Anti-Tumor Mechanisms Associated With Regulation of Non-Coding RNA by Active Ingredients of Chinese Medicine: A Review

Tian-Jia Liu, Shuang Hu, Zhi-Dong Qiu* and Da Liu*

School of Pharmacy, Changchun University of Chinese Medicine, Changchun, China

Cancer has become the second leading cause of death worldwide; however, its complex pathogenesis remains largely unclear. Previous research has shown that cancer development and progression are closely associated with various non-coding RNAs, including long non-coding RNAs and microRNAs, which regulate gene expression. Target gene abnormalities are regulated and engaged in the complex mechanism underlying tumor formation, thereby controlling apoptosis, invasion, and migration of tumor cells and providing potentially effective targets for the treatment of malignant tumors. Chemotherapy is a commonly used therapeutic strategy for cancer; however, its effectiveness is limited by general toxicity and tumor cell drug resistance. Therefore, increasing attention has been paid to developing new cancer treatment modalities using traditional Chinese medicines, which exert regulatory effects on multiple components, targets, and pathways. Several active ingredients in Chinese medicine, including ginsenoside, baicalin, and matrine have been found to regulate ncRNA expression levels, thus, exerting anti-tumor effects. This review summarizes the scientific progress made regarding the anti-tumor mechanisms elicited by various active ingredients of Chinese medicine in regulating non-coding RNAs, to provide a theoretical foundation for treating tumors using traditional Chinese medicine.

Keywords: microRNA, lncRNA, non-coding RNA, active ingredients of Chinese medicine, anti-cancer

INTRODUCTION

The incidence of cancer has tripled over the past three decades and is expected to increase five-fold by 2030 (1). Nevertheless, the precise mechanism associated with cancer pathogenesis remains largely unclear as it is highly complex and diverse. Since the 1970s, gene therapy has become an increasingly attractive strategy for the treatment of various diseases. Accordingly, more recently, the focus has shifted toward identifying specific genetic etiologies of cancer to design effective gene

Abbreviations: ncRNA, non-coding RNA; lncRNA, long non-coding RNA; miRNA, microRNA; siRNA, small interfering RNA; piRNA, Pwi-interacting RNA; rRNA, ribosomal RNA; tRNA, transfer RNA; snRNA, small nuclear RNA; EMT, epithelial-mesenchymal transition; cERNA, competing endogenous RNA; T-ALL, T-cell acute lymphoblastic leukemia; B-ALL, B-cell acute lymphoblastic leukemia; PKM2, pyruvate kinase M2; MMPs, Matrix metalloproteinases; circRNA, circular RNA.
therapies to overcome the challenges associated with traditional cancer treatment modalities. As the human genome is gradually deciphered, RNA has been shown to play an auxiliary role as an intermediate vector of genetic information, and an increasing number of regulatory functions have been ascribed to this class of molecules. In particular, non-coding sequences, which account for 99% of the total human genome, have received greater attention (2). Most of the identified non-coding RNAs (ncRNAs), including long non-coding (lnc)RNAs, micro (mi) RNAs, small interfering (si)RNAs, Piwi-interacting (pi)RNAs, ribosomal (r)RNAs, transfer (t)RNAs, and small nuclear (sn) RNAs, participate in the translation, modification, and other cellular functions. Among these molecules, lncRNAs and miRNAs have been researched more intensively to decipher their fundamental roles in many diseases, including cancer (3). In fact, lncRNAs were initially believed to be the “noise” of genome transcription, a by-product of RNA polymerase II transcription, and were considered biologically non-functional (4). However, recent studies have shown that lncRNAs play an essential role in cancer signal transduction pathways by interacting with proteins and RNA (5) and are reportedly associated with various cancers, including those of the stomach (6–8), lung (9, 10), breast (11, 12), and prostate (13, 14). Specifically, inhibition of lncRNA H19 and lncRNA PVTT1 expression can effectively inhibit the cancerization, metastasis (15), and angiogenesis (7) of gastric cancer.

miRNA is a class of small (18–22 nucleotides) ncRNA molecules; it is present in all eukaryotic cells, with over 2,000 of these RNAs being identified in humans (3). However, ncRNAs have also been described in insects, plants, fungi, bacteria, and viruses (16, 17). Compared with lncRNA, the regulatory mechanism of miRNA is relatively simple and clear. It regulates gene expression by either suppressing mRNA translation or degrading mRNA molecules (18). Previous studies have found that the abnormal expression of miRNAs can disrupt many signaling pathways resulting in reduced proliferation, migration, and invasion of cancer cells and the promotion of apoptosis (19–21). Numerous carcinogenic miRNAs, including miR-638, miR-155, miR-31, miR-21, miR-221, miR-222, and miR-294 among others, are overexpressed in various malignant tumors (22–24), whereas others, including miR-429, miR-211, miR-1271, and miR-34a, exert anti-cancer effects and are under-expressed in cancer cells (25, 26).

The emergence of ncRNA provides new alternatives for cancer treatment, but its effective application in clinical cancer treatment remains challenging. At present, chemotherapy is one of the most important means of treating malignant tumors. However, its efficacy is limited by systemic toxicity and tumor cell resistance (27). Traditional Chinese medicine has been practiced for thousands of years because of its safety and minimal side effects. To date, many cancer patients have used traditional Chinese medicine as an alternative therapy for cancer treatment (28). Moreover, some of the active ingredients of Chinese medicine have been shown to exert anti-cancer effects by regulating ncRNAs and acting on various signaling pathways and cancer-related molecular targets, thus, inhibiting tumor proliferation, metastasis, and invasion and inducing cancer cell apoptosis (29). For instance, the isoflavone calycosin inhibits nasopharyngeal carcinoma cell growth by regulating the lncRNA EWSAT1 and its downstream TRAF6 pathways (30). Additionally, curcumin upregulates miR-145 expression to inhibit cell proliferation and invasion in vitro, while inducing cell cycle arrest (31). These reports suggested that ncRNAs have anti-tumor abilities that regulate cancer cell apoptosis, proliferation, resistance, metastasis, and invasion.

ACTIVE INGREDIENTS OF TRADITIONAL CHINESE MEDICINE REGULATE THE ANTI-TUMOR MECHANISM OF MiRNA

Over the past decades, miRNA has been shown to play a regulatory role in many cancer signaling pathways (32). The active ingredients in traditional Chinese medicine act through different mechanisms to upregulate the expression of tumor-suppressing miRNAs and downregulate the expression of oncogenic miRNAs (33). They also inhibit tumor occurrence and development by inducing cell apoptosis to inhibit tumor metastasis, enhancing cell cycle arrest to reduce drug resistance, and by downregulating other pathways (34) (Table 1).

ACTIVE INGREDIENTS OF CHINESE MEDICINE TARGETING MiRNA INDUCE TUMOR APOPTOSIS

Apoptosis is a basic biological phenomenon, that involves the activation, expression, and regulation of a series of genes. The active ingredients of traditional Chinese medicine regulate target genes by influencing an abnormal expression of miRNAs and inducing tumor cell apoptosis (Figure 1). miR-21 inhibits apoptosis in various tumor cells (71–73). Ginsenoside Rh2 is a natural monosome of ginseng total saponin, and its anti-cancer effects have been demonstrated in various tumors. A former report showed that ginsenoside Rh2 inhibited Bcl-2 by increasing miR-21 levels, which induced apoptosis and significantly decreased leukemia cell viability (35). PTEN is a classical anti-oncogene, the inhibition of PTEN is key for cell apoptosis, mainly relying on the phosphorylation and dephosphorylation of Akt. In FTC-133 human follicular thyroid cells, the alkaloid Chinese medicine active ingredient matrine is induced by upregulating the PTEN/Akt signaling pathway via the downregulating miR-21 (39) it induces apoptosis of TPC-1 human thyroid cancer cells (40). Similarly, the reverse quantitative polymerase chain reaction of an extract of Magnolia officinalis revealed that magnolol could induce abnormal expression of miRNA in human osteosarcoma cells, with miR-21 showing a very strong ability to downregulate miRNAs. Recent evidence has suggested that Honokiol is able to suppress the PI3K/AKT signaling pathway; however, it was reactivated by miR-21 overexpression. Honokiol inhibits proliferation and induces apoptosis by regulating the miR-21/
PTEN/P13K/Ark signaling pathway in human osteosarcoma cells (41).

A previous report described that Rh2 reduces the expression levels of MCL1 and Nrf2, suppresses colony formation, and induces HepG2 cell apoptosis by inhibiting miR-146a-5p in HepG2 cells (36). Berberine is a quaternary ammonium alkaloid isolated from Coptis chinensis. It inhibits the growth of non-small-cell lung cancer via the miR-19a/TF/MAPK axis and promotes apoptosis. A previous study of the mechanism of anti-tumor baicalin in human colon cancer showed that baicalin induced colon cancer cell apoptosis via the Wnt signaling pathway mediated by miR-217/DDK1, in which DDK1 was identified as a direct downstream target gene of miR-217 (33). A previous study showed that resveratrol regulated the apoptosis and cell cycle of breast cancer cells by regulating miRNAs such as miR-125b-5p, miR-200C-3p, miR-409-3p, miR-122-5p, and miR-542-3p. Resveratrol-mediated miRNA modulation regulates key anti-apoptotic and cell cycle proteins, including Bcl-2, X-linked inhibitor of apoptosis protein, and CDKs, which are critical for its activity. Among these, miR-542-3p and miR-122-5p play key roles in resveratrol-mediated apoptosis of MCF-7 and MDA-MB-231 breast cancer cells, respectively (44). Resveratrol significantly reduced miR-196b/miR-1290 expression in the T-ALL (T-cell acute lymphoblastic leukemia) SUP-B15 cell lines and upregulated the expression of IGFBP3. As a miR-196b/miR-1290 inhibitor, resveratrol was further demonstrated to exert antitumor effects on ALL cells including antiproliferation, cell cycle arrest, apoptosis and inhibition of migration (45). Pyruvate kinase PKM2 is highly expressed in various tumors. The expression of miR-326 was

---

**TABLE 1** | Detailed information on Chinese medicine active ingredients targeting miRNAs.

| Active Compound | Types of cancer | miRNA | Target Genes | Related Hallmark | Reference |
|-----------------|----------------|-------|--------------|------------------|-----------|
| Ginsenoside Rh2 | Acute myeloid leukemia | mR-21 | Bcl-2 | Induce apoptosis | (35) |
| Ginsenoside Rh2 | Human liver cancer | mR-21 | MCL1/Nrl2/Bcl-2 | Induce apoptosis | (36) |
| Ginsenoside Rh2 | Prostate cancer | mR-4295 | CDK11A | Anti-proliferation | (37) |
| Ginsenoside Rh2 | Lung adenocarcinoma | mR-491 | MMP-9 | Anti-metastasis | (38) |
| Matrine | Human thyroid cancer | mR-21 | PTEN/p-Akt | Induce apoptosis | (39, 40) |
| Honokiol | Osteosarcoma | mR-21 | PTEN/P13K/Ark | Induce apoptosis | (41) |
| Berberine | Non-small cell lung cancer | mR-19a | TF/MAPK | Induce apoptosis | (42) |
| Baicalin | Colon cancer | mR-217 | DKK1 | Induce apoptosis | (43) |
| Baicalin | Hepatoma | mR-3127-5p | PI3K/Akt | Cell cycle arrest | (44) |
| Resveratrol | Breast cancer | mR-122-5p/miR-542-3p | XIAP/Bcl-2 | Induce apoptosis | (45) |
| Resveratrol | Acute lymphoblastic leukemia | mR-196b/miR-1290 | Caspase-3 | Induce apoptosis | (46) |
| Resveratrol | Cancer | mR-326 | PKM2 | Induce apoptosis | (47) |
| Resveratrol | Breast cancer | mR-34a/miR-424/miR-503 | Bcl2/p53 | Anti-proliferation | (48) |
| Triacetylar | Pancreatic cancer | mR-200 | Shh | Anti-MET process/Anti-metastasis | (49) |
| Resveratrol | Low invasive breast cancer | mR-122-5p | Bcl2/CDKs | Enhance chemosensitivity | (50) |
| Resveratrol | Colorectal cancer | mR-200c | Vimentin/EB1 | Anti-MET process/Anti-metastasis | (51) |
| Ginsenoside Rg3 | Oral squamous cell carcinoma | mR-221 | P53/Ark, MAPK/ERK | Anti-EMT process | (52) |
| Ginsenoside Rg3 | Ovarian cancer | mR-145 | DNMT3A/FSN1 | Anti-EMT process | (53) |
| Camptothecin | Cancer | mR-125b | Baf1/Mcl1/p53 | Induce apoptosis | (54) |
| Camptothecin | Cervical cancer | mR-15a/16 | Rictor | Enhance chemosensitivity | (55) |
| Paeoniforin | Gastric carcinoma | mR-124 | P53/Akt/STAT3 | Anti-proliferation | (56) |
| Paeoniforin | Human glioma cells | mR-16 | MMP-9 | Anti-proliferation/induce apoptosis | (57) |
| Paeoniforin | Multiple myeloma | mR-29b | MMP-2 | Anti-proliferation/induce apoptosis | (58) |
| Shikonin | Glioblastoma | mR-143 | BAG3 | Induce apoptosis | (59) |
| Shikonin | Endometrioid endometrial cancer | mR-106b | Akt/mTOR | Anti-proliferation/Induce apoptosis | (60) |
| Shikonin | Gastric carcinoma | mR-195 | P53/Akt | Anti-proliferation Anti-invasion | (61) |
| Shikonin | Cervical Cancer | mR-163-5p | E-cadherin | Anti-proliferation Anti-invasion | (62) |
| Shikonin | Retinoblastoma | mR-34a/miR-202 | MYCN | Anti-proliferation | (63) |
| Celastrol | Ovarian carcinoma | mR-21 | P53/p-Akt/NF-xB | Induce apoptosis | (64) |
| Celastrol | Colon cancer | mR-21 | P53/Akt/GSK-3B | Anti-proliferation | (65) |
| Celastrol | Gastric cancer | mR-21 | MMP9|Vimentin | Anti-proliferation/Induce cell cycle arrest | (66) |
| Celastrol | Gastric cancer | mR-21 | P27/mTOR | Induces cell cycle arrest | (67) |
| Celastrol | Prostate cancer | mR-101 | NA | Induces autophagy | (68) |
| Celastrol | Prostate cancer | mR-17-92a | NA | Induces autophagy | (69) |
| Celastrol | Lung adenocarcinoma | mR-24/miR-181b | STAT3 | Anti-proliferation | (70) |
| Celastrol | Lung adenocarcinoma | mR-33a-5p | mTOR/p-p70S6K/p-4EBP1 | Enhance chemosensitivity | (71) |
increased after resveratrol treatment, and miR-326/PKM2-mediated stress and mitochondrial dysfunction were involved in apoptosis induced by resveratrol (46). Camptothecin, a cytotoxic quinoline alkaloid, is an anti-cancer compound found in plants. Deep sequencing analysis of miRNA expression profiles during the camptothecin-induced apoptosis showed that 79 miRNAs were downregulated post-treatment (74). A study of camptothecin verified that miR-125b was down-regulated in camptothecin induced apoptosis in cancer cells. Camptothecin induced apoptosis in cancer cells through miR-125b-mediated mitochondrial pathways by targeting the 3’-untranslated (UTR) regions of Bak1, Mcl1, and p53 (53). In glioblastoma stem cells, miR-143 expression was downregulated after shikonin administration, whereas the regulation factor BAG3 was upregulated. Notably, miR-143 overexpression reversed this phenomenon and enhanced the anti-tumor activity of shikonin in glioblastoma stem cells (58). Celastrol is found in the root of Celastrus orbiculatus, belonging to the family Celastraceae. It can regulate apoptosis-promoting signaling pathways (75). Celastrol caused G2/M cell cycle arrest that was accompanied by the down-regulation of miR-21 expression. Further study showed that celastrol inhibited p27 protein degradation by inhibiting the miR-21 and mTOR signaling pathways in BGC-823 and MGC-803 cells. The effect of celastrol on cell cycle arrest of gastric cancer cells was due to an increase in the p27 protein level via inhibition of the miR-21-mTOR signaling pathway (66).

ACTIVE INGREDIENTS OF CHINESE MEDICINE TARGET MIRNAS TO BLOCK TUMOR CELL CYCLE

The occurrence of most tumors is related to the disruption of cell cycle regulation, leading to uncontrolled cell growth. Many active ingredients of Chinese medicine play an anti-tumor role by blocking the tumor cell cycle and inhibiting cell proliferation (Figure 1). For instance, in patients with acute lymphoblastic leukemia (ALL), a study demonstrated that the expression of IGFBP3 was decreased in ALL patients. The authors further identified that miR-196b and miR-1290 were overexpressed in T-ALL TALL-104 and B-ALL SUP-B15 cell lines, respectively. As an miR-196b/miR-1290 inhibitor, resveratrol was further demonstrated to exert antitumor effects on ALL cells including cell cycle arrest. Resveratrol blocks T-ALL T-ALL-104 cells during the G1 phase and the B-ALL SUP-B15 cells in the S phase by inhibiting miR-196b/miR-1290 (45). Baicalin upregulates miR-3127-5p, which increases p21/CDKN1A and P27/CDKN1B expression to inhibit cell proliferation arresting the cell cycle in S and G2/M phases in Bel-7402 cells (43). Celastrol caused G2/M cell cycle arrest that was accompanied by the down-regulation of miR-21 expression. Further study showed that celastrol inhibited p27 protein degradation by inhibiting the miR-21 and mTOR signaling pathways in BGC-823 and MGC-803 cells. The effect of celastrol on cell cycle arrest of gastric cancer cells was due to an increase in the p27 protein level via inhibition of the miR-21-mTOR signaling pathway (66).

ACTIVE INGREDIENTS OF CHINESE MEDICINE TARGETING MIRNA INHIBIT TUMOR CELL PROLIFERATION

Many traditional Chinese medicines regulate cell proliferation through miRNAs (Figure 2). Paeoniinol is a monoterpene glycoside with various anti-cancer activities and is derived
from *Paeonia lactiflora*. Studies have shown that paeoniflorin has broad-spectrum anti-tumor activities against various cancers (76), including those of liver (77), lungs (78), breast (79), and pancreas (80). miR-124 levels are significantly increased in paeoniflorin-treated MGC-803 cells, which inhibits PI3K/Akt and p-STAT3 expression. A PI3K agonist or STAT3 overexpression can reverse effects of paeoniflorin on MGC-803 cell proliferation (55).

Shikonin, a natural naphthoquinone isolated from traditional Chinese herbs. miR-106b is one of the most significantly downregulated miRNAs among the several miRNAs dysregulated by shikonin. miR-106b targets the tumor suppressor gene phosphatase and tensin homolog (PTEN), thereby modulating AKT/mTOR signaling pathway and ultimately inhibiting the proliferation of endometrial cancer cells (59). An earlier report investigated changes in the proliferation of the retinoblastoma cell lines Y-79 and Weri-RB-1 after shikonin administration. The results revealed that shikonin upregulated miR-34a and miR-202 expression and directly targeted the oncogene MYCN to degrade its mRNA while inhibiting the proliferation of retinoblastoma cells (62).

Several studies have shown that celastrol can inhibit tumor cell proliferation in several types of cancers. For example, in colon cancer cells, the overexpression of miR-21 enhanced cell viability, inhibited apoptosis, increase Bcl-2 expression, and decreased Bax levels; these effects were reversed by celastrol. As enzymes are involved in cell survival, the PI3K/AKT/GSK-3β pathway provides important signals for tumor cell proliferation. Celastrol may inhibit colon cancer cell proliferation by negatively regulating the PI3K/AKT/GSK-3β pathways via miR-21 (64). Similar results were reported in lung adenocarcinoma, in which celastrol inhibited cell proliferation and induced apoptosis by regulating the expression levels of miR-24 and miR-181b (69).

Another study showed that ginsenoside Rh2 inhibited the proliferation of prostate cancer cells in a dose-dependent manner, and no CDKN1A cell cycle inhibitor was observed in the increased protein of ginsenoside Rh2. Screening all candidate miRNAs for binding to the 3′-untranslated region of CDKN1A showed that miR-4295 was dose-dependently inhibited by ginsenoside Rh2. Therefore, comprehensive experimental investigations revealed that ginsenoside Rh2 inhibits prostate cancer cell growth by inhibiting miRNA-4295, which activates CDKN1A (37).

**ACTIVE INGREDIENTS OF CHINESE MEDICINE TARGETING MiRNA INHIBIT TUMOR CELL METASTASIS AND INVASION**

The metastasis and invasion are essential feature characterizing the biological behavior of malignant tumors. The active
ingredients of traditional Chinese medicine can inhibit the invasion and metastasis of tumors by regulating miRNA (Figure 3). EMT is an important prerequisite for tumor cell metastasis. The miR-200 family inhibits EMT, thereby inhibiting tumor metastasis. A previous study reported that triacetyl resveratrol, a derivative of resveratrol, inhibited pancreatic cancer growth and EMT by upregulating the expression of the members of the miR-200 family and targeting the Shh pathway (48). Moreover, resveratrol increased the expression of miR-200c to inhibit cell proliferation and invasion in HCT116 cells (50). Ginseng saponin Rg3 suppressed EMT in oral squamous cell carcinoma and ovarian cancer via miR-221 (51) and miR-145 (52). E-cadherin, the most common EMT protein, plays an important role in tumor invasion, and the loss of E-cadherin expression promotes tumor and EMT. In the cervical cancer cell lines HeLa and C33a, Shikonin inhibits EMT by inducing miR-183-5p expression via E-cadherin (61). Similarly, miR-17-5p expression was upregulated in triple-negative breast cancer. The PTEN is a direct target of miR-17-5p. Studies have shown that increased expression of PTEN can inhibit miR-17-5p and reduce the expression of Akt and P-Akt, thereby inhibiting EMT and the migration and invasion of triple-negative breast cancer cells (81).

Shikonin can inhibit tumor migration and invasion via modulating miRNA-mediated regulation of multiple pathways. miR-195 is an important member of the micro-15/16/195/424/497 family and can be used as a diagnostic biomarker in breast cancer (82). In NCI-N87 cells, shikonin inhibited the proliferation, migration, and invasion by regulating miR-195 to inhibit the PI3K/AKT signaling pathway (60). Matrix metalloproteinases (MMPs) play important roles in mediating angiogenesis, metastasis, and invasion. MMP-2/9 expression is related to the progression of many tumors, such as colon cancer (83), neuroblastoma (84), and bladder cancer (85). Paoniflorin regulated miR-16-29b, which targeted MMP-9/2 (56) to inhibit the growth and invasion of multiple myeloma cells (57). Celastrol can downregulate miR-21 and MMP9 and regulate the expression of the cell migration protein vimentin; this reduces the migration and invasion ability of MKN45 gastric cancer cells (65). Resveratrol significantly inhibited cell migration in T-cell ALL T-ALL-104 and B-cell ALL SUP-B15 cells by inhibiting miR-196b/miR-1290 (45).

**ACTIVE INGREDIENTS OF CHINESE MEDICINE TARGETING MiRNA REVERSE TUMOR CELL RESISTANCE**

Increasing evidence has revealed that dysfunctional miRNAs significantly affect chemotherapy resistance. Active ingredients of Chinese medicine play an important role in reducing the toxic and side effects of chemotherapy and improving resistance to chemotherapy (Figure 3). A previous study showed that low-invasive breast cancer cells were resistant to amycin and this resistance was reversed by resveratrol, which also targeted the regulatory inhibitor miR-122-5p to influence the cell cycle and apoptosis (49). Increased autophagy during chemotherapy can promote tumor apoptosis or mediate autophagy-related apoptosis. miR-15a and miR-16 effectively induce autophagy,
enhancing the therapeutic effect of camptothecin (54). Celastrol reduced mTOR, P-P70S6K, and p-4EBP1 expression by increased miR33a-5p to inhibited tumor growth (70).

THE ACTIVE INGREDIENTS OF TRADITIONAL CHINESE MEDICINE REGULATE THE ANTI-TUMOR MECHANISM OF LncRNAs

Generally, lncRNAs are defined as molecules comprising more than 200 nucleotides lacking protein-coding capacity. However, more recently, lncRNAs have been reported to regulate gene expression (86). Meanwhile, various active ingredients in Chinese medicines, such as curcumin and resveratrol, modulate tumor development via lncRNA expression regulation in vitro and in vivo (Table 2). In gemcitabine-resistant pancreatic ductal adenocarcinoma cell, a phenolic compound extracted from turmeric, curcumin, desensitizes chemotherapy-resistant pancreatic ductal adenocarcinoma via inhibiting the PRC2-PVT1-c-Myc axis. Hence, emerging evidence suggested that curcumin may be an effective sensitizing agent for chemotherapeutic drugs (96). Moreover, curcumin induces the expression of the lncRNA PINT to inhibit acute lymphoblastic leukemia cell growth (88). Resveratrol is a non-flavonoid polyphenol compound with a wide pharmacological spectrum of anti-cancer, anti-inflammatory, anti-microbial, and antioxidant activity (97). One study on lung cancer reported the upregulation of 21 lncRNAs and downregulation of 19 lncRNAs resveratrol treated A549 cells. Among these, decreased levels of the lncRNA AK001796 weakened the inhibitory effect of resveratrol on cell proliferation (91). Resveratrol inhibits cell proliferation, migration, and invasion by downregulating AK001796 and NEAT1 in lung cancer and multiple myeloma (91, 92). Similarly, triptolide and isoflavone calycosin inhibit cancer cell growth by inhibiting specific lncRNAs in nasopharyngeal cancer. Triptonide inhibits human nasopharyngeal carcinoma cell growth via disrupting lncRNA THOR-IGF2BP1 signaling. Conversely, ectopic lncRNA THOR overexpression inhibits Triptonide-induced cytotoxicity in NPC cells (95).

One of the representative lncRNAs, H19, is recognized as a cancer biomarker and is associated with the occurrence of esophageal cancer (98), colorectal cancer (99), liver cancer (100), breast cancer (101), bladder cancer (102), and stomach cancer. Furthermore, reduced expression of H19 can inhibit cancer development (103, 104). Specifically, curcumin inhibited cell proliferation via c-Myc/H19 pathway, which reduced the expression of H19 in stomach cancer cells. This indicated that curcumin is a potential drug for gastric cancer (87). Moreover, microarray data identified H19 as a potential target of Huaier (a fungal parasite on locust trees), the extract from which reduced the expression of H19, while also reducing the viability of breast cancer cells by inducing apoptosis via regulation of the H19-miR-675-5p-CBL axis (105). Besides, certain lncRNAs and miRNAs mutually restrict and regulate target genes to achieve tumor inhibition. For example, in bladder cancer, H19 can directly bind miR-29b-3p to derepress the target DNMT3B. Further, upregulating H19 antagonizes miR-29b-3p-mediated proliferation, migration, and epithelial-mesenchymal transition (EMT) suppression in bladder cells. This evidence demonstrated, for the first time, that H19 may function as a competing endogenous RNA (ceRNA) for miR-29b-3p and relieve the suppression of DNMT3B, leading to EMT and metastasis of bladder cancer (106). In 2011, a new theory was proposed that ceRNAs and miRNA response elements could mediate the interactions between mRNA pseudogenes and some ncRNAs to form a large-scale regulatory network in the transcriptome and serve as a “new language” for “mutual conversation” (107) (Figure 4). These networks are characterized by sponge activity, in which ncRNA interacts with the target gene to competitively bind or inhibit. In addition, ceRNAs have been identified as key regulatory factors in cancer (108, 109). PVT1, located downstream of the proto-oncogene Myc in chromosome 8q24, was used as a ceRNA of miR-216b and miR-152 in non-small-cell lung cancer and osteosarcoma to promote the tumor resistance to anti-cancer drugs (110, 111). In prostate cancer cells, lncRNA-ROR and the stem cell marker Oct4 mRNA contain binding regions for miR-145 and directly compete with this microRNA. Curcumin reduced the expression of endogenous lncRNA-ROR and effectively increased the available concentration of miR-145 in human prostate cancer stem cells.

| Active Compound | LncRNA | Cancer | Related Hallmark | Reference |
|----------------|--------|--------|----------------|-----------|
| Curcumin       | H19    | Gastric cancer | Proliferation | 87        |
| Curcumin       | GA57   | Breast cancer  | Apoptosis     | 12        |
| Curcumin       | PINT   | Acute lymphoblastic leukemia | Proliferation | 68        |
| Curcumin       | ROR    | Prostate cancer | Proliferation | 31        |
| Curcumin       | PANDAR | Colorectal cancer | Apoptosis | 69        |
| Curcumin       | MEG3   | Ovarian cancer  | Drug resistance | 90        |
| Resveratrol    | AK001796 | Lung cancer | Proliferation/cycle arrest | 91        |
| Resveratrol    | NEAT1  | Multiple myeloma | Proliferation/migration | 92        |
| Matrine        | LINC00472 | Bladder carcinoma | Growth/metastasis | 63        |
| Artesunate     | UCA1   | Prostate cancer  | Apoptosis/migration | 94        |
| Triptolide     | THOR   | Nasopharyngeal carcinoma | Growth | 95        |
| Calycosin      | EWAT1  | Nasopharyngeal carcinoma | Growth | 90        |
where miR-145 prevented cell proliferation by decreasing Oct4 expression (31). The ceRNA hypothesis has revealed new mechanisms of RNA interactions, which incentivized the analysis of ncRNA role in cancer development.

**REGULATION OF THE ANTI-TUMOR MECHANISM BY CIRCRNA AND OTHER NCRNAS**

As potential targets for the active ingredients of Chinese medicine, circRNA, siRNA, rRNA, and other non-coding RNAs are involved in tumor development. Some circRNAs affect cancer biogenesis in diverse manners, such as by functioning as miRNA sponges, combining with RNA-binding proteins, acting as transcription factors, and affecting protein translation (112). Matrine decreased circRNA-104075 and Bcl-9 expression significantly via inhibition of PI3K/AKT and Wnt-β-catenin pathways, it suppressed cell viability while inducing apoptosis and autophagy in glioma cell line U251 (113). Another study shows that matrine down-regulated the levels of circ_0027345 and HOXD3, and up-regulated miR-345-5p expression. Meanwhile, matrine restrained tumor growth, invasion and promoted autophagy of HCC by regulating the circ_0027345/miR-345-5p/HOXD3 axis in vivo (114). Curcumin has antioxidant and anti-cancer properties, and it has also been used as a radiosensitizer. A study compared the differences in circRNA levels in NPC cell lines after radiotherapy and after treatment with curcumin, using a high-throughput microarray. Finally, it was demonstrated by reverse transcription-quantitative polymerase chain reaction assay and wound healing assay that curcumin could enhance radiosensitization of NPC cell lines via mediating regulation of tumor stem-like cells by the “hsa_circRNA_102115”-“hsa-miR-335-3p”-“MAPK1” interaction network (115). At present, although circRNA has shown significant activity in the treatment of cancer, there are few reports on the regulation of circRNA by Active Ingredients of Chinese Medicine, which is also an important direction for future researchers to concern and research. circRNA has been expected to become a new molecular biomarker for the clinical diagnosis, treatment and prognosis, and the potential target for targeted therapy. siRNAs are double-stranded RNAs of 20-25 nucleotides and are involved in RNA interference; they regulate gene expression in a specific manner. Multiple synthetic siRNAs can achieve long-term silencing of target genes without interfering with endogenous microRNA pathways. Ginsenoside Rh2 downregulated P-STAT3/STAT3 and intracellular oxidative stress by upregulating PPAR. In response to siRNA-mediated knockdown of PPAR, STAT3 and intracellular oxidative stress were increased (116). rRNA is the most abundant type of RNA in cells. In lung cancer cells, triptolide interrupts rRNA synthesis by inhibiting transcriptional activation of RNA Pol I and UBF, thereby activating the apoptosis regulators caspase 9 and caspase 3 to inhibit BCL2 and induce apoptosis and cell cycle arrest (117).

**DISCUSSION**

During cancer development, abnormal ncRNAs modulate cell proliferation, migration, and invasion by regulating the expression of proto-oncogenes and tumor suppressor genes. Many active ingredients of traditional Chinese medicine, such as resveratrol, matrine, and berberine, have been evaluated in vivo and in vitro to target specific ncRNA and shown to play anti-cancer roles. This review summarized the finding regarding 16 active ingredients of traditional Chinese medicine that can target miRNAs, lncRNAs, and other ncRNAs, thereby playing an effective role in suppressing cancer growth. Among the ncRNAs regulated by Chinese medicine active ingredients, miR-21 is the most reported ncRNA and is extensively studied in various cancers. It is involved in most of the cancer-related processes, such as cell apoptosis, proliferation, migration, and cell cycle. These findings indicate that miR21 is one of the promising ncRNAs to develop targeted therapeutic agents for many types of cancer. Some active ingredients of traditional Chinese medicine, such as Ginsenoside Rh2 and Resveratrol, promote apoptosis by regulating ncRNAs to target common apoptosis-related target genes, such as BCL2 and Caspase3.
In conclusion, traditional Chinese medicine’s active ingredients significantly ameliorate malignant neoplasms via ncRNA regulation, suggesting that active ingredients of traditional Chinese medicine may become alternative therapeutic agents for cancer in the future. At present, most studies have reported that the active ingredients of traditional Chinese medicine mainly target one kind of ncRNA for cancer treatment. However, ceRNA mechanism suggests that several kinds of ncRNA have complex interactions in cancer treatment. Therefore, we need to further explore the detailed anti-cancer mechanism and clinical safety of each of the active ingredients of traditional Chinese medicine. We hope that this review on the regulation of ncRNA by active ingredients of traditional Chinese medicine on tumor will be helpful for future research studies on anti-cancer of traditional Chinese medicine and provide a reference for their clinical application.

REFERENCES

1. Sohyla R, Shrahram S, Alireza Z, Arash Z, Fariba S. Cancer CMJoT. A comparative study of spatial distribution of gastrointestinal cancers in poverty and affluent strata (kermanshah metropolis, iran). J Gastrointest Cancer (2018) 50(4):838–47. doi: 10.1007/s12029-018-0163-7
2. Hong M, Wang N, Tan HY, Tsao SW, Feng Y. MicroRNAs and chinese medicinal herbs: new possibilities in cancer therapy. Cancers (2015) 7 (3):1643–57. doi: 10.3390/cancers7030855
3. Romano G, Veneziano D, Acunzo M, Croce CM. Small non-coding RNA and cancer. Carcinogenesis (2017) 38(5):485–91. doi: 10.1093/carcin/bgw026
4. Long J, Xiong J, Bai Y, Mao J, Lin J, Xu W, et al. Construction and investigation of a IncRNA-associated cerna regulatory network in cholangiocarcinoma. Front Oncol (2019) 9:649. doi: 10.3389/fonc.2019.00649
5. Lin C, Yang L. Long noncoding RNA in cancer: wiring signaling circuitry. Trends Cell Biol (2018) 28(4):287–301. doi: 10.1016/j.tcb.2017.11.008
6. Hao NB, He YF, Li XQ, Wang K, Wang RL. The role of miRNA and IncRNA in gastric cancer. Oncotarget (2017) 8(46):81572–82. doi: 10.18632/oncotarget.19197
7. Zhao J, Du P, Cui P, Qin Y, Hu C, Wu J, et al. LncRNA PVT1 promotes angiogenesis via activating the STAT3/VGFA axis in gastric cancer. Oncogene (2018) 37(30):4094–109. doi: 10.1038/s41388-018-0250-z
8. Wei GH, Wang X. IncRNA MEG3 inhibit proliferation and metastasis of gastric cancer via p53 signaling pathway. Eur Rev Med Pharmacol Sci (2017) 21(17):3850–6
9. Nie W, Ge HJ, Yang XQ, Sun X, Huang H, Tao X, et al. LncRNA-UCA1 exerts oncogenic functions in non-small cell lung cancer by targeting mir-193a-3p. Cancer Lett (2016) 371(1):99–106. doi: 10.1016/j.canlet.2015.11.024
10. Fang Z, Chen W, Yuan Z, Liu X, Jiang H. LncRNA-MALAT1 contributes to the cisplatin-resistance of lung cancer by upregulating MRPI and MRD1 via STAT3 activation. Biomed Pharmacother (2018) 101:536–42. doi: 10.1016/j.biopha.2018.02.130
11. Chen F, Chen J, Yang L, Liu J, Zhang X, Zhang Y, et al. Extracellular vesicle-packaged HIF-1α stabilizing IncRNA from tumour-associated macrophages regulates aerobic glycolysis of breast cancer cells. Nat Cell Biol (2019) 21 (4):498–510. doi: 10.1038/s41556-019-0299-0
12. Gu J, Wang Y, Wang X, Zhou D, Shao C, Zhou M, et al. Downregulation of IncRNA GASS confers tamoxifen resistance by activating miR-222 in breast cancer. Cancer Lett (2018) 434:1–10. doi: 10.1016/j.canlet.2018.06.039
13. Zhang Y, Pitchaya S, Cieslik M, Niknafs YS, Tien JC, Hosono Y, et al. Analysis of the androgen receptor-regulated IncRNA landscape identifies a role for AR-LINC1 in prostate cancer progression. Nat Genet (2018) 50 (6):814–24. doi: 10.1038/s41588-018-0120-1

AUTHOR CONTRIBUTIONS

TL and SH participated in writing, editing, and making figures. ZQ and DL read and approved the final manuscript. All authors contributed to the article and approved the submitted version.

FUNDING

This work was supported by the National Natural Science Foundation of China (grant 81973712, 81803680,82003985), China Postdoctoral Science Foundation (grant 2020M670825, 2020T130568), Jilin Province Science and Technology Development Project in China (grant 201703090005Y, 20200504005YY), Jilin Province TCM science and technology project (grant 2020041).

10. Fang Z, Chen W, Yuan Z, Liu X, Jiang H. LncRNA-MALAT1 contributes to the cisplatin-resistance of lung cancer by upregulating MRPI and MRD1 via STAT3 activation. Biomed Pharmacother (2018) 101:536–42. doi: 10.1016/j.biopha.2018.02.130
11. Chen F, Chen J, Yang L, Liu J, Zhang X, Zhang Y, et al. Extracellular vesicle-packaged HIF-1α stabilizing IncRNA from tumour-associated macrophages regulates aerobic glycolysis of breast cancer cells. Nat Cell Biol (2019) 21 (4):498–510. doi: 10.1038/s41556-019-0299-0
12. Gu J, Wang Y, Wang X, Zhou D, Shao C, Zhou M, et al. Downregulation of IncRNA GASS confers tamoxifen resistance by activating miR-222 in breast cancer. Cancer Lett (2018) 434:1–10. doi: 10.1016/j.canlet.2018.06.039
13. Zhang Y, Pitchaya S, Cieslik M, Niknafs YS, Tien JC, Hosono Y, et al. Analysis of the androgen receptor-regulated IncRNA landscape identifies a role for AR-LINC1 in prostate cancer progression. Nat Genet (2018) 50 (6):814–24. doi: 10.1038/s41588-018-0120-1
64. Ni H, Han Y, Jin X. Celastrol inhibits colon cancer cell proliferation by downregulating miR-21 and PI3K/ATK/GSK-3β pathway. Int J Clin Exp Pathol (2019) 12(3):3008–16.
65. Guo J, Mei Y, Li K, Huang X, Wang H, Yang H. Downregulation of miR-17-92a cluster promotes autophagy induction in response to celastrol treatment in prostate cancer cells. Biochem Biophys Res Commun (2016) 478(2):804–10. doi: 10.1016/j.bbrc.2016.08.029
66. Yan YF, Zhang HH, Lv Q, Liu YM, Li YJ, Li BS, et al. Celastrol suppresses the proliferation of lung adenocarcinoma cells by regulating miR-24 and miR-181b. Oncol Lett (2018) 15(2):2515–21. doi: 10.3892/ol.2017.7593
67. Li YJ, Sun YX, Hao RM, Wu P, Zhang LJ, Ma X, et al. miR-33a-5p enhances pancreatic cancer cell growth by upregulating HTRA3 expression. Oncotarget (2016) 7(18):25470–9. doi: 10.18632/oncotarget.8810
68. Yao SS, Han L, Tian ZB, Yu YN, Zhang Q, Li XY, et al. Celastrol inhibits proliferation and invasion by targeting ETV1 in triple-negative breast cancer cell lines. Oncotarget.15353–60. doi: 10.18632/oncotarget.15353
69. Li L, Liu J, Xu X, Li L. Celastrol suppresses cisplatin resistance development partly via modulating extracellular vesicle-mediated transfer of MEG3 and miR-214 in ovarian cancer. Cancer Chemother Pharmacol (2017) 79(3):479–87. doi: 10.1007/s00280-017-3388-4
70. Yang Q, Xu E, Dai J, Liu B, Han Z, Wu J, et al. A novel long non-coding RNA AK001796 acts as an oncogene and is involved in cell growth inhibition by resveratrol in lung cancer. Toxicol Appl Pharmacol (2015) 285(2):79–88. doi:10.1016/j.taap.2015.04.003
71. Geng W, Guo X, Zhang L, Ma Y, Wang L, Liu Z, et al. Resveratrol inhibits proliferation, migration and invasion of multiple myeloma cells by NEAT1-mediated Wnt/β-catenin signaling pathway. Biomed Pharmacother. –. doi: 10.1016/j.biopha.2018.08.003
72. Li L, Qi F, Wang K. Matrine restrains cell growth and metastasis by upregulating LINC00472 in bladder carcinoma. Cancer Manage Res (2020) 12:1241–51. doi: 10.2147/cmar.s224701
73. Zhou Y, Wang X, Zhang J, He A, Wang YL, Han K, et al. Artesunate suppresses the viability and mobility of prostate cancer cells through UCA1, the sponge of miR-184. Oncotarget (2017) 8(11):18260–70. doi: 10.18632/oncotarget.13533
74. Wang SS, Lv Y, Xu XC, Zuo Y, Song Y, Wu GP, et al. Triptolide inhibits human nasopharyngeal carcinoma cell growth via disrupting Lnc-RNA THOR-IGF2BP1 signaling. Cancer Lett (2019) 443:13–4. doi: 10.1016/j.canlet.2018.11.028
75. Yoshida K, Toden S, Ravidranathan P, Han H, Goel A. Curcumin sensitizes pancreatic cancer cells to gemcitabine by attenuating PR23 subunit EZH2 and the LncRNA PVT1 expression. Carcinogenesis (2017) 38(10):1036–46. doi:10.1093/carcin/bgw065
76. Shukla D, Sharma A, Tuli HS, Sak M, Mukherjee T, Bishaye A. Molecular targets of celastrol in cancer: recent trends and advancements. Crit Rev Oncog/Herpatol (2018) 12870–81. doi:10.1016/j.critrevonc.2018.05.019
77. Xiang Y, Zhang Q, Wei S, Huang C, Li Z, Gao Y, Panorifin: a monoterpene glycoside from plants of Paeoniaceae family with diverse anticancer activities. J Pharm Pharmacol (2020) 72(4):483–95. doi:10.1111/jphp.13204
78. Liu H, Zang L, Zhao J, Wang Z, Li L. Paeoniflorin inhibits cell viability and invasion of liver cancer cells via inhibition of Skp2. Oncol Lett (2020) 19(4):3165–72. doi: 10.3892/ol.2020.11424
79. Lu Q, Chen GL, Li YJ, Chen Y, Lin FZ. Paeoniflorin inhibits macrophage-mediated lung cancer metastasis. Chin J Natural Medicines (2015) 13(12):925–32. doi: 10.1007/s11755-015-0908-4
80. Zhang J, Yu K, Han X, Zhen L, Liu M, Zhang X, et al. Panorifin influences breast cancer cell proliferation and invasion via inhibition of the Notch-1 signaling pathway. Mol Med Rep (2018) 17(1):1321–5. doi: 10.3892/mmr.2017.8002
81. Li Y, Gong L, Qi R, Sun Q, Xia X, He H, et al. Paeoniflorin suppresses pancreatic cancer cell growth by upregulating hTERT expression. Drug Design Dev Ther (2017) 11:2481–90. doi: 10.2147/dddt.s134518
82. Li J, Lai Y, Ma J, Liu Y, Bi J, Zhang L, et al. miR-17-5p suppresses cell proliferation and invasion by targeting ETVI in triple-negative breast cancer. BMC Cancer (2017) 17(1):345. doi: 10.1186/s12885-017-3674-3
83. Liu Y, Tang D, Zheng S, Su R, Tang Y. Serum microRNA-195 as a potential diagnostic biomarker for breast cancer: a systematic review and meta-analysis. Int J Clin Exp Pathol (2019) 12(11):3982–91.
1. Collette J, Le Bourhis X, Adriaenssens E. Regulation of human breast cancer by the long non-coding RNA H19. *Int J Mol Sci* (2017) 18(11):2319. doi: 10.3390/ijms18112319

2. Taheri M, Omrani MD, Ghafouri-Fard S. Long non-coding RNA expression in bladder cancer. *Biophys Rev* (2018) 10(4):1205–13. doi: 10.1007/s12551-017-0379-y

3. Zhang L, Zhou Y, Huang T, Cheng AS, Yu J, Kang W, et al. The interplay of LncRNA-H19 and its binding partners in physiological process and gastric carcinogenesis. *Int J Mol Sci* (2017) 18(2):450. doi: 10.3390/ijms18020450

4. Ghafouri-Fard S, Esmaeili M, Taheri M. H19 lncRNA: Roles in tumorigenesis. *Biomed Pharmacother* (2020) 123:109774. doi: 10.1016/j.biopha.2019.109774

5. Wang J, Wang X, Chen T, Jiang L, Yang Q. Huaier extract inhibits breast cancer progression through a LncRNA-H19/MiR-675-5p pathway. *Cell Physiol Biochem Int J Exp Cell Physiol Biochem Pharmacol* (2017) 44(2):581–93. doi: 10.1159/000485093

6. Lv M, Zhong Z, Huang M, Tian Q, Jiang R, Chen J. lncRNA H19 regulates epithelial-mesenchymal transition and metastasis of bladder cancer by miR-29b-3p as competing endogenous RNA. *Biochim Biophys Acta Mol Cell Res* (2017) 1864(10):1887–99. doi: 10.1016/j.bbamcr.2017.08.001

7. Salmena L, Poliseno L, Tay Y, Kats L, Pandolfini PP. A ceRNA hypothesis: the Rosetta Stone of a hidden RNA language? *Cell* (2011) 146(3):353–8. doi: 10.1016/j.cell.2011.07.014

8. Ogunwobi OI, Kumar A. Chemoresistance mediated by ceRNA networks associated with the PVT1 locus. *Front Oncol* (2019) 9:834. doi: 10.3389/fonc.2019.00834

9. Anastasiadou E, Jacob LS, Slack FJ. Non-coding RNA networks in cancer. *Nat Rev Cancer* (2018) 18(1):5–18. doi: 10.1038/nrc.2017.99

10. Chen L, Han X, Hu Z, Chen L. The PVT1/miR-216b/Becn1-1 regulates cisplatin sensitivity of NSCLC via modulating autophagy and apoptosis. *Cancer Chemother Pharmacol* (2019) 83(5):921–31. doi: 10.1007/s00280-019-03808-3

11. Sun ZY, Jian YK, Zhu HY, Li B. LncRNA-PVT1 targets miR-152 to enhance chemoresistance of osteosarcoma to gemcitabine through activating c-MET/PI3K/AKT pathway. *Pathology Res Pract* (2019) 215(3):555–63. doi: 10.1016/j.prp.2018.12.013

12. Shang Q, Yang Z, Jia R, Ge S. The novel roles of circRNAs in human cancer. *Mol Cancer* (2019) 18(1):6. doi: 10.1186/s12943-018-0934-6

13. Chi G, Xu D, Zhang B, Yang F. Matrine induces apoptosis and autophagy of glioma cell line U251 by regulation of circRNA-104075/BCL-9. *Chemico Biological Interact* (2019) 308:198–205. doi: 10.1016/j.cbi.2019.05.030

14. Lin S, Zhuang J, Zhu L, Jiang Z. Matrine inhibits cell growth, migration, invasion and promotes autophagy in hepatocellular carcinoma by regulation of circ_9027345/miR-345-5p/HOXD3 axis. *Cancer Cell Int* (2020) 20:246. doi: 10.1186/s12935-020-01293-w

15. Zhu D, Shao M, Yang J, Fang M, Liu S, Lou D, et al. Curcumin enhances radiosensitization of nasopharyngeal carcinoma via mediating regulation of tumor stem-like cells by a CircRNA network. *J Cancer* (2020) 11(8):2360–70. doi: 10.7150/jca.39511

16. Tong-Lin Wu T, Tong YC, Chen IH, Niu HS, Li Y, Cheng JT. Induction of apoptosis in prostate cancer by ginsenoside Rh2. *Oncotarget* (2018) 9(13):11109–18. doi: 10.18632/oncotarget.24326

17. Wang J, Zhang ZQ, Li FQ, Chen JN, Gong X, Cao BB, et al. Triptolide interrupts rRNA synthesis and induces the RPL23–MDM2–p53 pathway to repress lung cancer cells. *Oncol Rep* (2020) 43(6):1863–74. doi: 10.3892/or.2020.7569

**Conflict of Interest:** The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

Copyright © 2021 Liu, Hu, Qiu and Liu. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY). The use, distribution or reproduction in other forums is permitted, provided the original author(s) and the copyright owner(s) are credited and that the original publication in this journal is cited, in accordance with accepted academic practice. No use, distribution or reproduction is permitted which does not comply with these terms.