Review Article

Regulation of MicroRNAs by Natural Products and Bioactive Compounds Obtained From Common Medicinal Plants: Novel Strategy in Cancer Therapy

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ABSTRACT

MicroRNAs (miRNAs) are highly conserved non-protein coding small RNAs, known to contribute to the epigenetic regulation process in various cancer cells, including the regulation of progression, proliferation and metastasis of cancer cells, differentiation of the cells and process of apoptosis. In addition to, they are crucial for the regulation of cancer stem cells, and management the process of epithelial to mesenchymal transition of cancer cells, implicating in the cancer cells. Further to this, their roles are changeable depending on biological processes, for example miR-17, miR-20a, miR-19b-1, miR-18a, miR-19a, miR-92-1, miR-21, and miR-155 may have critical roles as oncogenic miRNAs (oncomiRs), while miR-15, miR-16, let-7, miR-34, miR-48, miR-84, miR-241 may have anticancer activities as tumor suppressor miRNAs. Therefore, the regulation of miRNAs levels by active natural compounds and/or products could be a promising strategy for cancer treatment, especially in order to inhibit cancer progression and proliferation, prevent metastasis, control the process of transition of cancer cells, and overcome chemotherapeutic resistance by increasing drug sensitivity as well. Recent studies and clinical trials which are aimed to find novel targets for the treatment of cancer, have emphasized the importance of the consumption of natural anticancer agents-rich diet. In the current review, we aimed to provide overview anticancer effects of natural compounds and/or products, isolated from medicinal plants, on miRNAs which are closely related to cancer progression and metastasis.

KEY WORDS: MicroRNAs, Cancer Therapy, Natural Products, Bioactive Molecules, Medicinal Plants, Nutri-Epigenetics.

INTRODUCTION

Cancer is a genetic disease, characterized by uncontrolled cell growth, which originates from one malignantly transformed normal cell. This cell both grows uncontrollably and multiplies quickly. Then, it spreads to other cells through body fluids such as blood and lymph nodes, which caused initiation of metastasis process.[1,2] According to statistical cancer reports on the prevalence and mortality of cancer globally, cancer is reported to be the second most common disease behind cardiovascular diseases. Besides high rate of prevalence, it lead to high rate of mortality worldwide. The statistical cancer reports show that it caused almost 8.8 million deaths among a total number of 17.5 million cancer cases in 2015. Furthermore, it is estimated that the prevalence of cancer will exceed 20 million every year by 2025, alarming fact on cancer cases. Therefore, in recent years, it has been a major and critical public health problem all over the world, it will probably continue to be more critical health problem in the following years.[2,3]

Even though, cancer risk and progression have been associated with many genetic and epigenetic factors such as genetic mutations, hormones, immune system, infectious

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agents, chemicals, radiation, smoking, consumption of alcohol, obesity, cancer history. Of which epigenetic factors, not causing any alterations in DNA sequences, have been found to be more linked with initiation and/or development of carcinogenesis.[3,4] Indeed, scientific evidences have been asserted that changes and alterations in genetic and epigenetic mechanisms have significantly contributed to increase incidence and prevalence of the cancer.[1,4]

In the recent years, medicinal plants have offered many natural bioactive compounds that involving in prevention and treatment many cancers, as natural anticancer agents. In addition to, they have play critical roles in discovering efficient and clinically useful therapeutic anticancer agents.[5,6] However, medicinal plants contain many natural products and compounds against the cancer, berberine, curcumin, genistein, daidzein, glyceollin, apigenin, quercetin, baicalein, resveratrol, luteolin, matrine, garcinol, silibinin, mangiferin, doxorubicin, and paclitaxel are common natural products and compounds found to associate with cell differentiation, proliferation and apoptosis that exhibit anticancer activities on various human cancer types.[7-9]

Plant derivatives natural products are capable of altering cellular signaling through epigenetic changes that include DNA methylation and histone modifications. These epigenetic changes lead to alter the expressions of miRNAs, while either increasing or decreasing of the expression levels.[7,8] Because of their anticancer effects as regulating expression levels of many miRNAs, taking dietary natural products are necessary for both the inhibition of activity of oncogenic miRNAs, and inducing the activity of tumor suppressor miRNAs, which will support to inhibit development and progression of tumorogenesis.[8-10]

The present review is aimed to provide viewpoint concerning to elucidate the relations between the alterations in expression levels of miRNAs and process of cancer development, likewise, relation between anticancer roles of natural products and regulating effects on the expression pattern of miRNAs involved in cancer process.

2. MicroRNAs and Their Roles in Cancer-Related Processes

MiRNAs are small (18-25 nucleotides) and evolutionarily highly conserved non-coding RNAs that are called as the key player in gene regulation through posttranscriptional silencing or activation.[8,11] Even though, miRNAs commonly localize in intergenic regions, the localization of them can differ from species to species. A single miRNA is able to target more than one hundred genes; additionally each gene contains multiple binding sides for miRNAs.[5] Thus, they are involved in many multiple signaling pathways including cancer regulation processes especially, cell proliferation, and migration, metastasis, apoptosis, and cell differentiation in numerous malignancies.[11,12]

In terms of their functions, they are classified into two different categorizes that are tumor suppressors miRNAs which are downregulated or completely lost in cancerous conditions, and oncogenic miRNAs which are overexpressed in many cancerous cases.[6,7] Among which tumor suppressing miRNAs, also called as gatekeepers, exhibit the reducing effect on tumor growth, as well as suppressing effect on the oncogenic signaling that controlled carcinogenesis mechanisms by negatively. Nevertheless, oncogenic miRNAs, also known as oncomiRs, lead to promote proto-oncogenes or block tumor suppressor genes by involving in oncogenic and tumor suppressor pathways.[9-12] The expression levels of the tumor suppressor genes and oncogenes are controlled by genetic and epigenetic mechanisms that significantly associated with development of cancer pathogenesis. Methylation and acetylation are the most common posttranscriptional regulation mechanisms in human which causing alterations in the expression patterns of miRNAs. Scientific evidences showed that hyper-methylated genes become silence and inactive, while, hypo-methylated genes become active. On the other hand, recent researches have suggested that methylation status of miRNAs have strongly associated with the regulation of them, while altering the expression levels of miRNAs.[11-13]

Indeed, the hypo-methylation in oncogenic miRNAs causes to overexpression of the oncogene, thereby proto-oncogenes can convert to the oncogenes. Besides the activation of oncogenic miRNAs, the hyper-methylation in tumor suppressor miRNAs leads transcriptional inactivation in tumor suppressor genes. In case of any of these situations, they will lead to the loss of control in cell growth and division resulting in development of cancer proliferation and metastasis.[13,14]

In the recent years, scientific researches related to evaluate changes and alterations in the expression patterns of miRNAs have gained significant attention, particularly recognizing miRNA biomarkers as an indicator in various cancer cases, owing to their changeable expression levels depending on the cancerous conditions.[7,8] Some of them such as miR-10b, miR-21, miR-27a, miR-155, miR-373, miR-424-5p, miR-520c have been identified as oncogenic miRNAs that found overexpressed in various cancers, whereas, the others including miR-15a, miR-16-1, miR-34, miR-126, miR-150, miR-183, miR-203, miR-206, miR-335, miR-495 have been identified as tumor

suppressor miRNAs that found down expressed in the cancers compared to normal cells.[13-15]

Despite the fact that many genetic and epigenetic alterations in the coding miRNA genes were determined, many of them are not tissue specific miRNA in diagnosis and prognosis of cancer, not suitable for clinical applications as well. Therefore, further researches should be focused on discovering cancer-related miRNAs which play significant roles in carcinogenic pathways.

Regulation of MicroRNAs Expressions by Dietary Compounds and Natural Bioactive Products

The expression levels of tumor suppressor miRNAs are induced, whereas, the expression levels of oncogenic miRNAs are suppressed or silencing by bioactive compounds and natural products, found in medicinal plants as natural anticancer agents.[5-8] These natural anticancer agents are obtained from various medicinal plants such as, *Allium* species, *Brassica* vegetables, *Magnolia* sp., *Ganoderma* sp., *Berberis aristata, Aloe vera*, *Mentha longifolia*, *Mentha spicata* L., *Citrus medica*, *Citrus limon* Burm. f., *Citrus paradise* Macf., *Betula pendula*, *Mimosa pudica*, *Passiflora incarnate*, *Cannabis sativa*, *Azadirachta indica*, *Calendula officinalis*, *Glycchericza glabra*, *Oraxylum indicum*, *Lithosprmum radix, Myrciaria floribunda, Thymus vulgaris, Xylopia frutescens, Neolitsea variabillima, Guatteria pogonopus, Tridax procumbens, Myrica gale, Boswellia carterii, Commiphora pyracanthoides, Amomum tsaoko, Zingiber officinale, Jasminum grandiflora,*

Table 1: Regulation of miRNAs by bioactive compounds

Bioactive compounds	Main known medicinal plants	Target tumor suppressor miRNAs	Target oncogenic miRNAs	Type of cancer
Apigenin	*Brassica* species, *Allium* species, *Matricaria recutita, Capsucum annuum*	miR-183	miR-103	Obesity and diabetes-induced cancer types
Baicalin and baicalein	*Scutellaria baicalensis*	miR-23a, miR-124	miR-181b, miR-199a-3p, miR-294, miR-378	Embryonic stem cells and neuronal cells
Berberine	*Berberis aristata, Coptis japonica, Coptis chinensis, Phellondendron amurense*	miR-21-3p, miR-34a, miR-141	miR-21, miR-99a~125b, miR-17~92, miR-106~25	Ovarian and breast cancer, hepatocellular carcinoma
Betulinic acid	*Platanus acerifolia*	miR-21	miR-27a, miR-33	Colon, breast and hepatoma cells
Boswellic acid and AKBA	*Boswellia serrata*	let-7, miR-34a, miR-200	miR-27a	Brain and colon cancers
Caffeine and caffeic acid	*Coffea arabica*	miR-124, miR-148a	miR-9, miR-125b, miR-146a, miR-155, miR-223	Breast cancer and hepatocarcinoma cells
Camptothecin (quinolone alkaloid)	*Camptotheca acuminata*	miR-15a, miR-16	miR-125b	Cervical carcinoma, ovarian, gastric and colorectal cancers
Catechin (tea polyphenols) and EGCG	*Camelia sinensis, Aspalathus linearis*	let-7b, let-7c, miR-1, miR-7-1, miR-16, miR-18, miR-25, miR-34a, miR-34b, miR-92, miR-99a, miR-126, miR-144-3p, miR-210, miR-330	miR-21, miR-30, miR-92, miR-93, miR-98-5p, miR-106b, miR-374c-5p, miR-449c-5p, miR-450a-2-3p, miR-453, miR-520-e, miR-608, miR-629	Lung and prostate cancers, hepatoma and neuroblastoma cells
Curcumin (turmeric), curcuminoid	*Curcuma longa*	miR-7, miR-9, miR-15, miR-16, miR-22, miR-29a, miR-145, miR-181, miR-192-5p, miR-200b/c, miR-203, miR-205-5p, miR-215, let-7	miR-17-5p, miR-20a, miR-21, miR-27a, miR-186, miR-208	Breast, colorectal, prostate and lung cancers, leukemia, WT1, hepatocellular carcinoma
Doxorubicin, docetaxel		miR-27b, miR-34a, miR-34b, miR-101, miR-125b, miR-127, miR-128, miR-193b, mir-199a, miR-200c, miR-205, miR-218, miR-450b-3p, miR-451, miR-497, miR-522, miR-542-3p	miR-10b, miR-21, miR-28, miR-106a, miR-181a, miR-202, miR-206, miR-221, miR-548c-3p	Breast cancer, glioblastoma and lymphoma cells

Bioactive compounds	Main known medicinal plants	Target tumor suppressor miRNAs	Target oncogenic miRNAs	Type of cancer
Garcinol and Gemcitabine	*Garcinia indica*	let-7, miR-453, miR-720, miR-128, miR-200b/c, miR-453, miR-638, miR-663, miR-720, miR-1280	miR-21, miR-196a, miR-495, miR-605, miR-483-3p, miR-494, miR-495, miR-1914, miR-1977	Breast and pancreas cancers
Genistein and soy isoflavones	*Glycine max, Pueraria lobata, Psoralea corylifolia, Scutellaria* species	let-7, miR-23b, miR-34a, miR-146a, miR-200, miR-574-3p, miR-1296	miR-21, miR-23b, miR-27a, miR-151, miR-155, miR-221, miR-222, miR-223, miR-1260b	Renal, ovarian, prostate and pancreas cancers
Glabridin	*Glycyrrhiza glabra*	miR-148a, miR-520a	------	Hepatocellular carcinoma and breast cancer
I3C and DIM (indole alkaloids)	*Brassica* species	let-7b/c/d/e, miR-21, miR-34, miR-146a, miR-200b/c, miR-212/132	miR-21, miR-31, miR-92, miR-130a, miR-146b, miR-221, miR-377	Prostate and pancreas
Luteolin	*Terminalia chebula*	----	miR-34a	Gastric cancer
Magnolol and honokiol	*Magnolia* species	miR-34a, miR-143, miR-200c	------	Colon, breast and bladder cancers
Mangiferin	*Mangifera indica*	miR-15b, miR-182	------	Lung, prostate, leukemia
Matrine	*Sophora flavescens*	-----	let-7b-5p, miR-10a-5p, miR-15b-5p, miR-18a-5p, miR-19a-3p, miR-19b-3p, miR-20b-5p, miR-21, mir-21-5p, miR-23a-3p, miR-26b-5p,	Gastric and breast cancers
Paclitaxel (taxol)	*Taxus brevifolia*	let-7b, miR-9, miR-10b, miR-16, miR-17, miR-17-5p, miR-34a, miR-122, miR-125a, miR-130a, miR-134, miR-141, miR-155, miR-200c, miR-218, miR-367, miR-494, miR-497, miR-647, miR-873, miR-877, miR-1204	miR-19a, miR-21, miR-22, miR-30a-5p, miR-129-5p, miR-130b, miR-149, miR-153, miR-133a/b, miR-197, miR-205, miR-320a, miR-361-3p, miR-375, miR-433, miR-490, miR-520h, miR-622, miR-663, miR-1307	Ovarian, breast and lung cancers
Palmitine	*Coptis japonica*	miR-34a, miR-141, miR-200c	-----	Prostate and breast cancers
Quercetin	*Allium* species*, Malus domestica, Phaseolus vulgaris, Vitis vinifera, Capparis sicula, Citrus* species	let-7, miR-16, miR-26, miR-34a, miR-142-3p, miR-146a	miR-27a, miR-125b-3p	Colon, lung and pancreas cancers
Resveratrol	*Arachis hypogaea, Muscadine berries, Vitis vinifera*	miR-34a/c, miR-122-5p, miR-141, miR-194, miR-200c, miR-299-5p, miR-338-3p, miR-582-3p, miR-622, miR-663, miR-758, miR-774	miR-17, miR-21, miR-25, miR-27a, miR-92a-2, miR-103-1, miR-103-2, miR-183, miR-200-3p, miR-520h, miR-542-3p, miR-17-92	Colorectal, lung, pancreas, prostate and gastric cancers
Rosmarinic acid	*Rosmarinus officinalis*	miR-124, miR-148a	miR-9, miR-125b, miR-146a, miR-155, miR-223	Brain, breast and lung cancers
Silibinin	*Silybum marianum*	miR-200c	miR-21	Lung cancers
Ursolic acid	*Radix actinidiae, Oldenlandia diffusa*	-----	miR-21	Glioma cells,
Vinca alkaloids (vinblastine, vincristine)	*Catharanthus roseus*	miR-25, miR-34a, miR-93, miR-93, miR-199a, miR-224, miR-424, miR-494, miR-497	miR-27a, miR-27b, miR-148a, miR-324-3p, miR-328, miR-451	B-cell lymphoma, breast, prostate and laryngeal cancers

Nectandra megapotamica, Matricaria chamomilla, Rosa damascena, Zanthoxylum rhoifolium Lam., *Lavandula angustifolia, Lavandula stoechas* ssp. *stoechas, Talauma ovata, Symphyopappus itatiayensis, Psidium cattleianum, Juniperus phoenicea, Malus domestica, Comptonia peregrina* L., *Artemisia indica, Litsea cubeba, Casearia sylvestris, Photinia serrulata* and *Plectranthus amboinicus*.[13-18] The miRNAs regulated by a selection of important anticancer natural products and compounds that obtained from main known medicinal plants are presented in Table 1.

As summarized in Table 1, recent studies and clinical trials which are aimed to find novel targets for the treatment of multiple types of cancers, have emphasized the importance of the consumption of natural agents-rich diet, including curcumin, berberine, alkaloids, mitomycin C, resveratrol, camptothecin, topotecan, trabectedin, matrine, honokiol, isoflovones, indole-3-carbinol, sulforaphane, water soluble vitamins, diallyl disulfide, 3,3'-diindolylmethane, epigallocatechin-3-gallate and hesperidin, etc., additionally syntheses of natural products by the liposome or nanoparticle formulations assays.[5,7,16-18]

The bioactive compounds and natural products have significant influences on the epigenetic changes in the cancer cells. For instance, they regulate the expression levels of miRNAs by effecting the several proteins that are involved in the stages of tumorogenesis both cancer initiation and development. [17,18] Apart from, they effect cell signaling and apoptotic pathways such as PI3K-Akt-mTOR, AR, Akt and ERK signaling, Wnt signaling, p53, Erb and MAPK signaling, Src/Ras/ERK and TGF-β signaling. From this point of view, intake of these natural agents by dietary regimes appears worthwhile for effective cancer therapy as a nutri-epigenetic approach, since approximately 30-35% cancer, a substantial proportion, can be prevented by dietary choices.[1,10,11] In addition, dietary interventions give opportunity to cure more efficiently with fewer side effects and toxicity.[7,8]

CONCLUSIONS AND FUTURE PERSPECTIVES

MicroRNAs as Novel Biomarkers in Cancer

Consequently, regulation of microRNAs by natural products and/or bioactive compounds obtained from common medicinal plants would likely provide a novel therapeutic agent for cancer therapy in the following years particularly, when provided to be certain that there are no side effects of dietary intake.

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CONFLICT OF INTERESTS

The authors have declared that no conflict of interest exists.

ABBREVIATIONS

AKBA: 3-acetyl-11-keto-b-boswellic acid; **Akt:** a serine/threonine kinase also known as protein kinase B [PKB]; **AR:** androgen receptor; **DIM:** 3,30-diindolylmethane; **EGCG:** [−] epigallocatechin-3-gallate; **ERK:** extracellular signal-regulated kinase; **I3C:** indole-3-carbinol; **mTOR:** mammalian target of rapamycin; **p53:** tumor protein 53; **PI3K:** phosphatidylinositol 3-kinase; **TGF-β:** transforming growth factor beta.

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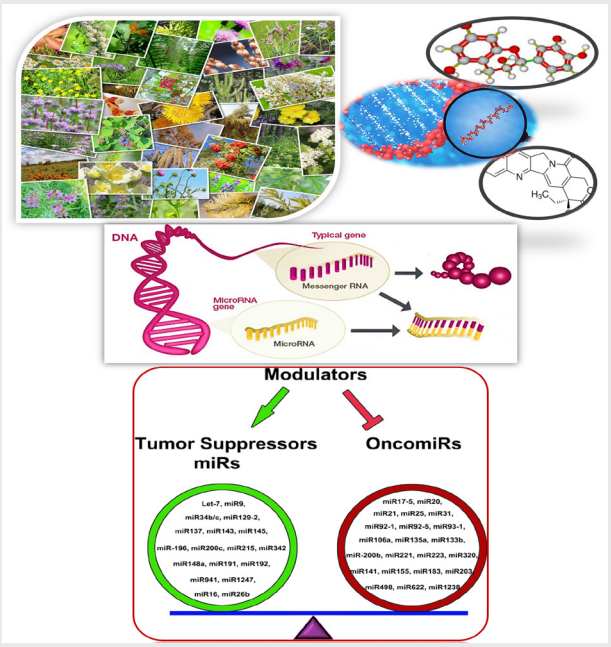
PICTORIAL ABSTRACT



SUMMARY

- MicroRNAs (miRNAs) contribute to the epigenetic regulation process in progression, proliferation and metastasis of cancer cells.
- They exhibit changeable expression levels depending on the biological process, so they play critical roles in cancerous conditions as oncogenic miRNAs (oncomiRs) or tumor suppressor miRNAs.
- Their expression levels can be suppressed or induced by active natural compounds and/or products, isolated from MAPs.
- • In the current review, we aimed to provide overview anticancer effects of natural compounds and/or products, isolated from MAPs, to emphasize the importance of the consumption of natural agents-rich diet for both cancer prevention and treatment as well.
- Overall, MAPs would likely provide a novel therapeutic strategy for cancer therapy in the following years particularly, when provided to be certain that there are no side effects of dietary intake

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