Research Progress on Anticancer Active Constituents and Mechanisms of Dendrobium Species (Postprint)

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Abstract

Dendrobium represents the second largest genus within the Orchidaceae family, with numerous species being traditional precious medicinal plants that exhibit significant antitumor activity. In recent years, remarkable advances have been achieved in antitumor research on Dendrobium. This review systematically summarizes the primary antitumor active constituents, extraction methodologies, and underlying antitumor mechanisms of Dendrobium species. The main antitumor active components encompass polysaccharides, alkaloids, phenanthrenes, bibenzyls, fluorenone compounds, among others. The antitumor mechanisms primarily include enhancement of immune function, inhibition of cancer cell proliferation, induction of cancer cell apoptosis, regulation or arrest of the cancer cell cycle, antioxidant and free radical scavenging activities, and modulation of signal pathway transduction. Building upon these findings, we further propose intensifying comprehensive investigations into the anticancer potential of Dendrobium, exploring additional Dendrobium medicinal resources and their characteristic constituents, elucidating their antitumor mechanisms in depth, establishing a holistic evaluation system, providing a theoretical foundation for the development of Dendrobium-based anticancer therapeutics, and furnishing scientific rationale for the rational and efficient utilization of Dendrobium resources.

Full Text

Preamble

Advances in Antitumor Active Ingredients and Mechanisms of *Dendrobium*

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Abstract

Dendrobium is the second largest genus in the Orchidaceae family. Many *Dendrobium* species are traditionally valued medicinal plants with significant antitumor pharmacological activities. In recent years, remarkable progress has been made in antitumor research on *Dendrobium*. This paper summarizes the main antitumor active ingredients, extraction methods, and antitumor mechanisms of *Dendrobium* plants. The primary antitumor active components include polysaccharides, alkaloids, phenanthrenes, bibenzyls, and fluorenones. The antitumor mechanisms mainly involve enhancing immune function, inhibiting cancer cell proliferation, promoting cancer cell apoptosis, regulating or blocking the cancer cell cycle, antioxidant and free radical scavenging activities, and modulating signal transduction pathways. Based on previous research, we propose that further efforts are needed to investigate the anticancer potential of *Dendrobium*. Specifically, future work should explore additional *Dendrobium* medicinal resources and their characteristic components, elucidate their antitumor mechanisms in greater depth, and establish comprehensive evaluation systems. This review provides theoretical foundations for developing anticancer drugs from *Dendrobium* and offers scientific guidance for the rational and effective utilization of *Dendrobium* resources.

Keywords: *Dendrobium*, antitumor, active ingredient, mechanism of action

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Dendrobium is the second largest genus in the Orchidaceae family, comprising numerous species that typically grow epiphytically on tree trunks in high-altitude forests or on moist rocks, preferring semi-shaded environments. The genus is widely distributed across Asia, Australia, and Europe (Chen et al., 2009). The English edition of Flora of China (2009) documented 78 *Dendrobium* species in China, primarily found in Yunnan, Guizhou, Guangxi, Guangdong, Hainan, and Taiwan (Chen et al., 2009). Traditional Chinese medicine texts record that *Dendrobium* possesses pharmacological effects such as nourishing yin, benefiting the stomach, and strengthening essence (Chinese Materia Medica Commission, 1999). In recent years, the medicinal value of *Dendrobium*, particularly its antitumor activity, has attracted increasing attention from researchers worldwide. Studies have demonstrated that multiple *Dendrobium* species exhibit significant antitumor effects. For example, *Dendrobium catenatum* (commonly known as Tie Pi Shi Hu) can inhibit the growth of mouse Lewis lung cancer cells, human hepatocellular carcinoma HepG2 cells, human lung cancer A549 cells, human teratocarcinoma stem cells NCCIT, and mouse teratocarcinoma stem cells F9, while also inducing apoptosis in HepG2 cells (Liu et al., 2014; Wang et al., 2014; Xing et al., 2018b; Luo et al., 2019). *Dendrobium nobile* can suppress the proliferation of colon adenocarcinoma Caco-2 cells and human

triple-negative breast cancer cells (Wang, 2015; Song, 2019). This review summarizes research progress on the main antitumor active ingredients, extraction methods, and antitumor mechanisms of *Dendrobium* to provide a reference for further research and application.

1. Main Antitumor Active Ingredients and Effects of *Dendrobium*

The main chemical constituents of *Dendrobium* include polysaccharides, alkaloids, phenanthrenes, bibenzyls, fluorenones, flavonoids, lignans, coumarins, anthraquinones, glycosides, esters, and other compounds (Wang et al., 2019). Research indicates that the primary antitumor active components are alkaloids, polysaccharides, and phenolic compounds (Wang, 2017; Zhou et al., 2018; Song, 2019), as detailed in Table 1 .

Table 1 Main active ingredients of *Dendrobium*

Active ingredient	Structural formula / molecular formula	Species	Cancer cell	References
Total polysaccharides of *D. catenatum*	—	*D. catenatum*	Salivary gland cancer A-253, lung cancer A549, teratoma NCCIT, Lewis lung cancer, liver cancer HepG2, cervical cancer HeLa	Xiang et al., 2013; Liu et al., 2014; Wang et al., 2014; Wang, 2017; Wei et al., 2018; Xing et al., 2018b; Yu et al., 2018

Active ingredient	Structural formula / molecular formula	Species	Cancer cell	References
Total polysaccharides of *D. nobile*	—	*D. nobile*	Sarcoma 180, acute promyelocytic leukemia HL-60, chronic myelogenous leukemia K-562, bone marrow monocyte leukemia WEHI-3, cervical cancer HeLa	Wang et al., 2010; Ge et al., 2015; Yan et al., 2015

Active ingredient	Structural formula / molecular formula	Species	Cancer cell	References
Total alkaloids of *D. nobile*	–	*D. nobile*	Breast cancer MCF-7, colon cancer Caco-2 and HT-29, liver cancer HepG2, gastric cancer MNK45, lung cancer A549, triple-negative breast cancer MDA-MB-231/MDA-MB-453	An et al., 2015; Wang, 2015; He, 2016; He et al., 2017; Song, 2019
Dendrobine	$C_{16}H_{25}NO_2$	*D. nobile*	A549 non-small cell lung cancer	Song et al., 2016; Song et al., 2019
Chrysotoxine	–	*D. chrysotoxum*	Chronic myelogenous leukemia K562, neuroblastoma SH-SY5Y	Wang et al., 1997; Song et al., 2012

Active ingredient	Structural formula / molecular formula	Species	Cancer cell	References
Erianin	$C_{18}H_{22}O_5$	*D. chrysotoxum*	Gastric cancer SGC-7901, hepatocellular carcinoma Huh7 and HepG2, pancreatic cancer MiaPaCa-2, breast cancer MDA-468 and MCF-7, colon cancer HCC-2998/HCT-116/Caco-2, lung cancer A549, bladder cancer EJ/T24, ER-positive breast cancer T47D, osteosarcoma 143B/Saos2, nasopharyngeal carcinoma NPC-039/NPC-BM	Hong et al., 2008; Su, 2011; Lam et al., 2012; Wang, 2013; Zhu, 2013; Cui et al., 2016; Sun et al., 2016a; Wang et al., 2016; Su et al., 2017; Liu et al., 2019; Zhu et al., 2019

Active ingredient	Structural formula / molecular formula	Species	Cancer cell	References
Moscatilin	$C_{17}H_{20}O_5$	*D. loddigesii*/*D. pulchellum*	Lung cancer A549, esophageal cancer CE81T/VGH and BE3, lung cancer H23	Tsai et al., 2010; Chen et al., 2013; Kowitdamrong et al., 2013; Chen et al., 2019
Gigantol	$C_{16}H_{18}O_4$	*D. catenatum*	Ovarian cancer A2780	Li, 2009
Densiflorol B	—	*D. catenatum*	Ovarian cancer A2780, gastric cancer BGC-823	Li, 2009
Dehydroorchinol	—	*D. chrysotoxum*	Hypopharynx squamous carcinoma	Nam et al., 2019
Ephemeranthol A	—	*D. chrysotoxum*	Hypopharynx squamous carcinoma	Nam et al., 2019

Active ingredient	Structural formula / molecular formula	Species	Cancer cell	References
Denbinobin	$C_{16}H_{12}O_5$	*D. nobile*/*D. moniliforme*	Lung cancer A549, ovarian cancer SK-OV-3, promyelocytic leukemia HL-60, chronic myelogenous leukemia K562, colon cancer COLO 205, prostate cancer PC3	Lee et al., 1995; Huang et al., 2005; Yang et al., 2005; Lu et al., 2014
Confusarin	$C_{17}H_{16}O_5$	*D. chrysotoxum*	Chronic myelogenous leukemia K562, osteosarcoma U2OS	Wang et al., 1997; Zhang et al., 2019
Nudol	$C_{16}H_{14}O_4$	*D. nobile*	Osteosarcoma U2OS	Zhang et al., 2019
Luciantridine/(−)- and (+)-denobilone A		*D. brymerianum*	Lung cancer H460	Pornprom et al., 2015

Active ingredient	Structural formula / molecular formula	Species	Cancer cell	References
Dendroflorin	$C_{15}H_{14}O_4$	*D. nobile*	Cervical cancer HeLa, breast cancer MCF-7, lung cancer A549	Zhou et al., 2016
4,5,4' -Trihydroxy-3,3' - dimethoxybibenzyl	–	*D. brymerianum*	Lung cancer H460	Pornprom et al., 2015
Cypripedin	–	*D. densiflorum*	Lung cancer H460, H23; hypopharynx squamous carcinoma	Treesuwan et al., 2018; Nam et al., 2019
Vicenin II	$C_{27}H_{30}O_{15}$	*D. catenatum*	Lung cancer A549, H1299; liver cancer HepG2	Luo et al., 2019; Luo et al., 2019
Isoviolanthin	$C_{27}H_{30}O_{14}$	*D. catenatum*	Liver cancer HCC	Xing et al., 2018a
Phoyunnanin E	$C_{33}H_{26}O_6$	*D. venustum*	Lung cancer H23	Phiboonchaiyanan et al., 2018

Note: The Latin name Dendrobium officinale* is commonly used for "铁皮石斛 (Tie Pi Shi Hu)" in most literature. After verification, this paper adopts *Dendrobium catenatum* instead of *D. officinale.**

1.1 Polysaccharides

Polysaccharides are the primary active components in *Dendrobium* plants, exhibiting anti-inflammatory, antioxidant, antiviral, antitumor, and immune-enhancing effects (Xing et al., 2013). They are mainly composed of glucose, galactose, xylose, arabinose, and mannose (Zhou et al., 2018). Studies have shown that *Dendrobium* polysaccharides effectively inhibit various tumor cells, including sarcoma 180 (Wang et al., 2010), H22 hepatocellular ascites cells (He et al., 2007), human hepatocellular carcinoma HepG2 cells (Xing et al., 2018b), human lung cancer A549 cells (Liu et al., 2014), and human teratocarcinoma stem cells NCCIT (Liu et al., 2014).

Dendrobium catenatum polysaccharides, when combined with interleukin-2 in vitro, significantly enhance the tumoricidal activity of LAK cells from umbilical cord blood and peripheral blood of cancer patients (Luo et al., 2000). Tong et al. (2016) investigated the antitumor activity and immunostimulatory effects of water-soluble polysaccharides from *Dendrobium devonianum* stems in S180 tumor-bearing mice, finding that these polysaccharides significantly inhibited transplanted tumor growth by improving specific and non-specific immune responses and increasing colonic short-chain fatty acid concentrations. Luo et al. (2007) studied the inhibitory effects of different concentrations of polysaccharides, ethanol extracts, and water extracts from *Dendrobium denneanum* on human hepatocellular carcinoma SMMC-7721 cells, demonstrating that polysaccharides exhibited the strongest inhibitory effect and represented the most effective antitumor component of *D. denneanum*. Liu et al. (2019) reviewed recent advances in antitumor activity of natural polysaccharides, suggesting their antitumor effects are associated with improving intestinal barrier function, preventing malnutrition, and enhancing immune homeostasis. Deng et al. (2018) investigated the structure, chemical properties, and immunomodulatory activity of *Dendrobium* polysaccharides, finding they could enhance macrophage immune functions including NO release and phagocytosis, suggesting potential as natural immunostimulants. Liu et al. (2019) demonstrated that *Dendrobium* polysaccharides improved macrophage viability and phagocytic capacity in immunosuppressed mice. Polysaccharides from *Dendrobium thyrsiflorum* significantly increased spleen weight, enhanced macrophage phagocytosis, accelerated carbon clearance, and stimulated B lymphocyte proliferation, indicating strong immunomodulatory activity (Song et al., 2006). Similarly, polysaccharides from *Dendrobium tosaense* increased natural killer cell numbers and cytotoxicity, enhanced macrophage phagocytosis, and induced IL-2 and IFN-γ production in spleen cells, demonstrating potent immunomodulatory effects (Yang et al., 2014). Therefore, the antitumor activity of *Dendrobium* polysaccharides appears closely related to their immunomodulatory properties.

1.2 Alkaloids

Fifty-two alkaloid components have been identified in *Dendrobium*, with seven species commonly containing alkaloids: *D. nobile*, *D. chrysanthum*, *D. crepi-*

datum, *D. findleyanum*, *D. friedericksianum*, *D. primulinum*, and *D. signatum* (Li et al., 2019). In 1932, Suzuki first extracted dendrobine from *D. nobile*, marking the earliest compound discovered in *Dendrobium* (Xu et al., 2010). Pharmacological effects of *Dendrobium* alkaloids include heat-clearing, detoxification, antitumor activity, hypoglycemic and hypolipidemic effects, antithrombotic activity, and improved cerebral blood supply (He, 2016; Zhang, 2016). These alkaloids inhibit various cancer cells, including breast cancer, colon cancer, and Lewis lung cancer cells. An et al. (2015) found that *Dendrobium* alkaloids induce apoptosis in breast cancer MCF-7 cells by regulating the cell cycle. He et al. (2017) demonstrated that lipid-soluble alkaloid extracts upregulate pro-apoptotic factors and trigger apoptosis in human colon cancer HT-29 cells through the mitochondrial pathway by releasing apoptotic factors that bind to Caspase-9. Wang et al. (2014) investigated the anti-Lewis lung cancer mechanism of fresh *D. catenatum* extracts and their effects on vascular endothelial growth factor (VEGF), proliferating cell nuclear antigen (PCNA), and microvessel density (MVD) in tumor tissues, revealing that *D. catenatum* alkaloids inhibit mouse Lewis lung cancer growth, possibly by promoting T cell subset growth and binding to T cell growth factor receptors on lymphocyte membranes to regulate cellular immunity, or through combined inhibition of VEGF, PCNA, and MVD expression by alkaloids and polysaccharides. Water-soluble alkaloids from *D. nobile* inhibit colon adenocarcinoma Caco-2 cell growth by inducing G1 phase arrest, while both water- and lipid-soluble alkaloid extracts activate Caspase-3 to induce apoptosis and suppress proliferation (Wang, 2015). Song (2019) investigated the effects and mechanisms of *D. nobile* alkaloids on triple-negative breast cancer cells, finding significant proliferation inhibition.

1.3 Phenolic Compounds

Phenolic compounds in *Dendrobium* mainly include phenanthrenes, bibenzyls, and fluorenones, with antitumor, hypoglycemic, and immune-enhancing effects (Zhou et al., 2010; Zhu et al., 2019). Studies show that gigantol inhibits epithelial-mesenchymal transition in non-small cell lung cancer H460 cells (Unahabhokha et al., 2016a), suppresses H460 cell migration (Charoenrungruang et al., 2014), inhibits hepatocellular carcinoma HepG2 cell growth, induces HepG2 apoptosis (Chen, 2017), and reduces breast cancer cell viability and migration (Yu et al., 2018). Among eight phenolic compounds isolated from methanol extracts of *Dendrobium brymerianum*, moscatilin, gigantol, lusianthridin, and dendroflorin exhibited significant cytotoxicity against human H460 lung cancer cells, demonstrating antitumor activity (Pornprom et al., 2015). Chrysotoxine from *Dendrobium chrysotoxum* showed 62.25% inhibition against Ehrlich ascites carcinoma (Ma et al., 1994). Bibenzyl compounds exhibit antioxidant and anticancer activities (Hu et al., 2008), with erianin being the most studied *Dendrobium* component in this class. Erianin induces apoptosis in bladder cancer cells (Zhu, 2013; Zhu et al., 2019), nasopharyngeal carcinoma cells (Liu et al., 2019), colon cancer SW480 cells (Cui et al., 2011), colon cancer Caco-2 cells (Cui et al., 2016), gastric cancer SGC-7901 cells (Hong et al., 2008),

and breast cancer T47D cells (Sun et al., 2016a), while significantly inhibiting proliferation of human hepatocellular carcinoma Huh7 and HepG2 cells (Su, 2011; Wang, 2013). Denbinobin, another bibenzyl compound from *Dendrobium*, induces typical apoptotic features in human colon cancer HCT-116 and lung cancer A549 cells (Chen et al., 2008; Kuo et al., 2008), inhibits prostate cancer migration by suppressing Rac1 activity (Lu et al., 2014), and inhibits proliferation and metastasis of human ovarian cancer HO-8910PM cells by upregulating CASP3, CASP9, CAV1 and downregulating SOX2 (Zhang et al., 2016). Cypripedin, a phenanthrenequinone from *D. densiflorum*, exhibits antimetastatic potential. Treesuwan et al. (2018) used H460 and H23 cells as in vitro models to demonstrate that cypripedin reduces epithelial-mesenchymal transition in non-small cell lung cancer cells by inhibiting Akt/GSK-3β signaling, showing promising pharmacological effects against lung cancer metastasis. Additionally, Wattanathamsan et al. (2018) found that cypripedin activates caspase-3 and downregulates anti-apoptotic proteins Bcl-2 and Bcl-xL, inducing apoptosis in human lung cancer H460 cells and enhancing cisplatin-mediated cancer cell death, suggesting potential as an anticancer agent or adjuvant to increase lung cancer treatment efficacy.

2. Extraction Methods for Main Antitumor Active Ingredients from *Dendrobium*

Extraction methods for *Dendrobium* active components include water extraction (Liu et al., 2019), ethanol extraction (Huang et al., 2017), water extraction followed by ethanol precipitation (He et al., 2018), supercritical fluid extraction (Ma, 2014), microwave extraction (Chai et al., 2018), ultrasonic extraction (Guo et al., 2019), enzymatic extraction (Ao et al., 2018), flash extraction (Cai et al., 2016), and semi-bionic extraction (Dai et al., 2018). Optimal process parameters for each method are typically determined through single-factor investigations combined with orthogonal optimization experiments.

2.1 Water Extraction

Water extraction is a traditional method where factors such as material-to-liquid ratio, extraction temperature, time, and number of extractions significantly affect efficiency. Liu et al. (2019) optimized water extraction of *D. catenatum* polysaccharides, proposing optimal conditions of 1:30 material-to-liquid ratio, three extractions, and 5 hours per extraction. Wang et al. (2019) used orthogonal experiments to determine maximum polysaccharide extraction efficiency from *D. catenatum* at 1:80 ratio, 80°C, three extractions for 2 hours each. Shan et al. (2017) identified optimal conditions as 1:70 ratio, 90°C, two extractions for 78.5 minutes each. Wang et al. (2017) found optimal extraction of *D. devonianum* polysaccharides at 1:25 ratio, 100°C, two extractions for 1 hour each. While simple to operate, water extraction requires high temperatures and multiple extractions for high efficiency, resulting in high energy consumption and costs compared to other methods.

2.2 Enzymatic Extraction

Enzymatic extraction offers high efficiency and has been increasingly applied in recent years (Tang et al., 2014). Factors affecting extraction efficiency include enzyme type, dosage, hydrolysis temperature, time, material-to-liquid ratio, and pH. Yang et al. (2017) used α-L-rhamnosidase to extract *D. catenatum* polysaccharides, achieving maximum efficiency with 2.5% enzyme at 40°C for 1 hour. Han et al. (2017) optimized pectinase extraction at 1,500 $U \cdot L^{-1}$, pH 6.0, and 60°C. Ao et al. (2018) optimized combined enzymatic extraction of alkaloids and polysaccharides from *D. nobile*, finding optimal conditions: papain (0.10 g enzyme, 1:50 ratio, 45°C, 2 hours), cellulase (0.30 g enzyme, 1:40 ratio, 50°C, 2 hours), and pectinase (0.45 g enzyme, 1:40 ratio, 2 hours). Enzymatic extraction offers high productivity, low energy consumption, and minimal pollution, but requires strict control of reaction conditions including temperature, time, and enzyme dosage, making operation challenging.

2.3 Ultrasonic Extraction

Ultrasonic extraction is simple, achieves high efficiency in short time, and is often used to assist other extraction techniques, offering advantages of short extraction time, low energy consumption, and high efficiency. Studies show that ultrasonic power, time, temperature, and material-to-liquid ratio affect extraction yield. Guo et al. (2019) determined optimal conditions for ultrasonic-assisted 60% methanol extraction of free amino acids from *Dendrobium henanense* as 1:40 ratio, 30 minutes, 240 W power, and four extractions. Yang et al. (2018) optimized ultrasonic-assisted 60% acidic ethanol extraction of anthocyanins from *D. catenatum* at 30% ethanol, 1:20 ratio, 40°C, 70 minutes, and 180 W power. Qiu et al. (2018) achieved maximum polysaccharide extraction from *D. catenatum* at 1:50.26 ratio, 41.74°C, and 28.65 minutes. Wei et al. (2016) optimized ultrasonic-assisted cellulase extraction of polyphenols from *D. huoshanense* at 2.1 $mg \cdot mL^{-1}$ enzyme, 57°C, 71 minutes, pH 5, 180 W ultrasonic power, and 20 minutes ultrasonic time. Yu et al. (2016) found optimal ultrasonic-assisted polysaccharide extraction from *D. nobile* at 1:25 ratio, 40 minutes ultrasonic time, 120 minutes water extraction, and 80°C.

2.4 Microwave Extraction

Microwave technology offers short reaction time, selective heating, energy efficiency, simple operation, and high reaction efficiency, demonstrating superior performance over traditional water extraction for natural active ingredients from traditional Chinese medicine (Chai et al., 2018). Factors affecting efficiency include microwave power, time, material-to-liquid ratio, and auxiliary parameters. Miao et al. (2019) reported maximum polysaccharide extraction from *D. catenatum* flowers using ultrasonic-microwave synergy at 1:50 ratio, 3 minutes microwave, 55 minutes ultrasonic, and 450 W power. Chen et al. (2017) applied microwave technology to *D. catenatum* polysaccharide extraction, obtaining optimal conditions of 1:45 ratio, 95°C, 30 minutes, and 900 W power.

Efficient extraction of active components is crucial for antitumor research on *Dendrobium*. Different extraction methods significantly affect antitumor activity. Zhang et al. (2019) found that ether extracts of *D. denneanum* showed stronger inhibitory effects on lung cancer cells compared to traditional ethanol or water extracts. Li et al. (2018) studied different polarity fractions from *D. nobile* and *D. denneanum* for lung cancer A549 cell inhibition, revealing that ether extracts exhibited stronger effects while water and ethanol extraction showed lower efficiency. Polysaccharide fractions purified from *D. catenatum* stems using water extraction and ethanol precipitation demonstrated potent antioxidant and antitumor activities (Xing et al., 2018b). Bao (2007) investigated water, petroleum ether, ethyl acetate, and n-butanol extracts from *D. huoshanense*, *D. catenatum*, *D. nobile*, and *D. fimhriatum*, finding different polarity fractions exhibited varying inhibition degrees against human cervical cancer HelsS3 and liver cancer HepG2 cells. Yan et al. (2015) studied water-soluble and alkali-soluble polysaccharides from *D. nobile* on HeLa cell proliferation, showing that high concentrations of water-soluble polysaccharides inhibited HeLa cell growth in a dose-dependent manner, while alkali-soluble polysaccharides showed opposite effects. In summary, optimal conditions for the same extraction method vary, and the applicability of different processes requires further investigation. However, optimization generally follows a pattern: identify influencing factors, conduct single-factor and orthogonal experiments, and determine optimal parameters.

3. Antitumor Mechanisms of *Dendrobium*

Dendrobium antitumor mechanisms primarily involve enhancing immunity, inhibiting cancer cell proliferation, promoting apoptosis, regulating/blocking cell cycle, antioxidant/free radical scavenging, and inhibiting signal pathway expression.

3.1 Enhancing Immune Function

The immune system plays a crucial role in natural cancer defense by eliminating or suppressing viral infections to protect against virus-induced tumors, promptly clearing pathogens and reducing inflammation to prevent tumor-promoting inflammatory environments, and specifically recognizing and eliminating tumor cells based on tumor-specific antigens or stress-induced molecular expression (Swann & Smyth, 2007). Studies show that *D. denneanum* polysaccharides enhance antitumor immune function by improving antioxidant capacity (Luo et al., 2007). Yang et al. (2017) demonstrated that polysaccharides from *D. Taiseed Tosnobile* (DTTPS) increase natural killer cell numbers and cytotoxicity, enhance macrophage phagocytosis, and induce IL-2 and IFN-γ production, suggesting DTTPS as an effective immunomodulator. Huang et al. (2015) investigated the immunomodulatory functions of *D. catenatum* stems and two polysaccharide fractions (crude and purified) in cyclophosphamide-induced immunosuppressed mice,

showing that cultivated *D. catenatum* had equivalent immunomodulatory activity to wild varieties, with purified O-acetyl-glucomannan polysaccharides being key bioactive components. The β-(1$\rightarrow$4)$glycosidicbondsandO-acetylgroupslikelyrepresentfunctionalstructuresresponsibleforimmunomodulatoryactivity.Heetal.(2016)coacetyl-glucomannanfrom*D.catenatum*exhibitssignificantimmunomodulatoryactivityviaupregulationof\kappa BandERK1/2signalingpathways.Huangetal.(2018)showedthat2,3-O-acetylated1,4-$-d-glucomannan from *D. catenatum* induces immune responses through TLR4-mediated NF- B activation, thereby regulating immune responses and enhancing immunity. Liang et al. (2019) demonstrated that *D. catenatum* polysaccharides enhance metabolic function of cytotoxic T lymphocytes (CTLs) in colorectal cancer tumor microenvironments, reduce mitochondrial loss in CTLs, suppress PD-1 expression, restore intestinal barrier function, and enhance intestinal antitumor immune responses to inhibit colorectal cancer. In summary, *Dendrobium* acts as an immunomodulator to enhance immune function and antitumor capacity.

3.2 Inhibiting Cancer Cell Proliferation

Inhibiting cancer cell proliferation prevents tumor expansion. Multiple *Dendrobium* extracts demonstrate antiproliferative effects. Erianin from *D. chrysotoxum* inhibits proliferation of human breast cancer T47D cells by reducing Bcl-2 expression, activating Caspase signaling, inducing apoptosis, suppressing cyclin-dependent kinase expression to cause cell cycle arrest, and regulating matrix metalloproteinase/tissue inhibitor of metalloproteinase balance to inhibit migration, without affecting normal breast epithelial MCF10A cells (Sun et al., 2016a). Ethanol extracts from *D. catenatum* of different growth years exhibit antiproliferative effects against human hepatocellular carcinoma HepG2 and cervical cancer HeLa cells, with longer growth periods showing stronger anti-HeLa activity (Lin et al., 2018). Ethanol extracts from *D. catenatum* stems inhibit proliferation of human nasopharyngeal carcinoma CNE1 and CNE2 cells (Deng, 2010). Ether extracts of *D. denneanum* interfere with cancer cell metabolism and adhesion, disrupt cell cycle regulation, impair self-repair mechanisms, and inhibit lung cancer A549 cell proliferation (Zhang et al., 2019). Flavonoids from *D. denneanum* inhibit HepG2 cell proliferation by inducing significant apoptosis (Zhou et al., 2018). Cyclin-dependent kinases play key roles in controlling cell proliferation by maintaining cell cycle progression (Zhang et al., 2015), and active components can inhibit cancer cell proliferation by suppressing their expression. In Huh7 cells, erianin inhibits proliferation by suppressing Akt kinase activity, downregulating Mcl-1 protein expression, and activating PARP (Su, 2011).

3.3 Promoting Cancer Cell Apoptosis

The primary obstacle in antitumor therapy is the anti-apoptotic capacity of malignant cells, making apoptosis induction a critical strategy (Magwere, 2009). Moscatilin from *D. denneanum* induces pancreatic cancer apoptosis by increas-

ing reactive oxygen species (ROS) generation and regulating Bax/Bcl-2 ratio (Zhang et al., 2017). *D. catenatum* polysaccharides induce HepG2 apoptosis by downregulating Bcl-2 and upregulating Bax, altering mitochondrial function, ROS production, and apoptosis-related protein expression (Xing et al., 2018b). In 1-methyl-3-nitro-1-nitrosoguanidine (MNNG)-induced rat gastric tumorigenesis, *D. catenatum* water extract downregulates MDA and 8-hydroxy-2' -deoxyguanosine (8-OHdG) while upregulating GSH-PX and IL-2 activity, demonstrating antioxidant effects and regulation of tumor-related cytokines to induce apoptosis and prevent gastric cancer (Zhao et al., 2016). Erianin induces apoptosis and cell cycle arrest in nasopharyngeal carcinoma cell lines (NPC-039 and NPC-BM) through mitochondrial membrane changes, death receptor activation, and caspase-3, -8, and -9 activation, with erianin and its inhibitors increasing apoptosis rates (Liu et al., 2019). Phoyunnanin E from *D. venustum* significantly induces H460 lung cancer apoptosis by activating caspase-3 and -9 and causing nuclear condensation and fragmentation, increasing intracellular p53 protein accumulation to mediate apoptosis via p53-dependent pathways, and also induces H23 lung cancer apoptosis (Phiboonchaiyanan et al., 2018).

3.4 Regulating or Blocking Cell Cycle

The G1-to-S and G2-to-M transitions represent periods of complex molecular changes vulnerable to environmental influences, making G1/S and G2/M blockage crucial for promoting cancer cell apoptosis. Erianin exhibits antitumor activity against osteosarcoma and bladder cancer by inducing G2/M phase arrest, apoptosis, and autophagy (Wang et al., 2016; Zhu et al., 2019). *Dendrobium moniliforme* reduces viability of human breast cancer MCF-7 cells by inducing G2/M phase arrest and regulating key biomarkers (Sun et al., 2016b). The phenanthrene derivative 3,4-dimethoxy-2,7-phenanthrenediol (Nudol) from *D. nobile* is a potent cyclin-dependent kinase inhibitor that exhibits antiproliferative activity against osteosarcoma U2OS cells by causing G2/M phase arrest (Zhang et al., 2019). Ethanol extracts of *D. chrysanthum* induce HeLa cell apoptosis by upregulating tumor suppressor p53 to interfere with cell cycle progression and cause S phase delay (Prasad et al., 2017). Ethanol extracts of *D. formosum* promote Dalton lymphoma apoptosis by blocking cells at G2/M phase, significantly increasing survival time in Dalton lymphoma mice (Prasad & Koch, 2014).

3.5 Antioxidation and Free Radical Scavenging

Cancer development is closely associated with excess free radicals (Stohs, 1995), making antioxidant activity crucial for cancer prevention and treatment. *D. catenatum* polysaccharides inhibit 8-OHdG activity and activate the NRF2 pathway and related antioxidant enzymes HO-1 and NQO-1, improving antioxidant activity and protecting gastric mucosal cells from oxidative damage to prevent MNNG-induced precancerous gastric lesions and subsequent liver/kidney damage (Zhao et al., 2019b). These polysaccharides also regulate nine endogenous

metabolites in precancerous gastric lesion rat models, with betaine being most important due to its strong antioxidant activity and antitumor potential (Zhao et al., 2019a). Paudel et al. (2019) evaluated antioxidant and cytotoxic activities of ethanol and acetone extracts from *D. crepidatum* stems, finding DPPH radical inhibition (IC_{50}) at 73.90 $g \cdot mL^{-1}$ and 99.44 $g \cdot mL^{-1}$, respectively. At 800 $g \cdot mL^{-1}$, chloroform extracts inhibited human cervical cancer HeLa cell growth by (81.49$±0.43)±$4.26)%, confirming both antioxidant and cancer cytotoxic activities.

3.6 Inhibiting Signal Pathway Expression

Inhibiting or altering cell signal pathway expression can enhance immunity, induce apoptosis, and inhibit cancer cell proliferation and migration. *D. catenatum* polysaccharides exert immunomodulatory effects through NF- B and ERK1/2 pathway upregulation (He et al., 2016). In HepG2 hepatocellular carcinoma cells, erianin-induced apoptosis involves multiple signaling pathways including Akt inhibition, JAK/STAT3 suppression, Wnt pathway inhibition, and TGF-$ $3l pathway modulation (Su, 2011). In HeLa cervical cancer cells, gigantol inhibits proliferation and promotes apoptosis by regulating ERK1/2 and mitochondrial apoptotic pathways (Li et al., 2018). Yu et al. (2018) found that gigantol treatment reduces phosphorylated LRP6, total LRP6, and cytoplasmic β-catenin levels in HEK293 cells, decreasing Wnt target genes Axin2 and Survivin expression, indicating gigantol is a novel Wnt/β-catenin pathway inhibitor that suppresses breast cancer cell viability and migration by downregulating phosphorylated LRP6 and β-catenin. *D. catenatum* extracts inhibit proliferation of hepatocellular carcinoma SMMC-7721, BEL-7404, and primary liver cancer cells by activating mitochondrial apoptosis and inducing Wnt/β-catenin pathway inhibition (Guo et al., 2019). Vicenin II, a crucial component for *D. catenatum* antimetastatic activity, inhibits TGF-$ 1−*inducedepithelial*−*mesenchymaltransitioninlungadenocarcinomaA*549*andH*1299*cellsbyinactivatingTGF*− /*SmadandPI*3*K*/*A*
2*pathways*(*Luoetal.*, 2019).*Isoviolanthinfrom*∗*D.catenatum*∗*leavesinhibitsTGF*− 1−*inducedepithelial*−*mesenchymaltransitioninHepG*2*andBel*−7402*hepatocellularcarcinomacellsbytargetingI* and PI3K/Akt/mTOR pathways, significantly reducing cancer cell migration and invasion (Xing et al., 2018a).

4. Prospects

Global cancer statistics for 2018 estimated 18.1 million new cancer cases and 9.6 million cancer deaths worldwide, with China accounting for 3.804 million new cases and 2.296 million deaths—over 10,000 new diagnoses daily, averaging seven people every minute (Bray et al., 2018). Chemotherapy remains a primary cancer treatment but causes severe side effects, and no definitive cure exists. Consequently, the antitumor effects of traditional Chinese medicine are gaining attention. The 2019 "Opinions of the CPC Central Committee and the State Council on Promoting the Inheritance and Innovation of Traditional Chinese Medicine" states that "Traditional Chinese medicine is a great cre-

ation of the Chinese nation, a treasure of ancient Chinese science, and a key to unlocking the treasure house of Chinese civilization, having made tremendous contributions to the survival and prosperity of the Chinese nation and positively impacting world civilization." With strong government support and policy implementation, traditional Chinese medicine development has become a national strategy. *Dendrobium*, a precious Chinese medicinal material known as the "foremost of the nine immortal herbs," has attracted increasing research attention on its antitumor active ingredients and mechanisms. Over 50 *Dendrobium* species have been identified as medicinally valuable in China (Zeng, 2015), offering broad medicinal resources with complex active components and diverse antitumor mechanisms and targets requiring further intensive study to provide scientific foundations for developing novel antitumor drugs and rationally utilizing China' s valuable *Dendrobium* resources. Future research should focus on: (1) Expanding antitumor activity studies beyond the few commonly investigated species (*D. catenatum*, *D. nobile*, *D. chrysotoxum*, *D. denneanum*, *D. chrysanthum*, *D. huoshanense*) to explore additional *Dendrobium* germplasm resources and medicinal values. (2) Current research focuses mainly on crude extracts and primary structural analysis, with limited structure-activity relationship studies requiring further exploration of the relationship between active component structures and mechanisms. (3) *Dendrobium* natural products serve as bioactive lead compounds, but structural modification studies remain scarce and require intensification to prepare for new drug development. (4) Although research on biosynthetic pathways of medicinal secondary metabolites and related regulatory genes has increased, deeper and more comprehensive studies using transcriptomics, genomics, metabolomics, and other multi-omics approaches are needed to identify key regulatory genes and metabolic pathways for effective active components, and to explore strategies for enhancing expression or heterologous biosynthesis to promote resource conservation and sustainable utilization. (5) Most pharmacological studies have focused on in vitro cells and mouse models, with limited research on in vivo metabolism, absorption mechanisms, and transformation stability, necessitating clinical studies when conditions permit.

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Note: Figure translations are in progress. See original paper for figures.