REVIEW

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Roles of plant-derived bioactive compounds and related microRNAs in cancer therapy

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Plant-derived bioactive compounds, often called phytochemicals, are active substances extracted from different plants. These bioactive compounds can release therapeutic potential abilities via reducing antitumor drugs side effects or directly killing cancer cells, and others also can adjust cancer initiation and progression via regulating microRNAs (miRNAs) expression, and miRNA can regulate protein-coding expression by restraining translation or degrading target mRNA. A mass of research showed that plant-derived bioactive compounds including tanshinones, astragaloside IV, berberine, ginsenosides and matrine can inhibit tumor growth and metastasis by rescuing aberrant miRNAs expression, which has influence on tumor progression, microenvironment and drug resistance in multifarious cancers. This review aims to provide a novel understanding of plant-derived bioactive compounds targeting miRNAs and shed light on their future clinical applications.

KEYWORDS
cancer, miRNAs, NcRNA, novel anticancer agents, phytochemicals, tanshinones

1 | INTRODUCTION

Cancer incidence and mortality are yearly growing, global cancer statistics showed about 18.1 million new cancer cases and 9.6 million cancer deaths in 2018 (Bray et al., 2018). Recently, precision medicine including chemotherapy, targeted therapy and immunotherapy have made tremendous achievements for cancer therapy due to the advances in genomics, cellular and molecular biology. However, cancer with metastasis, multidrug resistance and drug-induced toxicities are still thought to be the vital cause of cancer therapy failure. Therefore, it is urgent to find high-efficiency and non-toxic novel anticancer agents.

Plant-derived bioactive compounds are one of the popular alternative treatments for cancer, mostly by increasing host immune response and reducing harmful effect of chemotherapy such as traditional Chinese medicine (TCM). Over the last several decades, clinical research and experiment have confirmed that natural phytochemicals

could decrease toxicity and enhance the efficacy of radio-chemotherapy, prolong survival in patient with advanced cancer, and contribute to prevention, treatment of recurrence and metastasis (J. Liu, Wang, Zhang, Fan, & Lin, 2015). Plant-derived bioactive compounds are a class of substances with clear chemical structure extracted from certain medicinal plants. So far, studies on the anti-cancer effects of bioactive compounds have confirmed that some phytochemicals, including tanshinones, astragaloside IV, berberine, ginsenosides and matrine, showed obvious inhibitory effect on tumor progression.

MiRNAs are small non-coding RNAs (ncRNAs) which are endogenous RNAs of 18–24 nucleotides (nts) that regulate the expression of one third of protein coding genes through several mechanisms by binding to complementary sequences in the 3′-untranslated region (3′-UTR) of messenger RNAs (mRNA). Growing body of experimental evidence suggest an aberrant expression of miRNAs in plenty of disease such as cancer, kidney disease, cardiovascular and nervous system disease, diabetes and so on, which can act as disease-causing or suppressing gene (H. Li et al., 2019). In recent years, more and more studies also have demonstrated the role of phytochemicals related to regulate miRNAs

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expression. This review systematically showed the current studies on the relationship between miRNAs and some well-studied natural phytochemicals, to provide a novel understanding about the anti-tumor mechanisms of these plant-derived bioactive compounds.

2 | TANSHINONES AND MIRNAS

Tanshinones are the liposoluble components of *Salvia miltiorrhiza* (Danshen), a well-known herb in TCM. Since the day they were detected in the 1930s, more than 40 lipophilic tanshinones and structurally related components have been isolated from Danshen, which consist of 0.29% tanshinone IIA (T2A), 0.23% cryptotanshinone (CT), and 0.11% tanshinone I (T1) (S. Xu & Liu, 2013; Y. Zhang et al., 2012) (Figure 1). T2A, CT and T1 are main bioactive constituents which have been used for treating stroke, inflammatory diseases, atherosclerosis, cardiovascular diseases, and cancers (Tian & Wu, 2013).

T1 could restrain growth in many cancers including gastric cancer (GC) and osteosarcoma through suppressing proliferation and accelerating apoptosis (Jing et al., 2016; W. Wang et al., 2019). Recent studies demonstrated that T1 could sensitize prostate cancer (PC) PC-3 and DU145 cells to tumor necrosis factor related apoptosis inducing ligand (TRAIL) agent induced apoptosis via overexpression of miR-135a-3p mediated death receptor DR5 (TRAIL-R2) (Shin et al., 2014).

T2A has presented all sorts of anti-cancer effects including gastric, breast, lung cancer (Yu, Wang, Li, & Tang, 2017). Multiple studies have demonstrated that T2A could reverse the abnormal expression of miRNA in cancer cells. T2A treatment inhibited the proliferation of inflammatory HCT116 and HT-29 colon cancer (COAD) cells by reducing the expression of tumor necrosis factor α (TNF-α) and interleukin 6 (IL6), which produced by macrophage cell, whereas miR-155 was upregulated and bona fide target gene Phosphatidylinositol-3,4,5-trisphosphate 5-phosphatase 1 (SHIP1) was downregulated in macrophage cell. In other words, T2A ameliorates inflammatory macroenvironment of COAD cells via repression of miR-155 (Tu et al., 2012). T2A also suppressed cell proliferation and induced cycle arrest in Ec109 human esophagus cancer (ESAC) cells via upregulation of miR-122 expression mediated pyruvate kinase M2 (PKM2) down-regulation, which PKM2 play an important role in cancer occurrence and development (H. S. Zhang, Zhang, et al., 2016). Coincidentally, T2A induced hepatocellular carcinoma (HCC) cell death by inducing apoptosis and cell cycle arrest, when T2A treat HCC cells, miR-30b was down-regulated which was the upstream of tumor protein 53 (TP53), that is to say the underlying mechanism involved in T2A induced cell death may be miR-30b-p53 pathway (Ren et al., 2017). Meanwhile, miR-205 was predicted as the regulatory microRNA on surviving expression, recently studies showed that T2A also induced cell apoptosis by direct upregulation of miR-205 in ovarian carcinoma (OC) TOV-21G cells (N. Li, Yang, Zhang, & Chen, 2018).

CT has been utilized in traditional oriental medicine for treating multiple diseases, and anti-proliferation and pro-apoptosis activities also already known to the world in various cancer cells (Y. Zhang et al., 2012). Mechanism investigation showed that CT suppresses expression of epidermal growth factor receptor (EGFR) plays positive roles involved in tumorigenesis by upregulating the expression of miR-146a-5p in H1299 non-small cell lung cancer (NSCLC) cells (Qi et al., 2019).

There are more to anti-cancer roles of tanshinones via regulating miRNAs. TI, T2A and CT could suppress NSCLC through upregulating miR-137, which cause cell cycle arrest and increase cell apoptosis. Various miRNAs including let-7b, let-7c, miR-32, miR-25, miR-34a, miR-92a, miR-92b, miR-367, and miR-363 were also significantly up-regulated by tanshinones (B. Zhang, Ma, et al., 2016). Furthermore, miR-32 was illustrated target of aurora kinase A (AURKA) as an anti-oncogene in NSCLC, and tanshinones inhibits NSCLC via upregulating the expression of miR-32 mediate AURKA suppression (Ma et al., 2015). In addition, our lab's further research showed that T1 and T2A can also suppress NSCLC by up-regulating let-7a-5p expression level through directly targeting AURKA and BORA, and the upstream transcription factor LIN28B of let-7 family is downregulated by tanshinones.

## 3 | OTHER PLANT-DERIVED BIOACTIVE COMPOUNDS

With the improvement of extraction isolation and identification technology, an increasing number of natural compounds have discovered. Tanshinone is not the only one, but there are numerous other plant-derived bioactive compounds that exhibit extraordinary anti-cancer activity by rescuing the expression of miRNA. The following is partial summary about several hot plant-derived bioactive compounds including Astragaloside IV, Berberine, Ginsenosides, Matrine that are currently studied to against cancer through regulating miRNA expression (Figure 2).

Molecular formula: $C_{18}H_{12}O_3$
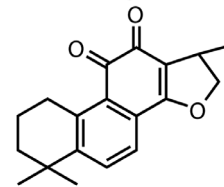Molecular weight: 276.291
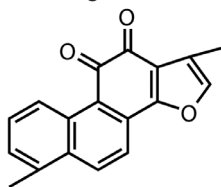
Molecular formula: $C_{19}H_{18}O_3$
Molecular weight: 294.35
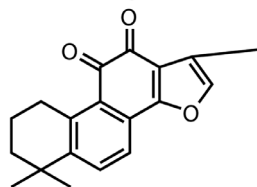
Molecular formula: $C_{19}H_{20}O_3$
Molecular weight: 296.366

Tanshinone I

Tanshinone IIA

Cryptotanshinone

FIGURE 1 The chemical structures of tanshinones

Molecular formula: C_{41}H_{68}O_{14}
Molecular weight: 784.981

Molecular formula: C_{20}H_{18}NO_4^+
Molecular weight: 336.366

Molecular formula: C_{15}H_{24}N_2O
Molecular weight: 248.37

Astragaloside IV

Berberine

Matrine

Molecular formula: C_{42}H_{72}O_{13}
Molecular weight: 785.025

Molecular formula: C_{36}H_{62}O_8
Molecular weight: 622.884

Molecular formula: C_{48}H_{82}O_{18}
Molecular weight: 947.166

Ginsenoside Rg3

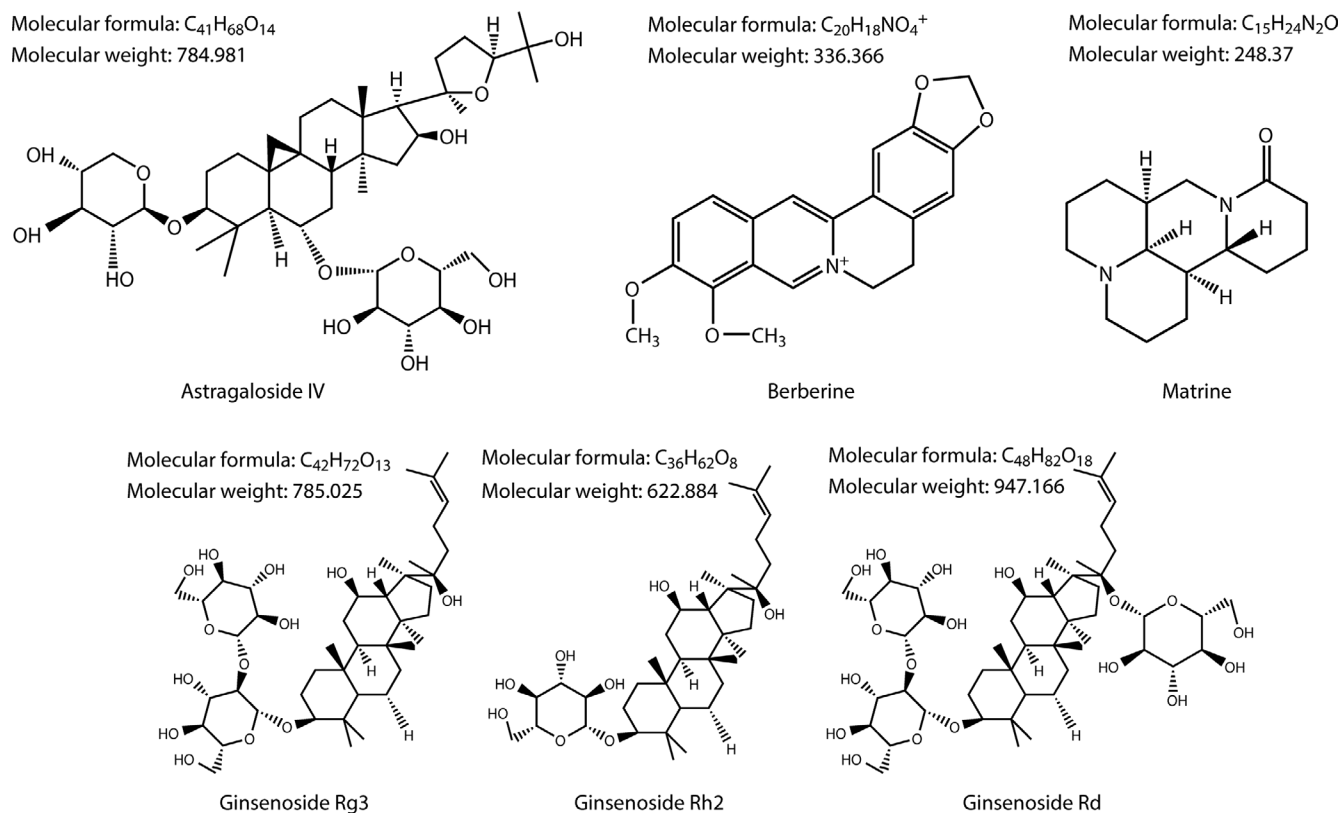Ginsenoside Rh2

Ginsenoside Rd

FIGURE 2 The chemical structures of some phytochemicals

3.1 | Astragaloside IV and miRNAs

Astragaloside IV (AS-IV) is a cycloartane-type triterpene glycoside, and is one of main monomer active substances isolated from Huangqi (*Astragalus membranaceus Bunge*) which has been widely illustrated to showed pharmacological effects in aspect of improve immunity, treat diabetes, anti-inflammation, anti-oxidant, and so forth (L. Li, Hou, Xu, Liu, & Tu, 2017). In recent years, a number of pharmacological studies have confirmed that AS-IV has significant anti-tumor activity and its value as an anti-cancer drug is gradually reflected (F. Xu et al., 2018).

Studies have showed that AS-IV up-regulates miR-214 and down-regulates miR-301a expression to suppress the stimulated capacities of gastric cancer associated fibroblast (GCAF) to MGC-823 human gastric cancer cell that aspect of proliferation, migration and invasion (Z. F. Wang, Ma, et al., 2017). Furthermore, macrophage colony-stimulating factor (M-CSF) and tissue inhibitor of metalloproteinase 2 (TIMP2) are illuminated targets of miR-214 and miR-301a, the abnormal expression of microRNA can affect M-CSF and TIMP2 expression accordingly in GCAFs, respectively. AS-IV may become an effective therapeutic drug for regulating the expression of miRNA leading to change microenvironment.

Latest studies showed that AS-IV treatment dose-dependently suppressed cell proliferation of SW620 and HCT116 colorectal cancer (CRC) cell lines, and caused cell cycle arrest in G0/G1 phase (S. Wang, Mou, Cui, Wang, & Zhang, 2018). B7-H3, a member of the B7 family, which regulates immune responses by participation of co-stimulatory and co-inhibitory of T cells, is commonly over-expressed in a wide range of cancers (Seaman et al., 2017). MiR-29c can directly bind to B7-H3 and AS-IV could significantly block the expression of B7-H3 by increasing the expression level of miR-29c, thereby inhibiting the growth of CRC cell. AS-IV also exhibited extraordinary effects of miR-134 in CRC (Ye, Su, Chen, Zheng, & Liu, 2017). In the CRC SW-480 cell line, miR-134 expression level was observably upregulated upon the treatment of AS-IV, and the protein level of several key regulators in epithelial mesenchymal transition (EMT) signaling was decreased, indicating that AS-IV has an inhibitory effect on EMT. Furthermore, it was found that AS-IV treatment can enhance the sensitivity of CRC cells to oxaliplatin (OXA) chemotherapy. cAMP responsive element binding protein 1 (CREB1) is proto-oncogene which is a target gene of miR-134, knockdown of CREB1 inhibited invasion and migration of SW-480 cells, and also dramatically induced cell apoptosis. In other words, AS-IV prevented the EMT of CRC by inducing expression of miR-134, and significantly down-regulated the expression level of CREB1, thereby increasing sensitivity to OXA chemotherapy.

AS-IV and curcumin also have a synergistic inhibitory effect on tumor growth in human HCC (S. Zhang et al., 2017). Studies have showed that the combination of AS-IV and curcumin can up-regulate miR-122 and down-regulate miR-221 expression compared with control group, and displayed synergistic inhibitory potency of vascular endothelial growth factor (VEGF), fibroblast growth factor-2 (FGF-2), matrix metalloproteinase-2 (MMP-2), hepatocyte growth factor (HGF)

and thrombosis-related factor tissue factor (TF) and hepatocyte growth factor (FVII).

3.2 | Berberine and miRNAs

Berberine (BBR) is an alkaloid initially extracted from roots, rhizome, and stem bark of several plants, such as *coptis chinensis* and *berberis aristata*, which was examined in many clinical trials for treatment of cancers, diarrhea, cardiovascular diseases, diabetes, hyper-lipemia, inflammation, schizo-phrenia and so on (Ayati et al., 2017; Luo et al., 2014; McCubrey et al., 2017; Yang et al., 2018). The targets and mechanisms of BBR remain unclean, and miRNAs are potential one of targets of BBR for cancer therapy.

The integration of miRNA-mRNA profiles showed that 347 upregulated and 93 downregulated miRNAs were confirmed in BBR-treated GC cells: 38 upregulated and 49 downregulated in the multiple myeloma (MM) (Luo et al., 2014; Yang et al., 2018). Multiple studies exhibited that BBR is able to modulate miRNA function in U266 and RPMI-8266 MM cells. BBR inhibits proliferation, induces cell cycle arrest and apoptosis through negatively regulates NF-κB via Set9 (lysine methyltransferase)-mediated lysine methylation, which leads to downregulate miR-21 and Bcl-2 levels (Hu et al., 2013). Likewise, treatments with BBR also could downregulate miR-21 levels possibly through interleukin 6 (IL6)/signal transducer and activator of transcription (STAT3), and led to increase programmed cell death 6 (PDCD6), a predicted miR-21 target as a tumor-suppressor gene in different cancer by inhibiting STAT3 activation, resulting in suppress the protein 53 (P53) signaling pathway (Gu et al., 2017). Furthermore, a number of studies showed that some miRNA cluster play a pivotal role in BBR-treated MM cells. The miRNAs clusters including miR-19a-92a, miR-99a~125b, miR-17-92, and miR-106b-25 were markedly downregulated in BBR-treated MM cells, likely via tumor protein 53 (TP53), Erb and MAPK signaling pathways, and miR-106b-25 cluster effectively suppressed P38 MAPK and phosphor-P38 MAPK which plays an important role in myeloma growth, survival, and drug resistance (Feng et al., 2015; Gu et al., 2017; Yin et al., 2018).

BBR is also able to drug-induce the abnormal expression of miRNA in HCC cells HepG2. MiR-21-3p was upregulated after BBR treatment in HCC cells, and directly decreases the expression of methionine adenosyltransferase 2A (MAT2A) and MAT2B, which result in reduced S-adenosylmethionine (SAM) contents, thereby suppressing growth and induced apoptosis (T. F. Lo, Tsai, & Chen, 2013). The up-regulation of miR-23a may mediate p53-inducable transactivation of tumor suppressive genes by BBR treatment, and induces cell cycle arrest and cell death in HCC cells (N. Wang et al., 2014).

Several studies have suggested that BBR could modulate miRNA expression and function in OC. In the cisplatin-resistant SKOV3 OC cells, decreased miR-21 expression and increased PDCD4 expression, a direct target of miR-21, resulting in sensitizes cells to cisplatin (DDP) after BBR treatment (S. Liu, Fang, Shen, Xu, & Li, 2013). Likewise, BBR could enhance the sensitivity of DDP through inhibiting miR-93

expression and function, and its target PTEN was upregulated as an important tumor suppressor in OC A2780 cells (Q. Chen, Qin, Fang, & Li, 2015).

Accumulated studies illustrated that BBR can be potential therapeutic agents for human CRC. BBR is able to downregulate miR-429 expression level and cause to suppress the progression of human CRC. Meanwhile, BBR showed prominent effect on the expression of miRNAs including miR-152, miR-29a, miR-429, and their corresponding DNA methyltransferases (DNMTs), especially miR-29a more obviously was downregulated (Huang, Liu, Gong, Wu, & Wen, 2017; H. Liu, Huang, Wu, & Wen, 2016). The combination of second generation heat shock protein 90 (Hsp90) inhibitor, NVP-AUY922 and BBR, can enhance the antiproliferation activity of drug through inducing of miR-296-5p mediate multiple oncogenic signaling pathways in CRC cells (Su et al., 2015).

BBR can also inhibit the proliferation, induce apoptosis and cell cycle arrest by reversing miRNA expression in other cancer cells. BBR significantly increased miR-21-3p and decreased aryl hydrocarbon receptor (AhR) activation, thereby suppressing the increase of functional cytochrome P450 A1 (CYPA1) protein expression in MCF-7 breast cancer (BC) cells (S. N. Lo et al., 2017). Recently, BBR was also found to suppress proliferation and metastasis of endometrial cancer (EC) cell line AN3 CA and HEC-1-A through miR-101 was upregulated and cyclooxygenase-2 (COX-2) was downregulated, and miR-101 directly target COX-2 (Y. Wang & Zhang, 2018). In particular, BBR treatment significantly induced miR-203 overexpression, and its target Bcl-w is decreased, resulting in reduces DDP resistance of SGC-7901 and BGC-823 GC cells (You, Xie, Zhang, Zhu, & Jiang, 2016).

3.3 | Ginsenosides and miRNAs

Ginsenosides are commonly believed to be the main bioactive constituent of ginseng which is widely used in orient as a traditional herb. The root of ginseng is abundant in ginsenosides, and novel structures continue to be determined. Ginsenosides have been isolated are classified into two categories: protopanaxatriol and protopanaxadiol, according to their glycosylation pattern (Dai, Zhang, Williams, Yuan, & Wang, 2017; Mohanan, Subramaniyam, Mathiyalagan, & Yang, 2018). Ginsenosides are associated with virous biological activities, such as tumorigenesis, angiogenesis and inflammation, but its underlying mechanism remain unclear. In recent years, some types of ginsenosides, including ginsenoside 20(S)-Rg3 (20(S)-Rg3), ginsenoside Rh2 (Rh2) and ginsenoside Rd (Rd), have been clearly demonstrated to inhibit cancer initiation and progression via regulating miRNA expression (Yi, 2019).

20(S)-Rg3, a steroidal saponin extracted from red ginseng, displays stereospecificity which showed antidiabetic and anticancer and readily dissolves compare with 20(R)-Rg3, has been proved to possess anti-tumorigenesis through impacting the expression of miRNA in different cancer (Y. Zhang, Yang, Wang, & Song, 2019). 20(S)-Rg3 reversed EMT to inhibit the migration and invasion of OC cells SKOV3 and 3AO via antagonizing DNMT3A-mediated downregulation of miR-145

to suppress target gene FSCN1 expression (J. Li, Lu, et al., 2017). Furthermore, recent studies showed that 20(S)-Rg3 could also positively regulated miR-532-3p and miR-324-5p to antagonize the Warburg effect, which is one of the major metabolic features for cancers, and the overexpression of miR-532-3p reduced HK2 and PKM2 expression, miR-324-5p reduced PMK2 and lncRNA H19 expression, cause to repress tumorigenesis in OC cell SKOV3 and A2780 (Zheng et al., 2018; Zhou et al., 2018). What's more, Rg3 inhibited oral squamous cell carcinoma (OSCC) cell SCC-9 and HSC-5 viability, proliferation and EMT process, but induced apoptosis via downregulating miR-221 and upregulating TIMP3, leading to inactivate PI3K/AKT and MAPK/ERK signal pathways (Cheng & Xing, 2019).

Rh2 is also one of the key components isolated from red ginseng with demonstrative therapeutic effects on various cancers, and its molecular targets and underlying mechanism continue to be illustrated (Y. S. Wang, Lin, et al., 2017). In human glioma cells (GBMLGG) U251, 14 human miRNAs were positively impacted and 12 were negatively impacted in miRNA array assay after Rh2 treatment, and Rh2 has been verified to inhibit proliferation and promote apoptosis in part through up-regulation of miR-128 and down-regulation of E2F3a which is a miR-128 target gene (Wu, Wu, Hu, Li, & Feng, 2011). Similarly, miRNA microarray analysis indicated that 44 and 24 miRNAs including let-7d, miR-150, miR-32 were upregulated and let-7e, miR-21, miR-486-5p were downregulated, displaying changes in Rh2-treated NSCLC cells (I. S. An, An, Kwon, Kim, & Bae, 2013). Furthermore, Rh2 was able to mediate the three specified drug-resistant miRNAs including miR-222, miR-34a and miR-29a expression to ease the drug resistance of breast cancer (Wen et al., 2015). In addition, Rh2 could also suppress PC3 and DU145 (PC) cell growth via suppression of miR-4,295 mediated to activate CDKN1A, which plays a pivotal role in the manage of cell cycle arrest and has been proved to be a miR-4,295-targeting gene (Q. Gao & Zheng, 2018). Recent studies investigated the effects of Rh2 on growth and progression of the human medulloblastoma (MBC) cell Daoy, Rh2 could down-regulate miR-31 to inhibit the Wnt/β-catein signaling pathway, which lead to attenuate the proliferation and migration, promote apoptosis of MBC cell (Y. Chen, Shang, Zhang, & Zhang, 2018). MiR-491 was upregulated in HCC after Rh2 treatment, and EGFR signaling was inhibited which has been related to tumorigenesis, resulting in Rh2 efficiently suppresses the progression of HCC in vitro and vivo (W. Chen & Qiu, 2015). Further studies showed that Rh2 also upregulated miR-146a-5p expression, and miR146a-5p overexpression enhances Rh2-induced anti-proliferation and the apoptosis of the liver cancer cell (W. Chen, Chu, Li, & Qiu, 2018). At the latest, Rh2 could also generate anti-metastasis activity via miR-491 regulates hypoxic tumor microenvironment in lung cancer cells A549 and H1299 (Y. Chen et al., 2019).

Rd is only individually studied contact with miRNA in cancer, but also exhibits high anticancer activity through influencing other molecular signaling (Phi et al., 2019). Rd treatment inhibits cell migration and invasion via decreasing the expression of miR-18a, and Smad2 expression level was downregulated which be a direct target of miR-18a in 4 T1 BC cells (P. Wang et al., 2016).

3.4 | Matrine and miRNAs

Matrine is a main alkaloid isolated from *Sophora flavescens* and has been proved to present antitumor activity in various cancer including GC, BC, NSCLC, COAD, but its mechanisms of action still lacked accord (Rashid, Xu, Muhammad, Wang, & Jiang, 2019). Last decade, matrine has been recognized that caused tumor cell death by up-regulating or down-regulating the cancer related miRNA expression level. For example, 68 miRNAs were upregulated, and 60 miRNAs were downregulated after matrine treatment in the SGC-7901 GC cell line (H. Li et al., 2014). Coincidentally, matrine can also alter miRNA expression profiles in the A549 human NSCLC, eventually causing the proliferation inhibition (Y. Q. Liu et al., 2014).

Matrine induced cell apoptosis and cell cycle arrest to inhibit BC cell line MCF-7 growth in a concentration-dependent manner, miR-21 was downregulated and its important downstream target phosphatase and tensin homolog (PTEN) was upregulated (L. Q. Li et al., 2012). Furthermore, matrine combined with sorafenib synergistically increases cytotoxic effects against HCC cells HepG2 and Hep3B by the suppression of miR-21 mediate to positively regulate PTEN (Lin et al., 2014). In addition, studies showed that there exist a correlation between miR-126 and matrine in NSCLC-derived cell lines, matrine can recover the expression of miR-126 which is often downregulated in NSCLC cells, and target VEGF was accordingly downregulated, resulting in cell cycle arrest and promoting apoptosis (Q. An et al., 2016). Recently, studies indicated that matrine could also inhibit cell proliferation and invasion and induce cell apoptosis, at least partially, via suppressing miR-19b-3p expression and the subsequent induction of PTEN in human A375 and SK-MEL-2 MMC cell lines (Wei et al., 2018).

4 | CONCLUSION AND PERSPECTIVE

In overall objective of this review is to exhibit the inhibitory effect of some well-studied plant-derived bioactive compounds on cancer initiation and progression by regulating multiple miRNAs (Table 1). Among these miRNAs regulated by natural compounds, miR-21 was the most presented miRNA that has been extensively investigated in different cancers, and PTEN is the common target genes regulated by miR-21. Another interesting observation is that the mechanism research of downstream signaling pathway is poor, but related to various anti-cancer mechanism (Figure 3). In short, the expression of miRNAs was regulated appears as a strong molecular mechanism by these natural monomers which participate in cancer biology.

Actually, our lab's previous studies proved that tanshinones can suppress NSCLC through upregulating let-7, miR-32, miR-137, miR-146a-5p, and miR-32 was illustrated target of AURKA, miR-146a-5p was illustrated target of EGFR as an anti-oncogene (Ma et al., 2015; Qi et al., 2019; B. Zhang, Ma, et al., 2016). Further, our findings also showed that T1 and T2A inhibit NSCLC via Upregulation of let-7a-5p targeting AURKA, and Lin28B-let-7-AURKA/BORA/MYC pathway was clarified in aspect of tanshinones treat NSCLC molecular

**TABLE 1** Anti-cancer phytochemicals targeting miRNAs

Phytochemicals	Cancer types	Cell models employed	miRNAs	Regulation	Target genes	Biological effect	Reference
AS-IV	GC	GCAF	miR-214 miR-301a	Up Down	M-CSF, TIMP2	Change microenvironment	(Z. F. Wang, Ma, et al., 2017)
	CRC	SW620, HCT116	miR-29c	Up	B7-H3	Anti-proliferation, induce cell cycle arrest	(S. Wang et al., 2018)
		SW-480	miR-134	Up	CREB1	Anti-MET, increase sensitivity to OXA	(Ye et al., 2017)
	HCC	HepG2	miR-122 miR-221	Up Down		Anti-angiogenesis	(S. Zhang et al., 2017)
T I	PC	PC-3, DU145	miR-135a-3p	Up	DR5	Anti-proliferation, induce apoptosis	(Shin et al., 2014)
T2A	COAD	HCT116, HT-29	miR-155	Down	SHIP1	Change macroenvironment	(Tu et al., 2012)
	ESAC	Ec109	MiR-122	Up	PKM2	Anti-proliferation, induced cycle arrest	(H. S. Zhang, Zhang, et al., 2016)
	HCC	HepG2	MiR-30b	Down	p53	Induce apoptosis and cell cycle arrest	(Ren et al., 2017)
	OC	TOV-21G	miR-205	Up		Induce apoptosis	(N. Li et al., 2018)
CT	NSCLC	H1299	MiR-146-5p	Up	EGFR	Anti-proliferation	(Qi et al., 2019)
T I, T2A, CT	NSCLC	A549, SPCA-1, H1299	miR-32 miR-137	Up Up	AURKA	Anti-proliferation, induce apoptosis and cell cycle arrest	(Ma et al., 2015; B. Zhang, Ma, et al., 2016)
BBR	MM	U266	miR-21	Down	NF-κB	Anti-proliferation, induce apoptosis and cell cycle arrest	(Hu et al., 2013)
		RPMI-8266, U226	miR-21	Down	PDCD4	Anti-proliferation	(Luo et al., 2014)
		RPMI-8266, U226	miR-19a-92a, miR-99a-125b, miR-106b-25 cluster	Down		Anti-proliferation	(Feng et al., 2015; Gu et al., 2017; Yin et al., 2018)
	HCC	HepG2	MiR-21-3p	Up	MAT2A, MAT2B	Anti-proliferation, induce apoptosis	(T. F. Lo et al., 2013)
		HepG2	miR-23a	Up	p53	Induce cell cycle arrest and apoptosis	(N. Wang et al., 2014)
	OC	SKOV3	miR-21	Down	PDCD4	Increase sensitivity to DDP	(S. Liu et al., 2013)
		A2780	miR-93	Down	PTEN	Increase sensitivity to DDP	(Q. Chen et al., 2015)
	CRC	Tumor tissue model	miR-429, miR-152, miR-29a	Down	DNMTs	Anti-tumorigenesis, anti-metastasis	(Huang et al., 2017; H. Liu et al., 2016)
		HT-29, HCT116	miR-296-5p	Up	Pin1	Combination of drug, anti-proliferative	(Su et al., 2015)
	BC	MCF-7	miR-21-3p	Up	CYPA1	Anti-inflammation	(S. N. Lo et al., 2017)
	EC	AN3 CA, HEC-1-A	miR-101	Up	COX-2	Anti-proliferation, anti-metastasis	(Y. Wang & Zhang, 2018)
	GC	SGC-7901, BGC-823	miR-203	Up	Bcl-w	Increase sensitivity to DDP	(You et al., 2016)

(Continues)

TABLE 1 (Continued)

Phytochemicals	Cancer types	Cell models employed	miRNAs	Regulation	Target genes	Biological effect	Reference
20(S)-Rg3	OC	SKOV3, 3AO	miR-145	Down	FSCN1	Anti-EMT	(J. Li, Lu, et al., 2017)
		SKOV3, A2780	miR-532-3p	Up	HK2	Anti-Warburg effect	(Zheng et al., 2018)
		SKOV3, A2780	miR-324-5p	Up	PKM2	Anti-Warburg effect	(Zhou et al., 2018)
	OSCC	SCC-9, HSC-5 cells	miR-221	Down	TIMP3	Anti-proliferation, EMT, induce apoptosis	(Cheng & Xing, 2019)
Rh2	GBMLGG	U251	miR-128	Up	E2F3a	Anti-proliferation, induce apoptosis	(Wu et al., 2011)
	BC	MCF-7	miR-222, miR-34a, miR-29a	Up		Anti-chemoresistance	(Wen et al., 2015)
	PC	PC3, DU145	miR-4,295	Down	CDKN1A	Anti-proliferation	(Q. Gao & Zheng, 2018)
	MBC	Daoy	miR-31	Down		Anti-proliferation, anti-migration	(Y. Chen, Shang, et al., 2018)
	HCC	SMMC-7721	MiR-491	Up	EGFR	Anti-proliferation and cell survival	(W. Chen & Qiu, 2015)
		HepG2	miR-146a-5p	Up		Anti-proliferation, induce apoptosis	(W. Chen, Chu, et al., 2018)
	NSCLC	A549, H1299	miR-491	Up		Anti-metastasis	(Y. Chen et al., 2019)
Rd	BC	4 T1	miR-18a	Down	Smad2	Anti-metastasis	(P. Wang et al., 2016)
Matrine	BC	MCF-7	miR-21	Down	PTEN	Induce apoptosis and cell cycle arrest	(L. Q. Li et al., 2012)
	HCC	HepG2, Hep3B	miR-21	Down	PTEN	Increase sensitivity to sorafenib	(Lin et al., 2014)
	NSCLC	A549	miR-126	Up	VEGF	Induce cell cycle arrest and apoptosis	(Q. An et al., 2016)
	MMC	A375, SK-MEL-2	miR-19b-3p	Down	PTEN	Anti-proliferation, induce apoptosis	(Wei et al., 2018)

FIGURE 3 Functional roles of miRNAs in various cancer. Selected miRNAs and their molecular partners or genomic targets are shown for cancer progression, drug resistance, microenvironment, angiogenesis and others. Red arrow promotes the expression of target protein, red T-shaped arrow inhibits the expression of target protein, green arrow indicates the regulatory effect of phytochemicals on miRNA, blue arrow indicates the biological effect of phytochemicals in cancer [Colour figure can be viewed at wileyonlinelibrary.com]
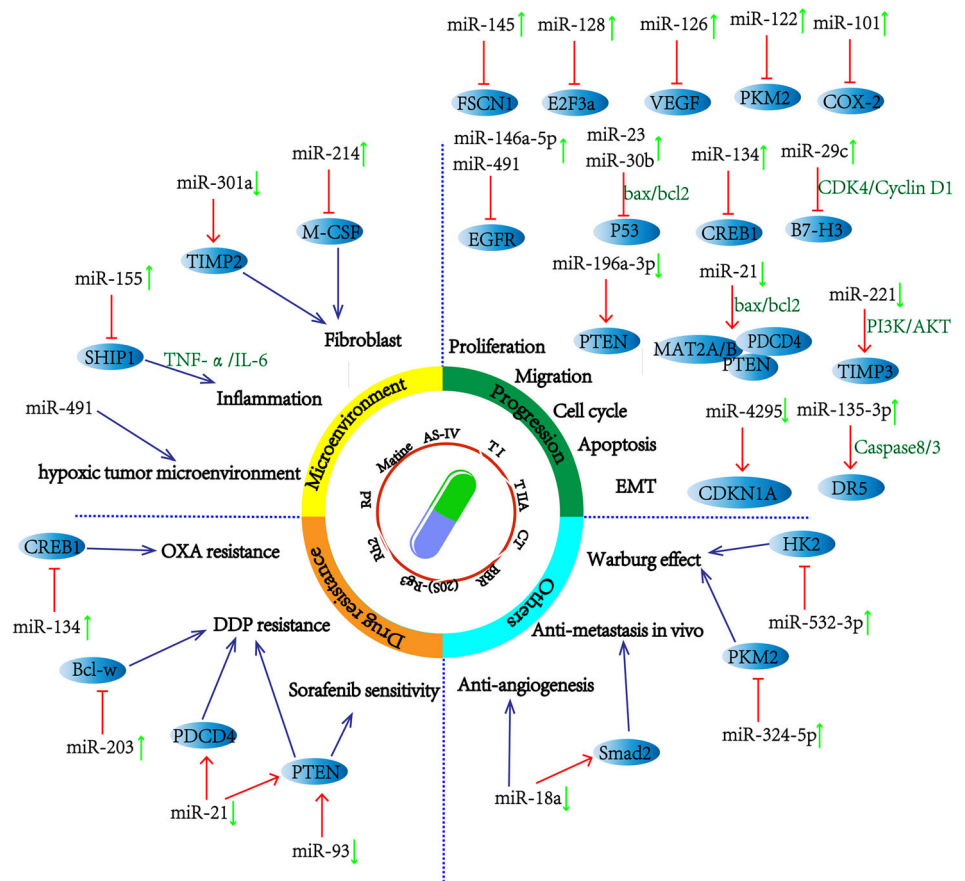
mechanism. Furthermore, our latest findings suggest that T1 and T2A inhibit NSCLC by down-regulating PD-L1 through miR-449a, which indicates that tanshinones may be involved in blocking immune checkpoint to suppress NSCLC. In following studies, we will seek whether tanshinones can involve in regulating other ncRNA while regulating miRNA expression. All in all, tanshinones may soon be the new star of cancer drugs.

Interestingly enough, most of the plant-derived bioactive compounds are small molecules (SM), and multidisciplinary researchers pay close attention to the miRNA-SM association studies. Nevertheless, biological experiment approach to identify the binding of miRNA-SM remain time-consuming and laborious, so it is a promising strategy to develop a computational prediction model of miRNA-SM association. In recent years, many computational methods have been developed to predict associations between phytochemicals and miRNAs (Guan, Sun, Ming, Li, & Chen, 2018; Lv et al., 2015). For example, a novel computational model of HeteSim-based inference for SM-miRNA Association prediction (HSSMMA) which can capture the semantics information under each path and predict potential miRNA-SM associations based on all the considered paths in the heterogeneous network (Qu et al., 2019). Similarly, a novel model named Symmetric Nonnegative Matrix Factorization for Small Molecule-MiRNA Association prediction (SNMFSMMA) was proposed, and case study results demonstrated the reliable predictive power of the model (Zhao, Chen, Yin, & Qu, 2020). More usefully, synergistic drug

combinations can also be further predicted based on the miRNA-SM association.

In addition to the plant-derived bioactive compounds and related microRNAs summarized in this review, newfound phytochemicals have been widely reported recently. Luteolin is a representative that has anti-tumor properties possibly involved the elevated expression of miR-203 on BC and upregulated miR-384 expressions on CRC (G. Gao, Ge, Li, & Liu, 2019; Yao, Rao, Zheng, & Wang, 2019), and it could also suppress tumorigenesis and promote apoptosis of NSCLC cells by upregulation of miR-34a-5p (Z. Q. Jiang et al., 2018). More than one, species of phytochemicals, such as baicalein and quercetin, showed excellent anti-cancer effect via regulating miRNA expression (Jiang, Song, Guo, Wang, & Lu, 2018; Nwaeburu, Abukiwan, Zhao, & Herr, 2017). Today, plant-derived bioactive compounds are important sources to develop therapeutic approaches and new drugs. A variety of plant-based foods in the diet can contribute to reduce the risk of chronic diseases, including cancer. Phytotherapy is gaining acceptance among scientists. Most of the supportive evidences show that the development of anticancer drugs from medicinal plants have many superiorities including the following: non-toxic side and remarkable anti-cancer effect. For instance, paclitaxel and curcumin is already very excellent phytochemicals as natural anti-cancer drugs in clinical cancer therapy. In addition, previous research showed that phytochemicals can significantly inhibited cancer progression including lung, breast, colorectal, liver cancer and so on, its underlying mechanism

partly may be to suppress the occurrence of a certain cancer-promoting signaling pathway and participate in immune response, and or resulting in sensitizes cancer cells to chemotherapeutic drugs via up or down-regulating miRNAs expression level. Yet, most of them are still at the experimental stage and thus many problems may occur. Promising research hotspot include low bioavailability and high difficulty in complete purification that need to be considered, co-treatment of multiple drugs synergistically reduces side effects, and improvement of pharmacological effects are interesting fields to future investigate. This review will contribute to a novel understanding of natural phytochemicals targeting miRNAs and shed light on their future clinical applications.

CONFLICT OF INTEREST

There were no conflicts of interest with regard to the publication of this study.

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REFERENCES

An, I. S., An, S., Kwon, K. J., Kim, Y. J., & Bae, S. (2013). Ginsenoside Rh2 mediates changes in the microRNA expression profile of human non-small cell lung cancer A549 cells. *Oncology Reports*, 29(2), 523–528. https://doi.org/10.3892/or.2012.2136

An, Q., Han, C., Zhou, Y., Li, F., Li, D., Zhang, X., … Kan, Q. (2016). Matrine induces cell cycle arrest and apoptosis with recovery of the expression of miR-126 in the A549 non-small cell lung cancer cell line. *Molecular Medicine Reports*, 14(5), 4042–4048. https://doi.org/10.3892/mmr.2016.5753

Ayati, S. H., Fazeli, B., Momtazi-Borojeni, A. A., Cicero, A. F. G., Pirro, M., & Sahebkar, A. (2017). Regulatory effects of berberine on microRNome in cancer and other conditions. *Critical Reviews in Oncology/Hematology*, 116, 147–158. https://doi.org/10.1016/j.critrevonc.2017.05.008

Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians*, 68(6), 394–424. https://doi.org/10.3322/caac.21492

Chen, Q., Qin, R., Fang, Y., & Li, H. (2015). Berberine sensitizes human ovarian cancer cells to cisplatin through miR-93/PTEN/Akt Signaling pathway. *Cellular Physiology and Biochemistry*, 36(3), 956–965. https://doi.org/10.1159/000430270

Chen, W., Chu, S., Li, H., & Qiu, Y. (2018). MicroRNA-146a-5p enhances ginsenoside Rh2-induced anti-proliferation and the apoptosis of the human liver cancer cell line HepG2. *Oncology Letters*, 16(4), 5367–5374. https://doi.org/10.3892/ol.2018.9235

Chen, W., & Qiu, Y. (2015). Ginsenoside Rh2 targets EGFR by up-regulation of miR-491 to enhance anti-tumor activity in hepatitis B

virus-related hepatocellular carcinoma. *Cell Biochemistry and Biophysics*, 72(2), 325–331. https://doi.org/10.1007/s12013-014-0456-9

Chen, Y., Shang, H., Zhang, S., & Zhang, X. (2018). Ginsenoside Rh2 inhibits proliferation and migration of medulloblastoma Daoy by down-regulation of microRNA-31. *Journal of Cellular Biochemistry*, 119(8), 6527–6534. https://doi.org/10.1002/jcb.26716

Chen, Y., Zhang, Y., Song, W., Zhang, Y., Dong, X., & Tan, M. (2019). Ginsenoside Rh2 inhibits migration of lung cancer cells under hypoxia via mir-491. *Anti-Cancer Agents in Medicinal Chemistry*, 19, 1633–1641. https://doi.org/10.2174/1871520619666190704165205

Cheng, Z., & Xing, D. (2019). Ginsenoside Rg3 inhibits growth and epithelial-mesenchymal transition of human oral squamous carcinoma cells by down-regulating miR-221. *European Journal of Pharmacology*, 853, 353–363. https://doi.org/10.1016/j.ejphar.2019.03.040

Dai, D., Zhang, C. F., Williams, S., Yuan, C. S., & Wang, C. Z. (2017). Ginseng on cancer: Potential role in modulating inflammation-mediated angiogenesis. *The American Journal of Chinese Medicine*, 45(1), 13–22. https://doi.org/10.1142/S0192415X17500021

Feng, M., Luo, X., Gu, C., Li, Y., Zhu, X., & Fei, J. (2015). Systematic analysis of berberine-induced signaling pathway between miRNA clusters and mRNAs and identification of mir-99a approximately 125b cluster function by seed-targeting inhibitors in multiple myeloma cells. *RNA Biology*, 12(1), 82–91. https://doi.org/10.1080/15476286.2015.1017219

Gao, G., Ge, R., Li, Y., & Liu, S. (2019). Luteolin exhibits anti-breast cancer property through up-regulating miR-203. *Artificial Cells, Nanomedicine, and Biotechnology*, 47(1), 3265–3271. https://doi.org/10.1080/21691401.2019.1646749

Gao, Q., & Zheng, J. (2018). Ginsenoside Rh2 inhibits prostate cancer cell growth through suppression of microRNA-4295 that activates CDKN1A. *Cell Proliferation*, 51(3), e12438. https://doi.org/10.1111/cpr.12438

Gu, C., Li, T., Yin, Z., Chen, S., Fei, J., Shen, J., & Zhang, Y. (2017). Integrative analysis of signaling pathways and diseases associated with the miR-106b/25 cluster and their function study in berberine-induced multiple myeloma cells. *Functional & Integrative Genomics*, 17(2–3), 253–262. https://doi.org/10.1007/s10142-016-0519-7

Guan, N. N., Sun, Y. Z., Ming, Z., Li, J. Q., & Chen, X. (2018). Prediction of potential small molecule-associated MicroRNAs using Graphlet interaction. *Frontiers in Pharmacology*, 9, 1152. https://doi.org/10.3389/fphar.2018.01152

Hu, H. Y., Li, K. P., Wang, X. J., Liu, Y., Lu, Z. G., Dong, R. H., … Zhang, M. X. (2013). Set9, NF-kappaB, and microRNA-21 mediate berberine-induced apoptosis of human multiple myeloma cells. *Acta Pharmacologica Sinica*, 34(1), 157–166. https://doi.org/10.1038/aps.2012.161

Huang, C., Liu, H., Gong, X. L., Wu, L. Y., & Wen, B. (2017). Effect of evodiamine and berberine on the interaction between DNMTs and target microRNAs during malignant transformation of the colon by TGF-beta1. *Oncology Reports*, 37(3), 1637–1645. https://doi.org/10.3892/or.2017.5379

Jiang, L., Song, H., Guo, H., Wang, C., & Lu, Z. (2018). Baicalein inhibits proliferation and migration of bladder cancer cell line T24 by down-regulation of microRNA-106. *Biomedicine & Pharmacotherapy*, 107, 1583–1590. https://doi.org/10.1016/j.biopha.2018.08.107

Jiang, Z. Q., Li, M. H., Qin, Y. M., Jiang, H. Y., Zhang, X., & Wu, M. H. (2018). Luteolin inhibits tumorigenesis and induces apoptosis of non-small cell lung cancer cells via regulation of MicroRNA-34a-5p. *International Journal of Molecular Sciences*, 19(2), 447. https://doi.org/10.3390/ijms19020447

Jing, X., Xu, Y., Cheng, W., Guo, S., Zou, Y., & He, L. (2016). Tanshinone I induces apoptosis and pro-survival autophagy in gastric cancers. *Cancer Chemotherapy and Pharmacology*, 77(6), 1171–1181. https://doi.org/10.1007/s00280-016-3034-6

Li, H., Fan, J., Zhao, Y., Zhang, X., Dai, B., Zhan, J., … Wang, D. W. (2019). Nuclear miR-320 mediates diabetes-induced cardiac dysfunction by

activating transcription of fatty acid metabolic genes to cause lipo-toxicity in the heart. *Circulation Research*, 125, 1106–1120. https://doi.org/10.1161/CIRCRESAHA.119.314898

Li, H., Xie, S., Liu, X., Wu, H., Lin, X., Gu, J., ... Duan, Y. (2014). Matrine alters microRNA expression profiles in SGC-7901 human gastric cancer cells. *Oncology Reports*, 32(5), 2118–2126. https://doi.org/10.3892/or.2014.3447

Li, J., Lu, J., Ye, Z., Han, X., Zheng, X., Hou, H., ... Zhao, L. (2017). 20(S)-Rg3 blocked epithelial-mesenchymal transition through DNMT3A/miR-145/FSCN1 in ovarian cancer. *Oncotarget*, 8(32), 53375–53386. https://doi.org/10.18632/oncotarget.18482

Li, L., Hou, X., Xu, R., Liu, C., & Tu, M. (2017). Research review on the pharmacological effects of astragaloside IV. *Fundamental & Clinical Pharmacology*, 31(1), 17–36. https://doi.org/10.1111/fcp.12232

Li, L. Q., Li, X. L., Wang, L., Du, W. J., Guo, R., Liang, H. H., ... Jiang, H. C. (2012). Matrine inhibits breast cancer growth via miR-21/PTEN/Akt pathway in MCF-7 cells. *Cellular Physiology and Biochemistry*, 30(3), 631–641. https://doi.org/10.1159/000341444

Li, N., Yang, L., Zhang, B., & Chen, S. (2018). Tanshinone IIA effects on ovarian cancer cell line. *The Journal of Pharmacy and Pharmacology*, 70(10), 1369–1377. https://doi.org/10.1111/jphp.12961

Lin, Y., Lin, L., Jin, Y., Wang, D., Tan, Y., & Zheng, C. (2014). Combination of matrine and sorafenib decreases the aggressive phenotypes of hepatocellular carcinoma cells. *Chemotherapy*, 60(2), 112–118. https://doi.org/10.1159/000371736

Liu, H., Huang, C., Wu, L., & Wen, B. (2016). Effect of evodiamine and berberine on miR-429 as an oncogene in human colorectal cancer. *Oncotargets and Therapy*, 9, 4121–4127. https://doi.org/10.2147/OTT.S104729

Liu, J., Wang, S., Zhang, Y., Fan, H. T., & Lin, H. S. (2015). Traditional Chinese medicine and cancer: History, present situation, and development. *Thoracic Cancer*, 6(5), 561–569. https://doi.org/10.1111/1759-7714.12270

Liu, S., Fang, Y., Shen, H., Xu, W., & Li, H. (2013). Berberine sensitizes ovarian cancer cells to cisplatin through miR-21/PDCD4 axis. *Acta Biochimica et Biophysica Sinica Shanghai*, 45(9), 756–762. https://doi.org/10.1093/abbs/gmt075

Liu, Y. Q., Li, Y., Qin, J., Wang, Q., She, Y. L., Luo, Y. L., ... Xie, X. D. (2014). Matrine reduces proliferation of human lung cancer cells by inducing apoptosis and changing miRNA expression profiles. *Asian Pacific Journal of Cancer Prevention*, 15(5), 2169–2177. https://doi.org/10.7314/apjcp.2014.15.5.2169

Lo, S. N., Wang, C. W., Chen, Y. S., Huang, C. C., Wu, T. S., Li, L. A., ... Ueng, Y. F. (2017). Berberine activates aryl hydrocarbon receptor but suppresses CYP1A1 induction through miR-21-3p stimulation in MCF-7 breast cancer cells. *Molecules*, 22(11), 1847–1860. https://doi.org/10.3390/molecules22111847

Lo, T. F., Tsai, W. C., & Chen, S. T. (2013). MicroRNA-21-3p, a berberine-induced miRNA, directly down-regulates human methionine adenosyltransferases 2A and 2B and inhibits hepatoma cell growth. *PLoS One*, 8(9), e75628. https://doi.org/10.1371/journal.pone.0075628

Luo, X., Gu, J., Zhu, R., Feng, M., Zhu, X., Li, Y., & Fei, J. (2014). Integrative analysis of differential miRNA and functional study of miR-21 by seed-targeting inhibition in multiple myeloma cells in response to berberine. *BMC Systems Biology*, 8, 82. https://doi.org/10.1186/1752-0509-8-82

Lv, Y., Wang, S., Meng, F., Yang, L., Wang, Z., Wang, J., ... Li, X. (2015). Identifying novel associations between small molecules and miRNAs based on integrated molecular networks. *Bioinformatics*, 31(22), 3638–3644. https://doi.org/10.1093/bioinformatics/btv417

Ma, Z. L., Zhang, B. J., Wang, D. T., Li, X., Wei, J. L., Zhao, B. T., ... Jin, Y. X. (2015). Tanshinones suppress AURKA through up-regulation of miR-32 expression in non-small cell lung cancer. *Oncotarget*, 6(24), 20111–20120. https://doi.org/10.18632/oncotarget.3933

McCubrey, J. A., Lertpiriyapong, K., Steelman, L. S., Abrams, S. L., Yang, L. V., Murata, R. M., ... Cervello, M. (2017). Effects of resveratrol, curcumin, berberine and other nutraceuticals on aging, cancer development, cancer stem cells and microRNAs. *Aging (Albany NY)*, 9(6), 1477–1536. https://doi.org/10.18632/aging.101250

Mohanan, P., Subramaniyam, S., Mathiyalagan, R., & Yang, D. C. (2018). Molecular signaling of ginsenosides Rb1, Rg1, and Rg3 and their mode of actions. *Journal of Ginseng Research*, 42(2), 123–132. https://doi.org/10.1016/j.jgr.2017.01.008

Nwaeburu, C. C., Abukiwan, A., Zhao, Z., & Herr, I. (2017). Quercetin-induced miR-200b-3p regulates the mode of self-renewing divisions in pancreatic cancer. *Molecular Cancer*, 16(1), 23. https://doi.org/10.1186/s12943-017-0589-8

Phi, L. T. H., Sari, I. N., Wijaya, Y. T., Kim, K. S., Park, K., Cho, A. E., & Kwon, H. Y. (2019). Ginsenoside Rd inhibits the metastasis of colorectal cancer via epidermal growth factor receptor Signaling Axis. *IUBMB Life*, 71(5), 601–610. https://doi.org/10.1002/iub.1984

Qi, P., Li, Y., Liu, X., Jafari, F. A., Zhang, X., Sun, Q., & Ma, Z. (2019). Cryptotanshinone suppresses non-small cell lung cancer via microRNA-146a-5p/EGFR Axis. *International Journal of Biological Sciences*, 15(5), 1072–1079. https://doi.org/10.7150/ijbs.31277

Qu, J., Chen, X., Sun, Y. Z., Zhao, Y., Cai, S. B., Ming, Z., ... Li, J. Q. (2019). In silico prediction of small molecule-miRNA associations based on the HeteSim algorithm. *Molecular Therapy-Nucleic Acids*, 14, 274–286. https://doi.org/10.1016/j.omtn.2018.12.002

Rashid, H. U., Xu, Y., Muhammad, Y., Wang, L., & Jiang, J. (2019). Research advances on anticancer activities of matrine and its derivatives: An updated overview. *European Journal of Medicinal Chemistry*, 161, 205–238. https://doi.org/10.1016/j.ejmech.2018.10.037

Ren, X., Wang, C., Xie, B., Hu, L., Chai, H., Ding, L., ... Dou, X. (2017). Tanshinone IIA induced cell death via miR30b-p53-PTPN11/SHP2 signaling pathway in human hepatocellular carcinoma cells. *European Journal of Pharmacology*, 796, 233–241. https://doi.org/10.1016/j.ejphar.2016.11.046

Seaman, S., Zhu, Z., Saha, S., Zhang, X. M., Yang, M. Y., Hilton, M. B., ... St Croix, B. (2017). Eradication of tumors through simultaneous ablation of CD276/B7-H3-positive tumor cells and tumor vasculature. *Cancer Cell*, 31(4), 501–515. https://doi.org/10.1016/j.ccell.2017.03.005

Shin, E. A., Sohn, E. J., Won, G., Choi, J. U., Jeong, M., Kim, B., ... Kim, S. H. (2014). Upregulation of microRNA135a-3p and death receptor 5 plays a critical role in Tanshinone I sensitized prostate cancer cells to TRAIL induced apoptosis. *Oncotarget*, 5(14), 5624–5636. https://doi.org/10.18632/oncotarget.2152

Su, Y. H., Tang, W. C., Cheng, Y. W., Sia, P., Huang, C. C., Lee, Y. C., ... Lee, K. H. (2015). Targeting of multiple oncogenic signaling pathways by Hsp90 inhibitor alone or in combination with berberine for treatment of colorectal cancer. *Biochimica et Biophysica Acta*, 1853(10 Pt A), 2261–2272. https://doi.org/10.1016/j.bbamcr.2015.05.012

Tian, X. H., & Wu, J. H. (2013). Tanshinone derivatives: A patent review (January 2006 - September 2012). *Expert Opinion on Therapeutic Patents*, 23(1), 19–29. https://doi.org/10.1517/13543776.2013.736494

Tu, J., Xing, Y., Guo, Y., Tang, F., Guo, L., & Xi, T. (2012). TanshinoneIIA ameliorates inflammatory microenvironment of colon cancer cells via repression of microRNA-155. *International Immunopharmacology*, 14(4), 353–361. https://doi.org/10.1016/j.intimp.2012.08.015

Wang, N., Zhu, M., Wang, X., Tan, H. Y., Tsao, S. W., & Feng, Y. (2014). Berberine-induced tumor suppressor p53 up-regulation gets involved in the regulatory network of MIR-23a in hepatocellular carcinoma. *Biochimica et Biophysica Acta*, 1839(9), 849–857. https://doi.org/10.1016/j.bbagrm.2014.05.027

Wang, P., Du, X., Xiong, M., Cui, J., Yang, Q., Wang, W., ... Zhang, T. (2016). Ginsenoside Rd attenuates breast cancer metastasis implicating derepressing microRNA-18a-regulated Smad2 expression. *Scientific Reports*, 6, 33709. https://doi.org/10.1038/srep33709

Wang, S., Mou, J., Cui, L., Wang, X., & Zhang, Z. (2018). Astragaloside IV inhibits cell proliferation of colorectal cancer cell lines through down-regulation of B7-H3. *Biomedicine & Pharmacotherapy*, *102*, 1037–1044. https://doi.org/10.1016/j.biopha.2018.03.127

Wang, W., Li, J., Ding, Z., Li, Y., Wang, J., Chen, S., & Miao, J. (2019). Tanshinone I inhibits the growth and metastasis of osteosarcoma via suppressing JAK/STAT3 signalling pathway. *Journal of Cellular and Molecular Medicine*, *23*(9), 6454–6465. https://doi.org/10.1111/jcmm.14539

Wang, Y., & Zhang, S. (2018). Berberine suppresses growth and metastasis of endometrial cancer cells via miR-101/COX-2. *Biomedicine & Pharmacotherapy*, *103*, 1287–1293. https://doi.org/10.1016/j.biopha.2018.04.161

Wang, Y. S., Lin, Y., Li, H., Li, Y., Song, Z., & Jin, Y. H. (2017). The identification of molecular target of (20S) ginsenoside Rh2 for its anti-cancer activity. *Scientific Reports*, *7*(1), 12408. https://doi.org/10.1038/s41598-017-12572-4

Wang, Z. F., Ma, D. G., Zhu, Z., Mu, Y. P., Yang, Y. Y., Feng, L., ... Lu, H. W. (2017). Astragaloside IV inhibits pathological functions of gastric cancer-associated fibroblasts. *World Journal of Gastroenterology*, *23*(48), 8512–8525. https://doi.org/10.3748/wjg.v23.i48.8512

Wei, Y. P., Wang, X. H., Liu, G., Zhang, J. F., Yang, Y. X., Zhang, J., ... Zhao, L. D. (2018). Matrine exerts inhibitory effects in melanoma through the regulation of miR-19b-3p/PTEN. *International Journal of Oncology*, *53*(2), 791–800. https://doi.org/10.3892/ijo.2018.4414

Wen, X., Zhang, H. D., Zhao, L., Yao, Y. F., Zhao, J. H., & Tang, J. H. (2015). Ginsenoside Rh2 differentially mediates microRNA expression to prevent chemoresistance of breast cancer. *Asian Pacific Journal of Cancer Prevention*, *16*(3), 1105–1109. https://doi.org/10.7314/apjcp.2015.16.3.1105

Wu, N., Wu, G. C., Hu, R., Li, M., & Feng, H. (2011). Ginsenoside Rh2 inhibits glioma cell proliferation by targeting microRNA-128. *Acta Pharmacologica Sinica*, *32*(3), 345–353. https://doi.org/10.1038/aps.2010.220

Xu, F., Cui, W. Q., Wei, Y., Cui, J., Qiu, J., Hu, L. L., ... Liu, B. J. (2018). Astragaloside IV inhibits lung cancer progression and metastasis by modulating macrophage polarization through AMPK signaling. *Journal of Experimental & Clinical Cancer Research*, *37*(1), 207. https://doi.org/10.1186/s13046-018-0878-0

Xu, S., & Liu, P. (2013). Tanshinone II-A: New perspectives for old remedies. *Expert Opinion on Therapeutic Patents*, *23*(2), 149–153. https://doi.org/10.1517/13543776.2013.743995

Yang, Y., Zhang, N., Li, K., Chen, J., Qiu, L., & Zhang, J. (2018). Integration of microRNA-mRNA profiles and pathway analysis of plant isoquinoline alkaloid berberine in SGC-7901 gastric cancers cells. *Drug Design, Development and Therapy*, *12*, 393–408. https://doi.org/10.2147/DDDT.S155993

Yao, Y., Rao, C., Zheng, G., & Wang, S. (2019). Luteolin suppresses colorectal cancer cell metastasis via regulation of the miR384/pleiotrophin axis. *Oncology Reports*, *42*(1), 131–141. https://doi.org/10.3892/or.2019.7136

Ye, Q., Su, L., Chen, D., Zheng, W., & Liu, Y. (2017). Astragaloside IV induced miR-134 expression reduces EMT and increases chemotherapeutic sensitivity by suppressing CREB1 Signaling in colorectal cancer cell line SW-480. *Cellular Physiology and Biochemistry*, *43*(4), 1617–1626. https://doi.org/10.1159/000482025

Yi, Y. S. (2019). Roles of ginsenosides in inflammasome activation. *Journal of Ginseng Research*, *43*(2), 172–178. https://doi.org/10.1016/j.jgr.2017.11.005

Yin, Z., Yang, J., Ning, R., Liu, Y., Feng, M., Gu, C., ... Li, Y. (2018). Signal pathways, diseases, and functions associated with the miR-19a/92a cluster and the use of berberine to modulate the expression of this cluster in multiple myeloma cells. *Journal of Biochemical and Molecular Toxicology*, *32*(6), e22057. https://doi.org/10.1002/jbt.22057

You, H. Y., Xie, X. M., Zhang, W. J., Zhu, H. L., & Jiang, F. Z. (2016). Berberine modulates cisplatin sensitivity of human gastric cancer cells by upregulation of miR-203. *In Vitro Cellular & Developmental Biology. Animal*, *52*(8), 857–863. https://doi.org/10.1007/s11626-016-0044-y

Yu, J., Wang, X., Li, Y., & Tang, B. (2017). Tanshinone IIA suppresses gastric cancer cell proliferation and migration by downregulation of FOXM1. *Oncology Reports*, *37*(3), 1394–1400. https://doi.org/10.3892/or.2017.5408

Zhang, B., Ma, Z., Li, X., Zhang, C., Shao, Y., Liu, Z., ... Jin, Y. (2016). Tanshinones suppress non-small cell lung cancer through up-regulating miR-137. *Acta Biochimica et Biophysica Sinica Shanghai*, *48*(8), 768–770. https://doi.org/10.1093/abbs/gmw053

Zhang, H. S., Zhang, F. J., Li, H., Liu, Y., Du, G. Y., & Huang, Y. H. (2016). Tanshinone a inhibits human esophageal cancer cell growth through miR-122-mediated PKM2 down-regulation. *Archives of Biochemistry and Biophysics*, *598*, 50–56. https://doi.org/10.1016/j.abb.2016.03.031

Zhang, S., Tang, D., Zang, W., Yin, G., Dai, J., Sun, Y. U., ... Guo, X. (2017). Synergistic inhibitory effect of traditional Chinese medicine Astragaloside IV and curcumin on tumor growth and angiogenesis in an Orthotopic nude-mouse model of human hepatocellular carcinoma. *Anticancer Research*, *37*(2), 465–473. https://doi.org/10.21873/anticanres.11338

Zhang, Y., Jiang, P., Ye, M., Kim, S. H., Jiang, C., & Lu, J. (2012). Tanshinones: Sources, pharmacokinetics and anti-cancer activities. *International Journal of Molecular Sciences*, *13*(10), 13621–13666. https://doi.org/10.3390/ijms131013621

Zhang, Y., Yang, X., Wang, S., & Song, S. (2019). Ginsenoside Rg3 prevents cognitive impairment by improving mitochondrial dysfunction in the rat model of Alzheimer's disease. *Journal of Agricultural and Food Chemistry*, *67*(36), 10048–10058. https://doi.org/10.1021/acs.jafc.9b03793

Zhao, Y., Chen, X., Yin, J., & Qu, J. (2020). SNMFSMMA: Using symmetric nonnegative matrix factorization and Kronecker regularized least squares to predict potential small molecule-microRNA association. *RNA Biology*, *17*(2), 281–291. https://doi.org/10.1080/15476286.2019.1694732

Zheng, X., Zhou, Y., Chen, W., Chen, L., Lu, J., He, F., ... Zhao, L. (2018). Ginsenoside 20(S)-Rg3 prevents PKM2-targeting miR-324-5p from H19 sponging to antagonize the Warburg effect in ovarian cancer cells. *Cellular Physiology and Biochemistry*, *51*(3), 1340–1353. https://doi.org/10.1159/000495552

Zhou, Y., Zheng, X., Lu, J., Chen, W., Li, X., & Zhao, L. (2018). Ginsenoside 20(S)-Rg3 inhibits the Warburg effect via modulating DNMT3A/ MiR-532-3p/HK2 pathway in ovarian cancer cells. *Cellular Physiology and Biochemistry*, *45*(6), 2548–2559. https://doi.org/10.1159/000488273