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Review

Regulation of miRNAs by herbal medicine: An emerging field in cancer therapies

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ABSTRACT

MicroRNAs' expression profiles have recently gained major attention as far as cancer research is concerned. MicroRNAs are able to inhibit target gene expression via binding to the 3′ UTR of target mRNA, resulting in target mRNA cleavage or translation inhibition. MicroRNAs play significant parts in a myriad of biological processes; studies have proven, on the other hand, that aberrant microRNA expression is, more often than not, associated with the growth and progression of cancers. MicroRNAs could act as oncogenes (oncomir) or tumor suppressors and can also be utilized as biomarkers for diagnosis, prognosis, and cancer therapy. Recent studies have shown that such herbal extracts as Shikonin, Sinomenium acutum, curcumin, Olea europaea, ginseng, and Coptidis Rhizoma could alter microRNA expression profiles through inhibiting cancer cell development, activating the apoptosis pathway, or increasing the efficacy of conventional cancer therapeutics. Such findings patently suggest that the novel specific targeting of microRNAs by herbal extracts could complete the restriction of tumors by killing the cancerous cells so as to recover survival results in patients diagnosed with malignancies. In this review, we summarized the current research about microRNA biogenesis, microRNAs in cancer, herbal compounds with anti-cancer effects and novel strategies for employing herbal extracts in order to target microRNAs for a better treatment of patients diagnosed with cancer.

Contents

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1. Introduction

Herbal extracts have long been considered as anti-septics, anti-depressants, anti-inflammatories, expectorants, immune system fortifiers and to have anti-cancer effects [1,2]. Like many therapies, people may use herbal medicine to feel healthier. Herbal medicines are among alternative and complementary medicines most commonly used by people specifically those diagnosed with cancers of any kind. Certain researches have demonstrated that as many as six out of every ten people with cancer (60%) use herbal medicine in addition to general cancer treatments [3–8]. There are many types of herbal medicines, some of which exist in different foods.

Herbal medicines, which use is increasing day by day, in pediatric oncology cases are, not infrequently, administered by parents. Herbal extracts are mainly useful, yet it must be noted in pediatric oncology cases, that certain herb-drug interactions occur between conventional drugs and herbal medicines, because herbal agents often contain various pharmacologically active components, while conventional drugs typically contain only one [3]. Several patients employ certain CAM (Complementary/alternative medicine) approaches hoping for therapeutic effects on tumor which might in turn cure their disease [9]. Herbal medicines are deemed by the general population to be safe, entail fewer side effects and be less likely to ensue drug dependency [10]. Nonetheless, little clinical research is conducted in English as to the use of CAM approaches in cancer and has superscripted the studies of anticancer treatments.

Natural compounds might modulate epigenetic phenomena to shift gene expression networks [11]. MicroRNAs are tissue-specific small noncoding RNAs that bind to regulatory sites of target mRNA, resulting in translational repression with decreased protein synthesis [12–14]. MicroRNAs carry significant information concerning tumor cells, serum and blood genome-wide gene expression profiling of clinical samples [15–19].

The role of herbal medicine in regulating miRNA is yet to be fully studied. Recently, numerous researchers have begun to recognize the importance of the anti-tumor effects of herbal medicine targeting miRNAs.

In the present, a literature review was performed in order to specify the herbal extract approaches associated with cancer and microRNA regulation reports and to determine which of these have been studied in the future research.

2. Background and history

With the industrial revolution and the discovery of modern medications, herbal plants were abandoned for a long period of time. However, thanks to the novel techniques and the increased interest in using natural compounds in medicine, obstacles in the way of studies regarding alternative medicines have recently been largely eliminated [20–24].

According to WHO statistics, 80% of people in the world use a certain form of herbal treatment [6]. From 1984 to 1994, 60% of the drugs confirmed by FDA were isolated from natural sources such as plants.

Among the 121 drugs prescribed for cancer treatment, 90 are from herbal sources. A study showed that out of the 65 new medicines recorded for cancer treatment during 1981–2002, 48 were derived from natural agents including:

- Vinca alkaloids
- Taxanes (paclitaxel, docetaxel)
- Podophyllotoxin and its derivations (topothecan, irinothecan)
- Anthracyclines (doxorubicin, daunorubicin, epirubicin, idarubicin) [25,26]. The invention of vincristine, vinblastine and vinca organic compounds and cytotoxic podophyllotoxin segregation, marked the beginning of the study of herbal origins for cancer treatments in 1959. These discoveries led the National Cancer Institute to launch a program called Plant Collect in 1960, which resulted in the detection of novel chemicals, with cytotoxic activities, containing the taxans, and camptothecins. It took thirty years (1960–1990) for these drugs to come into clinical usage [27].

3. Biogenesis of microRNA and its regulation of gene expression

Endogenous RNAs of 19–25 nucleotides (~22 nt in length) are a class of small non-coding RNAs generally known as microRNAs (miRNAs), regulating gene expressions through several mechanisms. Lin-4 is the first microRNA discovered in 1993 by the genetic analysis of Caenorhabditiselegans [28–30]. Years later, *let-7* was discovered as well in Caenorhabditiselegans [31]. Since then, a host of microRNAs have been discovered the functions of which have been investigated [32,33]. It has been surmised that microRNAs are involved in the regulation of several physiological and pathological activities in humans, animals, and plants.

Transcribed in the nucleus by polymerase II, MicroRNAs produce long primary transcripts (pri-miRNAs) containing one to several microRNAs. Pri-miRNAs are processed by DGCR8 (a double-stranded RNA binding protein) and Drosha (RNase III endonuclease) into microRNA precursors called pre-miRNA, which have the two-nucleotide 3′ overhang. The two-nucleotide 3′ overhang structure of the pre-miRNA is recognized by Exportin-5 (Ran–GTP-dependent nuclear export factor). The pre-miRNA is transported into the cytoplasm and cleaved by Dicer to a 22 nt mature microRNA [34–36] Subsequently, by binding to Ago2, the RNA duplex is detached into a single strand, called passenger strand, which is a degraded and functional guide strand binding to the target mRNA [36–38]. The mature miRNA is made complex via the RNA-induced silencing complex (RISC) which leads RISC to target mRNA [37]. Mature microRNAs regulate gene expression through binding to the 3′ untranslated region (3′UTR) of target mRNA, resulting in the inhibition of mRNA translation to functional proteins or the degradation of target mRNA(Fig. 1) [37,39].

miRNA gene transcribed by RNA polymerase II to pri-miRNA then pri-miRNA capped and polyadenylated. The pri-miRNA is processed by Drosha producing pre-miRNA in the nucleus. Then pre-miRNA is exported into the cytoplasm by exportin-5. Dicer removes loop structures of pre-miRNAs in cytoplasm and producing mature miRNA fragment. Helicase unwind the duplex miRNA. Mature miRNA molecule binds to RISC complex, then degrad or repress the translation of mRNA [40–42].

4. The functional role of microRNAs in cancer

Many researchers have studied microRNA expression in tumor patients and the fact that they are differentially expressed in normal and cancer tissues. Such differences are tumor-specific and, in some cases, are associated with prognosis [16,17,43]. MicroRNAs