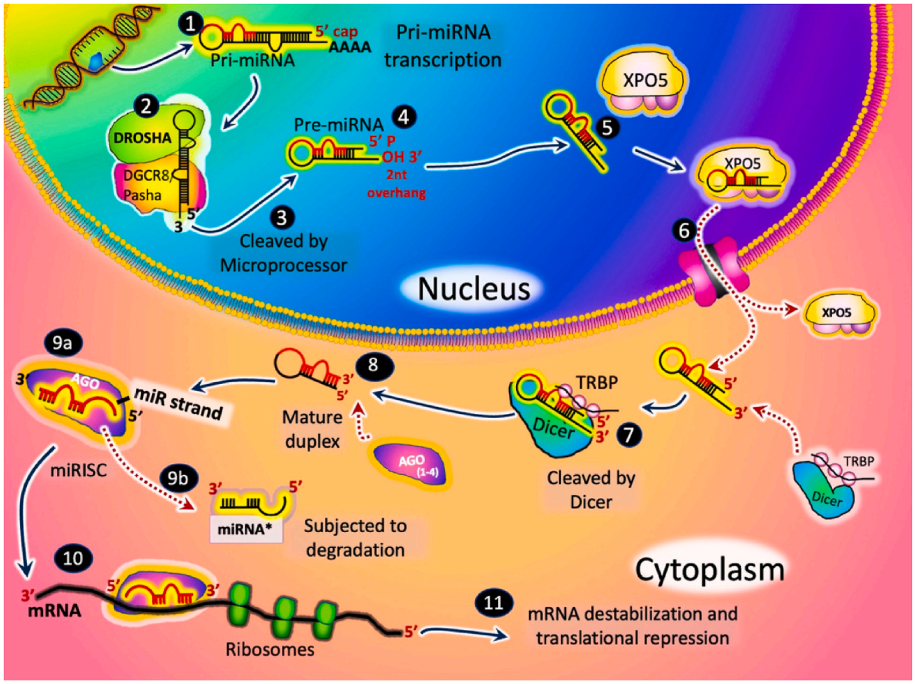

Fig. 2. Overview of microRNA (miRNA) biogenesis pathway. (1) Primary miRNAs (pri-miRNA) are transcribed by RNA polymerase II (2) Microprocessor, a multi-protein complex formed by Drosha and Pasha/DGCR8 recognizes the pri-miRNA (3) Drosha/DGCR8 proceeds to cleave pri-miRNA (4) This process generates a hairpin structure with approximately 70 nucleotides, known as pre-miRNA (5) pre-miRNA possesses ~ 2 nucleotide 3′ overhang that will trigger the binding of Exportin-5 (XPO5) (6) Exportin 5 transports pre-miRNAs to the cytoplasm. (7) an RNAse III-type endonuclease, termed Dicer identifies the pre-miRNA and cleave the loop structure about two helical turns from the base. (8) Due to Dicer processing, mature miRNA duplex is formed. (9a) Either 5p or 3p strands of mature miRNA duplex is loaded into Argonaute (AGO) family of proteins to form miRNA-induced silencing complex (miRISC) (9b) During this process, one of the mature strands is released (10) The miRNA guides the complex and post transcriptionally inhibits through 3′ UTR binding of messenger RNA (mRNA) (11) This event causes mRNA to become destabilised and translationally repressed.

formed [147–149]. The resulting pre-miRNA will possess ~2 nucleotide 3' overhang that will trigger the binding of Exportin-5 (XPO5) that subsequently directs and exports pre-miRNA via Ran-GTP dependent way [150] into the cytoplasm region [146]. Although these steps are essential for the canonical miRNA biogenesis pathway, another group of miRNAs identified as "mirtron" evades this complex microprocessor process by generating their pre-miRNA directly from intron splicing [151–153].

An additional cleaving process is required to liberate pre-miRNA hairpin into miRNA duplex. Hence, in the cytoplasm, an RNAse III-type endonuclease, termed Dicer, will identify and cleave the loop structure about two helical turns from the base [146] leaving, two RNA complementing strands (~21–22 nucleotides in length) linked by Watson-Crick base pairing. Due to RNAse III processing, the duplex strands are left distinctively with 3 nucleotide overhangs at each end [154–156]. The miRNA duplex will result in the typical characteristic of bulges and imperfect base matching. One of the mature strands will be anchored explicitly into the Ago protein when loaded into the Argonoute (Ago) family of RNA binding proteins, forming a complex known as the miRNA-Induced Silencing Complex (miRISC). Generally, the loaded miRNA strand will be referred to as the "miR" or "guide" strand. Notably, this strand may originate from either the 5′ side ('5p' strand) or the 3′ side ('3p' strand) of pre-miRNA. Only one miRNA strand predominates and defines the uniqueness of miRISC by the sequence complementarity between the miRNA strand and the 3′ UTR region of the target mRNA, albeit there is no set rule for which strand or arm is chosen for miRISC loading [157,158].

miRNA*, a passenger miRNA, refers to the opposite strand of the miRNA duplex. Chiefly, these miRNA* strands are expelled [159] from the Ago protein complex, through which they are eventually degraded. But according to other studies, both duplex strands or arms may result in mature, functional miRNAs that are equally accepted into the Ago protein complex for gene regulation [157,158]. For instance, it has been found that the human miR-34b-5p and miR-34b-3p have approximately similar levels and target different mRNAs, respectively [160,161]. This suggests that the less abundant miRNA* evolved their respective regulatory functions separately from their complementing guide strands [152,153]. Correspondingly, the limited existence of miRNA* was demonstrated to inhibit predicted target sites of mRNAs in mammals and flies, further corroborating its functional role [162,163]. The GW182 (Glycine-Tryptophan Repeat -Containing Protein of 182 kDa)--derived effector proteins and miRNA-are essential for miRISC-dependent gene silencing [164–168]. The presence of these proteins mediates miRNA-dependent translational suppression by behaving as molecular scaffolds linking Ago proteins with their downstream effector complexes [169,170]. The mechanism of miRNA-dependent translational repression mainly engages inhibition at the stage of translational initiation [119,169]. mRNAs are known to defend themselves from degradation by forming circular complexes, and the proteins associated with this mechanism are the Poly-A-Binding Proteins (PABPs) and eukaryotic initiation factors (eIFs) [171,172]. Progressively, the miRISC impedes breaking the initial physical interaction between PABPs and eIFS by dislodging the latter, hence de-circularizing and destabilization the target mRNAs [173–175].

Effector proteins produced from GW182 (Glycine-Tryptophan Repeat -Containing Protein of 182 kDa) play a crucial role in miRISC-dependent gene silencing in addition to miRNA [169,176–178]. The major cytoplasmic 5′-to-3′ exoribonuclease, Xrn1, targets the newly deadenylated mRNAs with decreased poly A tails for breakdown after they have been decapped by DCP2 (mRNA decapping enzymes) [179–182]. Nevertheless, target mRNA degradation does not seem the only way miRNA-dependent gene silencing works [183,184]. According to a few studies, the de-adenylated mRNAs do not further endure de-capping or degradation yet appear to be in a translationally silent state in a cell-free extract environment [185–189]. More research in *Caenorhabditis elegans* showed that the expression of the proteins *lin-14* and *lin-28* was decreased by the miRNA lin-4 regardless of either protein's mRNA expression levels [190,191]. Nevertheless, it has been shown that de-adenylation is a frequent side effect of miRISC-dependent transcriptional regulation, and that miRISC silencing typically results a more significant concentration of targeted miRNAs [181,192–194].

Commonly, miRNAs work by suppressing the expression of mRNA targets, but in some cases, miRNAs may not suppress these targets. For instance, during the arrestation of the cell cycle, the upregulation of target mRNAs is triggered by *let*-7 miRNA yet somehow inhibits translation in cells that are dividing rapidly [195]. Thomson & Dinger [196] have shown specific RNAs with miRNA binding sites to inhibit miRNA activity by sequestering it, which increases the expression of miRNA target genes. This implies that miRNAs may utilise multiple mechanisms to modulate target mRNA expressions or contributing factors such as cellular and development surroundings impacting the regulatory modes of miRISC.

6. microRNAs regulate apoptotic and anti-apoptotic proteins expression to induce apoptotic cell death

miRNAs play an essential role in regulating gene expression [197,198]. By doing so, it controls the biological process, including cell migration, differentiation, apoptosis, proliferation and homeostasis [199]. Regulation of miRNAs in cancer caused by uncontrollable cell growth [200] could be potentially curative molecules due to their functional nature in regulating the core mechanisms of cell proliferation and apoptosis at the post-transcriptional level.

Two pathways can trigger apoptosis; one is intrinsic, and the other is extrinsic. Intrinsic pathway facilitated by the mitochondrial membrane potential, releases cytochrome *c*, which attracts pro-caspase 9 and apoptotic peptidase activating factor 1 (Apaf-1), mediating apoptosome formation, preceded by caspase cascade activation, which also includes a host of other proteins that are essential for the induction of apoptosis such as Bcl-2-associated X protein (Bax), Bcl-2-antagonist/killer (Bak), BCL2-like 1 isoform 1 (Bcl-X_L), BH3 interacting domain death agonist (Bid), myeloid cell leukemia 1 (Mcl-1) and myeloid cell leukemia 1 (Bim) [201,202]. The second pathway is called the extrinsic apoptosis pathway. It is characterized by the participation of death ligands such as Fas ligand (FasL), tumor necrosis factor (TNF-α), TNF related-inducing ligand (TRAIL), TNF-like weak inducer of apoptosis (TWEAK) and initiate death-inducing signaling complex (DISC) after which the caspase cascade is activated [201–203].

A study report that one-third of human genes expressed to be controlled as miRNA targets [204]. The amount of expression of miRNA is associated with cancer-related biomarkers to determine the stage of disease and its therapeutic approach. The fact that miRNAs can repress the specific gene expression by attaching to their target mRNAs, miRNAs may function as oncogenes by directing genes involved in apoptosis or cell death or act as tumor suppressors (Fig. 3) by targeting genes involved in cell proliferation or anti-apoptotic mechanisms [205]. miRNA-based therapeutic approach can minimize off-course toxicity and reduce drug resistance issues [206,207].

A wide range of miRNAs in cancer cells was identified to regulate apoptotic proteins, as shown in Table 1. One of the main tumor suppressor genes is p53 which is generally mutated in cancer cells. It has been shown that miR-125b, which directly targets p53, is greatly upregulated in various malignancies. This inhibits apoptosis and promotes cell proliferation in cancer cells [208]. Furthermore, miR-33 was reportedly found to down-regulate the p53 to promote cell proliferation and oncogenesis [209]. By drastically downregulating p53, miR-504 has also been demonstrated to suppress and impede apoptosis and cell-cycle arrest [43]. Another such apoptotic protein is a member of the BH3-only family, which has been found to be mediated by several miRNAs. For example, the downregulation of miR-125b was also reportedly shown to upregulate Bak and induce apoptosis in cancer cells [210]. Beside that, miR-29b directly targets genes in the BH3-only family, bak, bim, bmf,

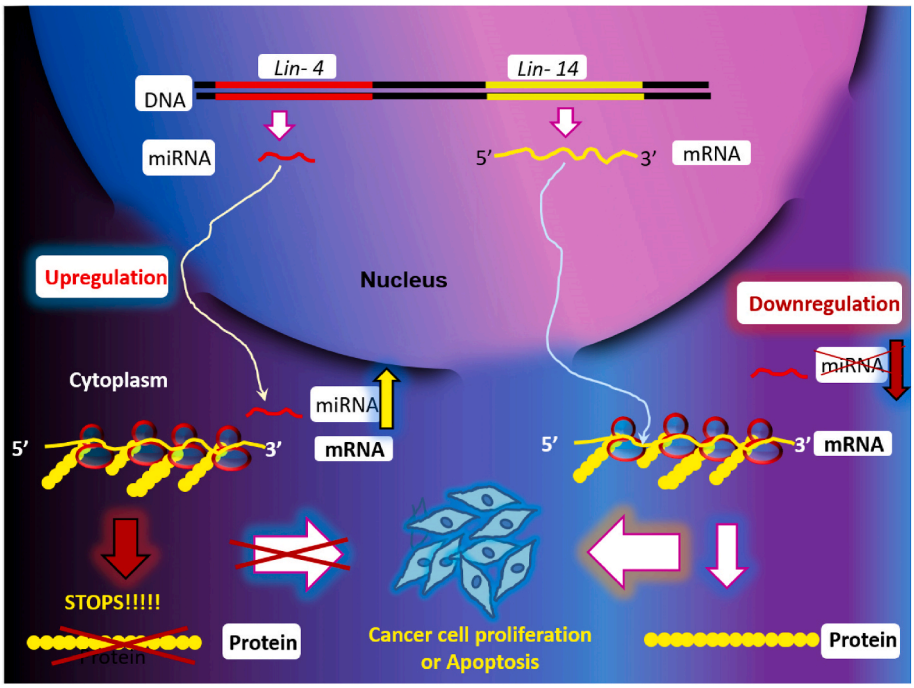

Fig. 3. Schematic diagram shows role of miRNAs in cancer cell in the regulation apoptotic and anti-apoptotic proteins.

Table 1
Regulation of pro-apoptotic proteins by miRNAs.

miRNA	Target	Cancer type	References
MiR-125b, miR-33, miR-504	Down-regulates p53	Colorectal cancer	Yin et al., 2015 [208] Herrera-Merchan et al., 2010 [209]
miR-22	Up-regulates p53	Cervical cancer	Wongjampa et al., 2018 [212]
miR-125b, miR-29b	Down regulates BAK1	Myelogenous leukimia	Zeng et al., 2012 [210] Kole et al., 2011 [211]
miR-125b	Down regulates PUMA	Myelogenous leukimia	Cacic et al., 2021 [213]
miR-222	Up regulates PUMA	Adenoid cystic carcinoma	Zhou et al., 2017 [214]

Table 2
Regulation of anti-apoptotic proteins by miRNAs.

miRNA	Target	Cancer type	References
miR-195, miR-24-2, miR-365-2, miR-204	Down regulates Bcl-2	Breast cancer cells, gastric cell	Singh et al., 2012 [215]
miR-15a, miR-16-1	Up regulates Bcl-2	Leukemia cells	
MiR-133a, MiR-608	Down-regulates Bcl-XL	primary human osteosarcoma 160 tissues, human chordoma	Zhang et al., 2014 [217] Ji et al., 2013 [216]
MiR-29, miR-113B, Mir-26, miR-101, miR-125a-5p, miR-106	Down regulates MCL-2	Cholangiocarcinoma, lung cancer, breast cancer, myeloma, endometrial cancer, colon cancer,	Opferman et al., 2003 [220] Taniai et al., 2004 [221] Konno et al., 2014 [112] Liu et al., 2015 [94]
miR-205	Upregulates MCL-2	Lung cancer	Zarogoulidis et al., 2015 [222]

hrk and puma were reported to inhibit neuronal apoptosis and induce maturation [211].

Numerous miRNAs have been bioinformatically as well as biochemically proven to target specific genes involved in cell proliferation, acting as tumor suppressor genes (Table 2). For instance, it has been observed that up-regulation of a variety of mRNAs, such as miR-195, miR-24-2, and miR-365-2, effectively silences Bcl-2 over-expression in human embryonic kidney cells (HEK-239T) and breast cancer cells (MCF7). This effectively induces apoptosis [215]. MiR-133a is another miRNA that functions in osteosarcoma cell lines as a tumour suppressor gene. It has been demonstrated that miR-133a preferentially targets and eventually suppresses Bcl-XL and Mcl-1 to promote apoptosis [216]. Similarly, miR-608 has been shown to target Bcl-XL and EGFR, which are reported to be elevated in cancer cells [217]. On the other hand, it has been observed that upregulating Bcl-2 and preventing apoptosis is possible by downregulating miR-15a and miR-16-1, which bind to Bcl-2 [218]. Another anti-apoptotic protein regulating miRNA is miR-204, which has been evidently shown to down-regulate Bcl-2 to induce apoptosis in gastric cell lines [219].

Mcl-1 was significantly up-regulated in numerous malignant cells and is known to inhibit TRAIL-induced cell death [223]. A broad range of miRNAs has been experimentally shown to target Mcl-1. For instance, transfection-based up-regulation of miR-29 and miR-133B by transfection significantly downregulates MCL-1 [221,220]. Moreover, miR-205 was reported to act as an oncogene by up-regulating Mcl-1, thus inducing cell proliferation [222].

7. Plant bioactive compounds regulate the miRNAs expressions in cancer cells

The expression profiles of miRNAs have drawn substantial attention in cancer research because they can suppress the expression of a target gene by binding to the 3′ untranslated regions (UTR) of the target mRNA and either inhibiting translation or cleaving the target mRNA [224]. This action is especially crucial because mounting data indicates that abnormal miRNA expression contributes significantly to the onset and

progression of cancer [225]. Therefore, they might influence the behavior of cancer cells as oncogenes or tumour suppressor genes, and they might be clinically valuable for the detection, prognosis, and therapy of cancer [224]. In this regard, it is anticipated that targeting and altering the specific expression profile of miRNAs could perhaps be a novel approach required to treat cancer effectively. Natural sources, primary derivatives from medicinal plants, have proven to be more straightforward, safe, and cost-effective and would probably offer a potential new drug for the cancer treatment through miRNA regulatory regulation [226].

Thanks to the novel approaches and a growing interest in employing medicinal plants in medicine, people have been using natural product-based therapy to treat diseases owing to the lower toxic side effects on the cells. This is mostly because medicinal plants rich in bioactive phytochemicals have long been valued for their biological activity, which includes antimicrobial, anti-inflammatory, antioxidant, and anti-cancerous properties [227]. Natural compounds have been among the most widely utilized alternative and complementary medicines to treat various diseases, specifically cancers since they could target several signaling pathways. Indeed, anticancer mechanistic studies demonstrate that naturally occurring bioactive chemicals can alter cellular communication in cancer cells through epigenetic alterations such as DNA methylation and histone alterations to exhibit their anti-cancer properties.

Indeed, mechanistic studies show that natural bioactive substances can modify cellular signaling via epigenetic changes in cancer cells, like DNA methylation and histone alterations, to exhibit their anti-cancer properties. Such epigenetic modifications then alter the expression of miRNAs, raising or lowering the levels of expression that may be linked to the ability to govern the development of human cancer cells [228, 229].

Although the regulation of miRNAs by medicinal plants remains scanty, many studies have begun acknowledging the anti-cancer effects of phytochemicals in medicinal plants by targeting miRNAs. Numerous plant compounds have indeed been identified as miRNA expression stimulators in different types of cancer cells [230]. This is essential because miRNAs mediate a plethora of biological mechanisms, including tumour development, progression, as well as cell death mechanism. Similarly, medicinal plants target multiple signaling pathways. As both medicinal plants and miRNAs wield an effect on a wide range of cellular targets, there is a solid perception that medicinal plants could modulate miRNAs' expression, thereby enhancing their anti-cancer potential [231]. Fascinatingly, it has been shown that miRNAs being prognostic and diagnostic biomarkers can be regulated by phytochemicals via proliferation, epithelial to mesenchymal transition (EMT), metastasis and drug resistance [232,233] predict response to therapies against malignancies like cancer cell inhibition and apoptosis. For example, plant bioactive compounds could affect numerous proteins linked to carcinogenesis at the initiation and development stages by modulating the miRNAs' expression levels [234]. Besides, they also have an impact on cell signaling and apoptotic pathways involving PI3K-AktmTOR, protein kinase B (Akt) and extracellular-signal-regulated kinase (ERK) signaling, Wnt signaling, p53, Erb, and mitogen-activated protein kinase (MAPK) signaling, Src/Ras/ERK, and TGF- signaling [235]. Consequently, the regulation of miRNA using medicinal plants, or their active fraction, has received more attention in recent years.

Herein, we summarized several medicinal plants extract or active fraction that targets miRNAs, alters their expression profiles, and could eventually be effective cancer treatments utilizing the molecular miRNA. These medicinal plants containing phytochemicals exhibit anti-cancer properties by either up-regulating or down-regulating tumor suppressor and oncogenic miRNA expression levels in humans, respectively [235]. For instance, in the present review paper, we discuss curcumin, resveratrol, EGCG, genistein, and other medicinal plants bioactive that are being linked with cell differentiation, proliferation, and apoptosis exhibiting their anti-cancer effect on a large number of miRNAs are implicated in the pathophysiology of cancer.

These groundbreaking discoveries blatantly imply that the precise targeting of miRNAs via the inclusion of medicinal plants could successfully limit tumors by triggering apoptosis in malignant cells to improve survival rates in malignancy patients. It is hoped that this breakthrough could open new windows for improved therapy strategies in the case of cancer, particularly by blending common medicinal plants as adjuvants with conventional therapeutics.

7.1. The role of curcumin in regulating miRNAs

A yellow polyphenolic flavonoid called curcumin (diferuloylmethane) was discovered in the rhizome of turmeric (*Curcuma longa)*. It has long been a crucial component of traditional Chinese and Indian treatments as well as Indian cuisine [236]. It has been established that turmeric exhibits a broad range of medicinal benefits, like chemopreventive and chemotherapeutic activities against many tumors, including breast, cervical, oral, gastric, melanoma, pancreatic, colon, and prostate [235]. Curcumin undergoes three steps of carcinogenesis suppression: tumor advancement, tumor proliferation, and angiogenesis via altering the expression of genes that control signaling pathways, including Akt, Nuclear Factor-B (NF-B), p53, and MAPK [237,238]. There is evidence that curcumin is essential in the fight against cancer by employing its therapeutic effects via miR-17-5p, miR-20a, and miR-21which are some of the oncogenic miRNAs that are down-regulated. In contrast, tumor-suppressor miRNAs such as miR-22, miR-185b, miR-15, miR-16, and the let-7 family are upregulated [235]. In research on curcumin treatment on the BxPC-3 human pancreatic cancer cell line, for example, in contrast to the untreated cell line, miRNA microarray data showed significant downregulation of miR-199a* and a huge overexpression of miR-22. The considerably upregulated miR-22 thereby suppressed the expression levels of the SP1 transcription factor and estrogen receptor 1 protein [233]. Another study found curcumin upregulated the tumor suppressors miR-15a and miR-16 while downregulating the expression of the key anti-apoptotic protein B-cell lymphoma 2 (Bcl-2) in MCF-7 breast cancer cells [239]. Besides MDA-MB 231 cell lines, curcumin increased the tumor suppressor miR1881b, which inhibits breast cancer metastasis [240]. In yet additional study, hematopoietic stem cells (HSCs) may have DNMT3b down-regulation as a result of curcumin overexpressing miRNA-29b, and the suppression of triggered HSCs may be caused by epigenetically mediated PTEN [241]. Furthermore, the induction of apoptosis and cell cycle arrest in human esophageal cancer cells (TE-7) has been reported with curcumin downregulating Notch-1 specific miR-21 and miR-34a, while triggering the tumor suppressor let-7 in these cancer cells [242]. As for studies done in colon cancer cells (RKO, HCT-116), a dose-dependent approach to curcumin interfered with the oncogenic miR-21 promoter activity. This is believed to be through enhancing the expression of the tumor suppressor gene Pdcd4 (programmed cell death protein 4), a target of miR-2 and blocking AP-1's ability to bind to the promoter. This resulted in decreased tumor growth and metastasis development [243]. Finally, in a different colon cancer cell lines (RKO, SW480) study, the target genes for SP repressors, ZBTB4/10, zinc finger including BTB-domain proteins identified as miR-17-5p, miR-20a, and miR-27a′s level of expressions were repressed by curcumin. This resulted in an increased development inhibition [244]. Owing to curcumin's remarkable ability to regulate a variety of miRNAs in various malignancies, the formulation of curcumin derivatives is becoming a key method for getting reliable anticancer medications.

7.2. The role of resveratrol in regulating miRNAs

The popular polyphenolic compound resveratrol (3,4′,5-trihydroxystilbene) is found in medicinal plants, including *Arachis hypogaea*, *Polygonum cuspidatum*, *Muscadine berries*, *Vitis vinifera* (which produces grapes, berries, plums, and peanuts). Resveratrol exerts

chemopreventive properties against several cancers by three main mechanisms, which block the proliferation of cancer cells, promote the stalling of the cell cycle, and induce cancer cell apoptosis [245]. The suppression of pro-inflammatory signaling pathways such as the ERK 1/2 signaling pathway, p53, Rb/E2F, cyclins, and many others are responsible for this anti-cancer effect. Several studies have suggested that resveratrol may lessen the chance of developing glioma, neuroblastoma, breast, lung, prostate, and colon malignancies. Besides, resveratrol has recently been shown to alter miRNAs by upregulating tumor suppressors like miR-34a/c, miR-122- 5p, miR-137, miR-194, and miR-200c and downregulating aggressive miRNAs like miR-17, miR-21, and miR-25 [235]. For instance, the overexpression of miR-663 and miR-774 in MCF-7 cells triggered by resveratrol inhibits cell growth and inhibits eukaryotic elongation factor IA2 (eEFIA2) both in terms of translation and transcription [246]. Reportedly, resveratrol inhibits glioblastoma cell tumor growth by downregulating oncomirs (miR-19, miR-21, and miR-30a-5p) and reactivating tumor suppressor miRNA expression [247]. Additionally, Venkatadri and co-authors [248] reported resveratrol effects on breast cancer cells by regulating critical tumor suppressors miRNAs such as miR-200c-3p, miR-125b-5p, miR-122-5p, miR-542-3p, and miR-409-3p, which can impact cancer cells' apoptosis and cell cycle. CDKs, X-linked inhibitors of apoptosis protein (*XIAP*), and B-cell lymphoma 2 (Bcl-2) are all controlled by resveratrol-mediated tumor suppressor miRNAs. Hence, it inhibits tumor development and induces breast malignant cell apoptosis. In yet another recent research, resveratrol has been studied to induce neuroblastoma cells to undergo apoptotic cell death by elevating miR-137 levels, including lowering the enhancer of zeste homolog 2 (EZH2) expression. This suppression in EZH2 expression could further initiate the downregulation of H3K27me3 and prompt the upregulation of CLU and NGFR, which are the tumor suppressor genes in neuroblastoma [249]. Regarding colorectal cancer, resveratrol could modulate the tumor suppressor miR-200c that attenuate cell viability, invasion, and EMT and induces cell death [250].

7.3. The role of epigallocatechin-3-gallate in regulating miRNAs

Green tea contains a significant amount of the polyphenol flavonoid epigallocatechin-3-gallate (EGCG) (*Camilla sinensis*), which is one of the most studied natural substances in terms of regulating miRNA production due to its potent anti-tumor activity apart from other pharmacological properties [251]. Previous studies have demonstrated that in various cancer types in both *in vitro* and *in vivo* models, by targeting several cellular signaling pathways, EGCG can have their proliferation reduced, apoptosis stimulated, and invasion, angiogenesis, and metastasis process restricted [239]. Next-generation sequencing was described in a prior study [252], which revealed that upon treatment with EGCG in lung cancer A549 cells, more than 205 miRNAs exhibited differential expression. Among them, 134 known miRNAs modulate the MAPK signaling pathway, which could serve as biomarkers for lung cancer diagnostics, prognostics, and therapeutics. miR-210 was one of the miRNAs that EGCG induced in lung cancer cells, which inhibited cell proliferation [238]. Besides, in various cancerous human cervical cells (HeLa, SiHa, CaSki, and C33A) infected with subtypes of human papillomavirus (HPV), EGCG exerted a suppressive effect on influencing the development of malignant cells via upregulating the tumor suppressor miRNAs (miR-29a, miR-125b, miR-210, and miR-203) [253]. Meanwhile, in colorectal cancer (CRC) cells, through the overexpression of miR-155-5p and the repression of the drug-resistance's gene expression for multi-drug resistance-1 (MDR1), EGCG could inhibit the NF-κB pathway and reduces resistance to treatment in cancer cells to 5-fluorouracil (5-FU) [254]. Moreover, In HepG2 hepatocellular carcinoma cells, treatment with EGCG transformed 61 miRNAs' expression patterns (13 upregulated and 48 downregulated), with miR-16 being one of the enhanced miRNAs. Bcl-2, one of its targets, was also downregulated by EGCG. miR-16 suppression was used to counterbalance the initiation of apoptosis and Bcl-2 downregulation affected by EGCG [255]. Lastly, in A549cisplatin-resistant cells, EGCG potentially inhibits the miR-485/CD44 axis from preventing features similar to cancer stem cell (CSC) [256]. These findings demonstrate that EGCG has anti-tumor potential by altering miRNAs, suggesting that EGCG might be used in the quest for a potent therapeutic target for the treatment and prevalence of cancer.

7.4. The role of genistein in regulating miRNAs

Several medicinal plants, including *Glycine max*, *Pueraria lobata*, *Psoralea corylifolia*, and *Scutellaria* sp., can be used to isolate the isoflavone chemical known as genistein, which is naturally present in fava beans, soybeans, and lupins [235,257]. Studies *in vitro* and *in vivo* have demonstrated this compound to function as a cytotoxic, anti-angiogenesis, and anti-metastatic drug in different cancers, including breast, prostate, gastric, lung, pancreatic, melanoma, and renal cancer [237,235]. Inhibition of the NFkB, Akt, ER, and androgen signaling pathways is the fundamental mechanism of their anti-cancer efficacy [258]. Most importantly, genistein inhibits the expression of several oncogenic miRNAs, while restoring the expression of tumor suppressor miRNAs. For instance, genistein increases expression levels of a target of miR-221 and miR-222, aplysia ras homolog I (ARH1), while these miRNAs undergo downregulation in PC-3 prostate cancer cells. Consequently, cell proliferation, colony formation, and invasion were all inhibited when ARH1 was overexpressed [259]. Likewise, genistein treatment positively impacted renal cancer cells (A498) as they interfered cyclin E2 while downregulating oncogenic miR-21. Subsequently, p21 and p38 MAPK (mitogen-activated protein kinase) were triggered [260]. According to Xia and colleagues [261], Genistein therapy prevented ovarian cancer cells from proliferating and migrating by suppressing miR-27a. In addition, the survivability of breast cancer, the expression of the miR-155, and related domains were examined to determine the anticancer effect of genistein. Genistein reduced the cell viability and induced programmed cell death in Hs578t breast cancer cells and metastatic MDA-MB-435 cells at lower clinically appropriate doses while having no impact on non-metastatic MCF-7 breast cancer cells in terms of viability. In addition, anti-cell and proapoptotic proliferative miR-155 targeted PTEN, FOXO3, p27, and casein kinase were boosted in Hs578t and MDA-MB-435 following genistein therapy, whereas miR-155 was downregulated [261]. Contrarily, in MCF-7 cells, genistein therapy continues to have no effects on the level of miR-155. Thus, it could be said that the miR-155's downregulation in breast cancer cells led to the anticancer impact. Thus, miR-155's downregulation in breast cancer cells led to anticancer implications [262].

7.5. The role of ginsenosides in regulating miRNAs

Ginsenosides are bioactive compounds found in the traditional medicinal plant ginseng, mainly in the root [263,264] with anticancer activity (including ginsenoside 20(S)-Rg3, ginsenoside Rh2 and ginsenoside Rd) by modulating the miRNA expression [265]. Ginsenoside 20(S)-Rg3, a steroidal saponin extracted from red ginseng, was recently shown to upregulate the miR-532-3p and miR-324-5p followed by a reduction of HK2, PKM2, PMK2 and lncRNA H19 expression, cause to repress tumorigenesis in SKOV3 and A2780 cells [266,267]. Furthermore, ginsenoside 20(S)-Rg3 treatment was also reported to inhibit SCC-9 and HSC-5 cell viability by downregulating the expression of the miR221 viability to induce apoptotic cell death via PI3K/AKT and MAPK/ERK signal pathways [268]. The miR-491 was upregulated, and the EGFR signaling was suppressed in HCC cells, resulting in the suppression of the progression of HCC *in vitro* and *in vivo* after being treated with Ginsenoside Rh2, a phytochemical isolated from red ginseng [269]. Besides, another study also reported that Ginsenoside Rh2 treatment in liver cancer cells upregulated the miR-146a-5p expression to trigger the anti-proliferation activity and apoptotic liver cancer cell death [270].

The 4 T1 cells treated with ginsenoside Rd were reported to suppress the 4 T1 cell migration and invasion by downregulating the expression of miR-18a and Smad2, which is the direct target of miR18a [271].

7.6. The role of tanshinones in regulating miRNAs

Tanshinones liposoluble compounds were isolated from Salvia miltiorrhiza (Danshen), which consist of tanshinone IIA (T2A), cryptotanshinone (CT), and tanshinone I (T1). T1 is effective against the prostate cancer (PC) PC-3 and DU145 cells and exhibits anticancer activities by regulating the miR-135a-3p expression [272]. Besides, T2A was also reported to inhibit cell proliferation and induce cycle arrest in Ec109 human esophagus cancer (ESAC) cells via upregulation of miR-122 expression in hepatocellular carcinoma (HCC) cells by down-regulating miR-30b, in ovarian carcinoma (OC) TOV-21G cells by direct upregulation of miR-205 [273]. Moreover, the CT was reported to upregulate the expression of miR-146a-5p in H1299 non-small cell lung cancer (NSCLC) cells [274] to initiate the anticancer effects.

7.7. The role of astragaloside IV (AS-IV) in regulating miRNAs

The cycloartane-type triterpene glycoside astragaloside IV (AS-IV) is isolated from *Astragalus membranaceus* Bunge [275], which has been reported to exhibit the anti-tumor activity [276]. The AS-IV was reported to upregulate miR-214 and down-regulate miR-301a expression to suppress gastric cancer [277]. In the treatment of AS-IV against the CRC SW-480 cell line, the expression of miR-134 level was upregulated and led to the decrease in the protein level of several key regulators in epithelial-mesenchymal transition (EMT) signalling, indicating that AS-IV has an inhibitory effect on EMT [278]. Furthermore, the combination of AS-IV and curcumin were reported to have a synergistic anti-tumor activity on human HCC [279], where the combination upregulates the miR-122 and downregulates the miR-221 expression compared with the control group.

7.8. The role of berberine (BBR) in regulating miRNAs

The alkaloid berberine (BBR) was isolated from the roots, rhizome, and stem bark of *Coptis chinensis* and *Berberis aristata*, exhibiting anticancer activity [280]. The BBR treatment against the HCC cells was reported to upregulate the miR-21-3p, which leads to diminutions in the expression of methionine adenosyltransferase 2A (MAT2A) and MAT2B, followed by the decline of S-adenosylmethionine (SAM) contents, thus conquering the cell growth by inducing apoptotic HCC cells death [281]. In addition, the treatment of BBR against the cisplatin-resistant SKOV3 OC cells causing in sensitizes the resistant cells to cisplatin (DDP) by decreasing the miR-21 expression followed by an increment of the DCD4 expression [282]. BBR also suppresses cancer cell growth, encouraging apoptosis and cell cycle arrest by reversing miRNA expression in various cancer cells. For example, the treatment of BBR against the MCF-7 breast cancer cells was also reported to increase significantly the expression of miR-21-3p followed by a decrease in aryl hydrocarbon receptor (AhR) activation, which leads to the suppression of the functional cytochrome P450 A1 (CYPA1) protein expression [283]. The BBR was also recently reported to suppress endometrial cancer (EC) cell line AN3 CA and HEC-1-A by upregulating the expression of the miR-101, which directly targets the cyclooxygenase-2 (COX-2) to downregulate COX-2 expression [284].

7.9. The role of matrine in regulating miRNAs

The alkaloid compound Matrine was isolated from *Sophora flavescens* and has been reported to possess good antitumor activity against numerous cancer [285]. The treatment of Matrine against the MCF-7 cell line was reported to downregulate the expression of the miR-21 and induces apoptotic cell death and cell cycle arrest to inhibit MCF-7 cell growth [286]. Furthermore, the combination therapy between matrine and sorafenib was reported to synergistically increase the cell cytotoxicity against the HepG2 and Hep3B cells by regulating the expression of miR-21 [287]. The latest study also revealed that the matrine treatment against the human A375 and SK-MEL-2 cell lines could suppress cell proliferation and invasion and induce apoptotic cell death by decreasing the miR-19b-3p expression.

7.10. The role of other medicinal plants in the regulation of miRNAs

The crude extract of medicinal herbs has been shown to have anticancer properties by inhibiting specific miRNAs in tumor cell lines. *Polyalthia longifolia* is a medicinal plant recently studied to have an anti-angiogenic influence on HeLa cells. Shanmugapriya & Sasidharan [288] reported that treatment of HeLa cells with *P. longifolia,* a plant rich in beneficial polyphenols, could induce apoptotic cell death by significantly suppressing the expression of miR-221-5p in comparison to the untreated HeLa cells. This plant's capability to have an effect on cancerous cells was discovered in an *in vitro* experiment using the MTT assay, which revealed the involvement of downregulated miRNA 221-5p in the induction of apoptosis of HeLa and showed that overexpression of miR-221-5p enhanced the proliferation rate of cells and survivability of HeLa cells treated with *P. longifolia* plant extract. Moreover, the flow cytometry evaluation indicated that the overexpressed miR-221-5p impeded apoptosis in HeLa cells when treated, proving the impact of miR-221-5p′s significance in blocking apoptosis in cancer cells. Finally, the depletion of caspase-3 in the overexpressed miR221-5p gene in HeLa cells displayed cell death functions of a downregulated miR-221-5p [263]. Coptidisrhizoma, also known as 'Huang Lian,' is another essential medicinal plant that contains several alkaloids, including berberine; it is a component of traditional Chinese medicine, which is used to treat several diseases [224]. The earliest evidence of miRNA up-regulation, which are the miRNA23a and miRNA21 in liver cancer cell lines after treatment with Coptidisrhizoma extract, reveals that *Coptidis rhizoma* aqueous extract (CRAE) targets these two genes, adding to the evidence that CRAE could be used to treat human cancer cells [289]. Apart from that, *Olea europaea*, a small tree that produces the well-known olive fruit, has long been used as a traditional cure for fever and tropical disorders like malaria [290]. In glioma stem cells (GSCs), miRNA-153, miRNA-145, and miRNA-137 transcription was considerably upregulated in response to *O. europaea* leaf extracts. In the T98G glioblastoma (GBM) cell line, *O. europaea* leaf extracts were also able to reduce the transcription of the target gene for these microRNAs, which are associated with anticancer properties and temozolomide (TMZ) response [291].

8. Novel strategies for cancer treatment: miRNA-Based gene therapy

Recent strides in molecular biology have sparked a paradigm shift, not just in our comprehension of fundamental biological processes but also in the realm of clinical oncology, particularly in anticancer therapeutics. Chief among these advancements is the discovery and elucidation of miRNAs, that exceed two thousand in humans alone. Operating at the posttranscriptional level, miRNAs intricately regulate gene expression, finely tuning protein output in response to diverse cellular cues. Their significance reverberates profoundly in cancer biology, where their dysregulation underpins numerous malignancies. MiRNAs have emerged as pivotal orchestrators in tumor initiation, progression, and metastasis. More than 39,174 publications related to miRNA and cancer are listed in the NCBI PubMed database and their number exponentially grows. Of particular interest is the distinct miRNA profiles observed across various cancer cell types, presenting a compelling target for therapeutic intervention. Among the growing strategies, miRNA-based gene therapy has emerged as a promising frontier in cancer care. Three primary approaches have surfaced: one aiming to quell the

activity of oncogenic miRNAs, often dubbed oncomiRs, when they are overexpressed; the other seeking to restore the function of tumor suppressor miRNAs when they are downregulated, and the last one pertains to chemical and dietary manipulations, employing small molecules and nutrients (Fig. 4). These procedures, aimed at reinstating physiological miRNA expression within tumor cells, hold substantial potential for tailored cancer treatments. In this dynamic convergence of science and clinical practice, the prospect of miRNA-based therapies reshaping cancer management is both tantalizing and transformative. As investigations delve deeper into the complexities of miRNA function and dysregulation in cancer, the promise of leveraging these diminutive molecules for therapeutic gain grows ever brighter.

Effective delivery of miRNA-based therapeutics is essential for their clinical application. Two main strategies, namely local and systemic delivery, are utilized to enhance efficacy and minimize off-target effects. Local delivery offers benefits such as decreased toxicity and targeted delivery to solid tumors; however, its applicability is limited in hematological malignancies and advanced metastatic cancers. Conversely, systemic delivery enables broad distribution of miRNA drugs, improving their accessibility to target tissues despite facing inherent challenges. Substantial progress has been achieved in both nonviral and viral delivery systems, each with distinct advantages and limitations, emphasizing the need for tailored delivery approaches to ensure the success of miRNA-based therapies.

8.1. Novel miRNA inhibition strategy for anticancer therapies

Innovative anticancer therapies leverage miRNA inhibition strategies to counter the overexpression of oncomiRs in tumor cells, with the goal of reinstating the normal function of tumor suppressor genes. Diverse methodologies are deployed for this purpose, spanning the utilization of antisense anti-miR oligonucleotides (AMO), locked nucleic acid (LNA), miRNA antagomirs, and miRNA sponges [292]. These approaches typically entail the introduction of chemically modified single-stranded RNAs that exhibit strong binding affinity towards target miRNAs. By forming stable complexes with these inhibitors, the targeted miRNAs are incapacitated from exerting translational repression. Consequently, the structure of endogenous miRNAs is altered, rendering them unrecognizable and thereby leading to their deactivation and removal from the RNA-induced silencing complex (RISC). This orchestrated process represents a promising avenue for the development of novel anticancer therapeutics.

AMOs represent chemically modified antisense oligonucleotides, typically comprising 17–22 nucleotides, strategically designed to complement specific miRNAs of interest [293]. By binding to the mature miRNA in a complementary manner, these oligonucleotides disrupt the interaction between the miRNA and its mRNA targets, thereby restoring normal translation processes. An exemplar of such modification is the introduction of locked nucleic acid (LNA). LNA-modified antisense oligonucleotides demonstrate enhanced thermal stability and affinity towards their target miRNA molecules, along with improved aqueous solubility and metabolic stability for effective *in vivo* delivery [294]. Notably, a study showcased the efficacy of LNA-modified antisense oligonucleotides in silencing overexpressed miR-21 in glioblastomas, resulting in a substantial reduction in cell viability and an increase in intracellular caspase levels [295]. Furthermore, *in vivo* experiments have validated the effectiveness of LNA-mediated miRNA silencing, even in non-human primates [294]. Notably, miravirsen, an LNA-derived inhibitor targeting miR-122, is currently undergoing phase 2 clinical trials for the management of hepatitis C virus infection [296].

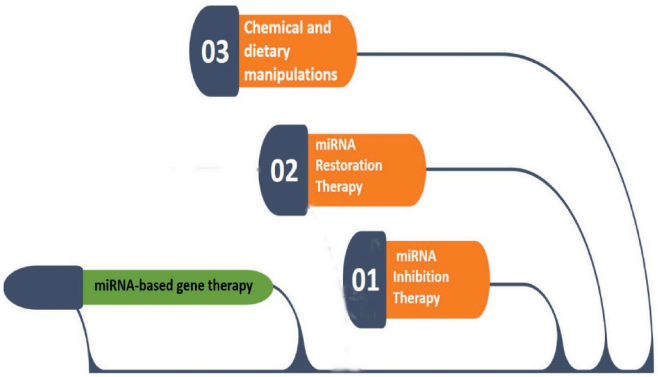

Fig. 4. The three miRNAs-based gene therapy strategies for cancer treatment.

Antagomirs, comprising chemically modified single-stranded 23 nucleotide RNA molecules, serve to stabilize targeted miRNAs and protect them from degradation [297,298]. Ma et al. demonstrated the effectiveness of antagomirs in suppressing metastasis by silencing miR-10b in a mouse mammary tumor model, leading to decreased miR-10b levels and elevated expression of the critical miR-10b target, HOXD10 [299].

Apart from LNA-based approaches, an artificial RNA decoy, known as a miRNA sponge, presents an alternative strategy for inhibiting oncomiRs. This miRNA sponge can be generated from a transgene, enabling stable expression even *in vivo* [300]. Interestingly, this artificial approach mirrors an endogenous regulatory mechanism involving long non-coding RNAs, termed competing endogenous RNAs (ceRNAs), which act as natural miRNA sponges [301]. While the prevalence of this phenomenon and its potential occurrence with different long noncoding RNAs remain subjects of debate [302], similar strategies have been observed in the case of herpesvirus saimiri, which produces an RNA decoy capable of titrating miR-27 [303]. These engineered RNAs contain multiple binding sites for specific miRNAs, competing with endogenous targets for miRNA interactions [304]. For instance, in breast cancer cells with heightened miR-9 levels suppressing CDH1 expression, miRNA sponges with numerous miR-9 binding sites effectively restored CDH1 expression, thereby impeding metastasis [305]. A recent advancement involves artificial circular RNA (circRNA) sponges, leveraging circRNAs' inherent ability to sequester miRNAs [306]. Liu et al. developed circRNA sponges targeting miR-21 and miR-221, demonstrating enhanced efficacy in inhibiting miRNA targets compared to linear counterparts in malignant melanoma cell lines [307]. Transfection of circRNA targeting miR-21 induced significant anti-proliferative effects in gastric cancer cells by inducing apoptosis and modulating global protein expression [307]. This pioneering approach underscores the therapeutic potential of circRNA-based miRNA inhibition strategies.

8.2. Novel miRNA replacement strategy for anticancer therapies

Artificial restoration of miRNA expression or function, known as "miRNA replacement therapy," offers a promising avenue for anticancer interventions. This approach involves reintroducing specific miRNAs, either through miRNA mimics or expression vectors, to re-establish cellular pathways crucial for normal function [308,309]. In cases where tumor suppressor miRNAs are downregulated in cancer cells, miRNA replacement therapy aims to induce apoptosis or inhibit proliferation by restoring their expression. MiRNA replacement therapy utilizes synthetic miRNA mimics or viral vectors expressing miRNAs. MiRNA mimics function by replacing lost miRNAs and restoring their normal function. Chemically modified RNA duplexes, resembling pre-miRNAs, are introduced into cells and loaded into the RNA-induced silencing complex (RISC) to inhibit target mRNAs downstream [292]. This strategy holds promise for targeted intervention in cancer by restoring the expression and function of specific miRNAs critical for tumor suppression.

Numerous studies have demonstrated the effectiveness of miRNA replacement therapy both *in vitro* and *in vivo*. For example, introduction of the miRNA mimic miR-15 into prostate cancer cell lines led to significant apoptosis and inhibition of proliferation, highlighting the

tumor-suppressive potential of miRNA replacement [310]. Similarly, intranasal administration of let-7 in K-ras mutant mice effectively suppressed tumor growth by blocking cell proliferation and cell cycle pathways [311,312]. Another approach involves the use of miRNA expression vectors, such as adenoviral, lentiviral, and retroviral vectors, to enhance miRNA expression for tumor suppression. Kota et al. observed reduced expression of miR-26 in human liver cancers compared to normal tissues. Ectopic expression of miR-26 induced cell cycle arrest in liver cancer cell lines, and intravenous injection of recombinant adenovirus carrying miR-26 inhibited tumorigenicity without inducing toxicity [313].

Clinical trials employing miRNA mimics are currently underway, with a miR-34 mimic showing promise in preclinical studies. Injection of a miR-34a mimic extended the survival of tumor-bearing mice and inhibited tumor growth while inducing apoptosis in a pancreatic xenograft cancer model [314]. The Mirna Therapeutics Company initiated a phase I study to assess the safety of MRX34, a liposome-formulated miR-34 mimic, in patients with primary liver cancer and advanced or metastatic cancer [315].

The advancements in miRNA replacement therapy hold significant promise for cancer treatment. By restoring aberrantly expressed miRNAs, this approach offers a targeted and potentially less toxic alternative to conventional therapies. Furthermore, the development of personalized miRNA-based treatments could revolutionize cancer care by tailoring therapies to individual patient profiles. However, challenges such as delivery efficiency, off-target effects, and the need for comprehensive understanding of miRNA function and regulation remain to be addressed. Continued research efforts and clinical trials are essential to validate the efficacy and safety of miRNA replacement therapy and pave the way for its integration into standard cancer treatment protocols. MiRNA replacement therapy represents a promising avenue for cancer treatment, leveraging the regulatory roles of miRNAs in cancer biology. Preclinical studies and ongoing clinical trials have demonstrated encouraging results, underscoring the therapeutic potential of this approach. With further advancements in delivery systems and deeper insights into miRNA function, miRNA replacement therapy holds promise for improving patient outcomes and advancing personalized cancer care in the future.

8.3. Chemical and dietary manipulations

In addition to nucleic acid-based approaches such as anti-miRs and miRNA sponges, small chemical molecules and nutrients capable of interfering with the processing of pre-miRNAs by Dicer represent a promising avenue for miRNA modulation. By targeting key enzymatic processes involved in miRNA biogenesis, these molecules offer a means to fine-tune miRNA expression levels and restore a nonpathogenic miRNA profile. Moreover, their ability to sensitize cancer cells to chemotherapy and radiotherapy underscores their therapeutic potential in personalized cancer treatment. Notably, modulation of specific miRNAs, such as microRNA-200c, has been shown to restore drug sensitivity and prevent tumor recurrence, highlighting the clinical relevance of chemical miRNA modulation [316]. Beyond chemical interventions, dietary factors play a pivotal role in modulating miRNA expression levels, offering a non-invasive and readily accessible approach to miRNA regulation. Various nutrients, including amino acids, carbohydrates, fatty acids, vitamins, and phytochemicals, have been implicated in miRNA modulation [317]. For instance, dietary fiber intake has been inversely associated with colorectal cancer risk, with short-chain fatty acids produced through microbial fermentation of fiber exerting miRNA-modulating effects [318]. By targeting oncogenic miRNAs in cancer cells, dietary interventions hold promise as adjunctive therapies in cancer management. The modulation of miRNA expression levels through chemical and dietary interventions represents a burgeoning frontier in cancer therapy. By leveraging small chemical molecules and dietary factors, clinicians may fine-tune miRNA profiles to restore nonpathogenic states and enhance the efficacy of conventional anticancer therapies. Moreover, the advent of personalized medicine underscores the potential of dietary interventions in tailoring cancer treatment to individual patient needs. As research in this field progresses, the integration of chemical and dietary miRNA modulation promises to revolutionize cancer management, offering novel avenues for therapeutic intervention and improved patient outcomes.

8.4. Navigating the roadblocks: overcoming challenges in miRNA-Based therapeutics

Developing miRNA-based therapies for cancer treatment encounters numerous obstacles hindering their successful clinical implementation. A primary challenge revolves around effectively delivering miRNA antagonists or mimics to target tumor tissues, requiring penetration into the tumor mass amidst the constraints posed by abnormal tumor vasculature and leaky structures. This compromised blood perfusion diminishes delivery efficacy. Additionally, ensuring the integrity and stability of miRNAs in circulation is vital, as unmodified miRNAs face rapid degradation by serum nucleases and clearance through renal excretion, resulting in short systemic circulation half-lives. Systemic miRNA delivery can also trigger immunotoxicity, activating inflammatory cytokine secretion and interferon production via Toll-like receptors. Furthermore, the risk of off-target side effects remains significant, as miRNAs designed to target multiple pathways may inadvertently silence tumor suppressor genes, reducing therapeutic efficacy and inducing toxicities. Overcoming these challenges requires innovative strategies, including combinatorial approaches and multifunctional nanoparticles, to enhance specificity and efficacy while minimizing off-target effects.

9. Conclusion

Since immemorial times, medicinal plants have been gaining much attention for their usage as a healing agent because of their high social acceptance level, non-toxic nature, and negligible side effects. Since the initial detection of miRNAs, various research has focused on their roles in cancer. The proliferation, invasion, migration, and metastasis of cancer cells have been shown in studies to be caused by the deregulation of miRNAs. miRNAs are essential modulators for cellular pathways, so various plant bioactive compounds also deregulate the miRNA in cancer cells to inhibit the cancer cells by inducing cell apoptosis. Ultimately, the plant bioactive compounds driven miRNAs should be the unique approach for future green and gene cancer therapy. They can be a viable resource for gene therapy. The study of miRNA is in its early stage, and there is still a need to understand the biological pathways and targets for miRNA with the diagnostic and prognostic potential of bioactive compounds. A large-scale population-based study is a need for future perspectives on therapeutic efficiencies in the field.

CRediT authorship contribution statement

Sahreen Sumaira: Data curation, Formal analysis, Investigation, Methodology, Writing – original draft. **Soundararajan Vijayarathna:** Data curation, Formal analysis, Investigation, Writing – original draft. **Manisekaran Hemagirri:** Data curation, Formal analysis, Writing – original draft. **Mohd Adnan:** Formal analysis, Validation, Writing – review & editing. **Md Imtaiyaz Hassan:** Investigation, Validation, Writing – review & editing. **Mitesh Patel:** Formal analysis, Investigation, Methodology, Writing – review & editing. **Reena Gupta:** Formal analysis, Methodology, Writing – original draft. **Shanmugapriya:** Formal analysis, Methodology, Writing – original draft. **Yeng Chen:** Formal analysis, Investigation, Methodology, Writing – original draft. **Subash C.B. Gopinath:** Formal analysis, Investigation, Methodology, Writing – original draft. **Jagat R. Kanwar:** Data curation, Formal analysis, Investigation, Methodology, Writing – review & editing. **Sreenivasan Sasidharan:** Formal analysis, Investigation, Methodology,

Project administration, Resources, Supervision, Validation, Writing – review & editing.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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