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REVIEW

Long non-coding RNAs are emerging targets of phytochemicals for cancer and other chronic diseases

Shruti Mishra[1] · Sumit S. Verma[1] · Vipin Rai[1] · Nikee Awasthee[1] · Srinivas Chava[2] · Kam Man Hui[3] · Alan Prem Kumar[4] · Kishore B. Challagundla[2] · Gautam Sethi[4] · Subash C. Gupta[1]

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Abstract

The long non-coding RNAs (lncRNAs) are the crucial regulators of human chronic diseases. Therefore, approaches such as antisense oligonucleotides, RNAi technology, and small molecule inhibitors have been used for the therapeutic targeting of lncRNAs. During the last decade, phytochemicals and nutraceuticals have been explored for their potential against lncRNAs. The common lncRNAs known to be modulated by phytochemicals include ROR, PVT1, HOTAIR, MALAT1, H19, MEG3, PCAT29, PANDAR, NEAT1, and GAS5. The phytochemicals such as curcumin, resveratrol, sulforaphane, berberine, EGCG, and gambogic acid have been examined against lncRNAs. In some cases, formulation of phytochemicals has also been used. The disease models where phytochemicals have been demonstrated to modulate lncRNAs expression include cancer, rheumatoid arthritis, osteoarthritis, and nonalcoholic fatty liver disease. The regulation of lncRNAs by phytochemicals can affect multi-steps of tumor development. When administered in combination with the conventional drugs, phytochemicals can also produce synergistic effects on lncRNAs leading to the sensitization of cancer cells. Phytochemicals target lncRNAs either directly or indirectly by affecting a wide variety of upstream molecules. However, the potential of phytochemicals against lncRNAs has been demonstrated mostly by preclinical studies in cancer models. How the modulation of lncRNAs by phytochemicals produce therapeutic effects on cancer and other chronic diseases is discussed in this review.

Keywords Chemosensitization · Non-coding RNA · Nutraceutical · Therapy · Tumor

Abbreviations

3′UTR	Three prime untranslated region
AIDS	Acquired immunodeficiency syndrome
AKT	AKT8 virus oncogene cellular homolog
ALL	Acute lymphoblastic leukemia
ANRIL	Antisense non-coding RNA in the INK4 locus
ASOs	Antisense oligonucleotides
BCRP	Breast cancer resistance protein
BIK	Bcl-2-interacting killer
CAS9	CRISPR-associated protein 9
CASC2	Cancer susceptibility candidate 2
CDK6	Cyclin-dependent kinase 6
CRISPR	Clustered regularly interspaced short palindromic repeats
CTR1	Copper transporter 1
DNA	Deoxyribo nucleic acid
dsDNA	Double-stranded deoxyribonucleic acid
EGCG	Epigallocatechin gallate
EIF4A3	Eukaryotic translation initiation factor 4A3
EMT	Epithelial-to-mesenchymal transition
ERα	Estrogen receptor α
FLS	Fibroblast-like synoviocytes

✉ Kishore B. Challagundla
kishore.challagundla@unmc.edu

✉ Gautam Sethi
phcgs@nus.edu.sg

✉ Subash C. Gupta
sgupta@bhu.ac.in

[1] Department of Biochemistry, Institute of Science, Banaras Hindu University, Varanasi, Uttar Pradesh 221005, India

[2] Department of Biochemistry and Molecular Biology, and Fred & Pamela Buffett Cancer Center, University of Nebraska Medical Center, Omaha, NE 68198, USA

[3] Division of Cellular and Molecular Research, Humphrey Oei Institute of Cancer Research, National Cancer Centre, Singapore 169610, Singapore

[4] Department of Pharmacology, Yong Loo Lin School of Medicine, National University of Singapore, Singapore 117600, Singapore

GAPDH	Glyceraldehyde 3-phosphate dehydrogenase
GAS5	Growth arrest-specific 5
GUCY2GP	Guanylate cyclase 2G homolog pseudogene
H2AFY	H2A histone family member Y
H2BFXP	H2B histone family member X pseudogene
H3K4	Histone H3 lysine 4
HFD	High-fat diet
HMGCR	3-Hydroxy-3-methylglutaryl-coenzyme A reductase
HOTAIR	HOX transcript antisense intergenic RNA
IL-6	Interleukin 6
INSIG1	Insulin-induced gene 1
JAK	Janus kinase
LINC	Long intergenic non-protein-coding RNA
linc-PINT	Long intergenic non-protein-coding RNA p53 induced transcript
LncRNA	Long non-coding RNA
MAP1LC3B2	Microtubule-associated proteins 1A/1B light chain 3B
MCP-1	Monocyte chemoattractant protein-1
MDR1/P-gp	Multidrug resistance protein 1/P-glycoprotein 1
MEG3	Human maternally expressed gene 3
MIR155HG	MicroRNA155 host gene
miRNA	MicroRNA
mRNA	Messenger RNA
MRP	Multidrug resistance-associated protein
mTOR	Mammalian target of rapamycin
NAFLD	Nonalcoholic fatty liver disease
NEAT1	Nuclear paraspeckle assembly transcript 1
NF-κB	Nuclear factor kappa-light-chain-enhancer of activated B cells
Nrf2	Nuclear factor erythroid 2-related factor 2
NSCLC	Non-small-cell lung carcinoma
PANDAR	Promoter of CDKN1A antisense DNA damage-activated RNA
PDK4	Pyruvate dehydrogenase kinase 4
PI3K	Phosphoinositide 3-kinase
PUMA	p53 up-regulated modulator of apoptosis
PVT1	Plasmacytoma variant translocation gene
RA	Rheumatoid arthritis
RNA pol II	RNA polymerase II
RNA	Ribo nucleic acid
RNAi	RNA interference
ROR	Regulator of reprogramming
ST7OT1	ST7 antisense RNA 1
STAT	Signal transducer and activator of transcription
TGM2	Transglutaminase 2
TMEM25	Transmembrane protein 25
TNF-α	Tumor necrosis factor alpha
TNM	Tumor nodes and metastasis
TUG1	Taurine-up-regulated gene 1
TUSC7	Tumor suppressor candidate 7
Zbtb20	Zinc finger and BTB domain-containing protein 20
ZEB1	Zinc-finger E-box-binding homeobox 1
ZFAS1	ZNFX1 antisense RNA 1

Introduction

The long non-coding RNAs (lncRNAs) are highly conserved and potentially functional molecules with an ability to regulate gene expression in a *cis*- or *trans*-manner [1–4]. During the past decade, lncRNAs have emerged as the key player for normal and pathological conditions. The lncRNAs play a crucial role in cell-cycle regulation, innate immunity, and pluripotency [5]. The lncRNAs, transcribed by RNA pol II, are ≥ 200 nucleotides in length [6]. Normally located in the cytosol and the nucleus, the lncRNAs undergo post-transcriptional modifications such as polyadenylation, capping, and splicing [7–10]. The lncRNAs play a crucial role in diverse biological processes such as epigenetic regulation [11, 12], transcriptional regulation of gene expression [13, 14], organization of protein complexes, cell–cell communications, and the formation of nuclear sub-structures [15]. The lncRNAs also play a role during development [16, 17], somatic cell reprogramming, and stem cell pluripotency [17, 18]. Although the mechanism of lncRNAs function varies under different conditions, studies suggest that lncRNAs and miRNAs can display potential cross-talk especially during carcinogenesis [19–22].

Often expressed in a development-, tissue-, or disease-specific manner, lncRNAs can be targeted therapeutically [23–28]. Indeed, strategies such as antisense oligonucleotides (ASOs), RNAi technology, and small molecule inhibitors have been used for lncRNAs' targeting [29, 30]. The lncRNAs have also been used for the selective killing of cancer cells [31]. During recent years, phytochemicals derived from natural sources have demonstrated potential against lncRNAs. The phytochemicals are reported to be cost-effective with an ability to modulate multiple cell signaling pathways [32, 33]. Moreover, these agents have been consumed for ages and, thus, are known to be safe. The sources of phytochemicals include fruits, vegetables, spices, cereals, etc. The consumption of fruits and vegetables is associated with reduced risk of chronic diseases [34–38]. Phytochemicals can affect lncRNA expression either directly or indirectly through the involvement of miRNAs, protein kinases, enzymes, and transcription factors (Table 1). In the cancer model, phytochemicals can suppress the expression of oncogenic lncRNAs or can restore the functions of tumor

Table 1 Molecular targets affected during modulation of lncRNAs by phytochemicals

Molecular targets	Phytochemicals
miRNAs	
hsa-mir-98-5p	Epigallocatechin gallate
miR-101	Gambogic acid
miR-34a, miR-141	Genistein
miR-181a, miR-194	Paclitaxel
miR-29a, miR-185, miR-214	Curcumin
Enzymes	
DNMT1, DNMT3A, DNMT3B	Curcumin
EzH2	Curcumin, paclitaxel, gambogic acid
HMGCR	Epigallocatechin gallate
mTOR	Sanguinarine
PI3K	Silibinin, quercetin, sanguinarine
Protein kinases	
AKT	Silibinin, genistein, quercetin, sanguinarine, anacardic acid
BIK	Paclitaxel
Transcription factors	
EIF4A3	Sanguinarine
NF-κB	Emodin, anacardic acid, sanguinarine, bharangin
Notch	Emodin
Nrf2, ZBTB20	Berberine
ZEB1	Paclitaxel, silibinin
β-Catenin	Resveratrol, silibinin, paclitaxel
Others	
CPEB2, NOXA	Paclitaxel
CTR1	Epigallocatechin gallate
H2AFY, MAP1LC3B2	Sulforaphane

AKT AKT8 virus oncogene cellular homolog, *BIK* BCL2 interacting killer, *CPEB2* cytoplasmic polyadenylation element-binding protein 2, *CTR 1* copper transporter 1, *DNMTs* DNA methyltransferases, *EzH2* enhancer of zeste homologue 2, *HMGCR* 3-hydroxy-3-methylglutaryl coenzyme A reductase, *MAP1LC3B2* microtubule associated protein 1 light chain 3 beta 2, *miRNA* microRNA, *mTOR* mammalian target of rapamycin, *NF-κB* nuclear factor kappa-light-chain-enhancer of activated B cells, *Nrf2* nuclear factor erythroid 2-related factor 2, *PI3K* phosphatidylinositol-3-kinase, *ZEB1* zinc-finger E-box-binding homeobox 1

suppressor lncRNAs. The modulation of lncRNAs by phytochemicals can produce therapeutic effects in some cancer types (Table 2). The disease models where phytochemicals have been demonstrated to modulate lncRNAs include cancer, rheumatoid arthritis, osteoarthritis, and nonalcoholic fatty liver disease (Fig. 1). In disease models, phytochemicals can both up-regulate and down-regulate lncRNAs (Fig. 2). The most common phytochemicals known to have potential to target lncRNAs include curcumin, resveratrol, sulforaphane, berberine, EGCG, gambogic acid, genistein, paclitaxel (taxol), quercetin, sanguinarine, silibinin, anacardic acid, and calycosin (Fig. 3). Moreover, the modulation of lncRNAs by phytochemicals can lead to the inhibition of survival, proliferation, migration, invasion, metastasis, and epithelial-to-mesenchymal transition (Fig. 4). The modulation of lncRNAs expression by phytochemicals can also lead to chemosensitization and radiosensitization of cancer cells (Fig. 4). How phytochemicals affect lncRNA expression in diverse diseases is discussed in the following section. The positives and negatives associated with the targeting of lncRNAs by phytochemicals are also discussed.

Effects of phytochemicals on lncRNA expression

Phytochemicals can modulate multiple cell signaling molecules including kinases, adhesion molecules, cell-cycle regulators, receptors, miRNAs, etc. [32, 39–56]. During the last 5 years, phytochemicals have also been reported to modulate lncRNA expression. The common phytochemicals known to have potential to target lncRNAs include curcumin, resveratrol, sulforaphane, berberine, EGCG, gambogic acid, genistein, paclitaxel (taxol), quercetin, sanguinarine, silibinin,

Table 2 Modulation of lncRNAs by phytochemicals affect pathogenesis of several cancer types

Cancer types	Phytochemicals
Acute lymphoblastic leukemia	Curcumin
Bladder cancer	Curcumin, silibinin, gambogic acid
Breast cancer	Curcumin, anacardic acid, sanguinarine, bharangin, genistein, calycosin, paclitaxel
Cervical cancer	Paclitaxel
Colorectal cancer	Resveratrol, curcumin
Gastric cancer	Sanguinarine, curcumin, paclitaxel
Glioma	Resveratrol
Hepatocellular cancer	Curcumin
Laryngeal squamous cell carcinoma	Paclitaxel
Lung cancer	Sanguinarine, silibinin, resveratrol
Nasopharyngeal carcinoma	Curcumin, paclitaxel
Non-small cell lung cancer	Paclitaxel, sanguinarine, silibinin
Ovarian cancer	Curcumin, paclitaxel, sanguinarine
Pancreatic cancer	Sanguinarine
Renal cell carcinoma	Curcumin, silibinin, genistein

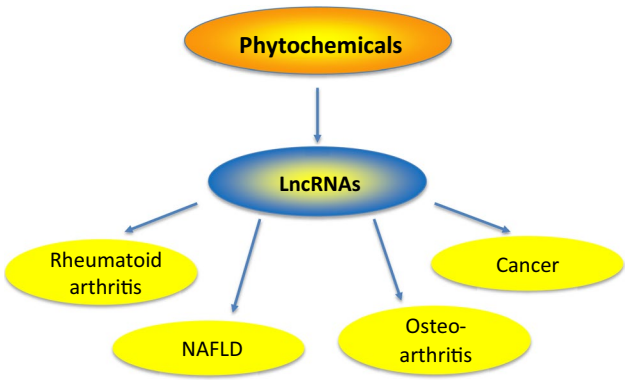

Fig. 1 A list of human diseases affected by phytochemicals through modulation of lncRNAs. NAFLD: nonalcoholic fatty liver disease

anacardic acid, and calycosin. In the following section, we have discussed the effects of phytochemicals on lncRNA expression in human disease models.

Curcumin

Curcumin (diferuloylmethane) is a yellow-color polyphenol derived from the yellow spice turmeric (*Curcuma longa*) [57]. The biological activities of this polyphenol have been reported against various human diseases including cancer, diabetes, cardiovascular disorders, obesity, and neurodegenerative diseases. This pleiotropic molecule can affect several signaling molecules such as adhesion molecules, enzymes, growth factors, inflammatory molecules, kinases, reductases, receptors, transcription factors, chemokines, DNA, RNA, and proteins involved in cell-cycle regulation, survival, and drug resistance [58]. Recent studies suggest that curcumin can also modulate lncRNAs in human disease models. The common lncRNAs modulated by curcumin include AF086415, AK056098, AK095147, AK294004, FLJ36000, GUCY2GP, H19, H2BFXP, HOTAIR, LINC00623, LOC100506835, MEG3, MUDENG, PANDAR, PVT1, RP1-179N16.3, and ZRANB2-AS2.

The oncogenic H19 is constitutively present in multiple myeloma [59] and in breast [60], gallbladder [61], esophageal [62], ovarian [63], and lung [62, 64] cancers. The expression of H19 also correlates with NF-κB activation [59, 65]. Curcumin suppressed the expression of oncogenic H19 in tumor cell lines such as Cal-27, Detroit-562, HCT-116, HeLa, Hep-2, and SW-620 without exerting any effect on normal cells [66]. Curcumin was also found to suppress H19 and c-Myc, and to enhance p53 expression in gastric cancer cells [67]. The polyphenol exhibited anti-proliferative activities and induced apoptosis in gastric cancer cells. Curcumin-induced p53 up-regulation and anti-proliferative effects were reversed by the ectopic expression of H19. When c-Myc was overexpressed, curcumin-induced down-regulation of H19 was reversed. It can be concluded that curcumin inhibits the proliferation of gastric cancer cells by negatively regulating the c-Myc/H19 pathway. The regulator of reprogramming (ROR) is an lncRNA that functions to regulate the activity and reprogramming of pluripotent stem cells. The activity of ROR is tightly regulated by stem cell related molecules such as SOX2, OCT4, and NANOG [68]. ROR is an oncogene with constitutive expression in multiple cancer types such as breast cancer [69], gallbladder cancer [70], nasopharyngeal carcinoma [71], pancreatic cancer [68], and prostate cancer [72]. Curcumin is reported to produce inhibitory effects on

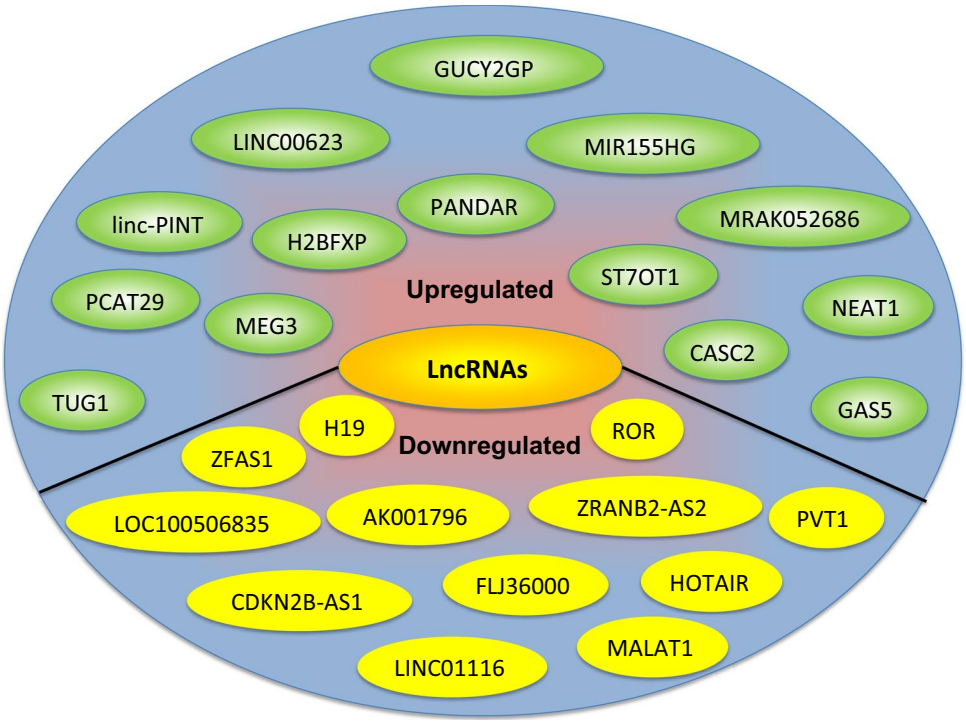

Fig. 2 A list of lncRNAs modulated by phytochemicals. *CASC2* cancer susceptibility 2, *CDKN2B-AS1* CDKN2B antisense RNA 1, *GAS5* growth arrest-specific 5, *GUCY2GP* guanylate cyclase 2G pseudogene, *H2BFXP* H2B histone family member X pseudogene, *HOTAIR* HOX transcript antisense RNA, *LINC00623* long intergenic non-protein-coding RNA 623, *LINC01116* long intergenic non-protein-coding RNA 1116, *linc-PINT* long intergenic non-protein-coding RNA-p53 induced transcript, *MALAT1* metastasis-associated lung adenocarcinoma transcript-1, *MEG3* maternally expressed gene 3, *MIR155HG* MIR155 host gene, *NEAT1* nuclear-enriched abundant transcript 1, *PANDAR* promoter of CDKN1A antisense DNA damage-activated RNA, *PCAT29* prostate cancer-associated transcript 29, *PVT1* plasmacytoma variant translocation 1, *ROR* regulator of reprogramming, *ST7OT1* ST7 overlapping transcript 1, *TUG1* taurine up-regulated gene 1, *ZFAS1* zinc finger antisense 1

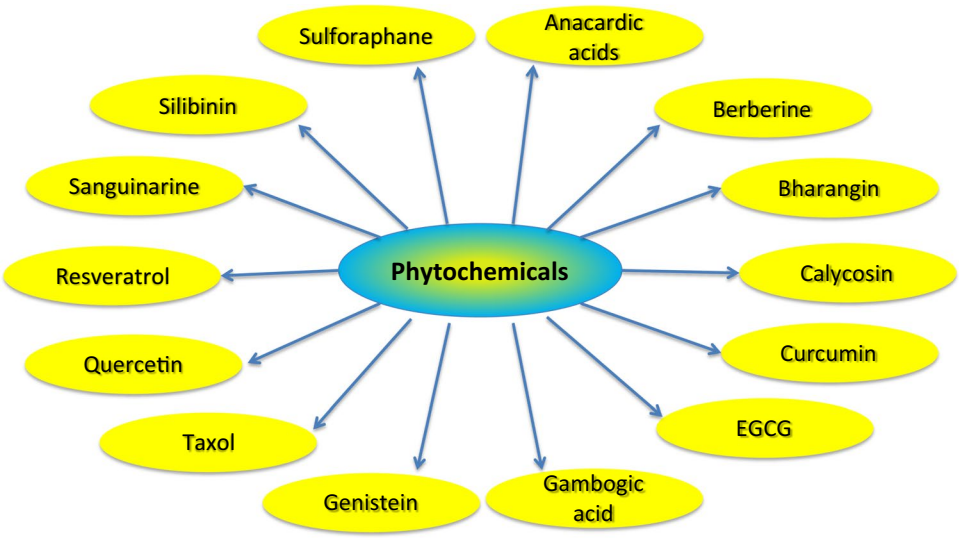

Fig. 3 A list of phytochemicals known to have the potential to target lncRNAs. EGCG: epigallocatechin gallate

prostate cancer stem cells by suppressing ROR expression [73]. Curcumin can also up-regulate linc-PINT, which is frequently down-regulated in acute lymphoblastic leukemia (ALL) [74] and suppresses the migration capacity of most cancer cells [75]. Growth arrest specific 5 (GAS5) is a tumor suppressor lncRNA with potential to induce apoptosis and suppress the proliferation of tumor cells [76]. The expression of this lncRNA is significantly enhanced during the growth

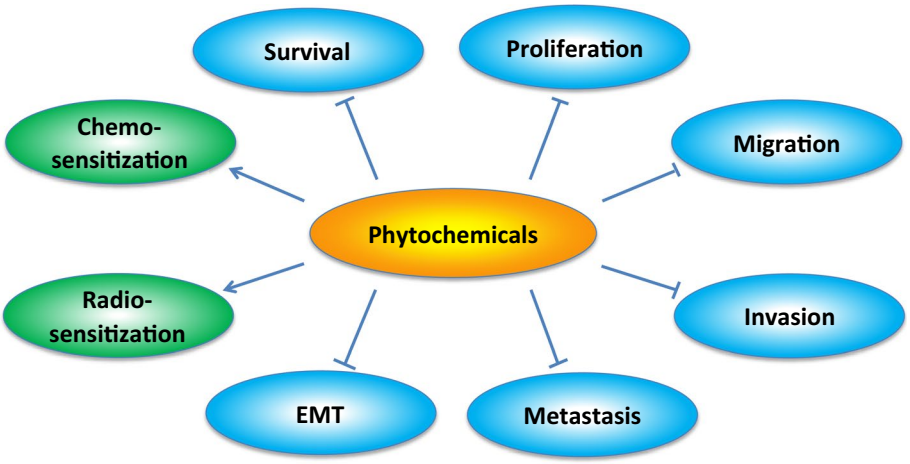

Fig. 4 The steps of tumorigenesis affected by phytochemicals through modulation of lncRNAs. EMT: epithelial-to-mesenchymal transition

arrest of the tumor cells [77]. Curcumin can also modulate GAS5 expression in breast cancer cells [78].

The promoter of CDKN1A antisense DNA damage-activated RNA (PANDAR) is an lncRNA with 1506 nucleotides in length [79]. With a function to promote proliferation and migration, this lncRNA is up-regulated in several cancer types including bladder, gastric, and colorectal cancers [80–84]. Whether PANDAR contributes to the efficacy of curcumin against colorectal cancer was investigated [85]. An identical expression pattern of PANDAR was observed in CRC tissues and in normal tissues. The proliferation of CRC DLD-1 cells was not affected by the knockdown of PANDAR. Curcumin at lower doses induced senescence and up-regulated PANDAR without any effect on apoptosis in DLD-1 cells. Curcumin's effect on apoptosis under the elevated level of PANDAR was investigated. The silencing of PANDAR enhanced apoptosis and attenuated senescence in curcumin-treated DLD-1 cells. Overall these results suggest that low-dose curcumin can induce PANDAR. Furthermore, PANDAR silencing can also switch cells from senescence to apoptosis partly by stimulating the expression of the p53-up-regulated modulator of apoptosis (PUMA). Further experiments will demonstrate the involvement of PUMA in PANDAR mediated apoptosis in CRC cells under curcumin treatment. HOX transcript antisense intergenic RNA (HOTAIR) is located at mammalian HOXC gene locus, and is associated with tumor progression and metastasis by binding and targeting polycomb repressive complex 2 [86]. Curcumin can suppress HOTAIR-induced migration of renal cell carcinoma (RCC) cells [87].

In certain cases, nanocurcumin has also been tested for its efficacy against lncRNA. For example, dendrosomal curcumin (DNC) with improved bioavailability [88, 89] can induce the tumor suppressor maternally expressed gene 3 (MEG3) in hepatocellular cancer (HCC) [90]. Under normal conditions, MEG3 is expressed at low level partly due to methylation of its promoter region. Although expressed at low level, MEG3 is known to stimulate p53, and can suppress proliferation, invasion, and migration of cancer cells [91]. The up-regulation in MEG3 expression by DNC was mediated through enhanced expression of miR-29a and miR-185 that down-regulated the expression of DNA methyltransferases (DNMTs) such as DNMT1, DNMT3A, and 3B. It was concluded that induction of DNA hypomethylation and MEG3 by DNC could be an effective choice for epigenetic therapy of HCC.

Curcumin is also known to sensitize cancer cells to chemotherapy and radiotherapy through modulation of lncRNA expression. Polycomb Repressive Complex 2 (PRC2) consisting of the Enhancer of Zeste Homolog-2 (EZH2) is reported to maintain the cancer stem cell population by regulating stemness-associated genes [92, 93]. EZH2 can interact with lncRNAs leading to resistance-associated phenomenon such as epithelial–mesenchymal transition and cancer stemness [94–98]. An interesting study was aimed to delineate the underlying mechanism of gemcitabine resistance in pancreatic ductal adenocarcinoma (PDAC) cell line [99]. The plasmacytoma variant translocation 1 (PVT1) is an oncogenic lncRNA that stabilizes the MYC protein [100]. Curcumin-sensitized chemoresistant PDAC cells were linked with the inhibition of EZH2 and lncRNA PVT1 [99]. Consistent with these observations, PVT1 is known to play a role in the sensitization of human pancreatic cancer cells to gemcitabine [98]. Curcumin also suppressed the spheroid formation by resistant cells and down-regulated several self-renewal driving genes, indicating the potential of this polyphenol against cancer stem cells (CSCs). Curcumin also attenuated gemcitabine-resistant tumor growth in vivo. Because CSCs contribute to chemoresistance [92, 101–105], the combination of curcumin and chemotherapy appears promising. However, further validation is required before these observations can be translated to the clinic. The extracellular vesicles (EVs) containing lncRNA and miRNAs are known to induce drug resistance in cancer cells [106–108].

Whether curcumin can overcome the cisplatin resistance in ovarian cancer was investigated [109]. The EVs from cisplatin-resistant ovarian cancer cells without or with curcumin treatment were analyzed. The EVs were found to induce drug resistance in ovarian cancer cells that were weakened by curcumin treatment. Furthermore, curcumin up-regulated MEG3 expression and induced demethylation in its promoter region. Curcumin also significantly reduced miR-214 in cells and in EVs that were associated with weakened chemoresistance. It was concluded that MEG3 could reduce drug resistance in ovarian cancer cells by suppressing EVs mediated transfer of miR-214. However, further studies using multiple cell lines and other preclinical models are required before these observations can be validated in the clinic.

Curcumin can radiosensitize nasopharyngeal CNE-2 carcinoma cells [110]. Furthermore, curcumin significantly up-regulated the expression of lncRNAs such as GUCY2GP, H2BFXP, and LINC00623, while the expression of ZRANB2-AS2, LOC100506835, and FLJ36000 IncRNA was down-regulated [110]. In another study, curcumin-induced radiosensitization of nasopharyngeal carcinoma cells was mediated partly through modulation of lncRNAs such as AF086415, AK056098, AK095147, AK294004, MUDENG, and RP1-179N16.3 [110].

In summary, curcumin's ability to modulate lncRNA expression has provided a new molecular basis for its biological activities. However, the studies have been performed mostly in the cancer models. Curcumin's potential to modulate lncRNAs in the other disease models remains to be explored. Future studies should also elucidate if curcumin can effectively regulate lncRNA expression in human subjects.

Resveratrol

Resveratrol is a polyphenolic phytoalexin derived from berries, grapes, peanuts, pistachio, plums, and white hellebore [111]. Although resveratrol exists in both *cis*- and *trans*-isomeric forms, the latter is of considerable interest [112]. The pleiotropic activities of this polyphenol originate from its ability to modulate several oncogenic signaling cascades [113–115].

The prostate cancer-associated transcript 29 (PCAT29) is a tumor suppressor lncRNA that is frequently down-regulated in prostate cancer tumors possibly through androgen signaling [116]. The lower levels of PCAT29 have also been observed in DU145 and LNCaP cells as compared to normal prostate cells [116]. This lncRNA is reported to inhibit proliferation and migration of prostate cancer cells [117, 118]. Whether resveratrol exhibits its anti-cancer activities against prostate cancer through modulation of PCAT29 was examined [116]. IL-6 was found to activate STAT3 and reduce the level of PCAT29 in both DU145 and LNCaP cells. The PCAT29 expression was enhanced by the inhibition of miR-21, which is downstream to STAT3. Resveratrol treatment stimulated the basal level of PCAT29 expression. Furthermore, the IL-6-induced suppression of PCAT29 was also reversed by resveratrol. Concomitantly, the viability of DU145 and LNCaP cells was also suppressed by resveratrol. Thus, the IL-6/STAT3/miR-21 pathway could regulate both the expression and function of PCAT29 and resveratrol induces expression and the functions of PCAT29 through the inhibition of this signaling pathway [116]. In another study, resveratrol modulated the expression of lncRNAs in lung cancer A549 cells [119]. Among various lncRNAs, AK001796 was overexpressed in lung cancer tissues and cell lines. However, resveratrol treatment reduced the expression of AK001796 in lung cancer cells. Furthermore, the knockdown of AK001796 was associated with a significant reduction in the viability of lung cancer cells and reduced tumor growth. The lncRNA metastasis-associated lung adenocarcinoma transcript 1 (MALAT1) is reported crucial for the progression of several cancer types including those of liver, renal, cervical, colorectal, bladder, and osteosarcoma [120]. Originally discovered as a prognostic marker for lung cancer patients, MALAT1 is now reported to be evolutionary conserved [121]. However, mice deficient in MALAT1 lack any obvious phenotype under normal physiological conditions [122, 123]. In CRC cell lines, resveratrol inhibited the invasion and metastasis of CRC cells through MALAT1-mediated Wnt/β-catenin signaling and its downstream targets [124]. Some other lncRNAs known to be up-regulated in response to resveratrol include MEG3, ST7OT1, NEAT1, and MIR155HG in glioma cell lines [125].

Paclitaxel (Taxol)

Paclitaxel (brand name Taxol) is an anti-cancer agent that was first isolated from the bark of the Pacific yew tree in 1971 [126]. Approved in 1993 for its anti-cancer activities, taxol is an antimitotic agent that blocks tumor growth by stopping cell division. Taxol has been found effective against several cancer types such as breast, ovarian, pancreatic, non-small cell lung cancer, and AIDS-related Kaposi sarcoma [127, 128]. During recent years, this antimitotic agent was also demonstrated to modulate lncRNAs expression.

The tumor suppressor GAS5 is significantly lower in breast cancer tissues than in the adjacent non-tumor tissues [129]. The decreased expression of GAS5 correlates with TNM stage and lymph-node metastasis of breast cancer. GAS5 expression was also significantly low in paclitaxel-resistant breast cancer cells. Furthermore, GAS5 was positively correlated with p21 but in a negative manner with CDK6. The overexpression of GAS5 in paclitaxel-resistant breast cancer cells suppressed the migration and invasion, and enhanced susceptibility to paclitaxel. In the

tumor-bearing nude mouse models, GAS5 overexpression enhanced the inhibitory effect of paclitaxel on tumor growth and lung metastasis by reversing the EMT. It was concluded that a decreased expression of GAS5 promotes lung metastasis of breast cancer by inducing EMT, thereby suggesting the therapeutic potential of this lncRNA against breast cancer [129]. In ERα-positive breast cancer cells, the high expression of H19 was correlated with paclitaxel (PTX) resistance [130]. H19 attenuated paclitaxel-induced apoptosis by inhibiting the transcription of BIK and NOXA (pro-apoptotic genes). Furthermore, H19 suppressed the promoter activity of BIK by recruiting EZH2 and by trimethylating the histone H3 at lysine 27. H19 was found to be one of the downstream target molecules of ERα. Overall, these observations suggest that the ERα–H19–BIK axis is crucial for the development of paclitaxel chemoresistance in ERα-positive breast cancer cells. One study was aimed to investigate the effects of lncRNA RP11-770J1.3 and transmembrane protein 25 (TMEM25) on paclitaxel-resistant human breast cancer (MCF-7/PR) cell line [131]. The parental MCF-7 cells (paclitaxel sensitive) were also used for the comparison. A higher expression of RP11-770J1.3 and TMEM25 was observed in MCF-7/PR cells. The MCF-7/PR cells were sensitized to paclitaxel after the gene silencing of RP11-770J1.3 and TMEM25. In agreement with these observations, the expression of MDR1/P-gp, MRP, and BCRP was also suppressed. Thus, RP11-770J1.3 and TMEM25 represent a novel target for enhancing the sensitivity of resistant breast cancer cells to paclitaxel. Similarly, MAPT-AS1 lncRNA can correlate with the growth, invasion, and paclitaxel resistance in ER-negative breast cancer cells [132]. The genetic polymorphisms of GAS5 can also predict the response of nasopharyngeal carcinoma patients to paclitaxel [133]. The inhibition of MA-linc1 enhances cell death in cancer cells induced by paclitaxel [134].

The RNA-sequencing in the A2780 ovarian cancer cell line and the A2780/PTX paclitaxel-resistant cell line was carried out [135]. Results indicated that five lncRNAs were up-regulated, while four lncRNAs were down-regulated in both multidrug-resistant ovarian and colon cancer cell lines. Furthermore, the lncRNA CTD-2589M5.4 was co-expressed with the multidrug-resistant genes (ABCB1, ABCB4, ABCC3, and ABCG2). Nuclear-enriched abundant transcript 1 (NEAT1) can act as both oncogene and tumor suppressor depending upon the cancer type [136, 137]. NEAT1 can also contribute to paclitaxel resistance of ovarian cancer cells partly by up-regulating ZEB1 expression and sponging miR-194 [138]. Some lncRNAs are dysregulated in paclitaxel-resistant lung adenocarcinoma cells as compared to parental A549 cells [139].

ZNFX1 antisense RNA 1 (ZFAS1) is known to act both as an oncogene and as a tumor suppressor in multiple cancer types [140–143]. ZFAS1 can modulate notch signaling and various other tumor-associated genes, and induce epithelial-to-mesenchymal transition in multiple cancer types [144–147]. The elevated expression of the lncRNA, ZFAS1, is observed in gastric cancer specimens as compared to the para-carcinoma tissues [135]. The knockdown of ZFAS1 can suppress the growth, proliferation, cell-cycle progression, migration, and invasion. Furthermore, the ZFAS1 gene silencing suppressed Wnt/β-catenin signaling and enhanced the sensitivity of SGC7901 gastric cancer cells to paclitaxel. Similarly, PVT1 is expressed at a higher level in human gastric cancer tissues than in adjacent non-cancerous tissues [148]. The expression level of PVT1 was also reported to be high in SGC7901 paclitaxel-resistant cells compared with that observed in SGC7901 cells [148].

The tumor suppressor TUSC7 can enhance the sensitivity of endometrial carcinoma to paclitaxel by targeting miR-23b [149]. Paclitaxel is also known to reduce the expression of CDKN2B-AS1, HOTAIR, and MALAT1 laryngeal squamous cell carcinoma [150]. PVT1 can affect the response of cervical cancer cells to paclitaxel by regulating EMT [151]. CCAT1 controls the sensitivity of nasopharyngeal carcinoma (NPC) cells to paclitaxel via miR-181a/CPEB2 axis [152]. Some other lncRNAs associated with paclitaxel resistance include H19 in breast cancer [153]; SNHG12 in NSCLC [152]; XR_938728, XR_947831, XR_938392, XR_948297, NR_036503, NR_073113, and NR_103801 in ovarian cancer [152]; LINC00672 in endometrial cancer [154]; n375709 in nasopharyngeal carcinoma [155]; HIF1A-AS2 and AK124454 in triple-negative breast cancer [156]; linc-ROR in breast cancer [157]; KCNQ1OT1 and ANRIL in lung adenocarcinoma [158]; and RP11-381N20.2 in cervical cancer [159].

Overall, these results suggest that lncRNAs contribute to paclitaxel resistance and, thus, could be targeted to enhance the sensitivity of cancer cells.

Epigallocatechin gallate

Epigallocatechin gallate (EGCG) is a type of catechin chiefly present in green tea. This catechin has been extensively studied for its potential health benefits by both preclinical and clinical studies [160–167]. The tea catechins have been closely linked with the maintenance of normal LDL-cholesterol level [168]. EGCG can modulate multiple cell signaling pathways in tumor cells [169, 170].

One study was aimed to elucidate the possible role of lncRNAs in the cholesterol modulatory effects of EGCG in hepatocytes [171]. When HepG2 cells were treated with EGCG, 15 genes related to cholesterol metabolism and 285 lncRNAs were dysregulated. Bioinformatic analyses revealed five matched lncRNA–mRNA pairs for five differentially expressed lncRNAs and four differentially expressed mRNA. The identification of lncRNA AT102202 and its

potential mRNA target, 3-hydroxy-3-methylglutaryl coenzyme A reductase (HMGCR) was of particular importance. The quantitative PCR analyses revealed a down-regulation in the mRNA level of HMGCR and an up-regulation in AT102202. Furthermore, silencing of AT102202 was associated with an increased expression of HMGCR. The authors of this study concluded that AT102202 is involved in the improvement of cholesterol metabolism by EGCG. However, further studies using the animal models are required before these claims can be translated to the clinic.

Platinum-based chemotherapy, such as cisplatin (cDDP), has been used for non-small cell lung cancer (NSCLC) patients [172]. Copper transporter 1 (CTR1) facilitates cDDP internalization in tumor cells [173–175]. The association of cDDP uptake with CTR1 levels has been confirmed by some studies [175, 176]. Interestingly, whereas CTR1 up-regulation can sensitize tumor cells to platinum drugs, its down-regulation contributes to resistance [175]. EGCG has been reported to induce CTR1 expression in ovarian cancer cells and mouse xenografts [177]. EGCG can also enhance the sensitivity of ovarian cancer cells to cDDP [177]. In another study, EGCG was found to up-regulate CTR1 expression and to increase platinum accumulation in NSCLC cells (H460, H1299, and A549), cDDP-resistant A549 cells and in a nude mouse xenograft model [156]. EGCG also enhanced the cell growth inhibitory effects of cisplatin both in vitro and in vivo. While miRNA hsa-mir-98-5p suppressed CTR1 expression, the lncRNA NEAT1 positively regulated CTR1 expression. The hsa-mir-98-5p harbors specific complementary binding sites for NEAT1. NEAT1 was found to compete with hsa-mir-98-5p and enhanced EGCG-induced CTR1 in NSCLC. Overall, these results suggest that NEAT1 plays a crucial role in sensitizing NSCLC cells to cisplatin. Thus, EGCG could be used as an effective adjuvant for lung cancer chemotherapy.

Genistein

Genistein is a dietary isoflavone known to modulate cell signaling pathways such as JAK/STAT, AKT, and Wnt pathway [178–181]. Genistein also acts as protein tyrosine kinase inhibitor and exhibits activities against multiple cancer types [182–187]. One study was aimed to investigate the mechanism by which the isoflavones such as calycosin and genistein exhibit activities against breast cancer [188]. Both genistein and calycosin inhibited proliferation and induced apoptosis in MCF-7 cells. However, calycosin was more effective as compared to genistein. Furthermore, both isoflavones decreased AKT phosphorylation and HOTAIR expression. Calycosin was concluded to be superior in inhibiting breast cancer growth in comparison to genistein. It was also concluded that the suppression of AKT phosphorylation and HOTAIR expression contribute to the anti-cancer activities of these isoflavones. However, more experiments are required to support these claims.

In renal cell carcinoma, genistein can suppress HOTAIR expression while up-regulating miR-141 expression [189]. MiR-141 has been inversely correlated with the tumorigenicity and invasiveness of several cancer types [190]. Conversely, the oncogenic role of HOTAIR has been demonstrated by some studies [191–193]. The observations that genistein down-regulates HOTAIR and up-regulates miR-141 further support the anti-cancer property of this soy isoflavone. In prostate cancer PC3 and DU145 cell lines, genistein down-regulated HOTAIR expression [194]. Furthermore, the gene silencing of HOTAIR was associated with a decrease in the proliferation, migration and invasion, while an induction in cell-cycle arrest and apoptosis was observed. The tumor suppressor miR-34a was also up-regulated by genistein in prostate cancer cells. Overall, up-regulation in miR-34a and suppression in HOTAIR may contribute to the anti-cancer activities of genistein against prostate cancer.

Silibinin

Silibinin is an active constituent of silymarin, which is derived from the seeds of milk thistle (*Silybum marianum*). Chemically, silibinin is a polyphenolic flavonolignan with potential against a variety of cancer types such as bladder [195, 196], brain [197], breast [198, 199], colon [200, 201], kidney [202, 203], lung [204, 205], pancreas [206], prostate [198, 207, 208], and skin [209, 210] cancers. The potential of silibinin against human bladder cancer cells was examined [211]. Silibinin significantly suppressed multi-steps of tumor development such as proliferation, migration, and invasion. Furthermore, this molecule also induced apoptosis in UM-UC-3 and T24 human bladder cancer cells. Silibinin also suppressed the actin cytoskeleton and PI3K/AKT signaling pathways, both of which cross-talk via *RAS* oncogene. Silibinin also reduced histone H3 lysine 4 (H3K4) trimethylation and H3 acetylation at the *KRAS* promoter suggesting the role of this agent in histone modifications. Furthermore, silibinin significantly attenuated the expression of oncogenic lncRNAs, HOTAIR, and ZFAS1 without any effect on MALAT1, MEG3, and GAS5. The use of wortmannin (PI3K inhibitor) suppressed HOTAIR expression in human bladder cancer cells [211]. Consistent with these observations, HOTAIR is linked with the recurrence of bladder cancer [212]. HOTAIR is also up-regulated by KRAS [213] and PI3K pathways [15]. Thus, silibinin may exert its effects through the modulation of oncogenic lncRNAs. It is also likely that multiple signaling pathways modulated by silibinin contribute to its activities against bladder cancer. Whether silibinin exhibits anti-cancer activities through

modulation of HOTAIR in other cancer types remains to be explored.

Emodin

Emodin, an active anthraquinone isolated especially from *Rhamnus frangula*, is known to exhibit anti-cancer activities by some preclinical studies [214]. Furthermore, emodin can sensitize resistant cancer cells to chemotherapeutic agents. This anthraquinone has also demonstrated potential against osteoarthritis (OA), which is a chronic disease involving adipose tissues, articular cartilage, ligaments, subchondral bone, synovium, and tendons [215]. Characterized by pain, joint dysfunction and deformity, OA constitutes the leading cause of disability and compromises patients' life quality [215–217]. The potential of emodin against OA was examined in vitro [218]. The murine chondrogenic ATDC5 cells were treated with lipopolysaccharide to mimic the OA model. The effects of emodin on viability, apoptosis, and release of cytokines (TNF-α, IL-6, and MCP-1) in LPS-treated ATDC5 cells were examined. The expression of taurine-up-regulated gene 1 (TUG1) lncRNA, and Notch and NF-κB signaling pathways were also examined in emodin-treated ATDC5 cells. The LPS stimulation induced a decrease in cell viability, an increase in apoptosis and pro-inflammatory cytokines expression, and alterations in the expression of apoptosis-related proteins. LPS-induced changes in these parameters were all mitigated by emodin in ATDC5 cells. While TUG1 was up-regulated, the NF-κB and Notch pathways were inhibited by emodin treatment. An up-regulation in TUG1 expression by emodin was found to inactivate Notch and NF-κB pathways. These observations provide a new mechanism for the therapeutic potential of emodin against OA. The previous studies have demonstrated that TUG1 functions as an oncogene in multiple cancer types [219–221]. For example, TUG1 modulates cancer cell proliferation and invasion by targeting miR-219, miR-145/ZEB1, and Wnt/β-catenin signaling pathways [222–224]. Whether emodin modulates the functions of TUG1 in cancer models remains to be elucidated.

Gambogic acid

Gambogic acid (GA) is a xanthonoid derived from the resin of Garcinia. This xanthonoid exhibits anti-inflammatory, antioxidant, antiviral, and parasiticidal activities [225]. GA also exhibit anti-cancer activities with minimal toxicity to normal cells [226–228]. Exposure of bladder cancer cells to GA induces apoptosis in bladder cancer cells by inhibiting EZH2 methyltransferase expression [229].

The lncRNA GAS5 negatively correlates with the clinical stage of bladder cancer [230]. Furthermore, GAS5 overexpression reduces viability and induces apoptosis in EJ and T24 bladder cancer cells. Mechanistically, GAS5 represses EZH2 transcription by direct interaction and recruitment of E2F4 to the EZH2 promoter. Moreover, GAS5-induced down-regulation in EZH2 was associated with overexpression of miR-101. Furthermore, GA induces GAS5 expression and produces pro-apoptotic effects in bladder cancer cells. Interestingly, GA-induced apoptosis in bladder cancer cells was suppressed by knockdown of GAS5. Overall these results suggest that GAS5 functions as a tumor suppressor by inhibiting EZH2 expression. In addition, induction of GAS5 by gambogic acid may contribute to its anti-cancer activities against bladder cancer.

Anacardic acid

Anacardic acid is a phenolic lipid chiefly present in cashew nuts. Chemically, anacardic acid is a mixture of saturated and unsaturated organic molecules [231]. This polyphenol has demonstrated potential against some cancer types including breast cancer [232–234]. The potential regulators involved in the activities of anacardic acid against ER-positive MCF-7 and triple-negative MDA-MB-231 cells was examined by next generation transcriptomic sequencing (RNA-Seq) and network analysis [233]. While 80 genes were dysregulated including lncRNA MIR22HG in MCF7 cells, 886 genes were identified in MDA-MB-231 cells in response to anacardic acid. The genes down-regulated by anacardic acid in both cell lines included SCD, INSIG1, and TGM2, while the up-regulated genes were PDK4, GPR176, and ZBT20. The molecular modeling indicated that anacardic acid could inhibit monounsaturated fatty acid biosynthesis in both cell lines and enhance endoplasmic reticulum stress in MDA-MB-231 cells. Furthermore, anacardic acid inhibited TNFα-induced NF-κB reporter activity in MCF-7 cells. Overall, this study uncovered new targets of anacardic acid that may contribute to its anti-proliferative and pro-apoptotic activities against breast cancer.

Berberine

Berberine is an alkaloid derived chiefly from herbs [235]. It has demonstrated potential against various conditions including cancer, diabetes, cardiovascular diseases, infectious diseases, and depression [236–240]. One study examined the therapeutic effects of berberine against nonalcoholic fatty liver disease (NAFLD), which is a common liver disorder [241]. Whether berberine can modulate the expression of mRNAs and lncRNAs in a high-fat diet (HFD)-induced steatotic animal model was examined. Berberine was found to reverse the expression pattern of a list of steatotic liver associated genes including 881 mRNAs and 538 lncRNAs. These observations suggest that berberine may produce a global effect on hepatic gene expression. Berberine was

found to regulate a list of genes related to liver metabolism and NAFLD. More specifically, Nrf2 was strongly correlated with the lncRNA MRAK052686 and both of these were down-regulated in the steatotic liver. Furthermore, berberine completely reversed the reduced expression of MRAK052686 and Nrf2. The protein-coding gene Zbtb20, which regulates glucose homeostasis harbor MRAK052686 in its 3′UTR region. Berberine prevented oleic acid-induced steatosis in human Huh7 cells by reversing ZBTB20 expression. Overall, these observations provide new mechanistic insights into the therapeutic effects of berberine against NAFLD.

Quercetin

Quercetin is a dietary flavonoid with potential anti-cancer activities [242, 243]. This flavonoid can also prevent and protect the oxidative stress and β-cell damage induced by streptozotocin in the rat pancreas [244]. The flavonoid has demonstrated potential in the management of arthritis [245], and can inhibit the release of macrophage-derived cytokines and nitric oxide [246].

Rheumatoid arthritis (RA), a chronic disease of the joint, is characterized by the proliferation of cytokines and chemokines producing synoviocytes [247]. RA compromises the expectancy and quality of life and is also a cause of atherosclerosis [248]. The hallmarks of RA are the expansion of fibroblast-like synoviocytes (FLS) and leukocytic infiltration of the synovium [249, 250]. In one study, quercetin decreased the viability and induced apoptosis in RAFLS [251]. Consistent with these observations, an increase in MALAT1 expression was observed after quercetin treatment. The knockdown of MALAT1 enhanced the activation of PI3K/AKT pathway and reduced apoptosis. It is likely that the induction of MALAT1 contributes to quercetin-induced apoptosis in RAFLS. However, more studies are required to support this claim.

Sanguinarine

Sanguinarine is an alkaloid with anti-microbial, anti-fungal, anti-inflammatory, and anti-tumor activities [252]. This alkaloid has demonstrated significant anti-cancer activities against non-small cell lung cancer [253], pancreatic cancer [254], gastric cancer [255], and breast cancer [256]. Conversely, the alkaloid can also produce carcinogenic effects [257]. One study investigated the possible anti-tumor activities and the underlying mechanism of sanguinarine's action against epithelial ovarian cancer [258]. Sanguinarine suppressed the viability, migration, and invasion, and induced apoptosis in SKOV3 cells. The alkaloid also induced the expression of cancer susceptibility candidate 2 (CASC2) lncRNA, the silencing of which reversed the effects of sanguinarine. While ovarian cancer tissues and cells expressed low levels of CASC2, an increased expression of eukaryotic translation initiation factor 4A3 (EIF4A3) was observed. EIF4A3 could bind to CASC2; the knockdown of EIF4A3 reversed the effects of sanguinarine plus CASC2 silencing. Sanguinarine also markedly reduced the activation of PI3K/AKT/mTOR or NF-κB activation cascades; both these effects were reversed by CASC2 silencing. Furthermore, the effects of sanguinarine plus CASC2 silencing on the modulation of NF-κB and PI3K/AKT/mTOR pathways were reversed by the EIF4A3 knockdown. Overall, these results suggest the anti-tumor activities of sanguinarine against epithelial ovarian cancer cells may be mediated through CASC2–EIF4A3 axis and/or PI3K/AKT/mTOR and NF-κB signaling pathways. Because CASC2 is well-known tumor suppressor with reduced expression in multiple cancer types [259–266], up-regulation of this lncRNA provides a potential avenue for anti-cancer drug development. That sanguinarine can up-regulate CASC2 further support its anti-cancer activities. Whether sanguinarine modulates CASC2 expression in cancer patients remains to be elucidated.

Sulforaphane

Sulforaphane (SFN) is an isothiocyanate group of organosulfur compounds obtained from the cruciferous vegetables [267]. In one study, normal human prostate epithelial cells and SFN-treated prostate cancer cells were subjected to whole-genome RNA-sequencing [268]. SFN modulated the expression of lncRNAs associated with cell-cycle regulation, signal transduction, and metabolism. Notably, the expression of LINC01116, which is an oncogene and over-expressed in several cancer types [268, 269], was significantly suppressed by SFN. The knockdown of LINC01116 significantly decreased the proliferation of prostate cancer cells and up-regulated the expression of genes involved in glycolysis (GAPDH), chromatin structure (H2AFY), and autophagy (MAP1LC3B2). The disruption of LINC01116 using CRISPR/CAS9 method suppressed the colony-forming ability of PC-3 cells by fourfold. The computational analyses indicated that LINC01116 could potentially interact with target genes through ssRNA:dsDNA triplexes. Overall, these results suggest that the modulation of lncRNAs by SFN may contribute to its activities against prostate cancer.

Bharangin

Bharangin is a diterpenoid quinonemethide derived from the roots of a medicinal plant, *Pygmacopremna herbacea* [270–272]. The parts of the plant are known to exhibit a range of biological activities [273–275]. The plant extract has also been shown to exhibit activities against breast cancer, leukemia, lymphoma, and multiple myeloma [276–279].

Recently, our group demonstrated that the diterpenoid can modulate the expression of long non-coding RNAs in breast cancer cells [60]. While the expression of tumor suppressor lncRNAs such as growth arrest specific-5 (GAS-5) and maternally expressed-3 (MEG-3) was induced, the expression of H19 (oncogenic lncRNA) was suppressed by the diterpenoid. We also observed that the diterpenoid suppresses the NF-κB activation induced by okadaic acid in breast cancer cells. It is likely that bharangin exhibits anti-cancer activities by modulating lncRNA expression and abrogating NF-κB activation. We are further exploring the in-depth mechanism for the activities of bharangin against breast cancer.

Conclusions and future prospects

Despite enormous expenses in the health sector, chronic diseases continue to affect millions of people worldwide. As most chronic diseases are caused by chronic inflammation, long-term treatment is required. The US-FDA has approved multiple drugs against chronic diseases such as steroids, statins, and metformin. However, the long-term use of these drugs is associated with numerous side effects. Moreover, these drugs are highly expensive and cannot be afforded by low-income and middle-income people. The phytochemicals derived from spices, fruits, vegetables, cereals, and medicinal plants have been consumed since ancient time. Thus, the safety of these agents is well proven. Moreover, these agents are readily available and produce minimum toxicity. Modern science has provided a molecular basis for the efficacy of these phytochemicals.

As discussed in this review, lncRNAs have emerged as a crucial player in the pathogenesis of chronic diseases with over 18,000 publications listed on PubMed database, most of which appeared during the last decade. The fact that lncRNAs exhibit cell/tissue/tumor-specific expression makes them potential target for the therapeutic development. However, lncRNAs are not very specific in the context of human diseases. For example, MALTA1 is dysregulated during multiple disease conditions such as cancer, cardiovascular diseases, and neurological disorders. During the last 5 years, phytochemicals have been shown to target lncRNAs. In most of the studies, the phytochemicals were found to up-regulate or down-regulate the expression of specific lncRNAs. Although most of the studies have been performed in cancer models, phytochemicals have also been demonstrated to modulate lncRNAs in the other disease models such as rheumatoid arthritis, osteoarthritis, and nonalcoholic fatty liver. In some cases, modifications have been performed to enhance phytochemicals bioavailability and efficacy against lncRNAs. Whether phytochemicals modulate lncRNAs in human subjects remains to be explored. The phytochemicals discussed in this review have been shown to hit several other disease-associated molecular targets. Because most chronic diseases are caused by dysregulation of multiple genes, phytochemicals possess promise against these diseases.

In summary, the discovery of lncRNAs has opened new avenue for the treatment of chronic human diseases. This has also provided a new molecular basis for the pleiotropic activities of phytochemicals. However, the in-depth mechanism by which phytochemicals modulate lncRNAs is lacking. Whether phytochemicals regulate copy number, subcellular localization, and protein-binding capacity of lncRNAs remains to be elucidated. Future studies in this direction would lead to a more deeper understanding of the beneficial effects of phytochemicals against chronic diseases. Future studies should also examine if phytochemicals target lncRNAs in normal cells. Eventually, this would lead to a more effective approach for the disease treatment.

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