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Therapeutic potential of phytochemicals in targeting long non-coding RNA (lncRNA) mediated Cancer Metastasis

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ABSTRACT

Cancer metastasis is a major challenge in cancer treatment and is regulated by several molecular mechanisms, including long non-coding RNAs (lncRNAs). LncRNAs are non-protein-coding RNA molecules that play important roles in cancer progression, epithelial–mesenchymal transition (EMT), invasion, migration, angiogenesis, and drug resistance. Recent studies suggest that phytochemicals can modulate the expression and activity of cancer-associated lncRNAs and may therefore provide a promising natural approach for controlling metastasis. Several phytochemicals, including curcumin, resveratrol, epigallocatechin gallate (EGCG), genistein, silibinin, emodin, sanguinarine, quercetin, naringenin, bharangin, artemisinin, anacardic acid, and gambogic acid, have demonstrated anticancer and antimetastatic activities through regulation of lncRNAs and related signaling pathways. These compounds can influence oncogenic and tumor-suppressive lncRNAs such as HOX transcript antisense intergenic RNA (HOTAIR), Metastasis-associated lung adenocarcinoma transcript 1 (MALAT1), H19 imprinted maternally expressed transcript (H19), Nuclear paraspeckle assembly transcript 1 (NEAT1), Growth arrest-specific 5 (GAS5), Maternally expressed gene 3 (MEG3), Plasmacytoma variant translocation 1 (PVT1), and Prostate cancer-associated transcript 29 (PCAT29), thereby affecting EMT, apoptosis, cell proliferation, invasion, and metastasis. Overall, phytochemical-mediated modulation of lncRNAs represents a promising therapeutic strategy for cancer metastasis and may provide opportunities for the development of safer and more effective anticancer approaches.

Key words: Cancer metastasis, Phytochemicals, Long non-coding RNA, lncRNA, Epithelial-mesenchymal transition (EMT), HOTAIR, MALAT1, Anticancer activity.

1. INTRODUCTION

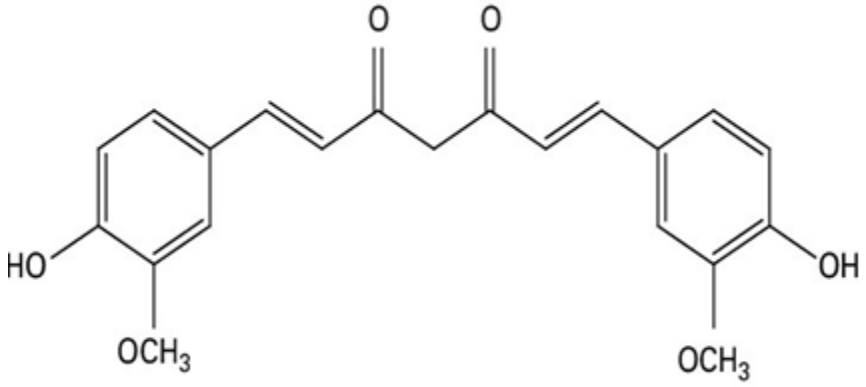
Cancer is a major global health issue and one of the leading causes of mortality worldwide, with around 19.3 million new cases and nearly 10 million deaths reported in 2020.[1] Cancer development is a complex and multistep process involving various mechanisms such as uncontrolled cell proliferation, dysregulated apoptosis, metastasis, changes in the tumor microenvironment, immune system dysfunction, and genetic abnormalities.[2] These alterations allow cancer cells to survive, multiply continuously, invade surrounding tissues, and spread to distant organs. Conventional cancer treatments such as surgery, chemotherapy, and radiotherapy remain the main therapeutic options for cancer management. However, these treatments may cause several adverse effects, development of drug resistance, recurrence, and limited efficacy in some patients. These limitations have encouraged researchers to explore alternative and complementary therapeutic approaches, including naturally occurring bioactive compounds and phytochemicals. [3] Long non-coding RNAs (lncRNAs) have emerged as important regulators of cancer development and progression. They significantly influence tumor angiogenesis, epithelial–mesenchymal transition (EMT), invasion, and metastasis. lncRNAs regulate these processes by modulating oncogenic signaling pathways, angiogenic factors, gene expression, and epigenetic modifications in various cancer types, including gastrointestinal, lung, breast, and brain cancers.[4] Several metastasis-associated lncRNAs, such as MALAT1, UBE2CP3, Highly upregulated in liver cancer (HULC), UCA1, and Prostate cancer antigen 3 (PCA3), contribute to cancer progression and metastasis by regulating the expression and

activity of important genes and signaling pathways[5,6]

LncRNAs are non-coding RNA molecules generally longer than 200 nucleotides that do not encode functional proteins but participate in various cellular processes, including cell growth, differentiation, proliferation, migration, and programmed cell death.[7] During the last decade, lncRNAs have gained considerable scientific attention because of their important roles in normal physiological functions and disease development, including innate immunity, maintenance of pluripotency, cell cycle regulation, and cellular homeostasis.[8] Their tissue- and cancer-specific expression patterns make lncRNAs promising molecular biomarkers for cancer diagnosis, prognosis, and therapeutic targeting.[9] Recent studies have demonstrated that bioactive phytochemicals can regulate the expression and function of lncRNAs involved in cancer development and metastasis. By influencing specific lncRNAs and their downstream molecular pathways, phytochemicals may inhibit cancer cell proliferation, migration, invasion, angiogenesis, and EMT. Therefore, modulation of lncRNAs by phytochemicals represents a potential therapeutic strategy for cancer treatment, with the possibility of reducing treatment-related adverse effects. [10] In addition to lncRNAs, other non-coding RNAs, including circular RNAs (circRNAs) and microRNAs (miRNAs), also play important roles in cancer initiation, progression, invasion, and metastasis, even though they do not directly code for proteins. [11] CircRNAs are abundant and stable non-coding RNA molecules found in eukaryotic cells. They participate in gene expression regulation at transcriptional, post-transcriptional, and translational levels and are primarily generated from the exons of protein-coding genes through back-splicing mechanisms. [12] miRNAs are short endogenous non-coding RNA molecules that regulate gene expression mainly by binding to target messenger RNAs. They influence several important biological processes, including metabolism, cell proliferation, cell cycle progression, differentiation, apoptosis, and cellular development. [13] study is here shown that, phytochemicals have the ability to influence lncRNA expression and associated molecular pathways involved in cancer progression and metastasis. Therefore, targeting lncRNAs using bioactive phytochemicals may provide a promising and relatively safer approach for the prevention and management of cancer. Further research is required to understand the precise molecular mechanisms through which phytochemicals regulate lncRNAs and to determine their potential clinical applications.

2. Phytochemicals as Antitumor Agents: Targeting LncRNAs and modulating LncRNA Expression

2.1 Curcumin



IUPAC Name: 1,7-bis-(4-hydroxy-3-methoxy-phenyl)-hepta-1,6-diene-3,5-dione

Molecular Formula: $C_{21}H_{20}O_6$, Molecular Weight: 368.39 g/mol

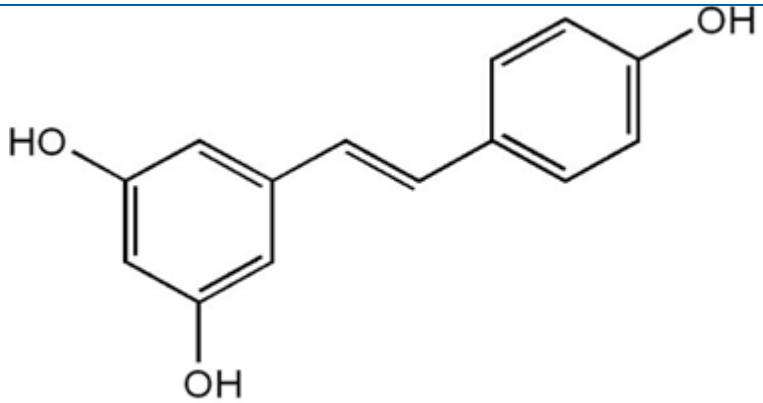
Chemical Class: Polyphenol, diarylheptanoid, αβ diketone, and enone

Physical Appearance: Bright orange-yellow crystalline powder

Biological Source: It is obtained from the dried rhizomes of *Curcuma longa* L. (syn. *Curcuma domestica* Valeton) Family: Zingiberaceae. Common Names: Turmeric, Haldi, Indian Saffron, Haridra

Curcumin, also known as diferuloylmethane, is a yellow-colored polyphenol derived from the spice turmeric (*Curcuma longa*) [14]. It belongs to the diarylheptanoid class of compounds and exhibits a wide range of biological activities, including chemopreventive, anti-cancer, and anti-inflammatory effects. Curcumin has also been identified as an epithelial–mesenchymal transition (EMT) suppressor in several types of cancer [15]. In vitro studies using breast cancer cell lines (MDA-MB-231, MCF-7, HCC1806, and SK-BR-3) have shown that curcumin regulates key signaling pathways involved in angiogenesis, metastasis, apoptosis, and cell proliferation [16,17]. Curcumin inhibits Akt phosphorylation in both MDA-MB-231 and MCF-7 cells in a time- and dose-dependent manner, with MCF-7 cells showing greater sensitivity when curcumin is combined with an Akt inhibitor [18]. Recent studies have demonstrated that curcumin can regulate the expression of several long non-coding RNAs (lncRNAs), including AF086415, AK056098, AK095147, AK294004, FLJ36000, GUCY2GP, H19, H2BFXP, HOTAIR, LINC00623, LOC100506835, MEG3, MUDENG, Promoter of CDKN1A antisense DNA damage activated RNA (PANDAR), PVT1, RP1-179N16.3, and ZRANB2-AS2, in different human disease models [19]. Curcumin also exerts anti-proliferative effects and induces apoptosis in gastric cancer cells. Its ability to up-regulate p53 and inhibit cell proliferation is reduced by H19 expression, while overexpression of c-Myc reverses the curcumin-induced down-regulation of H19. These findings suggest that curcumin suppresses gastric cancer cell proliferation through negative regulation of the c-Myc/H19 signaling pathway [20]. Furthermore, curcumin enhances the sensitivity of cancer cells to chemotherapy and radiotherapy by modulating lncRNA expression. It also influences cancer stem cell-related pathways involving the Polycomb Repressive Complex 2 (PRC2), which contains Enhancer of Zeste Homolog-2 (EZH2) and regulates stemness-associated genes [21,22]. In nasopharyngeal carcinoma, curcumin enhances radiosensitivity by modulating lncRNAs such as AF086415, AK056098, AK095147, AK294004, MUDENG, and RP1-179N. [23]

2.2 Resveratrol



IUPAC Name: 3,5,4'-trihydroxystilbene (or 3,4',5-Trihydroxystilbene)

Molecular Formula: $C_{14}H_{12}O_3$, Molecular Weight: 228.24 g/mol, CAS Number: 501-36-0

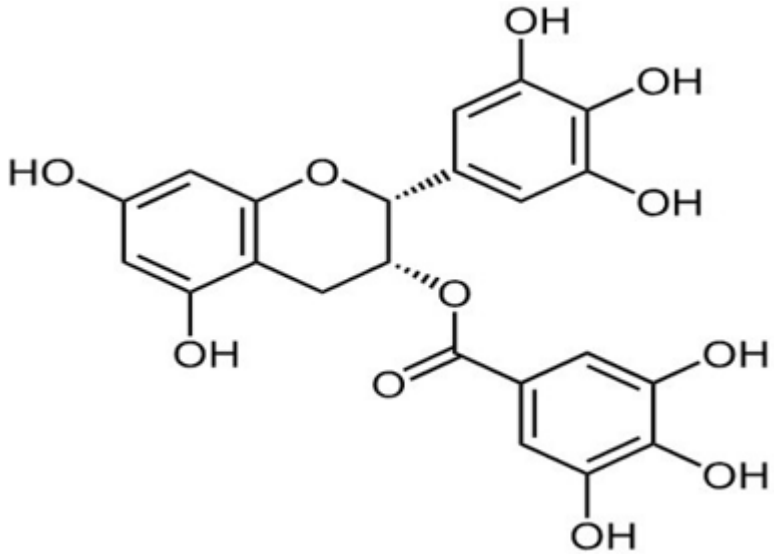
Isomers: Exists in two geometric isomers: trans-resveratrol (biologically active and more abundant) and cis-resveratrol, which can isomerize under ultraviolet (UV) radiation.

Physical Appearance: white to off-white or light yellow powder/solid

Biological Source: It is obtained from grapes, apples, blueberries, plums, and peanut.

Resveratrol (RSV, 17) is a naturally occurring polyphenol with good health effects in many areas [24]. RSV is considered a bioactive substance in red wine, and for this reason, has been the focus of much attention in the conduct of various studies. [25 The prostate cancer-associated transcript 29 (PCAT29) is a tumor suppressor lncRNA that is often down-regulated in prostate cancer tumors, potentially through androgen signaling. PCAT29 levels were also decreased in DU145 and LNCaP cells relative to normal prostate cells [26] Different regulation mechanisms were found in different cancer cell lines under the RSV. treatment. The miR-200 family of miRNAs is an important regulator of the EMT process in metastasis and cancer progression. miR-200c expression was increased in RSV-treated colorectal cancer HCT-116 cells and shifted from an EMT to a Mesenchymal–Epithelial Transition (MET) phenotype [27]. Other lncRNAs that have been shown to be up-regulated in glioma cell lines in response to resveratrol include MEG3, ST7OT1, NEAT1, and MIR155HG. [28]

2.3. Epigallocatechin gallate



Common Names: EGCG, Epigallocatechin-3-gallate, (-)-Epigallocatechin gallate

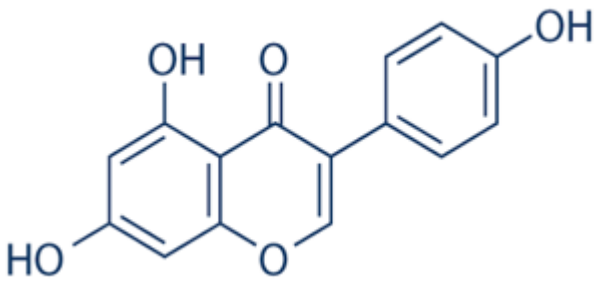
IUPAC Name: [(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-chromen-3-yl] 3,4,5-trihydroxybenzoate (or [(2R,3R)-5,7-dihydroxy-2-(3,4,5-trihydroxyphenyl)-3,4-dihydro-2H-1-benzopyran-3-yl] 3,4,5-trihydroxybenzoate)

Molecular Formula: $C_{22}H_{18}O_{11}$, **Molecular Weight:** 458.37 g/mol, **CAS Number:** 989-51-5

Biological Source: It is extracted primarily from the dried leaves of the tea plant *Camellia sinensis*

Epigallocatechin gallate EGCG, a natural polyphenol compound, possesses cancer-preventive and therapeutic properties. [29,30] Epigallocatechin gallate (EGCG) is a catechin found mainly in green tea, notable for its potential health benefits, as supported by numerous preclinical and clinical studies. [31.32.33,34,35,36,37,38] EGCG induces apoptosis and reduces proliferation by activating caspases, suppressing NF-κB activation, and modifying cell cycle regulatory protein expression, as shown by in vitro and in vivo studies[39]. EGCG can influence various cell signaling pathways in tumor cells. [40,41. Platinum-based chemotherapy, including cisplatin (cDDP), is utilized for patients with non-small cell lung cancer (NSCLC)[42].Cisplatin is a key drug in treating various cancers, notably non-small cell lung cancer (NSCLC). The copper transporter protein 1 (CTR1) is crucial for determining cisplatin sensitivity. [43] CTR1, a target gene of miR-98-5p, shows increased expression due to upregulation in NEAT1. EGCG enhances cisplatin sensitivity 5p/CTR1 axis in both in vivo and in vitro settings. [44] by modulating the NEAT1/miR-98- .

2.4. Genistein



IUPAC Name: 5,7-dihydroxy-3-(4-hydroxyphenyl)chromen-4-one

Molecular Formula: $C_{15}H_{10}O_5$, Molecular Weight: 270.24 g/mol, CAS No.:446-72-0

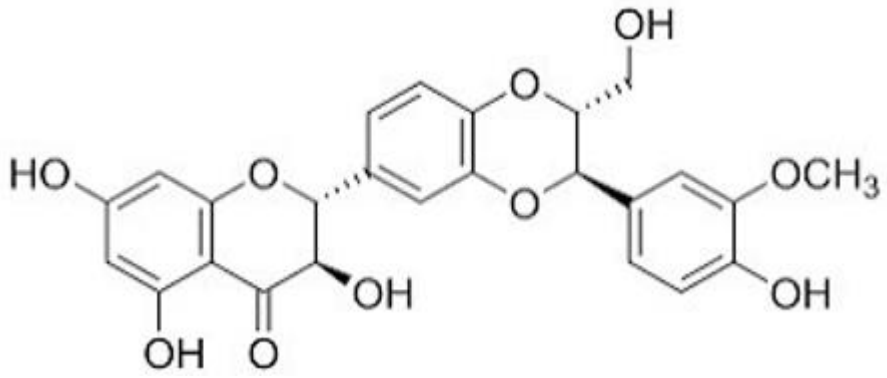
Physical appearance: white to off-white, light yellow, or light orange fine powder or small crystals.

Biological Source: Genistein is a natural isoflavone and phytoestrogen found primarily in plants (Apios Americana, Glycine max, etc.,) belonging to the Fabaceae (legume) family

Genistein (5,7-trihydroxyisoflavone), a naturally occurring isoflavone abundant in soybeans, exhibits potent anti-inflammatory, antioxidant, and antiangiogenic activities. It exerts significant anticancer effects by inducing apoptosis and suppressing cell cycle progression, angiogenesis, and metastasis, thereby inhibiting tumor growth and progression. [45,46] In breast cancer, treatment of MCF-7 cells with genistein and calycosin promotes apoptosis and inhibits cell proliferation through the downregulation of phosphorylated Akt (p-Akt) and the oncogenic lncRNA HOTAIR, with calycosin showing greater inhibitory activity than genistein [47]. Additionally, genistein acts as a protein tyrosine kinase inhibitor and has demonstrated broad-spectrum anticancer activity against multiple cancer types. [48–53] In colorectal cancer, genistein treatment (50 μM) significantly reduces the viability and migratory capacity of SW480 cells by suppressing the expression of lncRNA

TTTY18 and inhibiting the Akt, SGK1, and p38 MAPK signaling pathways [54].

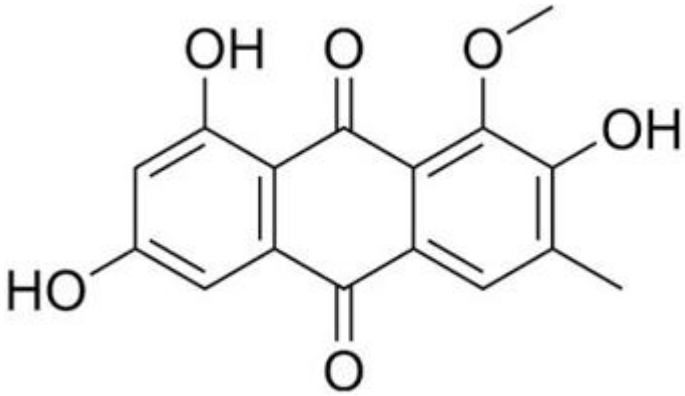
2.5. Silibinin



IUPAC Name of Silybin A: (2R,3R)-2-[(2R,3R)-2,3-dihydro-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-1,4-benzodioxin-6-yl]-2,3-dihydro-3,5,7-trihydroxy-4H-1-benzopyran-4-one

Molecular Formula: $C_{25}H_{22}O_{10}$, **Molecular Weight:** 482.44 g/mol, **CAS Number:** 22888-70-6

Physical Appearance: pale yellow, white-like crystalline powder



IUPAC Name of Silybin B: (2R,3R)-3,5,7-trihydroxy-2-[(2S,3S)-3-(4-hydroxy-3-methoxyphenyl)-2-(hydroxymethyl)-2,3-dihydro-1,4-benzodioxin-6-yl]-2,3-dihydrochromen-4- one

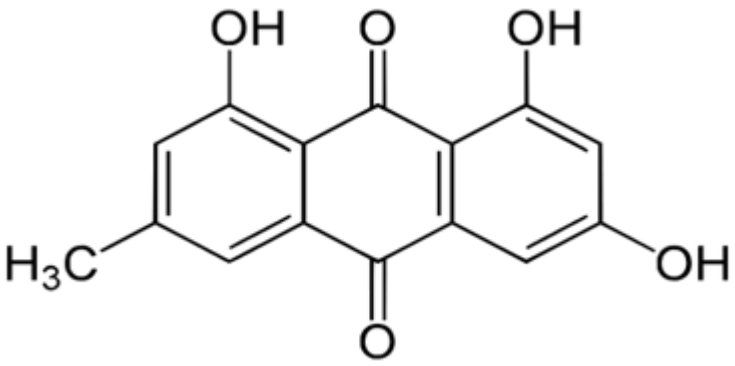
Molecular Formula: $C_{25}H_{22}O_{10}$, Molecular Weight: 482.44 g/mol, CAS Number: 22888-70-6 (mixture/general), with distinct CAS numbers for individual stereoisomers, Physical Appearance: pale yellow, white-like crystalline powder

Biological Source: It is primarily obtained from the seeds and fruits of the *Silybum marianum*

It has been demonstrated that silibinin, the main active ingredient in silymarin, has significant anticancer effects in a range of malignancies. Silibinin can dramatically increase apoptosis and prevent invasion, migration, and proliferation by downregulating the PI3K/Akt and Signal transducer and activator of transcription (STAT) signaling pathways, [55] According to reports, silibinin significantly inhibits invasion, migration, and proliferation, among other stages of tumor progression. Furthermore, it causes the human bladder cancer cell lines T24 and UM-UC-3 to

undergo apoptosis. Additionally, silibinin inhibits the actin cytoskeleton and Phosphoinositide 3-kinase (PI3K)/ Protein kinase B (AKT) signaling pathways, which interact via the RAS oncogene. Moreover, it reduces H3 acetylation and H3 lysine 4 (H3K4) trimethylation at the Kirsten rat sarcoma virus (KRAS) promoter, indicating its role in epigenetic regulation through histone alterations. Furthermore, silibinin had no discernible impact on MALAT1, MEG3, or GAS5, although it did considerably lower the expression of the carcinogenic lncRNAs ZFAS1 and HOTAIR. The PI3K inhibitor wortmannin similarly decreased HOTAIR expression in human bladder cancer cells. [56] HOTAIR has been linked to the recurrence of bladder cancer, which is consistent with these findings. [57] As a result, silibinin may modulate carcinogenic lncRNAs to produce its anticancer effects. The anti-bladder cancer action of silibinin may also be attributed to other signaling pathways. Whether silibinin controls HOTAIR in other cancer types, to have comparable anticancer effects is still unknown, though.

2.6. Emodin



IUPAC Name: 1,3,8-trihydroxy-6-methylanthracene-9,10-dione

Molecular Formula: $C_{15}H_{10}O_5$, Molecular Weight: 270.24 g/mol, CAS Number: 518-82-1

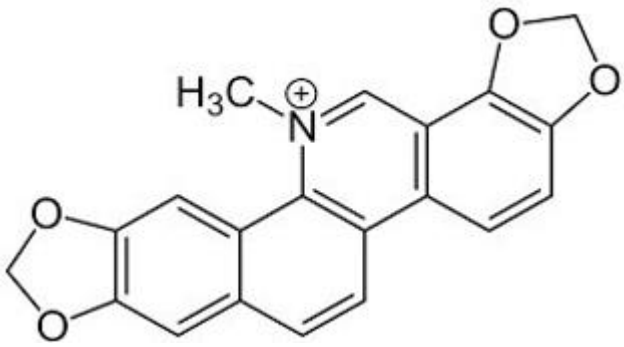
Physical **Appearance:** Orange-yellow crystalline solid or powder with a melting point of 256–257 °C.

Biological Source: Emodin is a naturally occurring anthraquinone derivative obtained from the roots and rhizomes of Rheum palmatum (rhubarb), the roots of Reynoutria japonica (Japanese knotweed), and species of buckthorn (Rhamnus). It is also produced by certain fungi.

Some preclinical studies show that the active anthraquinone emodin, especially isolated from *Rhamnus frangula*, has anti-cancer activities [58]. Emodin has been studied for its regulation of EMT, mainly in two aspects: anti-cancer and anti-fibrosis. Emodin exerts anti-invasion and anti-migration effects by regulating EMT in different types of cancer cells through different pathways. Ectopic expression of EMT regulator TWIST1 in head and neck carcinoma FaDu cells to induce EMT and acquire mesenchymal phenotype. Emodin reversed this process successfully and inhibited TWIST1-induced invasion. The in vivo effect was evaluated by the detection of pulmonary colonization from tumor cells injected intravenously. Mechanistically, emodin suppressed the transcription of E-cadherin by inhibiting TWIST1 binding to the E-cadherin promoter. [59] Additionally, emodin can sensitize resistant cancer cells to chemotherapeutic agents. This anthraquinone has also shown promise for the treatment of osteoarthritis (OA), a chronic disease that affects adipose tissue, articular cartilage, ligaments, subchondral bone, synovium and tendons. [60] In pancreatic cancers, miR-1271 down-regulation promoted the occurrence of EMT

and metastasis; emodin increased the expression of miR-1271 and significantly inhibited the EMT process and invasion. [61].However, it is not known whether emodin regulates the functions of TUG1 in cancer models.

2.7. Sanguinarine



IUPAC Name: 13-methyl[1,3]benzodioxolo[5,6-c]-1,3-dioxolo[4,5-i]phenanthridin-13-ium

Molecular Formula: $C_{20}H_{14}NO_4^+$

Molecular Weight: Approximately 332.33 g/mol

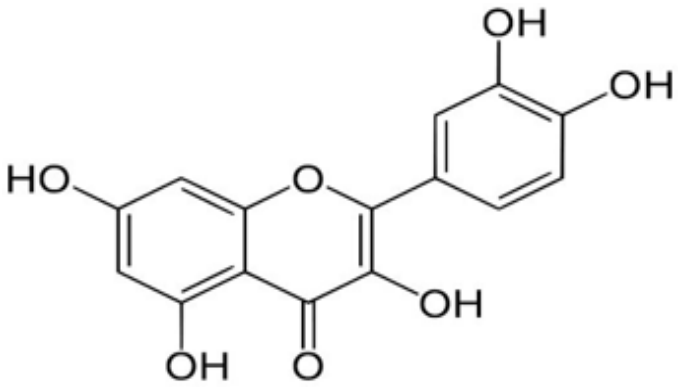
CAS Number: 2447-54-3

Physical Appearance: Orange-red to red crystalline powder.

Biological Source: Sanguinarine is an isoquinoline alkaloid obtained from the roots and rhizomes of Sanguinaria canadensis (Bloodroot), and from plants such as Chelidonium majus and Macleaya cordata.

Sanguinarine, a benzo-phenanthridine alkaloid found in the rhizomes of Sanguinaria canadensis, demonstrate significant biological activity and anti-cancer properties. [62] Sanguinarine is an alkaloid noted for its anti-microbial, anti-fungal, anti-inflammatory, and anti-tumor properties. It has shown significant anti-cancer effects against various cancer types, including non-small cell lung, pancreatic, gastric, and breast cancer. [63,64.65,66,67] Sanguinarine induces apoptosis via mechanisms including free radical initiation and mitochondrial dysfunction, impacting proteins such as STAT3, p53, BCL2 family members, caspases, Inhibitor of apoptosis protein (IAP), and Extracellular signal-regulated kinase (ERK)1/2. It promotes apoptosis in MDA-MB-231 Breast cancer (BC) cells by up-regulating pro-apoptotic proteins and inhibiting anti-apoptotic proteins. [68] In the MCF-7 BC cell line, the combination of SANG with a sub-lethal dosage of digitonin enhances cytotoxic effects. [69]

2.8 Quercetin



IUPAC Name: 2-(3,4-dihydroxyphenyl)-3,5,7-trihydroxy-4H-1-benzopyran-4-one.

Molecular Formula: $C_{15}H_{10}O_7$ Molecular Weight: 302.24 g/mol, CAS Registry Number: 117-39-5.

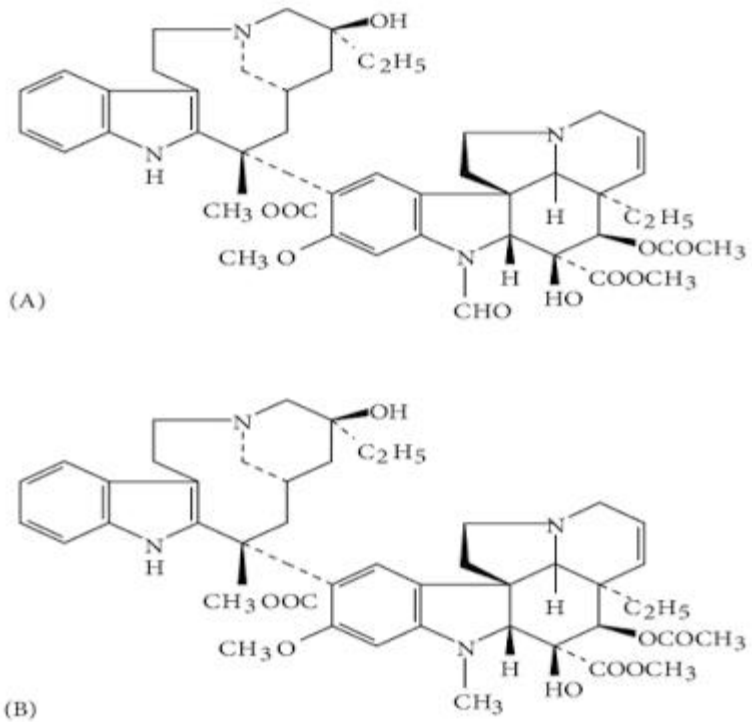
Physical Appearance: Bright lemon-yellow crystalline powder. It is poorly soluble in cold water but soluble in alcohol and lipids.

Biological Source: It is obtained from various plants such as *Curcuma domestica valeton*, *Cuscuta reflexa*, *Daucus carota*, *Emblica officinalis*, *Foeniculum vulgare*, *Glycyrrhiza glabra*, *Mangifera indica*, *Momordica charantia*, etc.

Quercetin is a dietary flavonoid widely present in fruits, vegetables, and grains, with antioxidant, anti-inflammatory, and anticancer properties. [70,71] Studies have shown that quercetin can suppress EMT and reduce cancer cell growth, migration, and invasion. In glioblastoma, quercetin inhibited EMT through the Glycogen synthase kinase-3 beta (GSK-3β)/β-catenin/Zinc finger E-box-binding homeobox 1 (ZEB1) pathway and reduced tumor growth in vivo. [72] In triple-negative breast cancer, it reversed EMT by regulating Insulin-like growth factor 1 (IGF1)/Insulin-like growth factor 1 receptor (IGF1R) signaling and β-catenin target genes [73,74]. In prostate cancer, quercetin suppressed EMT through the Epidermal growth factor receptor (EGFR)/PI3K/AKT pathway and by regulating the lncRNA MALAT1. [75,76] It also inhibited STAT3 signaling and reversed IL-6-induced EMT in pancreatic cancer cells, thereby reducing invasion. [77] Quercetin further showed anti-fibrotic effects by suppressing EMT through Hedgehog signaling in renal fibrosis and reducing bleomycin-induced EMT in pulmonary fibrosis. [78,79] Moreover, quercetin enhanced the response to erlotinib and cisplatin by suppressing EMT through Pyruvate kinase M2 (PKM2) and Yes-associated protein (YAP)/Hippo pathway regulation, respectively. [80,81] Many therapeutic plants, particularly *Catharanthus roseus*, also known as Madagascar periwinkle, are significant in the Indian community. Notably, *C. roseus* is recognized for its phytoremediation capabilities, specifically in lowering heavy metal accumulation such as cadmium (Cd). It has also been utilized in treating various diseases, including diabetes, wasp stings, and cold symptoms. [82] *C. roseus* contains bioactive compounds such as terpenoids, flavonoids, and alkaloids, which have chelating and antioxidant properties, potentially protecting against Cd-induced cytotoxicity by reducing cellular damage and oxidative stress. [83] Vinca alkaloids and terpenes have been studied in breast cancer models, including MCF-7, T47D, and MDA-MB-231[84]. These compounds could reduce cell viability, induce apoptosis, and stop cell migration and invasion. Vinca alkaloids are safe adjunct natural alkaloids that boost chemotherapeutic agents like doxorubicin and cyclophosphamide, while also lessening drug resistance, a key hurdle in treating various malignancies, including breast cancer. [85,86,87,88,89] Alkaloids target spindles through mechanisms like disrupting microtubule dynamics

and inducing apoptosis, but vinca alkaloids can cause side effects such as neurotoxicity and gastrointestinal issues. In contrast, terpenes show low toxicity and minimal liver impact, indicating their non-carcinogenic nature in normal cells. [90]

2.9. Alkaloids from *Catharanthus roseus* (Vinca Alkaloids)



Vinca Alkaloids: A- Vincristin, B- Vinblastin

Vincristine IUPAC Name: (3aR,3a1R,4R,5S,5aR,10bR)-methyl • (3aR,3a1R,4R,5S,5aR,10bR)-methyl 4-acetoxy-3a-ethyl-9-((5S,7S,9S)-5-ethyl-5-hydroxy-9-(methoxycarbonyl)-2,4,5,6,7,8,9,10-octahydro-1H-3,7-methano[1]azacycloundecino[5,4-b]indol-9-yl)-6-formyl-5-hydroxy-8-methoxy-3a,3a1,4,5,5a,6,11,12-octahydro-1H-indolizino[8,1-cd]carbazole-5-carboxylate

Alternative IUPAC Name: (2′β)-22-Oxovincaleukoblastine

Molecular Formula: $C_{46}H_{56}N_4O_{10}$, Molecular Weight**:** 824.96 g/mol

CAS Number**:** 57-22-7

Appearance**:** White crystalline solid (free base)

Vinblastin

IUPAC Name:

Dimethyl(2β,3β,4β,5α,12β,19α)-15-[(5S,9S)-5-ethyl-5-hydroxy-9-(methoxycarbonyl)-1,4,5,6,7,8,9,10-octahydro-2H-3,7-methanoazacycloundecino[5,4-b,indol-9-yl]-3-hydroxy-16-methoxy-1-methyl-6,7-didehydroaspidospermidine-3,4-dicarboxylate

Molecular Formula: $C_{46}H_{58}N_4O_9$, Molecular Weight**:** 810.97 g/mol, CAS Number: 865-21-4

Biological Source: Vinca alkaloids are obtained from the periwinkle plant *Catharanthus roseus*, formerly *Vinca rosea*.

2.10. Naringenin

Naringenin is a flavanone found in citrus fruits, similar in structure to hesperedin, and is generally considered a safe supplement with beneficial health effects. [91] Emerging studies suggest that naringenin possesses anti-cancer properties, particularly in glioblastoma cells, where it inhibits invasion and metastasis by modulating epithelial-mesenchymal transition (EMT), as indicated by changes in EMT biomarkers. [92] Naringenin inhibits the Transforming growth factor-beta (TGF-β)/Smad3 pathway in pancreatic cancer of EMT markers and a decrease in cell invasiveness and metastasis. [93]

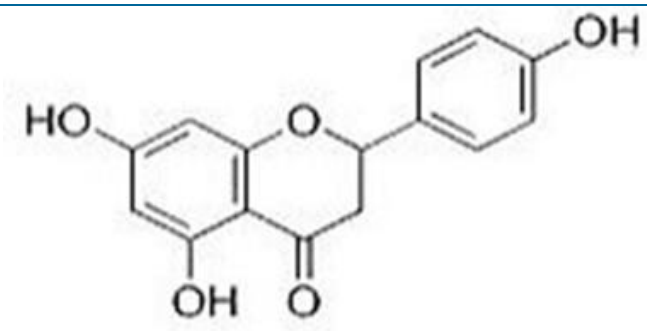
IUPAC Name: 5,7-dihydroxy-2-(4-hydroxyphenyl)-2,3-dihydrochromen-4-one

Molecular Formula: $C_{15}H_{12}O_5$. , Molecular Weight**:** 272.26 g/mol

Physical Appearance:is a solid organic compound that typically appears as a white, off-white, pale yellow-brown,

Biological Source: It is obtained primarily from the roots and root nodules of *Premna herbacea* Roxb.

2.11. Bharangin



IUPACName: (3S)-15-hydroxy-3,7,7-trimethyl-13-propan-2-yl-4-oxatricyclo[9.4.0.0^{3},^{8}]pentadeca-1(15),8,10,12-tetraene-5,14-dione.

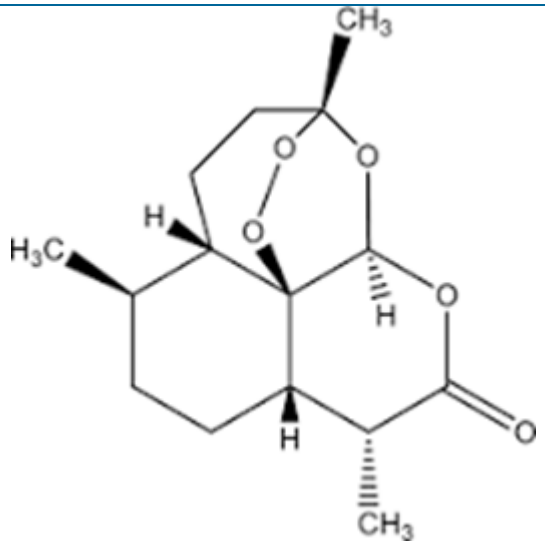
Chemical Formula: $C_{20}H_{24}O_4$. , Molar Mass: 328.40 g·mol, CAS Number**:** 72711-84-3

Physical Appearance: Amorphous orange solid**.**

Biological Source: Reported in Premna herbacea.

Bharangin is a diterpenoid quinonemethide, isolated from the roots of the medicinal plant Pygmacopremna herbacea [94,95,96]. It is known that various parts of the plant exhibit a range of biological activities. [97-99] Diterpenoid induced the expression of tumor suppressor lncRNAs, growth arrest specific-5 (GAS-5) and maternally expressed-3 (MEG-3) but suppressed the expression of oncogenic lncRNA, H19. Furthermore, it was observed that the diterpenoid inhibited NF-κB activation induced by okadaic acid in breast cancer cells. Bharangin most likely exerts anticancer activities through modulating the expression of lncRNA and abrogating the activation of NF-κB.

2.12 Artemisinin



IUPAC Name: (3R,5aS,6R,8aS,9R,12S,12aR)-octahydro-3,6,9-trimethyl-3,12-epoxy-12H-pyrano[4,3-j]-1,2-benzodioxepin-10(3H)-one

Molecular Formula: $C_{15}H_{22}O_5$, **Molecular Weight:** 282.33 g/mol, **CAS No.:** 63968-64-9

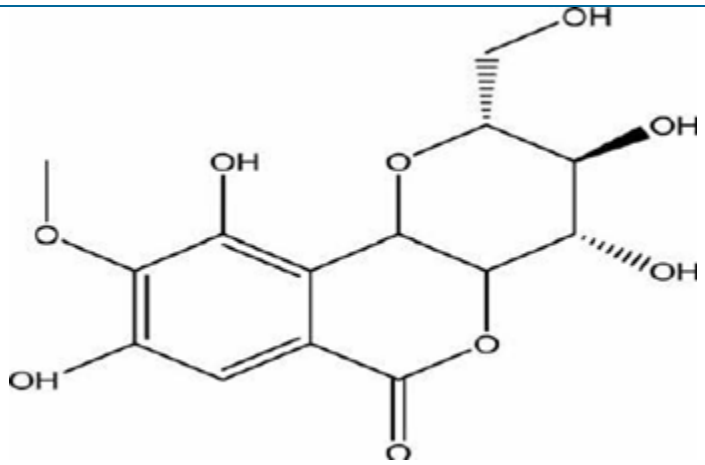
Physical Appearance: colorless, needle-shaped crystals or a white to off-white crystalline powder

Biological Source: It is obtained is naturally from the leaves and flowers of the sweet wormwood plant, scientifically known as *Artemisia annua*, Family: Asteraceae.

Biological Source: It is obtained is naturally from the leaves and flowers of the sweet wormwood plant, scientifically known as *Artemisia annua*, Family: Asteraceae. *Artemisia annua* by Chinese scientists, has been used as a powerful anti-malarial drug in clinics [100] A study demonstrated that artemisinin reversed celecoxib-induced EMT in human ovarian epithelial adenocarcinoma SKOV3 cells.

Dihydroartemisinin was found to inhibit EMT in esophageal, laryngeal, oral squamous and breast cancer cells through different regulatory pathway Dihydroartemisinin-induced autophagy inhibits esophageal cancer cell migration [101].The Dihydroartemisinin-elicited EMT inhibition in breast cancers was clarified by using canine mammary tumor cells, which are a suitable model for studies of human breast cancer research [102,103].

2.13 Anacardic acid



IUPAC Name: Saturated form: 2-Hydroxy-6-pentadecylbenzoic acid.

Diene form: 2-Hydroxy-6-[(8Z,11Z)-pentadeca-8,11-dien-1-yl]benzoic acid.

Triene form: 2-Hydroxy-6-[(8Z,11Z)-pentadeca-8,11,14-trien-1-yl]benzoic acid.

Molecular Formulas: Saturated: $C_{22}H_{36}O_3$-Diene: $C_{22}H_{32}O_3$-Triene: $C_{22}H_{30}O_3$

CAS No.: Saturated: 16611-84-0,Diene: 103904-74-1,Triene: 103904-73-0

Physical Appearance: Yellowish oily liquid in naturally occurring mixtures; appearance may vary depending on purity and composition.

Biological Source: Anacardic acid is a naturally occurring phenolic compound predominantly found in cashew nut shell liquid (CNSL), obtained from the shells of Anacardium occidentale L.

Anacardic acid is a phenolic lipid primarily found in cashew nuts, consisting of a mixture of saturated and unsaturated organic molecules. [104] This polyphenol has shown potential against various cancer types, including breast cancer[105-107]. It was identified 80 dysregulated genes, including lncRNA MIR22HG, in MCF7 cells and 886 genes in MDA-MB-231 cells in response to anacardic acid. Key down-regulated genes across both cell lines included SCD, INSIG1, and TGM2, while up-regulated genes were PDK4, GPR176, and ZBT20.

Molecular modeling suggested that anacardic acid inhibits monounsaturated fatty acid synthesis and increases endoplasmic reticulum stress in MDA-MB-231 cells. Additionally, it inhibited TNFα-induced Nuclear factor kappa B (NFκB) activity in MCF-7 cells, revealing new targets that may enhance its anti-proliferative and proapoptotic effects against breast cancer

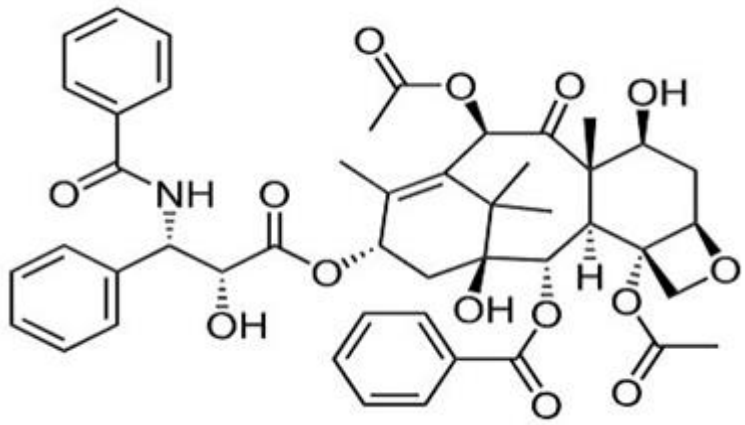
2.14. Gambogic acid (GA)

Gambogic acid (GA) is a xanthonoid obtained from Garcinia resin, known for its anti-inflammatory, antioxidant, antiviral, and parasiticidal properties. [108] The lncRNA GAS5 is negatively correlated with the clinical stage of bladder cancer[109]. GAS5 overexpression leads to reduced viability and apoptosis in EJ and T24 bladder cancer cells by repressing Enhancer of zeste homolog 2 (EZH2) transcription through direct interaction and recruitment of E2F

transcription factor 4 (E2F4) to the EZH2 promoter. This downregulation of EZH2 is linked to the overexpression of miR-101. Additionally, gambogic acid (GA) induces GAS5 expression, promoting pro-apoptotic effects, which are negated by GAS5 knockdown. Overall, GAS5 acts as a tumor suppressor by inhibiting EZH2

expression, and its induction by GA contributes to anti-cancer activities against bladder can.

2.15. Paclitaxel



IUPACName: (1S,2S,4S,7R,9S,10S,12R,15S)-4,12-bis(acetyloxy)-1,9-dihydroxy-15-{[(2R,3S)-2-hydroxy-3-phenyl-3-(phenylformamido)propanoyl]oxy}-10,14,17,17-tetramethyl-11-oxo-6-oxatetracyclo[11.3.1.0^{3},^{10}.0^{4},^{7}]heptadec-13-en-2-yl benzoate.

Molecular Formula: $C_{47}H_{51}NO_{14}$, Molecular Weight: 853.91 g/mol

CAS Registry Number: 33069-62-4

Appearance: White to off-white crystalline powder

Biological Source: Paclitaxel is a naturally occurring diterpenoid originally isolated from the bark of the Pacific yew tree, Taxus brevifolia.

Paclitaxel, known by the brand name Taxol, is an anti-cancer drug first isolated from the bark of the Pacific yew tree in 1971. [110]

Taxol, approved in 1993 for its anti-cancer properties, is an antimitotic agent that inhibits tumor growth by preventing cell division. It is effective against various cancers, including breast, ovarian, pancreatic, non-small cell lung cancer, and AIDS related Kaposi sarcoma. [111,112] GAS5, a tumor suppressor, is significantly reduced in breast cancer tissues compared to adjacent non-tumor tissues. Its lower expression correlates with advanced Tumor, node and metastasis (TNM) stages and lymph-node metastasis, as well as resistance to paclitaxel. Overexpressing GAS5 in resistant cancer cells inhibited migration and invasion while increasing sensitivity to paclitaxel.

In nude mouse models, GAS5 overexpression enhanced the anti-tumor effects of paclitaxel and decreased lung metastasis by reversing epithelial-mesenchymal transition (EMT). The findings indicate that reduced GAS5 expression contributes to lung metastasis in breast cancer, highlighting its therapeutic potential. [113] The tumor suppressor Tumor suppressor candidate 7 (TUSC7) enhances endometrial carcinoma sensitivity to paclitaxel by targeting miR-23b. [114] Paclitaxel decreases the expression of CDKN2B-AS1, HOTAIR, and MALAT1 in laryngeal squamous cell carcinoma. [115] PVT1 can affect the response of cervical cancer cells to paclitaxel by regulating EMT[116].The expression level of PVT1 was significantly higher in SGC7901 paclitaxel-resistant cells compared to SGC7901 cells[117].

Table 1. lncRNAs in Cancer Metastasis and Their Potential Phytochemical ligands

lncRNA	Type/role	Major molecular function	Effect on metastasis	Potential phytochemical regulator
HOTAIR	Oncogenic lncRNA	Regulates oncogenic signaling and gene expression	Promotes invasion and metastasis	Curcumin, Genistein, Silibinin
MALAT1	Oncogenic lncRNA	Regulates cell migration and EMT	Promotes metastasis	Quercetin, Paclitaxel
H19	Oncogenic lncRNA	Regulates proliferation and signaling	Promotes cancer progression	Curcumin, Bharangin
NEAT1	Cancer-associated lncRNA	Regulates signaling and drug response	Supports cancer progression	EGCG, Resveratrol
GAS5	Tumor-suppressor lncRNA	Promotes apoptosis and suppresses EZH2	Suppresses tumor progression	Bharangin, Gambogic acid, Paclitaxel
MEG3	Tumor-suppressor lncRNA	Regulates tumor-suppressive responses	May inhibit cancer progression	Curcumin, Resveratrol, Bharangin
PVT1	Oncogenic lncRNA	Regulates proliferation and chemoresistance	Promotes progression/metastasis	Curcumin, Paclitaxel
PCAT29	Tumor-suppressor lncRNA	Associated with androgen signaling	Suppresses prostate cancer progression	Resveratrol

3. CONCLUSION

Phytochemicals have shown promising anticancer and antimetastatic effects by regulating long non-coding RNAs (lncRNAs) and their associated signaling pathways. Compounds such as curcumin, resveratrol, EGCG, genistein, silibinin, quercetin, naringenin, bharangin, artemisinin, gambogic acid and paclitaxel can influence oncogenic and tumor-suppressive lncRNA genes involved in EMT, apoptosis, proliferation, invasion and metastasis. Modulation of lncRNA genes expression such as HOTAIR, MALAT1, H19, NEAT1, GAS5, MEG3 and PVT1 may therefore represent a promising approach for controlling cancer progression and metastasis. However, further mechanistic, preclinical and clinical studies are required to establish their therapeutic potential and safety. Overall, targeting lncRNA genes with phytochemicals may provide a promising natural strategy for the development of novel anticancer therapies.

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