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Review

New insights of medicinal plant therapeutic activity—The miRNA transfer

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ABSTRACT

MicroRNA (miRNA) has become the spotlight of the biomedical research around the world and is considered to be a major post-transcriptional gene regulator. This small, endogenous RNA (21–25 nucleotides long) plays an important role by targeting specific mRNAs in plants, animals and humans. Herbal medicine has been used for thousands of years, however little is known about its molecular mechanism of action. Since the discovery of plant miRNA in human tissue and sera after ingestion, the connection between the two kingdoms is presented under a new perspective. Forward pharmacology, such as miRNA therapeutics could be the next best step toward identifying novel therapeutic options involving medicinal plants. Besides reporting the latest findings regarding the cross-kingdom transfer of miRNA and its therapeutic application, this review can inform further investigations that could lead to a modern definition of herbal medicine.

Contents

1. Introduction

MicroRNAs (miRNAs) are a class of small, endogenous post-transcriptional RNAs of 21–25 nucleotides. They play an important role in post-transcriptional regulation in animals and plants by targeting specific mRNAs for degradation or translation repression [1]. A single miRNA can target several hundred genes. In addition, one target gene often contains binding sites for multiple miRNAs, allowing them to play an important role in every aspect of biology.

Since the discovery of the first miRNA, lin-4 (*Caenorhabditis elegans*) [2] in 1993, these novel molecules are a continuous growing family. Different computational methods and more than 10 public databases for microRNA:mRNA target prediction are used as research tools for miRNA gene identification and miRNA target prediction, using different algorithms and approaches [3]. This discovery has provided new platforms for controlling gene expression. Several preclinical and clinical studies have been initiated, and it seems that miRNA-based therapeutics are making a grand entrance in the pharmaceutical industry [4].

Plant miRNAs were first discovered in 2002 in *Arabidopsis* [5]. Their methylation at their 3′ ends by HEN1, distinguishes plant miRNAs from those of the animals because most animal miRNA genes are not methylated [6]. The major differences between the two kingdoms are related to target recognition. In animals, the complementary sites are located at the 3-UTR of genes, but in plants they can exist anywhere within the gene [7]. Animal miRNAs bind with mismatches, while plant miRNAs present a

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lower number of mismatches. A central mismatch facilitates the translational repression mechanism but disregards degradation, allowing small animal RNAs to regulate gene expression by translational repression and transcriptional silencing, while in plants the regulation occurs mostly by direct cleavage of target mRNAs due to the high degree of complementarity. In other words, the level of miRNA–mRNA complementarity plays an important role in the regulatory process [8].

To date, using direct cloning and sequencing, as well as bioinformatics and computational prediction methods, there are over 7385 mature miRNAs reported from 72 plant species in miRBASE (version 20) [9]. However, once a miRNA is identified, the understanding of its function or regulatory targets is not immediately evident.

The plants have played a vital role in the treatment of diseases for centuries. Natural active products such as polyphenols, alkaloids, saponins and tannins have been highly focused on as an important tool for production of less side effect drugs [10].

A new interest in plant molecular mechanism of action was brought forward in 2012, when Zhang et al. published their results suggesting that exogenous plant miRNAs in food can regulate the expression of target genes in mammals through food intake [11]. A cascade of articles was subsequently published supporting or arguing Zhang's hypothesis. Although the majority of follow-up studies used dietary plants such as corn [12] or soy [13], several studies used computational identification of miRNAs in medicinal plants. This finding triggers an important biological question: whether or not these miRNAs can enter the bloodstream and have a functional role in human metabolism. This review summarizes the existing knowledge regarding medicinal plant miRNAs and their capability to cross inter-kingdom boundaries.

2. The extracellular circulating miRNAs—a new way of signaling

The first evidence of miRNAs being encapsulated into nanovesicles was provided by Valadi et al. [14], who reported that exosomes containing miRNA and RNA from mouse can be passed into both human and murine cells. After this discovery, more and more articles sustained the idea that miRNAs constitute a form of cell-to-cell communication. In fact, miRNAs have been found in several body fluids like plasma, serum, urine, saliva, breast milk, seminal fluid, etc [15]. There are three different possibilities in which miRNAs can be packed: (a) into lipid-based carriers such as exosomes, ectosomes, apoptotic bodies, microparticles; (b) into lipoproteins carriers (HDL, LDL); (c) into vesicle-independent form (Ago2) [16]. Despite substantial research efforts in this field, little is known about the mechanism by which miRNAs are packed.

Choosing the type of carrier seems to be a miRNA-specific phenomenon, because some miRNAs are exclusively associated only with one type of vesicle or complex carrier. This may lead to the hypothesis that each form of transport have a highly defined role, yet to be discovered [17]. By understanding the role of the circulating miRNAs, scientists are a step closer to fill the gap regarding cross-kingdom communication. The most well-known example is the research by Zhang et al. who reported that miRNAs from exogenous plant consumed by mammals can survive the gastrointestinal tract (via exosomes) and are present in the serum and tissues after food intake [11]. But the hypothesis that sparked many controversies was that exogenous plant miRNAs can regulate

Table 1
Medicinal plants with identified miRNAs.

Medicinal plant	Main known active compound	No. of miRNA sequences	Ref.
Arachis hypogaea (Fabaceae)	Resveratrol	23	[23]
Artemisia annua (Asteraceae)	Artemisinin	6	[24]
Brassica napus (Brassicaceae)	3,3′-Diindolylmethane (DIM)	90	[25]
Brassica olearacea (Brassicaceae)	3,3′-Diindolylmethane (DIM)	10	[26]
Camellia sinensis (Theaceae)	Catechins, caffeine	11	[27]
Carica papaya (Caricaceae)	Papain	79	[28]
Carthamus tinctorius (Asteraceae)	Linoleic acid,carthamin	236	[29]
Catharanthus roseus (Apocyanaceae)	Vinblastine, vincristine	2	[30]
Citrus sp. (Rutaceae)	Vitamin C, pectine	38	[31]
Coffea Arabica (Rubiaceae)	Caffeine	67	[32]
Curcuma longa (Zingiberaceae)	Curcumin	12	[33]
Cynara cardunculus (Asteraceae)	Cynarin, cynaropicrin	48	[34]
Digitalis purpurea (Scrophulariaceae)	Digoxin, digitoxin	13	[35]
Eucalyptus grandis (Myrtaceae)	Eucalyptol	26	[36]
Glycine max (Fabaceae)	Genistein	639	[13]
Gmelina arborea (Verbenaceae)	Gmelanone	6	[37]
Helianthus annus (Asteraceae)	Oleic, linoleic acid	17	[38]
Linum usitatissimum (Linaceae)	Linamarin, linoleic acids	116	[39]
Manihot esculenta (Euphorbiaceae)	Cyanogenic glycosides	169	[40]
Nicotiana tabacum (Solanaceae)	Nicotine, tabacinine	165	[41]
Panax ginseng (Araliaceae)	Steroidal glycosides	73	[42]
Picea abies (Coniferophyta)	Picein, piceatannol	44	[43]
Pinus densata (Coniferophyta)	Pinen, vitamin C	34	[44]
Pinus taeda (Coniferophyta)	Pinen, vitamin C	36	[45]
Populus euphratica (Salicaceae)	Salicin	72	[46]
Populus trichocarpa (Salicaceae)	Salicin	272	[47]
Rehmannia glutinosa (Lamiaceae)	Iridoids, norcarotenoids	37	[48]
Ricinus communis (Euphorbiaceae)	Ricinolein, ricin	95	[49]
Salvia miltiorrhiza (Lamiaceae)	Salvianolic acid B	492	[50]
Salvia sclarea (Lamiaceae)	Linalyl acetate, linalool	18	[51]
Senecio vulgaris (Asteraceae)	Senecionine, tannins	10	[52]
Stevia rebaudiana (Asteraceae)	Stevioside, rebaudioside	112	[53]
Theobroma cacao (Malvaceae)	Theobromine	83	[54]
Vaccinium corymbosum (Ericaceae)	Anthocyanins	9	[55]
Vitis vinifera (Vitaceae)	Stilbenoids, anthocyanins	186	[56]
Zea mays (Gramineae)	Flavonoids, alkaloids	321	[12]