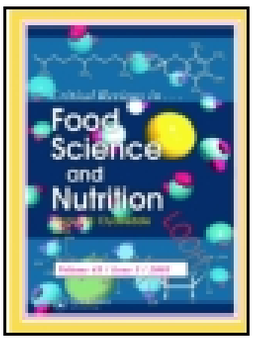

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REVIEW

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Targeting long non coding RNA by natural products: Implications for cancer therapy

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ABSTRACT

In spite of achieving substantial progress in its therapeutic strategies, cancer-associated prevalence and mortality are persistently rising globally. However, most malignant cancers either cannot be adequately diagnosed at the primary phase or resist against multiple treatments such as chemotherapy, surgery, radiotherapy as well as targeting therapy. In recent decades, overwhelming evidences have provided more convincing words on the undeniable roles of long non-coding RNAs (lncRNAs) in incidence and development of various cancer types. Recently, phytochemical and nutraceutical compounds have received a great deal of attention due to their inhibitory and stimulatory effects on oncogenic and tumor suppressor lncRNAs respectively that finally may lead to attenuate various processes of cancer cells such as growth, proliferation, metastasis and invasion. Therefore, application of phytochemicals with anticancer characteristics can be considered as an innovative approach for treating cancer and increasing the sensitivity of cancer cells to standard prevailing therapies. The purpose of this review was to investigate the effect of various phytochemicals on regulation of lncRNAs in different human cancer and evaluate their capabilities for cancer treatment and prevention.

KEYWORDS

Apoptosis; cancer therapy; long non-coding RNA (lncRNA); metastasis; natural product; phytochemical; proliferation

Introduction

As one of significant leading causes of human death, cancer have been attracted a great deal of attention owning to its rising morbidity and mortality rates (Liu et al. 2019). It is reported that the global burden of cancer in 2020 has grown to 19.3 million cases and 10 million deaths (Siegel et al. 2021). Female breast cancer had the highest incidence rate among other types followed by lung, colorectal, prostate and stomach cancers. However, lung cancer had the highest mortality and colorectal, liver, stomach and female breast cancers were respectively in the next orders (Siegel et al. 2021). Cancer is considered as a complex set of heterogeneous diseases connected with unlimited cellular growth which causes irregularity in cell proliferation and differentiation and finally through spreading the affected cells, other body tissues would be infected (Liu et al. 2019; Rathinasamy and Velmurugan 2018). Since different cancers are classified based on the affected tissue or organ, their signals and symptoms are significantly different depending upon involved organ, generating location and types of genetic mutation (Blackadar 2016). It is believed genetic abnormalities is the main inducer of cancer development (Whiteman and Wilson 2016). In fact, Human's tumorigenesis is mostly regarded as a multiphase process in which dysfunction of tumor suppressor genes or/and upregulation of oncogenes may lead to pre-cancerous cells transform into malignant ones (Chen and Zhu 2013; Reddy 2015). Various evidences in the area of molecular etiology of cancer have been revealed restriction of DNA damages or repairing them can prevent cancer cells from growing and eventually reduce cancer progress (Abdulridha et al. 2019; Chen, Wang, et al. 2016). Several attempts have illustrated variables such as age, sex, race, family history of cancer, obesity, physical inactivity, alcohol consumption, cigarette smoking and specific chemicals, radiations, and diet known as the most important risk factors of cancer occurrence, contribute substantially to cancer development via changing the expression of genes associating with cellular proliferation and differentiation (Karimi et al. 2014; Wu et al. 2016). In addition to genetic anomalies, epigenetic transformation including DNA methylation/demethylation, histone acetylation/deacetylation, transcription ingredients and post-transcriptional modulators namely RNA-binding proteins, micro RNA (miRNAs), circular RNAs (cirRNAs) and long non-coding RNAs (lncRNAs) have a crucial role in the cancer progress (Verma et al., 2014). Currently, the most prevalent therapeutic approaches for management of cancer are chemotherapy together with surgery, radiotherapy and combination therapy. In spite of impressive developments in the traditional method of cancer treatment, sufferings still not favorably respond to therapeutic procedures (Mansoori et al. 2017). Hence, introducing

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practical novel targets and treatments are of considerable importance.

However, Numerous investigations, comparing functions of cancer cells with their normal equivalent, have demonstrated alterations in lncRNA expression may affect gene expression and consequently, neoplastic transformation would be possible (Huarte 2015). It is proved around 2% of entire human genome is coded for proteins or regulatory operations and about its 90% remains as non-coding RNAs (ncRNAs) (Kung, Colognori, and Lee 2013). Initially, they were regarded as junk or noise of the transcription process owning to have any roles in protein production (Palazzo and Lee 2015). However, in parallel with identifying human genomic sequences, pivotal functions of ncRNAs as regulator of various biological process have been disclosed (Guttman and Rinn 2012). Based on their size, ncRNAs are divided into two general categories as small non-coding RNAs (sncRNAs) with less than 200 nucleotides in length and long non-coding RNA with more than 200 nucleotides in length without any limitations in open reading frames (ORF) (Harrow et al. 2012). sncRNAs are more split into microRNAs (miRNAs), short interfering RNAs (siRNAs), and piwi-interacting RNAs (piRNAs). Similar to sncRNAs such as miRNAs, acting as a tumor suppressor or an oncogenic factor, lncRNAs are related to human disorders including cancer due to their identical role in cellular expression and also their subcellular positioning (Cabili et al. 2015). In spite of well-known roles of miRNA in cancer pathogenesis, less is recognized about lncRNAs. Since lncRNAs control numerous cellular functions particularly gene expression and additionally have a prominent role in various cancer types, they have been considered as a noteworthy target for cancer treatments.

Recently, phytochemicals extracted from various plant sources such as fruit, vegetable, spices, cereal, etc., have revealed a great potential against cancer through targeting lncRNAs (Bishayee and Sethi 2016). Various observations have suggested phytochemicals as cost-effective and safe compounds, can regulate various cellular signaling pathways (Reddy, Odhav, and Bhoola 2003). Phytochemicals can alter regulation of lncRNAs via the intervention in functions of miRNAs, transcription factors, protein kinases, and enzymes (Hasanpourghadi et al. 2017). Several studies have reported phytochemicals have illustrated therapeutic potentials against some cancer types through downregulating the expression of oncogenic lncRNAs or upregulating the expression of tumor suppressor lncRNAs (Mishra et al. 2019). Furthermore, targeting lncRNAs by different phytochemicals can prevent cancer cells from proliferation, survival, invasion, metastasis, angiogenesis and epithelial to mesenchymal transition (EMT) (Saghafi et al. 2019). The purpose of the present investigation was to review the experimental reports that have considered the influence of phytochemicals/lncRNAs platforms on various mechanisms involving in cancer incidences and development.

Long non-coding RNAs biogenesis and function

Biogenesis of lncRNAs is a phenomenon depending on the type and growth phase of each cell. In respect of their biogenesis and structure, messenger RNAs (mRNAs) and lncRNAs are more similar than being different. However, lncRNAs own individual characteristics that make them distinguishable from mRNA such as polyadenylation of 3′-terminal, capping of 5′-terminal via 7-methyl guanosine (m7G), absence of translated ORFs, *cis*-regulatory functions, intron splicing and patterning of nucleic acid polymerization (Figure 1a) (Statello et al. 2021).

Transcription and processing of long non-coding RNAs

In comparison with mRNAs, a considerable quantity of lncRNAs is restricted in nucleus (Tian and Manley 2017). The results of dissection of the mRNAs and lncRNAs have demonstrated lncRNAs gens are less protected and expressed and also own comparatively fewer exons in proportion with mRNAs (Quinn et al. 2016). Although a low extent of lncRNAs is probably associated with repressive histone modifications, their transcription procedures is defined by their other distinctive qualities (Melé et al. 2017). Remarkable proportions of lncRNAs are transcribed by phosphorylation-dysregulated Pol II (Pol II). These types of lncRNAs are less spliced through co-transcription; therefore, termination of transcription in such genes is not determined by polyadenylation signals that causes lncRNAs to accumulate temporally on the chromatin and finally they are degraded by RNA exosome (Figure 1b) (Schlackow et al. 2017).

These procedures represent the reasons of existing parts of lncRNAs in the nuclear and it can be inferred that in order to great accumulation of lncRNAs in particular types of cells, functional lncRNAs ought to leave the process of nuclear monitoring. Nevertheless, some chromatin-associated lncRNAs are frequently not the target of the nuclear monitoring process. Certain chromatin- localized lncRNAs encompass high binding sites of U1 small nuclear RNA which engage U1 small nuclear ribonucleoprotein (U1-snRNP) to transcriptionally recruited Pol II, leading to connecting the great number of ncRNAs to chromatin (Figure 1c) (Yin et al. 2020). Eliminating the operation of elongation factor SPT6 associated with Pol II may lead to the presence of some lncRNAs on chromatin. Lack of SPT6 cause trimethylated histone H3 to redistribute at Lys36 (H3K36me6; a sign indicating active transcription) from protein coding genes to lncRNAs ones which eventually may elevate the transcription of lncRNAs. Simultaneously, loss of SPT6 disrupts the contributions of chromatin of the transcription termination complex, resulting in gathering of long non-coding transcripts on chromatin in the part of damaged R-loops of DNA (Nojima et al. 2018).

In comparison with mRNAs, lncRNAs are less systemically spliced, establish fewer internal splicing signals, have the further distance between 3′ splice site and branch point and also differential expression of their specific splicing regulators leads to most lncRNAs remain in the nuclear (Figure 1d) (Melé et al. 2017). Additionally, lncRNAs frequently possess inserted sequence patterns that can engage specific nuclear factors contributing to the nuclear

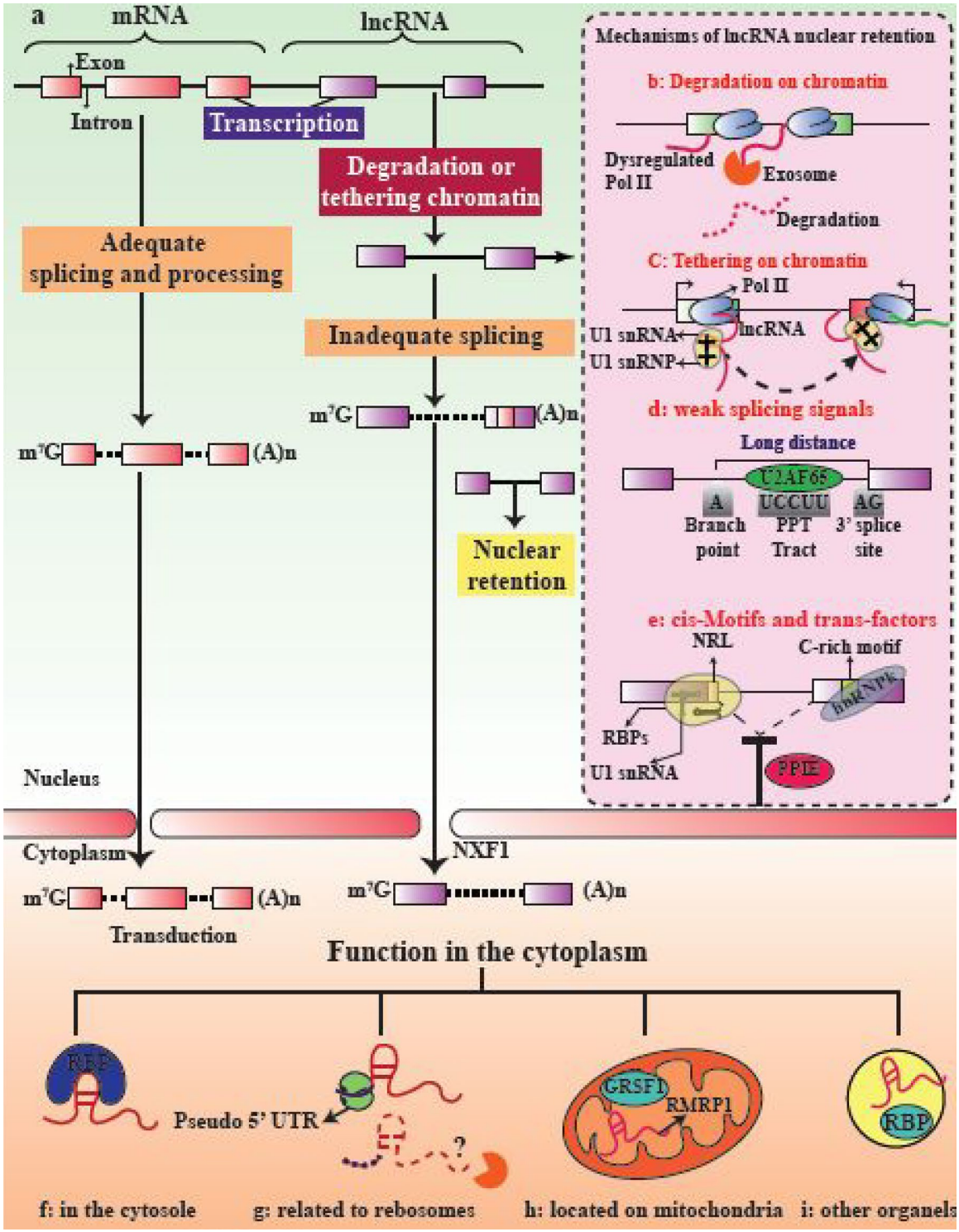

Figure 1. The biogenesis process of lncRNA. **a)** Common procedures of lncRNAs in nucleus and cytoplasm; **b)** transcription of lncRNAs on chromatin via dysregulated RNA polymerase II. **c)** tethering of lncRNA on chromatin as a consequence of association of lncRNAs enjoying U1 small nuclear RNA (U1 snRNA) part with RNA polymerase II by employing U1 small nuclear ribonucleoprotein (U1 snRNP); **d)** weak splicing signals as a result of the longer sequence between the branch point and the 3′ splice site; **e)** involvement of cis-motifs and trans-factors in unclear localization of lncRNAs; **f)** interaction of lncRNAs with different RBPs; **g)** association of lncRNAs with ribosome in cytoplasm by pseudo 5′ untranslated regions (UTRs); **h)** assortment of some lncRNAs into mitochondria via undisclosed processes; **i)** isolation of several lncRNAs in other organelle (shapes adapted from Statello et al. 2021).

localization and action of lncRNAs (Figure 1e). For instance, the lncRNA maternally expressed 3 (MEG3), in association with U1 snRNP, enjoys a 365-nuclear nucleotide retention component which maintain MEG3 in the nucleus (Azam et al. 2019). Furthermore, resent studies have demonstrated a C-rich pattern acquired from Alu repeated elements that can stimulate the lncRNAs nuclear localization via their connection with a complex nuclear protein of heterogeneous nuclear ribonucleoprotein K (hnRNPK) (Figure 1e) (Lubelsky and Ulitsky 2018). Therefore, it can be concluded the

nuclear restriction of lncRNAs are modulated at different stages of transcription, processing and nuclear export by *cis*- and *trans*-functions.

Export of long non-coding RNAs to the cytosol

A high fragment of lncRNAs exported to the cytosol, operationally undergoes processing and export pathways similar to mRNAs. Long A/U-rich transcripts owning one or few exons are exported to the cytosol via a nuclear RNA export factor 1 (NXF1) pathway. In fact, because of having fewer exons than mRNAs, lncRNAs prefer to select this pathway (Zuckerman et al. 2020). Arriving in the cytoplasm, lncRNAs probably encounter particular subdividing procedures that allocate different lncRNAs to certain organelles or are portioned in the cytoplasm and relates to different RNA-binding proteins (RBPs) (Figure 1f) (Carlevaro-Fita et al. 2016). Specific *cis* components such as pseudo-5′ untranslated parts are associated with localization of lncRNAs with ribosomes (Figure 1g).

Degradation of lncRNAs connected with ribosomes may be promoted by a type of translational process which is unknown. However, the investigations into the human mitochondrial transcriptomes suggested that RNA exported to the cytoplasm may be collected in mitochondria (Statello et al. 2021). For example, the RNA section of mitochondrial RNA-processing endoribonuclease (RMRP) is originated from RBP HuR in the nucleus exported to the cytoplasm through exportin 1. Upon appearing at mitochondria, RMRP participates in an interaction with G-rich RNA sequence-binding factor 1 (GRSF1) leading to accumulation of RMRP at mitochondria (Figure 1h) (Noh et al. 2016). Also, studies on the RNA motif of human blood exosome have disclosed exosomes contain numerous lncRNAs. It is assumed the underlying mechanism of lncRNAs sorting into exosomes is their binding to RBPs (Figure 1i) (Li, Li, et al. 2018).

Long non-coding RNAs functions

As mentioned previously, greater part of lncRNAs are located in the nucleus, but some of them have been founded in cytoplasm (Chi et al. 2019). Furthermore, exosomes by intercellular trafficking can transfer lncRNAs to contagious cells and also serum (Qu et al. 2016). lncRNAs, based on their position in the genomes, are classified into four groups: (1) the intergenic lncRNAs that their transcriptional units (TU) are located between two coding genes; (2) the intronic lncRNAs that are settled in an intron without any overlap with exons; (3) sense lncRNAs, which have an overlap with an axon of a different transcript in the similar direction; (4) antisense lncRNAs that are overlapped with an axon of another transcripts at the 5′ (head to head) or 3′-ends (tail to tail); (5) bidirectional lncRNAs launching in different direction of either promotor or enhancer and eventually producing enhancer-related RNAs (eRNAs) or promoter-related long RNAs (plRNAs) (Figure 2). Moreover, according to their roles, lncRNAs are basically categorized into three classes as nonfunctional lncRNA that are possibly to be as a consequence of transcriptional noise; lncRNAs that their transcriptional activity is adequate for their function but their transcripts are not essential; and functional lncRNAs that have the capability of regulating gene expression in a *cis*- or *trans*-manner (Kornienko et al. 2013; Ulitsky and Bartel 2013). Based on recent studies, functional lncRNAs are involved in up-regulation and downregulation of certain gens through various molecular mechanisms of scaffold, decoy and guide (Figure 3).

The scaffold process is related to epigenetic modulations including chromatin remodeling or histone modification, the decoy process is associated with transcription and translation inhabitations as well as RNA-RNA interactions, the guide mechanism controls precursors of medium-, small- and - and micro-RNAs and various RNAs processes

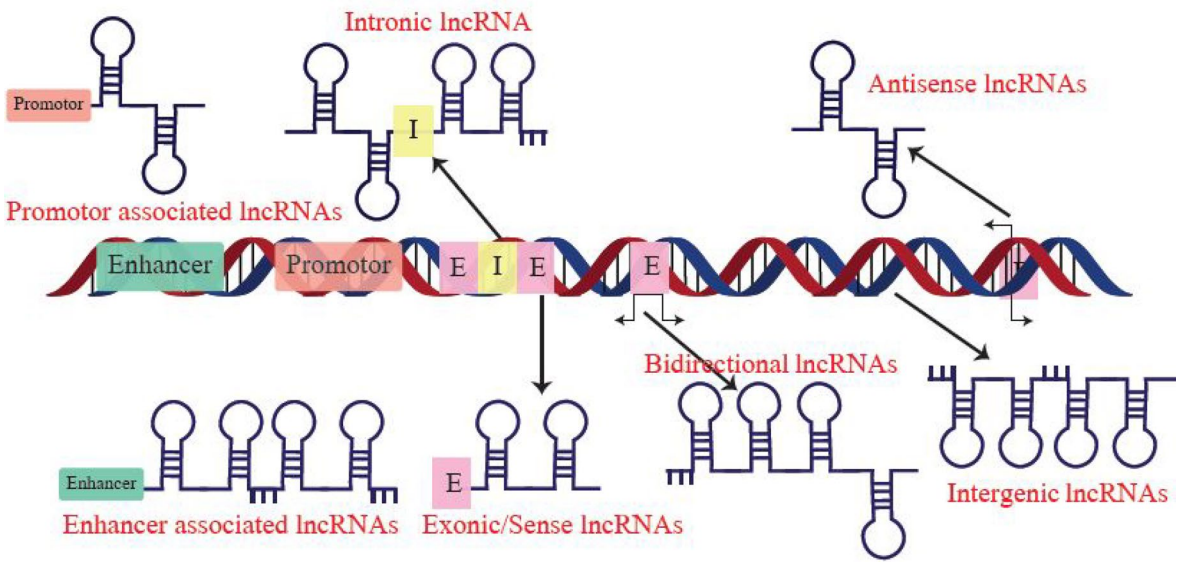

Figure 2. Classification of lncRNAs based on their positions.

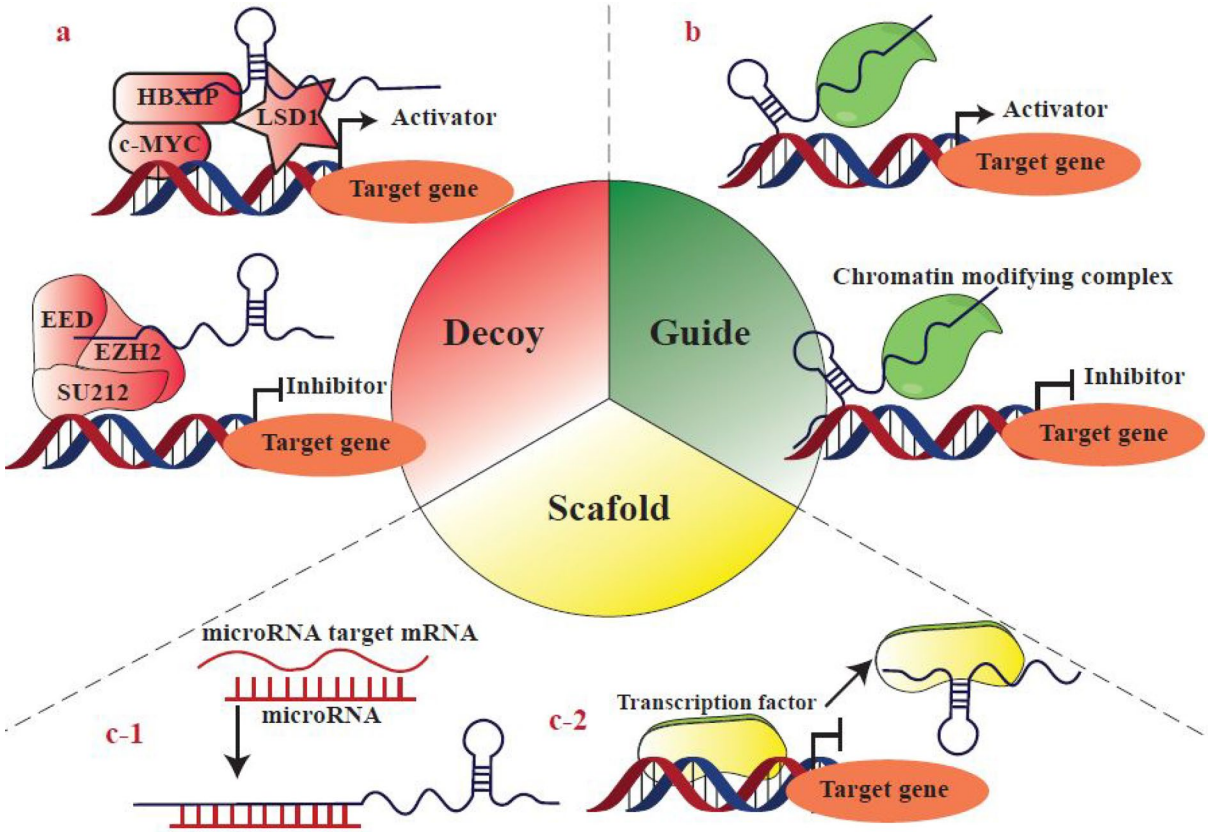

Figure 3. Various function of lncRNAs. **a)** lncRNAs act as a scaffold to trigger formation of chromatin remodeling complexes; **b)** lncRNAs serve as a guide for transcription factors toward particular genomic positions in order to modulation of gene expression; **c-1)** lncRNAs function as a sponge to inhibit miRNAs from binding to mRNA target; **c-2)** lncRNAs perform as a decoy, interact with numerous proteins such as transcription factors and detached them from chromatin.

such as splicing, editing, turnover and degradation and finally the molecular signaling machinery by which miRNA regulation and translation and transcription activation for gene expression are conducted (Dahariya et al. 2019). Additionally, there are other various mechanisms by which lncRNAs manage cellular operations such as grafting antisense transcripts onto overlapping sense ones to trigger alternative splicing, Dicer activation as a result of sense-antisense grafting causing siRNA to produce in the cells and attaching to the particular proteins to change the function or localization of cells (Wilusz, Sunwoo, and Spector 2009).

The role of long non coding RNA in cancer progression

As previously declared, convincing evidences have revealed lncRNAs are one of the chief modulators of gene expression in the context of cell proliferation, segregation, movement and survival. Since, altered functionalities of lncRNAs are coupled with cancer progress and metastasis, it is claimed they are credible biomarkers in identification and treatments of different cancers (Figure 4) (Sanchez Calle et al. 2018). A summary of the roles lncRNAs in various types of cancer have been presented in Tables 1 and 2.

Role of long non-coding RNAs in epigenetic processes

Recent research has presented lncRNAs stimulate structural changes in chromatin through intrachromosomal (*cis*-modulation) and interchromosomal genes (*trans*-modulation). Furthermore, the interaction between lncRNAs and chromatin, promoting the histone modification, regulates the gene expression in both *cis* and *trans* manners (Khalil et al. 2009). As about 38% of expressed functional lncRNAs of human genome are physically bound to various modified chromatin complexes, lncRNAs by assisting chromatin remodeling are able to regulate gene expression (Rathinasamy and Velmurugan 2018). The other mechanisms by which lncRNAs play their roles in the gene expression processes are eliminating regulatory proteins and transcription elements from chromatin, employing chromatin modifier factors in both *cis* and *trans* genes; boosting combinational activities of several transcript components, proceeding the arrangements of numerous proteins as a scaffold in order to generate ribonucleoprotein complexes to trigger histone modification, interacting with DNA methyltransferase enzymes to induce DNA methylation in both *cis* and *trans* genes (Wang and Chang 2011; Zhao, Sun, and Wang 2016). Considering the prominent roles of lncRNAs as epigenetic modulators, recruiting them in cancer therapeutic interventions may be a promising approach.

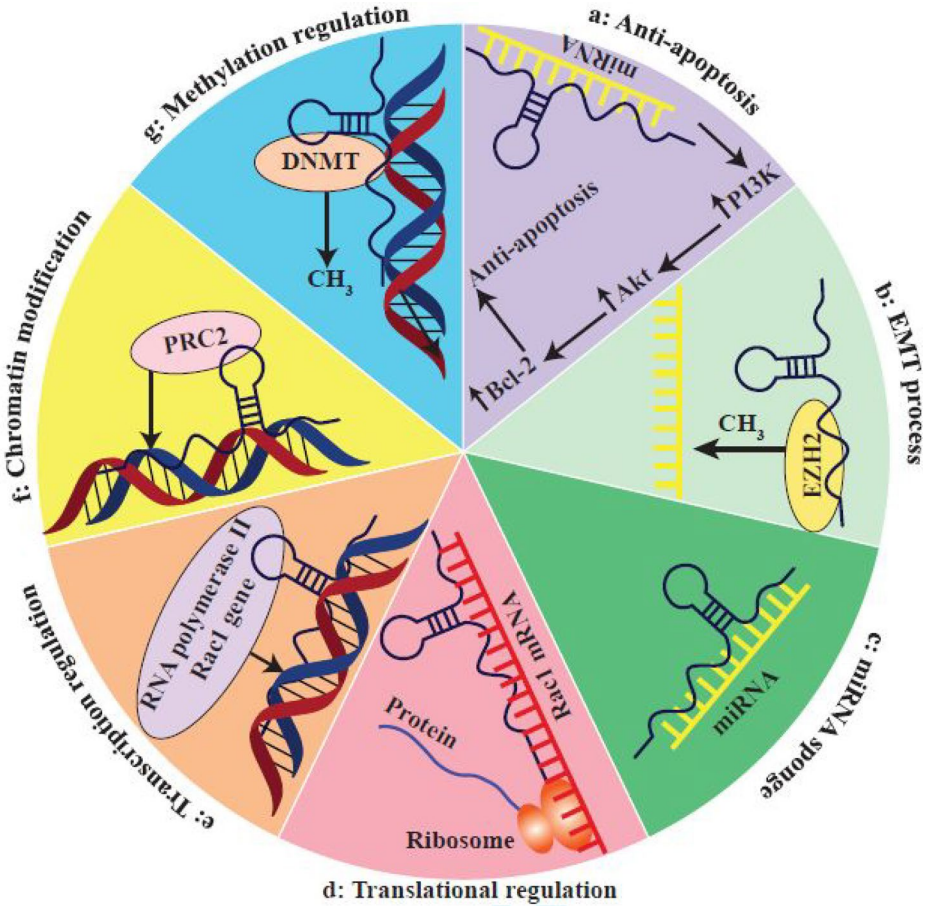

Figure 4. Different roles of lncRNAs in cancer. a) lncRNAs present a crucial role in apoptosis and change the level of miRNAs by which inhibit apoptosis induction; b) lncRNAs promote EMT process through interacting with EZH2 and increasing levels of H3K27me3 on miRNA; c) lncRNAs operate as miRNA sponge and opposite their function as an oncogene factor; d) lncRNAs change gene expression in translation levels; e) lncRNAs alter regulation of genes in transcriptional levels, f) lncRNAs can change gene regulation via association with chromatin modifying complexes; g) lncRNAs interact with different types of DNMT and interfere with DNA methylation process.

Table 1. Tumor suppressor functions of lncRNAs in various cancers.

LncRNAs	cytoband	Type of cancer	Related genes or miRNAs	Functions and Outcomes	References
MEG3	14q32.3	Breast, Gastric, Liver, Lung, Ovarian, Pancreatic,	↑: PTEN, QKI-5, SOX7, E-cadherin ↓: miR-21, PI3K/Akt, miR-9-5p, miR-21-5p, N-cadherin, Vimentin and Snail, β-catenin, PKM2, ki67, PCNA, MMP-2, MMP-9	Stimulation of apoptosis, prevention of cellular proliferation, migration and invasion, improvement of chemo-sensitivity, Suppressed glycolysis.	(Ma et al. 2018; Zheng, Li, et al. 2018; Dan et al. 2018; Wang, Shen, et al. 2017; Wu, Niu, et al. 2019; Zhu et al. 2019)
GAS5	1q25.1	Breast, colorectal, cervical, Gastric, Glioma, lung, Melanoma, Pancreatic, ovarian, osteosarcoma	↑: p21, PTEN, FOXO1 ↓: β-catenin/Wnt, Akt/mTOR, PI3K/Akt, miR-135b, IL-10, VGFA, NF-κB, miR-196a-5p, miR-103	Reduction of tumor growth and proliferation, triggered apoptosis, inhibited metastasis and invasion, arresting cell cycle.	(Li, Zhang, et al. 2017; Dong, Zhang, et al. 2019; Zhao et al. 2017; Song et al. 2019; Wen et al. 2017; Cai et al. 2017; Fotouhi Ghiam et al. 2017)

Role of long non-coding RNAs as tumor suppressor

Various studies have depicted the tumor suppressor role of lncRNAs is mostly associated with p53 pathway. p53, as one of the most significant tumor suppressor proteins, have a pivotal function in modulating the stability of genome. In order to adjust its downstream target genes, p53 attaches to particular p53 response element (p53RE). Since numerous investigations have announced p53RE is located in the genomic segment encoding lncRNAs, it encourages the possible functions of lncRNAs as a tumor suppressor (Liu et al. 2013; Sánchez et al. 2014). Additionally, it has been identified that various lncRNAs such as lncRNA-p21, loc28159, PANDA, TUG-1 and lncRNA-RoR have an active role in modulating the expression of genes participating in the p53 pathway (Zhang et al. 2013). An obvious example of the mentioned process is regulating the expression of p53 via a post-transcriptional procedure by a type of lncRNAs known as MT1JP. In this way, MT1JP reacts to TIAR, a kind of RNA binding protein, to develop the

Table 2. Oncogene functions of lncRNAs in various cancers.

LncRNAs	cytoband	Type of cancer	Related genes or miRNAs	Functions and Outcomes	Reference
CCAT1	8q24.21	Acute Myeloid Leukemia, Cervical, Multiple Myeloma, Melanoma, Osteosarcoma, Pancreatic, Retinoblastoma, Thyroid.	↑: c-Myc, Cyclin D1, Wnt/βcatenin, cyclin B1, VEGF, PI3k/Akt, MAPK, PIK3IPI, HOXA1 ↓: miR-148a, miR-33a. miR-181a-5p, miR-155, miR-143	Triggered cell proliferation, viability, migration and invasion and angiogenesis.	(Zhao and Cheng 2017; Yang, Wang, et al. 2018; Lv, Jia, and Chen 2018; Chen, Wang, et al. 2018; Chen, Wang, et al. 2016; Wang, Shen, et al. 2017; Yu et al. 2016)
H19	11p15.5	Breast, Cholangiocarcinoma, Colon, Gallbladder, Melanoma.	↑: IL-6, FOXM1, STAT3, DNMT1, NF-κB, PI3K/Akt, E2F3, Ras/MAPK ↓: miR-342-3p, miR-152, miR-106a-5p	Induction of inflammatory and oxidative stress, Enhancement of cell proliferation, migration and invasion,	(Yang, Wang, et al. 2018; Luan et al. 2018; Liao, Zhao, and Yang 2018; Li, Hao, et al. 2019; Li, Zhang, et al. 2017; Wang, Ma, et al. 2016; Wang, Ma, et al. 2016)
HOTAIR	12q13.13	Bladder, Cervical, Colorectal, Endometrial, Glioma, Melanoma, Nasopharyngeal Carcinoma, Osteosarcoma, Ovarian.	↑: cyclin J, Wnt/β-catenin, gelatinase, VEGF, glutaminase ↓: p53, miR-205, miR-203a-3p, miR-646, miR-15b, miR-126-5p, miR-206, miR-454-3p	Promotion of cell proliferation, invasion and migration, reduction of autophagy and induction of radio-resistance and chemo-resistance	(Bao et al. 2017; Chang, Guo, et al. 2018; Guo et al. 2019; Liu, Deng, et al. 2018; Sun et al. 2018; Sun et al. 2015; Tang et al. 2013; Zhou et al. 2018)
HULC	6p24.3	Colon, Glioma, Liver, Nasopharyngeal, Ovarian, Prostate.	↑: PI3K/Akt, RTKN, N-cadherin, vimentin, LC3 ↓: p53, p21, PTEN, E-cadherin, miR-125a-3p, miR-107, miR-15a, miR-613	Contribution in tumor growth, invasion and metastasis, stimulation of radio resistance, reduction of autophagy, promotion of angiogenesis	(Bao et al. 2017; Zhu et al. 2016; Zheng, Li, et al. 2018; Xin et al. 2018; Chen, Wang, et al. 2018; Chu, Xu, and Su 2019; Dong, Zhang, et al. 2019)
MALTA1	11q13.1	Colorectal, Hepatocellular, Lung, Oral, Osteosarcoma, Ovarian, Thyroid.	↑: RET/Akt, Bcl-2, cyclin D1, FGF2, NF-κB ↓: miR-216b, miR-101, p62, NOTCH1, Bax, miR-34a, miR-124	Promotion of chemo-resistance, Hamper apoptosis and autophagy	(Wu et al. 2018; Zhou et al. 2015; Huang et al. 2017; Bai et al. 2018; Chen, Wang, et al. 2018; Si et al. 2019; Yuan et al. 2016)
NEAT	11q13.1	Bladder, Colorectal, Gastric, Lung, Osteosarcoma, Ovarian.	↑: IGF-2, DNMT, snail, CDK4, cyclin D1, MMP2, STAT3, Akt, Bcl-2, Wnt/β-catenin ↓: let-7a, E-cadherin, miR-34a-5p, miR-506, Bax, miR-214-3p	Repressed apoptosis, induction EMT process, improve cell migration, proliferation and metastasis.	(Chen, Wang, et al. 2018; Peng, Wang, and Fan 2017; Tan et al. 2019; Ding et al. 2017; Li and Cheng 2018; Qi et al. 2018)
PVT1	8q24. 21	Bladder, Cervical, Gastric, Glioma, Hepatocellular, Lung, Nasopharyngeal Ovarian, Prostate.	↑: SOX2, EZH2, TWIST1, Bcl-2, VEGFC, HIF-1α, VEGFA, STAT3 ↓: miR-186, miR-128, miR-200b, miR-195	Correlation with cell proliferation and invasion, induction of cell cycle progress, angiogenesis and migration, acceleration of EMT process, Suppressing apoptosis	(Zhao et al. 2018; Wang et al. 2020; Du et al. 2019; Yu, Longfei, et al. 2019; Chang et al. 2018; Zhang, Zhang, and Liu 2016; Zou et al. 2018)
SNHG1	11q12.3	Colon, Gastric, Glioma, Hepatocellular, Neuroblastoma, Osteosarcoma, Prostate.	↑: CDK7, Wnt/β-catenin, DNMT1, c-Myc, cyclin D1, MATR3, NUAK1 ↓: E-cadherin, miR-195, miR-199a-3p, miR-577, miR-145-5p	Inhibited apoptosis, stimulation of cell proliferation, migration, metastasis and invasion	(Lan and Liu 2019; Hu et al. 2017; Wang, Shen, et al. 2017; Jiang, Chen, et al. 2018; Yang et al. 2019; Li, Zhang, et al. 2017; Yang, Wang, et al. 2018)
UCA1	19p13.12	Bladder, Gallbladder, Gastric, Glioma, Hepatocellular, Lung, Prostate, Thyroid.	↑: mTOR/STAT3, EZH2, ERK, FGFR1, Hippo JNK, cyclin D1, MAPK1, TGF-β, PI3K/Akt ↓: E-cadherin, p21, miR-143, miR-216b, miR-122	Stimulation of glucose metabolism, promotion of aggressive radio resistant, induction of tumor growth and metastasis, progress EMT process, Suppress apoptosis	(Cai et al. 2017; Fotouhi Ghiam et al. 2017; Wang, Ying, et al. 2015; Li, Hao, et al. 2019; Wang, Shen, et al. 2017; Jun et al. 2018; Li, Li, et al. 2018)
XIST	Xq13.2	Colorectal, Esophageal Carcinoma, Laryngeal Carcinoma, Lung, Pancreatic, Thyroid.	↑: EZH2, PI3K/Akt, Wnt/β-catenin, NOTCH3, EGFR, STAT3, ZEB1, MAPK1 ↓: miR-429, miR-124, miR-186-5p, miR-34a, miR-132-3p	Increased cell proliferation, migration and invasion, promotion of EMT process, inhibited apoptosis.	(Liu, Deng, et al. 2018; Wang, Shen, et al. 2017; Song et al. 2017; Shen et al. 2019; Chen, Huang, et al. 2019; Xiao, Cui, and Wang 2019)

expression of p53 genes. Different expression motif of MT1JP accompanying p53 regulation in tumor cells obviously indicates the anticancer characteristic of MT1JP. Hence, tumor suppressor functions of lncRNA in connection with the transcription factor of p53 can be regarded as potential strategy for cancer treatment.

Role of long non-coding RNAs as an oncogene

Beyond their tumor suppressor functions, lncRNAs may act as an oncogene factor according to many studies (Table 2). Thus, over expression of oncogenic lncRNAs can lead to survival, proliferation and invasion in different cancerous

cells (Inamura 2017). LncRNASs are able to exert their oncogenic effects through several mechanisms. RAS proteins (RASs), as a group of GTPase enzymes, are fundamental elements of signaling pathways that emerge from transmembrane receptors. The Oncogenic activity of RASs as a consequence of their mutation has been discovered in different types of cancer (Pylayeva-Gupta, Grabocka, and Bar-Sagi 2011). Orilnc1 is one of the lncRNAs that have the potential of promoting the oncogenic phenotypes via activity of RAS proteins. RAS-RAF-MEK-ERL is the pathway of adjusting ORilnc1 expression and increased levels of expressed ORilnc1 is correlated with high growth rates of cancer cells (Zhang, Zhang, et al. 2017). Furthermore, the elevated expression of oncogenic RAS is coupled with abnormal expressions of ANRIL and PAND; two significant lncRNAs regulating cellular senescence and apoptosis respectively (Kotake et al. 2016). Additionally, oncogenic lncRNAs through stimulating specific anti-apoptotic modulators can abolish the activity of tumor suppressor molecules. Some lncRNAs are regulated by miRNAs such as MIR31HG. Reportedly in pancreatic ductal adenocarcinoma (PDAC), miR-193b are bound to lncRNAs sequences and adversely upregulated the expression of MIR31HG. On the contrary, MIR31HG functions as an endogenous sponge for miR-139b to modulate the expression of its downstream targets (Yang, Liu, et al. 2016). MiRNAs sponge is regarded as a mechanism in which lncRNAs may manipulate the target gens at the posttranscriptional phase. In this way, lncRNAs act as a miRNAs sponge and reduce the interaction between endogenous miRNAs and downstream targets (Paraskevopoulou and Hatzigeorgiou 2016).

Targeting long non coding RNA by natural products

As mentioned previously, natural products and also their derivations have been applied as an anticancer drugs during recent decays. These types of compounds thanks to their valuable bilogical activities such as anti-oxidant, pro-apoptotic, anti-inflammatory and anticancer attributes have the capability of applying as chemoteraupic or chemopreventative agents for treating various cancers. Figure 5 represents some functions of natural biological ingredients in cancer cells or tissues. Herein, most practical phytochemical employed in cancer treatment have been introduced.

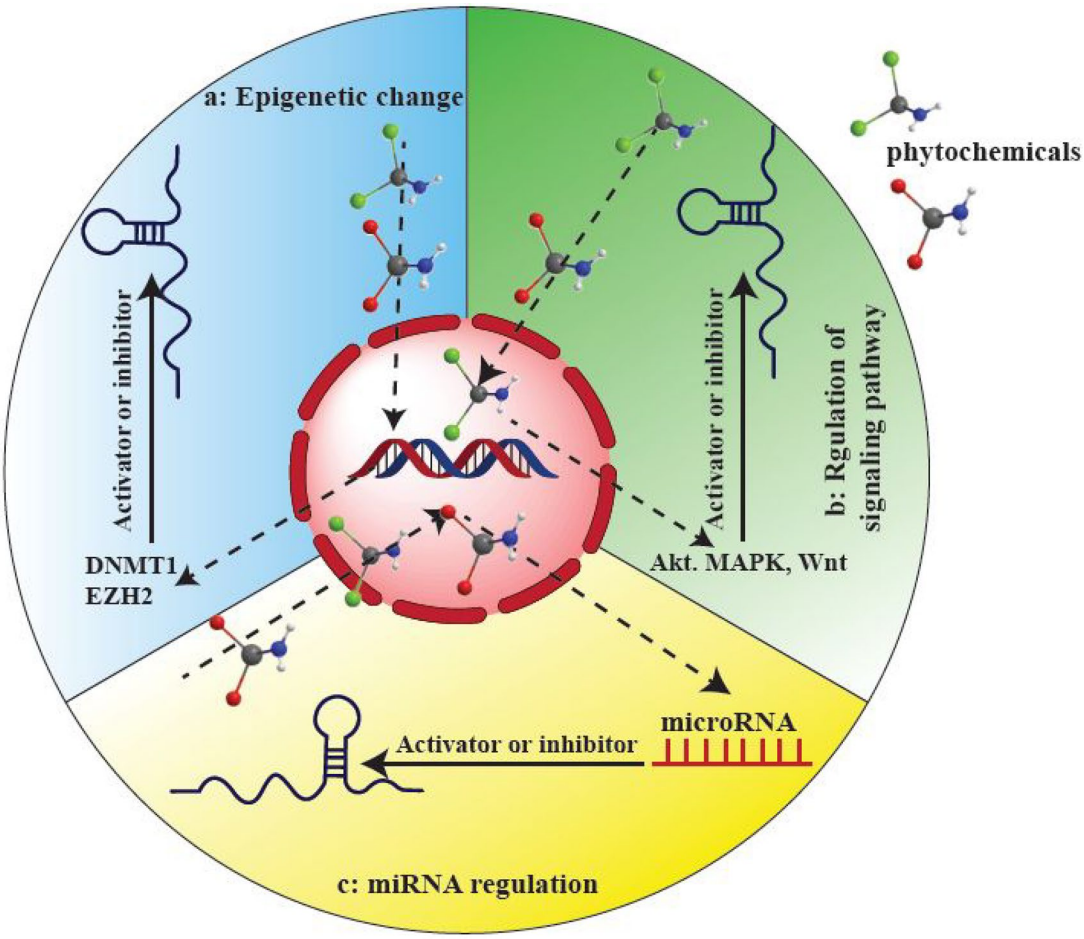

Figure 5. Biological functions of natural ingredients in cancer cells or tissues. a) natural compounds operate as epigenetic modifiers and change the expression of lncRNA; b) some natural products affect lncRNAs in cancer tissues by targeting various signaling pathway; c) phytochemicals modify regulation of lncRNA in cancer cells via targeting miRNAs.

Curcumin

Curcumin (diferuloylmethane) owning the chemical formulation of $C_{21}H_{20}O_6$ is a bright yellow polyphenol compound isolated from *Curcuma longa* (the rhizome of turmeric) (Ashrafizadeh et al. 2020). This powder thoroughly is implemented as a traditional herbal medicine in Asia especially China. Due to its unique structure, curcumin can suppress the generation of reactive oxygen species (ROS) and enjoys remarkable pharmacological functions such as anti-inflammatory, anti-analgesic, hepatoprotective, cardioprotective, and neuro-protective, anticancer as well as chemopreventive and chemotherapeutic effects. Accordingly, targeting lncRNAs by curcumin in different types of cancer has received considerable attention recent years (Grynkiewicz and Ślifirski 2012) and massive studies have been conducted presented in Table 3.

It is revealed the downregulation of lncRNA GAS5 (growth arrest-specific transcript 5) is linked to breast cancer by inducing cancer cell growth as well as reducing the apoptosis in various breast cancer cell lines (Pickard and Williams 2014). It is proved GAS5 via inactivation of PI3K/AKT/mTOR signaling axis prevent tumor cells from proliferation, migration and invasion (Wang et al., 2018). In an investigation conducted by Esmatabadi, Motamedrad (Esmatabadi, Motamedrad, and Sadeghizadeh 2018), it was speculated pretreatment of breast cancer cells with curcumin resulted in activation of GAS5 promotors which augment GAS5 expression; GAS5 induces apoptosis by means of suppressing the oncogenic pathways of MAPK/PI3K/PKB and eventually facilities tumor cell death. It has been observed that the expression of lncRNA KCNQ1OT1 (potassium voltage-gated channel subfamily Q member 1 opposite strand/antisense transcript1) increased in the cell line of cisplatin-resistant CRC, i.e. lymphoma 2) (Zheng et al. 2021). Zheng, You (Zheng et al. 2021) asserted treatment of HCT8/DDP with curcumin in concentration of 10 μM had an inhibitory impact on the expression of KCNQ1OT1. In this state, the elevated expression of miR-497 resulted in inducing apoptosis by inactivating Bcl-2 and restrained cell proliferation. It has been reported lncRNA PVT1 (plasmacytoma variant translocation1) is strongly associated with development of drug-resistant PDAC.

In this type of cancer, PRC2 (polycomb repressive complex-2) and its subunit, EZH2 (enhancer of zeste homolog-2), are remarked as key oncogenic elements in proliferation of chemo-resistant PDAC cells (Tseng et al. 2014). Furthermore, overexpression of c-MYC (cellular myelocytomatosis oncogene), is another inducer of chemo-resistant PDAC. It has been elucidated the expression of EZH2 and c-MYC and multi-drug resistance1 (MDR1) genes is regulated by PVT1 (Tseng et al. 2014; Yoshida et al. 2017). In an observation, it was clarified curcumin supplementation (20 μM) through downregulation of PVT1, PRC2, EZH2, MYC1 and MDR1 genes could re-sensitize drug-resistant PDAC tumors to gemcitabine and inhibit cell viability (Yoshida et al. 2017).

LncRNA NBR2 (neighbor of BRCA1 lncRNA 2) is found adjoining to the tumor suppressor of BRCA1 (Breast cancer type 1). In the condition of glucose and energy deprivation, NBR2 and AMPK (adenosine monophosphate-activated protein kinase) stimulates the kinase activity of AMPK. Lack of NBR2 reduces activation of AMPK and as e consequence, downstream biological processes related to AMPK would be disrupted. It has been reported curcumin in a time and dose dependent manner (10 μM for 24 h) can control development of colorectal cancer through upregulation of NRB2 by which AMPK and mTOR signaling pathways would be activated and deactivated respectively (Yu, Longfei, et al. 2019). X-inactive specific transcript (XIST) is a class of lncRNAs, in spite of being transcribed from one X-chromosome, it deactivates the other X-chromosome through PRC2. Hence, XIST is indispensable for deactivation of X-chromosome in female cells. Relay on the type tissue, XIST can be an oncogenic or tumor suppressor. It has been claimed downregulation of XIST may lead to breast cancer (BC) and renal cell carcinoma (RCC) (Sun et al. 2019; Wu et al. 2017; Zheng, Li, et al. 2018).

Sun, Jia (Sun et al. 2019) have declared XIST was able to arrest RCC tumor growth through inhibiting the cell cycle at the G0/G1 phase and upregulating the expression of tumor suppressor gene of p21. XIST through binding and sponging miR-106b-5p, as the inhibitor of p21, can upregulate the expression of tumor suppressor gene of p21 and therefore, suppress the cell viability. The antitumor activity of curcumin in RCC is completely depends on XIST; It is demonstrated curcumin (at concentration of 20 μM for 24 h) upregulates p21 via targeting its 3'UTR sequence, and consequently, increase expression of XIST which in turn blocks miR-106-5p. in another study, Liu, Chi (Liu, Lin, et al. 2017) illustrated pretreatment of prostate cancer cells with curcumin (46.5 μM) reduced tumor cell survival through dysregulation of lncRNA ROR. Due to own active sites for interacting with miR-145, both ROR and oct4 (a type of stem cell known as the marker of chemotherapy resistance) molecules have an intense competition for binding miR-145.

In prostate cancer, ROR acts as a sponge for miR-145 which is an inhibitor of oct4; therefore, increasing the expressions ROR and oct4 would cause the production of cell cycle kinase to continue that trigger proliferation and invasion of tumors. In this study, it was demonstrated the administration of curcumin led to downregulation of ROR and upregulation of miR-145 by which Oct4 expression was diminished and cell proliferation was avoided. It has been announced overexpression of lncRNA UCA1 (urothelial carcinoma associated1), is attributed to tumor development and proliferation in non-small cell lung cancer (NSCLC) (Wang, Ying, et al. 2015). The underlying mechanism of oncogenic function of UCA1 can be explained via mTOR-STAT3/miR-143 loop and triggering glycolysis (Li et al. 2014). Wang, Chen (Wang et al., 2018) acclaimed incubation of A549 cells (lung cancer cell lines) with curcumin (at 0.6 μM) drastically alleviated the expression of UCA1 which led to dysfunction of mTOR and Wnt pathways. Proteins-associated Wnt signaling such as wnt3a, wnt5a and β-catenin causes lung cancer to

Table 3. Regulation of lncRNA by natural compounds in various cancers.

Phytochemical compounds	Type of cancer	Targeted lncRNAs	Effect on lncRNAs	Cell lines or animal models	Concentration and time of treatment	Related genes or miRNAs	Reference
Curcumin	Acute lymphoblastic leukemia	Linc-pint	Upregulation	HLB-589 and MOLT-4 cells	30 μM, 48 h	↑: HMOX1, ↓: cell cycle rate	(Garitano-Trojaola et al. 2018)
	Breast cancer	H19	Downregulation	MCF-7/TAMR cells	15 μM, 48 h	↑: E-cadherin ↓: N-cadherin, vimantin	(Cai et al. 2020)
		GAS5 and Tusc7	Upregulation	MCF7, MDA-MB231 and SKBR3 cells	13.5 μM, 48 h	↑: - ↓: -	(Esmatabadi, Motamedrad, and Sadeghizadeh 2018)
	Colorectal cancer	NBR2	Upregulation	HCT8, HCT116, SW480 and SW620 cells	10 μM, 24 h	↑: AMPK/ACC ↓: S6K-S6, mTOR	(Yu, Longfei, et al. 2019)
		KCNQ1OT1	Downregulation	DDP and HCT8 cells Xenograft mouse	50 μM, 72 h 1 g/kg/week	↑: Bax, , Cyt-c, miR-497, ↓: Bcl-2	(Zheng et al. 2021)
		PANDAR	Downregulation	DLD-1, HCT116, SW620 and patient samples	5 μM, 24 h	↑: PUMA ↓: -	(Collado, Blasco, and Serrano 2007)
	Gastric cancer	H19	Downregulation	GES-1 and SGC7901	50 μM, 72 h	↑: Bax, p53 ↓: Bcl-2, c-Myc	(Liu, Xiang, et al. 2016)
		LINC01021	Downregulation	BGC-823, GES-1, KATO III and SGC-7901 Xenograft mouse	4 μM, 48 h 20 mg/kg/day or 250 nmol/kg/kg	↑: E-cadherin, p53 ↓: Bcl-2, N-cadherin, p62, vimentin	(Xu et al. 2020)
	Hepatocellular cancer	MEG3 HOTAIR	Upregulation Downregulation	HepG2 and Huh-7 cells	18 μM, 48 h	↑: miR-185, miR-29a ↓: DNMT1, DNMT3A and DNMT3B	(Zamani et al. 2015)
		ROR	Downregulation	Huh-7, LO2 and SMMC7721 cells	16 μM, 48 h	↑: - ↓: c-MycCD44, CCND1, Oct3/4, Wnt/β-catenin,	(Shao et al. 2020)
	Lung cancer	UCA1	Downregulation	A-549	0.6 μM, 24 h	↑: caspase-3, caspase-9 ↓: Cyclin D1, Wnt/mTOR	(Wang et al., 2018)
	nasopharyngeal carcinoma	AK294004	Downregulation	CNE-2 cells	10 μM, 24 h	↑: CCND1 ↓: radio resistance	(Wang et al. 2014)
	Ovarian cancer	MEG3	Upregulation	A2780, OVCAR-3 and SKOV3 cells	1 μM, 36 h	↑: - ↓: miR-214	(Zhang, Zhang, et al. 2017)
		BC200 ABO73614, ANRIL, CCAT2, FAL1, LSINCT5, MALTA1	Upregulation Downregulation	HFSF-PI3, OVCAR3 and SKOV3	5 or 10 μM, 48 h	↑: - ↓: -	(Seyed Hosseini et al. 2019)
	Pancreatic ductal adenocarcinoma	PVT1	Downregulation	BxPC3, MiaPaCa2 and Panc1 PDAC Xenograft mouse	8 and 20 μM, 48 h 100 mg/kg/day	↑: p21 ↓: EZH2, Suz12, c-Myc	(Yoshida et al. 2017)
	Prostate cancer	ROR	Downregulation	22RV1 and Du145 cells Xenograft mouse	46.5 μM, 48 h 23.25 μM, 48 h for inserted cancer cells	↑: miR-145 ↓: CCND1, CDK4, Oct4, CD44, CD133	(Liu, Lin, et al. 2017)
	Renal cell carcinoma	XIST HOTAIR	Upregulation Downregulation	786-O, ACHN, Caki-1, Caki-2 and HK2 cells	20 μM, 24 h	↑: p21 ↓: miR-106b-5p	(Sun et al. 2019)
Resveratrol	Breast cancer	u-Eleaner	Downregulation	LTED and MCF-7 cells	50 μM, 48 h	↑: - ↓: Estrogen receptor-α	(Tomita et al. 2015)
	Colorectal cancer	MALTA1	Downregulation	HCT116 and LoVo cells	50 μM, 48 h	↑: ↓: β-catenin, c-Myc, MMP-7	(Ji et al. 2013)
	Liver cancer	Dleu2	Upregulation	AML-12	50 μM, 20 h	↑: - ↓: -	
	Lung cancer	AK001796	Downregulation	16HBE, A549, BEAS-2B and H446	25 μM, 48 h	↑: ↓: cell viability	(Yang et al. 2015)
	Multiple myeloma	NEAT1	downregulation	LP1 and U266	50 μM, 72 h	↑: - ↓: β-catenin, MMP-7, c-Myc, Survivin	(Geng et al. 2018)

	nasopharyngeal carcinoma	DANCR	Downregulation	5-8F and SUNE-1 cells Xenograft mouse	100 μM, 48 h 20 mg/kg/day	↑: PTEN ↓: -	(Zhang et al. 2020)
	Ovarian cancer	NBR2 GAS5, HULC, MEG3, PVT1, UCA1	Upregulation Downregulation	OVCAR-3 cells	100 μM, 24 h	↑: - ↓: -	(Vallino et al. 2020)
	Pancreatic cancer	MALTA	Downregulation	AsPC-1 and Panc-1 C57BL/6 J wild type mice	20 μM, 24 h 30 mg/kg	↑: miR-200b ↓: EZH2, H3K27ne3	(Lee et al. 2020)
	Prostate cancer	PCAT29	Upregulation	DU145, LNcaP and RWPE-1 cells	25 μM, 24 h	↑: PDCD4 ↓: IL-6, miR-21, STAT3	(Al Aameri et al. 2017)
	Benign prostatic hyperplasia	DIO3OS	Downregulation	BPH-1 and WPMY-1	20 μM, 72 h	↑: E-cadherin, miR-485-5p, miR-656-3p, p21 ↓: CCND1, CTGF, N-cadherin, ZEB1	(Chen, Ye, et al. 2021)
EGCG	Gastric cancer	LINC00511	Downregulation	AGS and SGC7901 cells	100 μM, 48 h	↑: miR-29b ↓: KDM2A	(Zhao et al. 2020)
	NSCLC	NEAT1	Upregulation	A549, H1299 and H460 Xenograft mouse	20 μM, 24 h 20 mg/kg/3 days	↑: CTR1 ↓: has-miR-98p	(Jiang et al. 2016)
		NEAT1	Upregulation	A549 and NCI-H460 cells Xenograft mouse	30 or 40 μM, 24 h 20 mg/kg/3 days	↑: CTR1, ROS ↓: ERK1/2, p-ERK1/2	(Chen, Jiang, et al. 2020)
		ENSG00000224063.1 ENSG00000235142.2, ENSG00000254054.2, ENSG00000260630.2, ENSG00000272796.1, ENSG00000226403.1, ENSG00000230109.1, ENSG00000251018.2, PSMC3IP SG00000130600.10	Upregulation Downregulation	A549 and NCI-H460 cells	80 μg/ml, 48 h	↑: - ↓: -	(Hu, Wang, et al. 2019)
	NSCLC stem cells	NEAT1	Downregulation	A549, H1299 and H460 cells	20 μM, 48 h	↑: CTR1, E-cadherin ↓: β- catenin, cCD133, CD44, yclinD1, MMP-2, MMP-9, N-cadherin, Nanog, Oct4, p-GSK-3β, Slug, Snail, Zeb1	(Jiang, Chen, et al. 2018)
	Osteosarcoma	SOX2OT variant 7	Downregulation	SaoS2 and U2OS cells Xenograft mouse	20 μg/ml, 72 h 30 mg/kg/day	↑: - ↓: ABCg2, c-Myc, Nanog, Oct4, p62 SOX2	(Wang et al., 2018)
Quercetin	NSCLC	SNHG7	Downregulation	16HBE, A549 and HCC8 27 cells Xenograft mouse	100 μM, 24 h 10 mg/kg/day	↑: miR-34a-5p, ↓: -	(Chai et al. 2021)
	Prostate cancer	MALTA1	Upregulation	PC-3 Xenograft mouse	50 μM, 48 h 75 mg/kg/day	↑: Bax, E-cadherin ↓: Bcl-2, N-cadherin, PI3K/Akt	(Lu et al. 2020)
Baicalein	Breast cancer	PAX8-AS1-N	Upregulation	MCF-7 and MDA-MB-231 cells Xenograft mouse	200 μM, 48 h 10 mg/kg/day	↑: PTNE, CNDK1A, ZBTB4 ↓: miR-17-5p	(Yu, Tang, et al. 2018)
	Cervical cancer	BDLNR	Downregulation	HeLa, ME-180 and SiHa cells Xenograft mouse	100 μM, 24 h 10 mg/kg/day	↑: - ↓: PIK3CA, Akt	(Yu, Tang, et al. 2018)
	Hepatocellular cancer	HSALNT0103092 HSALNT0167051 HSALNT0167051	Downregulation	Bel-7402	40 or 80 μM	↑: has-miR-443 ↓: Akt1	(Zhao et al. 2021)
		NKILA	Upregulation	Hep3B, HepG2, HCCLM3, QSG-7701 and SMMG-7721 Xenograft mouse	50 μM, 48 h 5 or 10 mg/kg/day	↑: - ↓: NF-κB	

(*Continued*)

Table 3. (*Continued*).

Phytochemical compounds	Type of cancer	Targeted lncRNAs	Effect on lncRNAs	Cell lines or animal models	Concentration and time of treatment	Related genes or miRNAs	Reference
	Prostate cancer	PCGEM1	Downregulation	LNCaP	15 µM, 24 h	↑: LC3-II ↓: p62	(Han et al. 2020)
Berberine	Colorectal cancer	CASC2	Upregulation	HCT116 and HT29 cells	40 µM, 48 h	↑: caspase-3, caspase-9 ↓: Bcl-2	(Dai et al., 2019)
	Colorectal cancer	CASC2	Upregulation	HCT116, HT29, LoVo, SW480 and SW620 cells	50 µM, 48 h	↑: caspase-3, caspase-9 ↓: Bcl-2	(Dai et al., 2019)
	NSCLC	HOTAIR	Downregulation	A549 and H1975 cells Xenograft Mouse	25 µM, 24 h 10 mg/kg	↑: E-cadherin, miR-3-5p ↓: N-cadgerin, Snail, vimentin	(Zheng et al. 2020)
Ginsenoside	Breast cancer	ATXN8OS	Downregulation	MCF-7, MCF-10A and MDA-MB-231 cells	20 or 50 µM, 24 h	↑: miR-424-5p ↓: CHRM3, DACH1, EYA1	(Kim et al. 2021)
		C3Orf67	Down regulation	MCF-10A, MCF-12A, MDA-MB-231 and T-47D cells	20 or 30 µM, 24 h	↑: - ↓: ACOX2, FAM107A, FAM3D	(Jeong et al. 2019)
		RFX3-AS1 STXBP5-AS1	Downregulation Upregulation	MCF-7	20 µM, 24 h	↑: PUM3, RFX3, SLCA1A, STXBP5 ↓: GRM1	(Ham et al. 2019)
		STXBP5-AS1	Upregulation	MCF-7, MCF-10A and MDA-MB-231 cells	20 µM, 24 h	↑: - ↓: miR-4425, FAM172A, RABGAP1L, RNF217	(Park et al. 2021)
	Colorectal cancer	CCAT	Downregulation	Caco-2 cells	50 µM, 24 h	↑: Bax, caspas-3, p53 ↓: Bcl-2, CCND1, MMP9, Vimentin, PI3k/Akt	(Li and Qi 2019)
	Hepatocellular carcinoma	HOTAIR	Downregulation	HEK293T, SK-Hep-1 and SMMC-7721 cells	8 µg/mL, 48 h	↑: - ↓: MMP-2, MMP-9, p-Akt, p-PI3K	(Pu et al. 2021)
	Liver cancer	LOC727924 and XLOC-004412 CTD-2215E18.3 RP11-218C14.5 RP11-430L16.1	Downregulation Upregulation	HepG2 cells	20 µg/mL, 24 h	↑: - ↓: MMP-2, MMP-9, p-Akt, p-PI3K	(Chen, Huang, et al. 2019)
	Ovarian cancer	H19	Downregulation	A2780 and SKOV3 cells	40 or 80 µg/mL, 48 h	↑: miR-324-5p ↓: PKM2	(Zheng, Li, et al. 2018)
	Pancreatic cancer	CASC2	Upregulation	Panc-1 and SW1990 Xenograft mouse	200 µg/mL, 48 h 40 mg/kg/day	↑: PTEN ↓: -	(Zou et al. 2020)
	Renal cancer	THOR	Downregulation	768-O, Caki-1 and HK-2 Xenograft mouse	40 µM, 48 h 0, 25, 50 and 75 mg/kg/day	↑: Bax, caspase-3, E-cadherin ↓: Bcl-2, MMP-2, MMP-9, N-cadherin, Vimentin	(Chen, Ye, et al. 2021)
Genistein	Breast cancer	HOTAIR	Downregulation	MCF-7 cells	80 µM, 48 h	↑: ↓: p-Akt	(Chen et al. 2015)
	Colorectal cancer	TTTY18	Downregulation	SW480 Xenograft mouse	0, 25, 50, 100 µM, 48 h 20, 30 and 60 mg/kg/day	↑: ↓: Akt, p38-MAPK, SGK1	(Chen, Jiang, et al. 2020)
	Colorectal, prostate and Renal cancer	HOTAIR	Downregulation	786-O, ACHN DU145, HK-2 and HT-29 cells	25µM, 96 h	↑: miR-141 ↓: -	(Chiyomaru et al. 2014)
	Prostate cancer	HOTAIR	Downregulation	LNCaP, DU145, PC3 and cells Xenograft mouse	25µM, 96 h 5×10^{6}	↑: miR-34 ↓: -	(Chiyomaru et al. 2013)
	Renal cancer	HOTAIR	Downregulation	786-O and ACHN cells	25µM, 96 h	↑: ARID1A, ZO-1 ↓: EZH2, SMARCB1, Snail, SUZ12	(Imai-Sumida et al. 2020)
Calyosin	Breast cancer	HOTAIR	Downregulation	MCF-7	80 µM, 48 h	↑: - ↓: p-Akt	(Chen et al. 2015)

		HOTAIR	Downregulation	MCF-7, MCF-10A, MDA-MB-231, MDA-MB-468 Xenograft mouse	16 μM, 48 h 55 mg/kg/day	↑: RASD1, WDR-7 ↓: Akt, EGFR, ER-α, ERK1/2, GPR30, miR-375, SRC	(Tian et al. 2017)
		RP11-65M17.3	Upregulation	HMEC-1, HUVECs, MCF-7 and T47D cells Xenograft mouse	20 μM, 48 h 8 mg/kg/day	↑: BRIP1, ERα ↓: Akt, ERK1/2	(Wang et al. 2021)
	nasopharyngeal carcinoma	EWSAT1		CNE1, CNE2, C666-1 and NP69 Xenograft mouse	50 μM, 48 h 60 mg/kg/day	↑: - ↓: p-c-Jun, p-IκB, p-TAK1, TRAF6	(Kong et al. 2018)
Gambogic acid	Bladder cancer	GAS5	Upregulation	EJ and T24T cells	2.5 μM, 48 h	↑: caspase-3, miR-101 ↓: E2F4, EZH2, GAPDH	(Wang et al., 2018)
		SPRY4-IT1	Downregulation	EJ, SV-HUC-1, T24 and UMUC3 cells Xenograft mouse	1 μM, 48 h Stable T24T cells (3×10^{6}, 200 μL)	↑: E-cadherin, miR-101-3p ↓: EZH2, vimentin	(Liu, Lin, et al. 2017)
DIM	Colon cancer	BCAR4 CCAT1-L Linc-POU3F3 HOTAIR TUG1	Downregulation	HCT-116 and HT-29	30 μM, 72 h SGC7901 cells (1.5×10^{6}) with or without FRLnc1	↑: - ↓: -	(Zinovieva et al. 2017)
	Prostate cancer	PCGEM1	Downregulation	CWR22Rv1 LNCaP Xenograft mouse	20 μM, 72 h 20 mg/kg/day	↑: - ↓: p54/nrb	(Ho et al. 2016)
Silibinin	Bladder cancer	HOTAIR ZFAS1	Downregulation	T24T and UM-UC-3 cells	10 μM, 48 h	↑: - ↓: DDR1, EGFR, H3K4, PI3K/Akt, Ras, SOS1	(Imai-Sumida et al. 2017)
Anacardic acid	Breast cancer	CFAR-AS1 MIR22HG UBL7-AS1	Downregulation	MCF-7 and MDA-MB-231 cells	13.5 or 35 μM, 6 h	↑: GPR176, PDK4 and ZBTB ↓: INSIG1, SCD, TGM2, TNFα	(Schultz et al. 2018)
Bharangin	Breast cancer	H19 GAS5 MEG3 MHRT NEAT1	Downregulation Upregulation	MCF-7, MDA-MB-231, MDA-MB-453, MDA-MB-468, SKBR3 and T-47D cells	5 μM, 6 h	↑: Bax ↓: Bcl-2, NF-κB	
Hyperoside	NSCLC	CCAT1	Downregulation	NCI-H1975 cells	87.4 μM, 48 h	↑: FoxO1 ↓: -	(Hu, Zhao, and Xu 2020)
Luteolin	Thyroid carcinoma	BANCR	Downregulation	8505C, FTC-133 and IHH-4 cells	10 μM, 24 h	↑: - ↓: CCDN1, p-CREB, PCNA, TSHR	(Liu, Lin, et al. 2017)
	Triple negative breast cancer	TINCR	Downregulation	BT549, MCF-10A, HCC1937 and SUM159PT cells Xenograft Mouse	10 μM, 24 h 50 mg/kg/day	↑: - ↓: miR-761 N-	(Zhang, Liu, and Li 2021)
Polydatin	Osteosarcoma	TUG	Downregulation	MG-63 and Saos-2 cells	150 μM, 24 h	↑: - ↓: p-Akt	(Hu, Wang, et al. 2019)
Sanguinarine	Ovarian cancer	CASC2	Upregulation	A2780, Caov3, OVCAR3 and SKOV3 cells	5 μM, 48 h	↑: Bax, caspase-3, caspase-9 ↓: Bcl-2, NF-κB, PI3K, p-Akt	(Zhang et al. 2018)
Sulforaphane	Colon cancer	Loc344887	Upregulation	LNCaP and PC-3 cells	15 μM, 24 h	↑: GADPH, H2AFY, MAP1LC3B2 ↓: -	(Johnson et al. 2017)
	Pancreatic cancer	H19	Downregulation	AsPC-1, BxGEM, BxPc-3, CRL-4023, LX2, MIA-PaCa2 and PANC1 cells	10 μM, 24 h	↑: ↓: APOBEC3G, SMAD2, TGFβ	(Luo et al. 2021)
	Prostate cancer	LINC01116	Downregulation	HCT116 and HT29 cells	15 μM, 24 h	↑: - ↓: -	(Beaver et al. 2017)

develop by interfering in cell proliferation and segregation.

On that account, curcumin by blocking the mentioned pathways may induce its pro-apoptotic and anti-metastasis characteristics in NSCLC. lncRNA PANDAR (promoter of CDKN1A antisense DNA damage-activated RNA), upregulated in various cancers, stimulates cell proliferation and migration through dysregulating pro-apoptotic genes (Lu et al. 2017). In the study on treatment of CRC by curcumin, it was disclosed at low concentration (5 μM), curcumin reduced PANDAR expression and caused the ability of cell proliferation to suppress via promoting senescence instead of apoptosis (Chen et al. 2017). Cellular senescence is considered as a phenomenon upon which cells lose the capability of proliferating following DNA damage (Collado, Blasco, and Serrano 2007). It has been revealed suspending PANDAR in CRC cells treated with curcumin alters senescence into apoptosis through inducing PUMA (p53 upregulated modulator of apoptosis). Administration of mice bearing CRC with high dosage of curcumin (0.2% by weight) may led to stimulate cell senescence because of impaired absorption of iron (Chin et al. 2014), therefore in order to treatment of CRC, the modest concentration of curcumin should be implemented.

Resveratrol

Resveratrol (trans-3,4′,5-trihydroxystilbene, $C_{14}H_{12}O_3$) is a natural polyphenolic phytoalexin derived from numerous food materials such as grape, red wine, berries, peanut, etc (Bishayee 2009). Resveratrol, basically owning stilbene structure, contains two phenolic rings attached by a styrene double bound to stablish 3, 5, 4- trihydroxystilbene (Honari et al. 2019). Resveratrol possesses both cis- and trans-isoforms that the latter one is the most abundant and stable conformation and extensively have been applied as a therapeutic agent (Borriello et al. 2014). In several studies, resveratrol has been identified as a great chemopreventive ingredient thanks to its low toxicity and the capacity of targeting various signaling molecules inducing cancer cell growth and viability (Cimino et al. 2012). Recently, several studies have proposed anti-proliferative and pro-apoptotic features of resveratrol is as a result of its interplay with lncRNAs. Yang, Xu (Yang et al. 2015) identified the capability of resveratrol in alteration the expression pattern of lncRNAs in A549 cancer cells. They observed resveratrol treatment (at a concentration of 25 μmol/L for 48 h) upregulated 21 lncRNAs and downregulated 19 lncRNAs in cancerous A549 cells in comparison with normal A549 cells. Among lncRNAs, AK001769 was of considerable importance.

Silencing the AK001769 gene in resveratrol-treated A549 cancer cells led to a cell-cycle block and attenuated cell proliferation. Mechanistically, deterrence of cell-cycle development is related to the promoted expressions of genes involved in the cell-cycle arrest along with declined expression of genes required for boosting various cell growth phases of G_1, S and M (Huang, Sramkoski, and Jacobberger 2013). PCAT29 (prostate cancer associated transcript 29) is a tumor suppressive lncRNA that its expressions dramatically reduce in the prostate cancer. It has been observed that IL-6 (interleukin 6) through activating STAT3/miR-21 axis downregulated the expression of PCAT29 (Prensner et al. 2011). Al Aameri, Sheth (Al Aameri et al. 2017) resveratrol-treated prostate cancer cells via inhibition of STAT3/miR-21 was able to upregulate the PCAT29 expression and decreased the proliferation cancer cells. In another study, Vallino, Ferraresi (Vallino et al. 2020) analyzed the profile of ncRNAs in ovarian cancer cells of OVCAR-3 t under the effect of have a resveratrol administration (100 μM) after 24 h. Amongst the fifteen lncRNAs that their regulation was altered by resveratrol, the expression of lncRNA PVT1, UCA1, HULC and GAS5 as tumor suppressive elements was amplified under the effect of resveratrol while the expression of oncogenic lncRNAs such as XIST, LINC00092, H19 and MALTA downregulated under the mentioned treatment. presumably, environmental toxicants trigger the aryl hydrocarbon receptor (AHR), a ligand with potential of inducing transcription factors, of which stimulation results in modulating numerous downstream processes such as cancer cell metabolism, inflammation and xenobiotic transformation (Kasai et al. 2006; Safe, Lee, and Jin 2013). However, various reports have exhibited activation of AHR with environmental toxicant elevates the expression of lncRNA MALTA1 (metastasis associated lung adenocarcinoma transcript1) in different cancer lines. Interaction of MALTA1 with EZH2, a histone methyl-transferase owning a epigenetic gene silencing operation, extensively amplifies the gene silencing through epigenetic machineries and lead to increased cancer cell proliferation and progress (Hirata et al. 2015).

It has been identified treatment of pancreatic cancer cells (PCC) with resveratrol dysregulate AHR-MALTA1-EZH2 signaling cascades and finally blocked the survival and growth of PCC (Lee et al. 2020). NEAT1 (Nuclear enriched abundant transcript1) is the other class of lncRNAs via upregulating the Wnt/β-catenin signaling stimulates migration and invasion in cancer cells (Mao et al. 2014). Geng, Guo (Geng et al. 2018) in their investigation claimed administration of resveratrol (30 μM and 72 h) in multiple myeloma (MM) cells could dysregulate NEAT1 molecules which in turn dysfunction the expression of Wnt/β-catenin, c-Myc, MMP-7 (matrix metalloproteinase-7) and Survivin and finally blocked metastasis and invasion procedures. In the other study, the similar inhibitory effect was depicted as a result of the interaction between resveratrol and MALTA1. Ji, Liu (Ji et al. 2013) revealed treatment of CRC cells with resveratrol at concentration of 50 μM for 72 h suppressed MALTA1 by which various pathways including Wnt/β-catenin, c-Myc, MMp-7 were targeted and arrested. Therefore, cancer cell transformation, metastasis and invasion were attenuated.

EGCG (epigallactocatchin-3-gallat)

Several studies have reported high consumption of the green tea (Camellia sinensis) diffusion, as the most universally popular beverage, is connected with health promotion effects

particularly chemo-preventive benefits (Siddiqui et al. 2011). Accumulative evidences have demonstrated the chemo-preventative efficacy of green tea against numerous cancers is attributed to catechin components. EGCG ((-)-epigallactocatchin-3-gallat) is the most abundant polyphenolic compounds of green tea that suppresses several inflammatory pathways resulting in transformation, initiation, proliferation and invasion of cancer cells (Khan et al. 2006; Sigler and Ruch 1993). Recent reports have displayed the capability of EGCG in suppressing different lncRNAs is the key factor in inhibiting cancer progress. Copper transporter 1 (CTR1) is a membrane transport protein that have a pivotal role in augmenting the internalization of cisplatin (cDDP) in tumor cells. Reportedly, the downregulation of CTR1 cause tumor cells to be resistant to cDDP. In a study on NSCLC, it was declared EGCG (at doses of 30 μM and 40 μM for A549 and H460 for 24 h) via generating reactive oxygen species (ROS) simultaneously increased the expression of NEAT1 and decreased the expression of ERK1/2 p-ERK1/2.

Aforementioned alterations, all together upregulated CTR1 and consequently promoted the sensitivity of NSCLC to cDDP (Chen, Jiang, et al. 2020). In a similar study, Jiang, Wu (Jiang et al. 2016) examined the effect of EGCG on cisplatin transportation and sensitivity in groups of NSCLC such as A549, H460 and H1299. Based on bioinformatics, has-miR-98-5p is a crucial ncRNA which not only has specific binding sites for NEAT1, but also it is an appropriate candidate for interaction with CTR1. Jiang, Wu (Jiang et al. 2016) claimed employing EGCG at concentration of 20 mg/kg of mouse body weight as a targeting agents induced the regulation of CT1. In parallel, NEAT1 suppressed the regulation has-miR-98-5p via the sponging mechanism. Accordingly, NEAT1 have an inhibitory effect on NSCLC by through upregulation of CT1 increasing the sensitivity of cancer cell lines to cDDP. In another study, the sensitivity of gastric cancer cells to gemcitabine under the influence of EGCG has been evaluated (Zhao et al. 2020). In this type of cancer overexpression of NINC0051 leads to silencing miR-29b followed by cancer development. In fact, as a consequence of miR-29b silencing, the level of KDM2A elevated that protected the concentration of LINC0051. Employing EGCG as a therapeutic approach could knockdown regulation of LINC0051. Zhao, Jiang (Zhao et al. 2020) reported EGCC by LINC0051/miR-29b/KDM2A signaling axis might improve the sensitivity of gastric cancer cells to gemcitabine. Increasing the level of lncRNA SOX2OT variant 2 (Sex determining region Y-Box transcription Factor 2 overlapping transcript) is one of the authentic indicator of several cancers specifically osteosarcoma. In a study on osteosarcoma, it was found EGCG-targeted lncRNA SOX2OT variant 7 in company with Doxorubicin (DOX) (in concentrations of 25 μM and 20 μg/mL respectively) developed synergic effects to catch the proliferation of osteosarcoma cells (Wang et al., 2018). In this strategy, EGCG by downregulation of SOX2OT variant7 could block the pro-survival autophagy process associated with DOX. As well, EGCG through targeting Notch3/DLL3 axis inactivated SOX2OT variant 7 which in turn declined the stemness capability and consequently DOX resistance in osteosarcoma cells.

Quercetin

Quercetin (3, 5, 7, 30, 40-pentahydroxyflavone) is a bioactive compound affiliated to the natural flavonol class, a subgroup of the flavonoid family (Hertog and Hollman 1996). As ubiquitously found in different fruits and vegetables, it is one of the most prevalent flavonols in the western diet (Boots, Haenen, and Bast 2008). Convincing evidences have demonstrated quercetin enjoys a board range of biological performances such as antioxidant, anti-inflammatory, anticancer as well as antidiabetic effects (Carullo et al. 2017). Conclusive proofs have disclosed that quercetin can be functioned as either oxidant or pro-oxidant compound determined by the quercetin levels and cell redox condition (Shafabakhsh and Asemi 2019). Indicating anti-oxidant and pro-oxidant attributes in low and high concentrations respectively cause quercetin to inhibit cancer promotion via generating a high frequency of oxidative stress (Ezzati et al. 2020). Providing numerous capability such as apoptosis induction, anti-proliferation effects and arresting cellular cycles resulted in regarding quercetin as an appropriate composition in cancer research (Reyes-Farias and Carrasco-Pozo 2019).

Currently, the effect of quercetin on lncRNAs in different classes of cancer have also been probed. Accordingly, in an investigation into CRC, Zhang, Li (Zhang et al. 2019) applied MTS assay and flow cytometry technique to evaluate the effect of quercetin on CRC cells. Along with inducing apoptosis and anti-proliferative effect, quercetin could alter the expression of 240 lncRNAs, 131 circRNAs, 83 miRNAs and 1415 mRNAS in quercetin-treated HCT-116 cells in comparison with untreated ones. Supposedly, the overexpression of lncRNA SNHG7 (small nucleolar RNA host gene 7) and downregulation of miR-34a-5p is the diagnostic feature of NSCLC cells than normal ones. Chai, Xu (Chai et al. 2021) indicated quercetin () through knockdown of SNHG7 and increase the expression of miR-34a-5p in NSCLC cells could accelerate tumor cell growth and inhibit cancer progress. MALTA1 and MIAT are lncRNAs related to angiogenesis. Esteghlal, Mokhtari (Esteghlal, Mokhtari, and Beyzaei 2021) showed incubation of human umbilical vein endothelial cells (HUVEC) with Quercetin significantly suppressed the expression of both MALTA and MIAT in a dose dependent manner and eventually reduced the survival rates of tumors. Overexpression of MALTA1 is one of hallmarks of prostate cancer. Lu, Chen (Lu et al. 2020) for the first time asserted treatment of prostate cancer cells with quercetin could effectively downregulate MALTA1 in a dose and time-dependent trend. Moreover, administration of quercetin in mouse bearing prostate cancer and consequently silencing MALTA1 led to inactivation of EMT process and PI3K/Akt signaling pathway and induction of apoptosis. Akt has a paramount effect in the apoptotic signaling in such a way that its phosphorylation stimulated the processes that

preserve cells against apoptosis. These alterations collectively inhibited proliferation and growth of tumors in the prostate cancer.

Baicalein

Baicalein (5, 6, 7- trihydroxyflavone) is a natural flavonoid compound derived from dried roots of Scutellaria baicalensis Georgi, a type of traditional Chinese herbs (Gao, Huang, and Xu 2001). According to several investigations, baicalein is favored with numerous pharmacological functions in particular antioxidant, anti-inflammatory and anticancer properties (Liu, Xiang, et al. 2016). Biacalein by inactivation cell proliferation, migration, inflammation as well as angiogenesis can control tumors development and invasion (Gao et al. 2016). Targeting lncRNAs is one of well-known mechanisms by which baicalein induces its anticancer quality. In a study on hepatocellular carcinoma (HCC), it was indicated application of baicalein (80 μM) and dimethyl sulfoxide in treatment of HCC led to differentially express of about 14 lncRNAs and 26 miRNAs of which HSALNT-lncRNAs (HSALNT0171251, HSALNT0103092 and HSALNT0167051) and hsa-miR-4443 respectively were of considerable importance.

Subsequent analysis illustrated the possible mechanism by which baicalein could inhibit the tumor development in HCC is HSALNT-lncRNAs/has-miR-433-A/Akt1 (Zhao et al. 2021). Yu, Tang (Yu, Tang, et al. 2018) disclosed anticancer effects of baicalein on HCC highly depended on the presence of NF-κB interacting lncRNA (NKILA). Downregulation of NLKILA in HCC might lead to reduced chance of survival in HCC patients. Generally, NKILA physically interacts with NF-κB/IκB complex, prevents IκB from phosphorylating, NF-κB from nuclear translocating and other activities (Liu et al. 2015). These function of NKILA vastly improved the inhibitory activities of baicalein (50 μM, 48 h) on NF-κB and following baicalein-promoted effects such as attenuating tumors growth and migration and also triggering cellular apoptosis. On the contrary, downregulation of NKILA inhibits the anticancer activities of baicalein (Yu, Tang, et al. 2018). The previous authors in their study on the effect of biacalein on the cervical cancer, identified an unknown lncRNA upregulated in cervical cancer and named it as baicalein down-regulated long non-coding RNA (BDLNR). The further investigations showed BDLNR by physically connecting to YBX1, a type of RBPs, caused YBX1 to bind to PIK3CA promotor, the catalytic subunit of PI3K. These variations led to overexpression of PIk3CA that its roles in cancer development is clarified. Pretreatment of cervical cancer cells with baicalein (100 μM, 24 h) inhibited cell proliferation and invasion through its effect on BDLNR/PI3k/Akt signaling axis (Yu, Tang, et al. 2018). In the treatment of breast cancer, baicalein in a dose-and time dependent manner increased the expression of lncRNA PAX8-AS1 and exerted its pro-apoptotic and anti-proliferation effects. In this approach, PAX8-AS1-N activated miR-17-5p which in turn upregulated the expression of tumor suppressor proteins such as PTEN (Phosphatase and tensin homolog), CDKN1A (Cyclin Dependent Kinase Inhibitor 1 A) and ZBTB4 (Zinc Finger and BTB Domain Containing 4). These alterations collectively inhibited cell viability, survival and cancer progress (Yu, Tang, et al. 2018).

Berberine

As a pentacyclic isoquinoline alkaloid, berberine is a natural compound extracted from *Berberis* genus plants and possesses a broad domain of pharmacological characteristics such as antiarrhythmic, antidiabetic, anti-obesity and anticancer (Habtemariam 2020). The health stimulating effects of berberine is related to its interaction with specific biological enzymes, receptors and ligands together with antioxidant and anti-inflammatory attributes (Song, Hao, and Fan 2020). As other phytochemicals, berberine with modulating lncRNAs can inhibit cancer progression. LncRNA cancer susceptibility candidate 2 (CASC2) is well known as a tumor suppressor gene in a variety of cancers such as NSCLC, breast cancer and CRC. Huang, Wu (Huang et al. 2016) demonstrated the strategy of CASC2 for controlling tumor proliferation and cell growth in CRC is prolonging the transition phase of G0/G1-S. Dai, Mu (Dai et al., 2019) in their observation showed interplay between berberine and CASC2 in CRC promoted apoptosis. It is widely accepted that as a consequence of silencing CSSC2 in CRC, Bcl-2 protein would be overexpressed. AU-binding factor 1 (AUF1) is a type of RBPs provoked translation of Bcl-2 without affecting its mRNA content (Lapucci et al. 2002). Recognized as heterogeneous nuclear ribonucleoprotein D (hnRNPD), AUF1 is individualized to interact with specific parts of mRNAs. In order to binding to A-U rich elements (AREs), AUF1 has the capability of targeting and degrading RNAs to release AREs (Zhang et al. 1993). It has proved that AUF1 protein is related to both Bcl-2 and CASC2 genes. Treatment of CRC cells with berberine (40 μM for 48 h) upregulated CASC2 which in turn prevented AUF1 from binding to Bcl-2 gene and finally translation of Bcle2 would be suppressed (Dai et al., 2019).

The same authors in another study elucidated berberine through CASC2/EZH2/Bcl-2 signaling pathways could induce apoptosis in CRC cell and repressed tumorigenesis and invasion processes (Dai et al., 2019). As the first discovered lncRNA, HOTAIR (Hox transcript antisense intergenic RNA) promote the metastasis process in various cancers through epigenetic modification (Pei et al. 2014). In treatment of NSCLC with gefitinib, applying berberine synergistically inhibit the migration and invasion processes. Incubation of NSCLS cells with combination of gefitinib (5 μM) and berberine (20 μM) led to downregulation of HATAIR functioning as miR-34a-5p sponge. Therefore, the expression of miR-34a-5p would be increased. Upregulated miR-34a-5p caused snail to suppress that resulted in increased level of E-cadherin by which EMT process arrested and finally migration and invasion in NSCLC cells were inhibited (Zheng et al. 2020).

Ginsenosides

Known as natural steroid glycosides, Ginsenosides are triterpene saponins that exclusively derived from ginseng roots (Nakhjavani et al. 2019). Based on the number of hydroxyl group in their chemical structure, ginsenosides are categorized in two main classes: the ones with six positions occupied by hydroxyl groups are regarded as protopanaxatriol (PPT) and the other ones with six position not accompanied by hydroxyl groups are known as protopanaxadiols (PPD). The PPT group chiefly contains the ginsenosides-Re, G1, Rg2 and Rh1 while the ginsenoside-Rb1, Rb2, Rb3, Rc, Rd, Rg3, and Rh2 belong to PDD. Ginsenosides are multifunctional bioactive ingredients (Xue et al. 2021). Similar to other phytochemicals, ginsenosides by targeting lncRNAs exerts their anticancer features. In a study on the breast cancer, recruiting ginsenosides-Rg3 as a therapeutic agent led to reduced cell proliferation and induced apoptosis as a result of downregulated lncRNA ATXN8OS. Further investigation revealed inhabitation of ATXN8OS in ginsenoside-treated breast cancer cells upregulated the expression of miR-242-5p by which three oncogenes including EYA1, DACH1 and CHRM3 were deactivated (Kim et al. 2021). In another examination on the breast cancer, it was illustrated ginsenoside-Rh2 through promotor hypomethylation positively regulated lncRNA STXBP-AS1 (Syntaxin Binding Protein 5) which acts as the sponge of oncogenic miR-4425. Subsequent of inactivation of miR-4425, upregulated RNF217 (Ring Finger Protein 217) exerts its pro-apoptotic characters and impaired tumor growth and survival (Park et al. 2021). RNF217 regulates a highly protected RING protein and suppresses HAX1 (HS-1-associated protein X-1), an anti-apoptotic protein (Parrow and Fleming 2021).

Overwhelming evidences have illuminated CCAT1 (colon cancer associated transcript 1) is a lncRNA upregulated in different types of CRC and has a prominent function in the cell proliferation, migration and invasion (Abedini et al. 2019). Li and Qi (Li and Qi 2019) in their investigation into CRC displayed ginsenoside-Rg3 (50 μM, 24 h) suppressed the expression of CCAT1 causing the reduced regulation of PI3K/Akt signaling. Consequently, the development of CRC would be declined. Incubation of hepatoma carcinoma cells with ginsenoside-Rg3 (8 μg/mL) suppressed the expression of lncRNA HOTAIR as a promotor of cancer cell proliferation, migration and invasion. Thereafter, the expression of p-PI3K, p-Akt, MMP-2 and MMP-9 reduced led to inhibited cancerous cell viability (Pu et al. 2021).

Genistein

As a type of phytoestrogens, genistein [4′, 5, 7-trihydroxyisoflavone ($C_{15}H_{10}O5$)], is a natural soy-derived isoflavone. Phytoestrogens or dietary estrogens are non-steroidal plant compositions owning to their similar structure to estrogens reveal estrogenic or anti-estrogenic properties (Ravishankar et al. 2013). Genistein enjoys various biological activity including antioxidant, tyrosine kinase inhibitor and anticancer. Regarding its chemotherapeutic properties, genistein modulates different cellular machineries such as cell cycle, apoptosis and angiogenesis (Meeran, Ahmed, and Tollefsbol 2010). It has been declared the epigenetic alteration is one of the main mechanisms by which genistein affect expression of cancer-associated genes and particularly lncRNAs (Teng et al. 2017). Chen, Wu (Chen, Jiang, et al. 2020) indicated that in CRC, the expression of transferrin growth factor beta-1 (TGF-β1), lncRNA TTTY18 elevated which is followed by upregulation of Ki-67, serum and glucocorticoid regulated kinase 1 (SGK1) as well as Akt. As a result of administration of genistein () to CRC cells, apoptosis was induced and cell viability and migration were declined. These variations in CRC cell occurred under the effect of downregulation of TTY18, SGK1, Akt/ser, p38 MAPK and TGF-β1. Furthermore, genistein through targeting chromatin remodeling factors HOTAIR could control cell proliferation and migration pathways in human renal carcinoma cells.

In this way, genistein (at concentration of 25 μM for 96 h) caused the levels of EED (embryonic ectoderm development) in PRC2 to decline and as consequence, the interaction between HOTAIR and PRC2 was interrupted which in turn led to increase transcription of the ZO-1 promotor. Moreover, genistein suppress the interaction between HOTAIR and both SMARCB1 (SWI/SNF-related matrix-associated actin-dependent regulator of chromatin subfamily B member 1) and ARID1A (AT-rich interactive domain-containing protein 1 A) as the subunits of the human SWI/SNF (SWItch/Sucrose Non-Fermentable) chromatin remodeling complex and subsequently, transcription of SNAIL was inhibited. Upregulation of ZO-1 and downregulation of ANAIL transcription controlled by genistein ultimately silenced EMT process followed by inhabitation of cancer development (Imai-Sumida et al. 2020).

Calycosin

Calycosin ($C_{16}H_{12}O_5$) is another isofalvone phytoestrogen derived from the Radix astragali (the dried roots of *Astragalus* spp) and exerts various biological functions (Wu, Niu, et al. 2019). Several studies have revealed the anti-carcinogenic effect of calycosin against osteosarcoma, colorectal, breast and liver cancers (Deng et al. 2021). EWSAT1 (Ewing sarcoma-associated transcript 1) is a kind of lncRNAs whose expressions significantly increases in nasopharyngeal carcinoma (NPC). Administration of calycosin in treatment of NPC cell in a dose dependent manner significantly declined the regulation of EWSAT1 and its downstream signaling molecules including TRAF6, p-TAK1, and p-IκBα/p-c-Jun and ultimately inhibit NPC cell proliferation and viability (Kong et al. 2018). WDR7-7 is a class of lncRNAs that suppresses the growth rate of cancer cells through decreasing the expression of GPR30 (G-protein coupled estrogen receptor 30). Tian, Wang (Tian et al. 2017) represented incubation of both estrogen receptor-positive (ER+) i.e., T47D and MCF-7 breast cancer cells and estrogen receptor-negative (ER-) i.e. SKBR3 and MDA-MB-468 breast

cancer cells with calycosin (16 μM) caused the growth of cancer cell to inhibit in a dose dependent manner. The underlying mechanism was upregulation of lncRNA WDR7-7 by which the expression of GPR30 diminished.

Thereby, the lessened phosphorylation rates of SRC, EGFR, and ERK1/2 led to viability of cancerous cells. In another phytoestrogen-associated inquiry, Chen, Lin (Chen et al. 2015) asserted both calycosin and genistein could significantly control the proliferation and induce apoptosis in MCF-7 cell lines. However, the former has considerable inhibitory effect on the breast cancer cells. More detailed observation showed both phytoestrogens through reducing the phosphorylation process of Akt and repressing its downstream target, HOTAIR was able to decrease the rate of cancer development.

Gambogic acid

Gambogic acid (GA) is a brownish colored resin obtained from the Garcinia hanburryi tree and is the main bioactive compound of gamboge (Hassan, Taher, and Susanti 2018). As a traditional medicine, GA has numerous biological functions such as antiviral, antioxidant, anti-inflammatory and anticancer activities with negligible toxicity (Yu, Longfei, et al. 2019). SPRY4-IT1 (Sprouty RTK Signaling Antagonist 4 intronic transcript) is a class of oncogenic lncRNAs firstly recognized in melanoma with high capability of inducing cellular growth, survival, apoptosis and invasion. In bladder cancer, Liu, Li (Liu, Lin, et al. 2017) asserted the regulation of SPRY4-IT1 significantly increased in cancer cells. They revealed treatment of malignant cells with GA in a dose dependent manner could knockdown the expression of SPRY4-IT1 followed by reduced viability and survival of cancer cells. In this way, downregulation of SPRY4-IT1 as a sponge of miR-101-3p led to raised expression of this miRNA.

The interaction between miR-101-3p and posttranscriptional EZH2 inhibited the EMT process via upregulating E-cadherin proteins and finally terminated cancer cell progression. Moreover, Wang, Guo (Wang et al., 2018) exhibited the signaling cascades that caused GA to exert its anticancer effects on bladder cancer cells was GAS5/E2F4/EZH2. Mechanistically, administration of GA in cancerous cells upregulated the expression of GAS5 which in turn impressively suppressed EZH2 in the transcriptional level by binding E2F4. Declined expression of EZH2 led to upregulation of miR-101, a miRNA with pro-apoptotic characteristic that consequently inhibited cancer cell progression and invasion.

3,3′-Diindolylmethane

Known as an indole-3-carbinol derivation, DIM (3, 3′-Diindolylmethane, $C_{17}H_{14}N_2$) is a type of phytochemicals presenting in various cruciferous vegetables such as kale, cabbage and broccoli (Licznerska and Baer-Dubowska 2016). DIM through targeting several signaling axis have the capability of modulating cancerous cell growth, survival, angiogenesis and apoptosis (Amare 2020). PCGEM1 (prostate cancer gene expression marker) is considered as one of the former identified oncogenic lncRNAs that is overexpressed in various cancers including ovarian and prostate. Ho, Huang (Ho et al. 2016) in their study on prostate cancer showed DIM with targeting p45/nrb as the transcriptional modulator of PCGEM1 could suppress the expression of this lncRNA and lessened the growth of prostate cancer cells and also their castration resistance. In another gastric cancer investigation, it was reported DIM indirectly prevented the Akt/FOXM1 (Forkhead box protein M1) pathway. FOXM1 change the expression level of several lncRNAs in gastric cancer cells and promotes cancer progression and metastasis (Cai et al. 2015). Furthermore, Zinovieva, Grineva (Zinovieva et al. 2017) distinguished the expression rates of oncogenic lncRNAs of HOTAIR and CCAT1-L augmented in the colon cancer cells while administration of DIM reduced the regulation of mentioned lncRNAs.

Other natural product

Silibinin is the main bioactive constituents of silymarin categorized as a class of folavonolignan polyphenol compounds. The anti-cancer properties of silibinin have been indicated in different types of cancers such as pancreas, lung, breast, kidney and colon (Polachi et al. 2016). In a study conducted by Imai-Sumida, Chiyomaru (Imai-Sumida et al. 2017), it was revealed treatment of the bladder cancer with silibinin (10 μM) decreased the expression of lncRNA HOTAIR and ZFAS1 elevating the expression of PI3K/Akt. Therefore, silibinin under the effect of HOTAIR-ZFAS1-PI3K/Akt pathways could suppress proliferation and progression of bladder cancer cells (Imai-Sumida et al. 2017).

Anacardic acid ($C_{22}H_{30}O_3$) as the main component of the resin oil is generally extracted from the mesocarp of cashew nut (Anacardium occidentale L.) shells (Morais et al. 2017). The basic structure of Anacardic acid is similar to salicylic acid together with a long hydrocarbon chain with the majority of 3 unsaturated bonds connected with its biological attributes. It has been reported, Anacardic acid possess various health promoting effects such as antimicrobial, antioxidant, anti-inflammatory and anticancer (de Araujo et al. 2021). In an investigation into the effect of Anacardic acid on two different breast cancer lines (MCF-7 and MDA-MB-468), de Araujo, Martin-Pastor (de Araujo et al. 2021) reported anacardic acid-treated cells owned radically different genome patterns in the field of mRNA, lncRNA and miRNA thau untreated ones. In addition, the type of altered regulation lncRNAs was completely distinctive in two cell lines. However, the behavior of six genes was similar in both cell lines; SDC, INSIG1, and TGM2 were downregulated while PDK4, GPR176 and ZBT20 were upregulated. The role of lncRNAs in anticancer properties of anacardic acid was not clarifierd. In MDA-MB-468 cells, arresting the biosynthesis of monounsaturated fatty acids and in MCF-7, suppressing TNFα-promoted NF-κB functions are the suggested anticancer mechanisms.

Bharangin, classified as a diterpenoid quinonemethide compound, is a phytochemical isolated from roots of *Pigmacopremna herbacea*, a type of medical plants (Murthy et al. 2006). In addition to antioxidant, antimicrobial and anti-rheumatism effects, various studies have proved its anti-carcinogenic features (Gupta et al., 2011). Awasthee, Rai (Awasthee et al. 2018) observed bharangin applied several processes for inhibiting growth and survival rates of breast cancer cells. Together with Preventing the production of cell survive proteins, inducing Bax production and mitochondrial depolarization, inhibiting the function of pro-inflammatory transcriptions such as NF-κB, bharangin through suppressing the expression of oncogenic H19 and also upregulation of tumor suppressors of MEG-3 and CAS-5 could cease the proliferation of cancer cells.

Delphinidin-3-glucoside ($C_{21}H_{20}O_{12}$) with is classified as an anthocyanin compound presented in different parts of pigmented fruits and vegetables such as blackcurrant, blueberry, huckleberry, bilberry, etc. This compound enjoys various biological benefits including antioxidant, anti-inflammatory and anti-cancer features (Harada et al. 2018). In an investigation on breast cancer conducted by Yang, Luo (Yang, Liu, et al. 2016), it was remarked delphinidin-3-glucoside through downregulation of HOTAIR blocked proliferation and growth processes of cancerous cell. In this regard, delphinidin-3-glucoside dysregulated expression of Akt and upregulated interferon regulatory factor-1 (IRF1). IRF1 interact with the promotors of HOTAIR and deactivated this lncRNA.

Hyperoside, chemically known as Quercetin-3-O-β-D-galactopyranoside ($C_{21}H_{20}O_{12}$), is categorized as flavonol glycoside compounds and generally extracted from *Hypericum perforatum* (Ersoy et al. 2020). Cumulative studies have proved the valuable biological activities of hyperoside in suppressing the survival of various tumors (Raza et al. 2017). The tumorigenic role of lncRNA CCAT1 have been observed in various cancer types such as colon, lung, kidney, hepatocellular, ovarian and breast (Guo and Hua 2017). Hu, Zhao (Hu, Zhao, and Xu 2020) in order to discover the inhibitory effect of hyperoside on NSCLC cells observed this phytochemical ingredient discontinued the expression of CCAT1 and indirectly caused the regulation of the downstream target of this lncRNA, i.e. FoxO1 enhanced and eventually growth and proliferation of NSCLC cells were halted through inducing the apoptosis process.

Flavonoid-associated Luteolin (3′, 4′, 5, 7-tetrahydroxy flavonoids) is a natural antioxidant found in enormous varieties of plants such as carrot, peppers, spinach, celery, apple, honeysuckle, perilla, etc. luteolin triggers its anticancer impacts through activation of the apoptosis processes and counteraction of cell survival machineries (Yuan et al. 2021). It has been identified only a few lncRNAs including BANCR (BRAF-activated long noncoding RNA), NAMA and PTCSC3 have indicated their carcinogenic roles in the thyroid cancer. Liu, Lin (Liu, Lin, et al. 2017) exhibited treatment of thyroid cancer cells with luteolin substantially reduced the expressed levels of BANCR and its downstream oncogenic targets especially thyroid stimulating hormone receptor (TSHR). Knockdown of BANCR/TSHR signaling through arresting the G0/G1 cell cycle phase withstood cancerous cell proliferation. In triple negative breast cancer (TNBC), luteolin inhibited cancer development via suppressing metastatic pathways (Zhang, Liu, and Li 2021). It was reported luteolin downregulated the TINCR/miR761 molecular module in a dose dependent manner and as a result, proliferation of TNBC cells was restrained through apoptotic inducement.

Polydatin ($C_{20}H_{22}O_8$) is the glycosylated structure of resveratrol that is mainly derived from dried roots and stems of Polygonum cuspidatum, a Chinese herb. Additionally, this compound also can be found in grape, wine and peanut (Du, Peng, and Zhang 2013). Polydatin enjoys several therapeutic attributes including antioxidant, free radical scavenging and shows protective effects against metabolic and infection diseases and malignant tumors (Sun, Wang, and Xu 2021). Hu, Fei (Hu, Wang, et al. 2019) reported the anti-proliferation and pro-apoptotic effects of polydatin in doxorubicin-resistant osteosarcoma cells. In this way, further analysis revealed that polydatin in a dose- and time-dependent behavior declined the expression of lncRNA TUG1 (Taurine-upregulated gene 1), being the mediator of Akt regulation. Accordingly, downregulation of TUG1/Akt followed by cellular apoptosis induced death of osteosarcoma cell lines.

Sanguinarine as a benzo-phenanthridine alkaloid compound is obtained from several sources in particular *Argemone Mexicana*, *Sanguinaria Canadensis* as well as *Chelidonium majus*. DNA damaging and cytotoxic capacities of sanguinarine have nominated it as a prospective candidate for cancer therapies (Su et al. 2021). It has been reported expression of CASC2, as a tumor inhibitor lncRNA, decreases in the ovarian cancer. Incubation of ovarian cancer cell lines with sanguinarine led to elevated expression of CASC2 succeeded by downregulation of ETIF4A3 (Eukaryotic Translation Initiation Factor 4A3) and eradication of the viability of cancer cells. It should be explained that ETIF4A3 is one of the elements of the exon junction complex and can be silenced through binding to CASC2 (Zhang et al. 2018).

Sulforaphane is a isothiocyanate component belonging to organosulfur chemical groups and presents in cruciferous vegetables such as broccoli, kale and cabbage (Sun et al. 2022). Beaver, Kuintzle (Beaver et al. 2017) declared pretreatment of prostate cancer cells with sulforaphane considerably change the regulation of about 100 lncRNAs. Among them, lncRNA LINC01116 owning to its essential role in a great number of cancers was selected for the subsequent investigations. It was reported that sulforaphane reversely regulated LINC01116 by which the proliferation of cancerous prostate cells was abolished. Furthermore, knockdown of LINC01116 led to increased expression of genes presenting in the glycolysis modulation (GADPH), the autophagy cascade (MAP1LC3B2) and the chromatin structure (H2AFY). In another study, it was shown sulforaphane through reducing the expression of H19-mediated APOBEC3G (a virus-stimulated tumor promoter) exerts its inhibitory effect on TFG-β (transforming growth factor-β)/Smad2 (Mothers

against decapentaplegic homolog 2) molecular axis and as a consequent, alleviate development of pancreatic cancer (Luo et al. 2021).

Conclusion and future perspective

Regardless of tremendous efforts for discovering practically impressive treatment strategies, various cancer types still affect a considerable number of people for cancer annually. Additionally, prevalent therapeutic methods are partially effective and more importantly, show inappropriate potential for inhibiting the cancer reoccurrence. The concept of substituting chemotherapy with chemoprevention strategies was firstly recommended by in the treatment of breast cancer. Afterwards, desperate attempts have been made over the following years to detect adequate signaling molecules as a target of functional natural compounds.

As a class of non-protein coding RNAs, lncRNAs are manage various cellular-related processes including apoptosis, differentiation and proliferation. Since dysfunction of oncogenic or tumor suppressor lncRNAs may result in cancer progression and metastasis, they have been considered as target molecules for phytochemicals in Precision medicine strategy of cancer treatment. As expressed in this review, laboratory studies have asserted the potential of phytochemicals for regulating the expression of lncRNAs, however; the clinical assessments of these approaches have been encountered with formidable challenges. It has been expressed the practical laboratory scale doses may be insufficient for clinical examination to present anticancer properties. Thus, extensive animal studies should be carried out together with in vivo analysis to provide suitable data for clinical considerations. Furthermore, poor solubility, low bioavailability and requiring high administration doses to presenting multifunctional bioactivities are parts of restrictive parameters reducing the efficacy of phytochemicals in clinical studies. Incorporation of nanotechnology and chemistry science is a promising approach for overcome deficiencies of natural compounds and enhance their anticancer adequacy. The other recommended method to improve the functionality of the mentioned approaches is employing combination of various phytochemical with diverse activities or their mixture with adjuvant chemotherapy drugs that can be considered for the subsequent investigations. In summary, phytochemicals enjoying various quality attributes such as availability, inexpensive, low toxicity and side effects can be regarded as an innovative and promising therapeutic method for inhibiting cancer and intensify the effect of current treatments.

Author's contributions

MH, ZA and BY contributed in conception, design and drafting of the manuscript.

Disclosure statement

No potential conflict of interest was reported by the authors.

Abbreviation

ABC: ATP-binding cassette;
AKT: protein kinase B;
AMPK: adenosine monophosphate-activated protein kinase;
ANRIL: antisense non-coding RNA in the INK4 locus; BANCR: BRAF-activated long noncoding RNA;
Bcl-2: B-cell lymphoma 2;
CCAT1: colon cancer-associated transcript 1;
CCAT2: colon cancer-associated transcript-2;
CCND1: cyclin D1;
CRC: colorectal cancer;
CTR1: copper transporter protein 1;
DIM: 3, 30-diindolylmethane;
DNMT: DNA methyl transferase;
EGCG: epigallocatechin-3-gallate;
EGFR: epidermal growth factor receptor;
EMT: epithelial-mesenchymal transition;
ERBB4: erb-B2 receptor tyrosine kinase 4;
ERK: extracellular signal-regulated kinase;
EWSAT1: Ewing sarcoma-associated transcript 1;
EZH2: enhancer of zeste homolog-2;
FAL1: focally amplified lncRNA on chromosome 1;
GAS5: growth arrest-specific 5;
HCC: hepatocellular carcinoma;
HIF-1α: hypoxia-inducible factor-1α;
HMOX1: heme oxygenase 1;
hnRNP: heterogeneous nuclear ribonucleoprotein;
HOTAIR: Hox transcript antisense intergenic RNA;
JNK: c-Jun N-terminal kinase;
KCNQ1: potassium voltage-gated channel subfamily Q member 1;
KCNQ1OT1: KCNQ1 opposite strand/antisense transcript 1;
LINC00511: long intergenic non-protein coding RNA 00511;
lncRNA: long non-coding RNAs;
MALAT1: metastasis-associated lung adenocarcinoma transcript 1;
MAPK: mitogen-activated protein kinase;
MDR1: multi-drug resistance-1;
MEG3: maternally expressed gene 3;
mRNAs: messenger RNAs;
mTOR: mammalian target of rapamycin;
ncRNA: non-coding RNA;
NF-κB: nuclear factor-B;
NKILA: NF-κB interacting lncRNA;
NPC: nasopharyngeal carcinoma;
NRB2: neighbor of BRCA1 lncRNA 2;
NSCLC: non-small cell lung cancer;
Oct4: octamer-binding transcription factor 4;
ORF: open reading frames;
PANDAR: promoter of CDKN1A antisense DNA damage activated RNA;
PCGEM1: Prostate cancer gene expression marker;
PDAC: pancreatic ductal adenocarcinoma;
PI3K: phosphatidylinositol 3-kinase;
PKB: protein kinase B;
PRC2: polycomb repressive complex-2;
PTEN: phosphatase and tensin homolog;
PUMA: P53 upregulated modulator of apoptosis;
PVT1: plasmacytoma variant translocation 1;
RCC: renal cell carcinoma;
ROS: reactive oxygen species;
Sox2: Sex-determining region Y-box2;
STAT3: signal transducer and activator of transcription 3;
SWI/SNF: Switching defective/sucrose nonfermenting.

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