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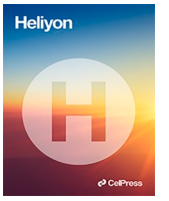

Review article

Research progress on the regulatory and pharmacological mechanism of chemical components of Dendrobium

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ABSTRACT

Dendrobium is a precious Chinese herbal medicine, which belongs to the genus Orchidaceae. Ancient records and modern pharmacological research show that Dendrobium has pharmacological effects such as anti-tumor, antioxidant regulating immunity and blood glucose, and anti-aging. Dendrobium contains polysaccharides, alkaloids, bibenzyl, sesquiterpenes, phenanthrene, polyphenols and other types of chemicals. Its pharmacological activity is closely related to these chemical components. For example, dendrobium extracts can achieve anti-tumor effects by inhibiting tumor cell proliferation and metastasis, promoting cell apoptosis and ferroptosis, or increasing cell sensitivity to chemotherapy drugs. It enhances immunity by regulating immune cell activity or cytokine release. In addition, it can alleviate neurodegenerative diseases by protecting nerve cells from apoptotic damage. In recent years, research reports on biologically active compounds in Dendrobium have shown a blowout growth, which makes us realize that it is meaningful to continuously update the research progress on the components and pharmacological regulatory mechanism of this traditional Chinese medicine. By classifying the collected chemical components according to different chemical structures and summarizing their pharmacological mechanisms, we investigated the current research progress of Dendrobium and provide a more comprehensive scientific foundation for the further development and clinical transformation of Dendrobium in the future.

1. Introduction

Dendrobium belongs to the Orchidaceae family. It is found all over Asia, including China, Thailand, Laos, and Vietnam, among

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Table 1
Types of compounds in dendrobium extracts, representative compound structures and their pharmacological effects.

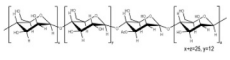
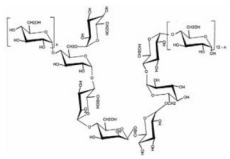
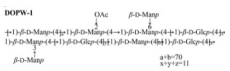
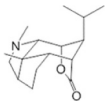
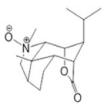
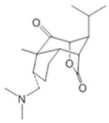
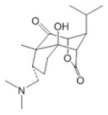
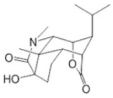
Compound type	Compound name	Compound structure	Pharmacological effects
Polysaccharides	Dendrobium huoshanense stem polysaccharide		Anti-diabetic [7,8], anti-fibrotic [9], skin protection [10,11], anticancer [12,13,14], improve cognitive dysfunction [15], regulate intestinal flora [16], anti-viral [17,18], regulate lipid metabolism [19], anti-arthritis [20,21], neuroprotection [20], anti-hypertensive [22], regulate immunity and anti-inflammatory [23,24], anti-aging [25,26], relieve dry eye syndrome [27], and antioxidant activity [28].
	D. officinale polysaccharide		
	A low-molecular polysaccharide from Dendrobium huoshanense		
	D. huoshanense polysaccharide 1 [29]		
	D. huoshanense polysaccharide 2 [29]		
	D. huoshanense polysaccharide 3 [29]		
	D. huoshanense polysaccharide 4 [29]		
	D. huoshanense polysaccharide 5 [29]		
Alkaloids	Dendrobine		Neuroprotective and anti-nerve damage effects [30,31–34], reduce cognitive dysfunction [35], improve abnormal liver lipid metabolism and intestinal metabolic function [36], regulate body metabolism [37], reduces acute liver injury [38–41], relieves acute lung injury [42], reduces bone ablation and bone destruction [43].
	Dendrobine-N-oxide		
	Nobilonine		
	Dendroxine		
	6-Hydroxy-nobilonine		
	13-Hydroxy-14-oxodendrobine		

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Table 1 (*continued*)

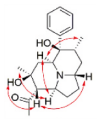
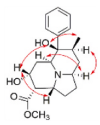
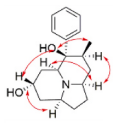
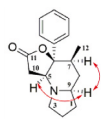
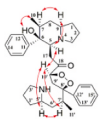
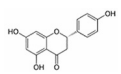
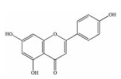
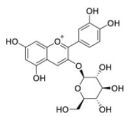
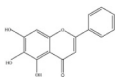
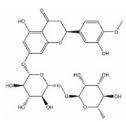
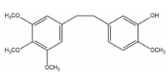
Compound type	Compound name	Compound structure	Pharmacological effects
	Dendrocrepidine A		
	Dendrocrepidine B		
	Dendrocrepidine C		
	Dendrocrepidine D		
	Dendrocrepidine E		
	(±)-Dendrocrepidine F		
Flavonoids	Naringenin		Antitumor [44,45], immunomodulatory and cardiovascular protective effects [46,47], neurodegenerative mitigation [48], antiviral and anti-inflammatory [49], antidiabetic [50], and osteoprotective effects [51].
	Apigenin		Anti-cancer [52,53], anti-diabetic [54,55], anti-inflammatory [56], anti-viral [57], anti-depressant [58], anti-neurodegenerative diseases [59], cardioprotective [60], bone-protective [51], immune modulation [61], and treatment of skin diseases [62,63]. Anti-neurodegeneration [64,65], cardiovascular protection [66], anti-inflammatory and anti-obesity [67, 68], anti-cancer [69,70], antioxidant and free radical scavenger [71].
	Anthocyanin		
	Baicalein		Anti-cancer [72], neurological and cardioprotective effects [73,74,75], antibacterial [76,77], anti-acute liver and kidney injury [78,79], joint protection [80], and anti-inflammatory effects [81].
	Hesperidin		Anti-pulmonary fibrosis [82], neuroprotection [83], anti-osteoporosis [84], anti-inflammatory and anti-oxidative stress [85,86], anti-cancer [87].
Bibenzyl	Erianin		Anti-tumor [88,89], anti-diabetic retinopathy [90], anti-angiogenic [91,92,93], Anti-arthritic and osteoprotective effects [94,95], immune modulation [96], anti-inflammatory [97,98], antibacterial [99,100], antiviral [101], alleviating neurodegeneration and cognitive dysfunction [102], anti-cataract [103,104].

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Table 1 (*continued*)

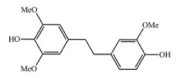
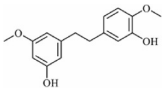
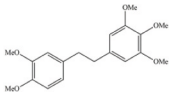
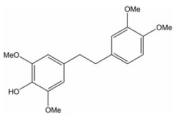
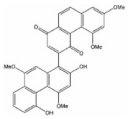
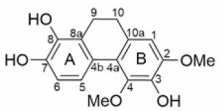
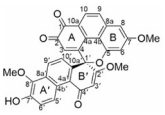
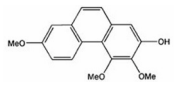
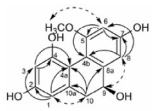
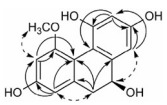
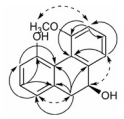
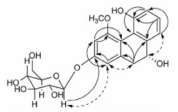
Compound type	Compound name	Compound structure	Pharmacological effects
	Moscatilin		
	Gigantol		
	Chrysotobibenzyl		
	Chrysotoxine		
Phenanthrenes	Dendropalpebrone		Anti-oxidize effect [105], immunomodulatory effect [106], antibacterial [107], anti-inflammatory [108], anti-tumor [109,110,111].
	Dendrocrumenol B		
	Dendrocrumenol D		
	Dendroscabrol A		
	2,5-Dihydroxy-4-methoxy-phenanthrene 2-O-a-L rhamnopyranosyl-(1–6)-b-D-glucopyranoside		
	5-Methoxy-2,4,7,9S-tetrahydroxy-9,10-dihydrophenanthrene		
	4-Methoxy-2,5,7,9S-tetrahydroxy-9,10-dihydrophenanthrene		
	5-Methoxy-4,7,9S-trihydroxy-9,10-dihydrophenanthrene		
	4-Methoxy-2,5,9R-trihydroxy-9,10-dihydrophenanthrene 2-O b-D-glucopyranoside		

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Table 1 (*continued*)

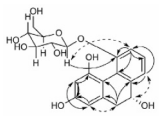
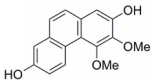
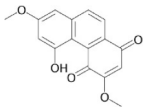
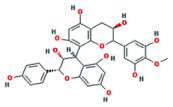
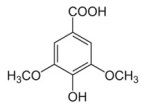
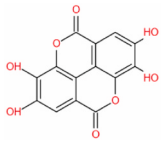
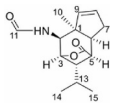
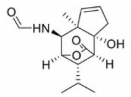
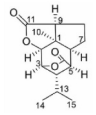
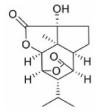
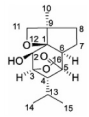
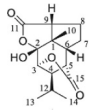
Compound type	Compound name	Compound structure	Pharmacological effects
	1,2,5,9R-Tetrahydroxy-9,10-dihydrophenanthrene 5-O-b-D glucopyranoside		
	Nudol		
	Denbinobin		
Polyphenols	Tannins (proanthocyanidins)		Anti-tumor [112], antioxidant, antibacterial and anti-infective [113,114], antidiabetic [115], antiviral [116], fights urinary tract infections [117], bone protection [118], regulate biological rhythms [119], regulate intestinal flora [120,121], cardioprotection [122,123], neuroprotection [51,124], Prevent liver damage and skin cancer [125,126], and anti-inflammatory [127].
	Syringic acid		
	Ellagic acid		
Sesquiterpenes	Dendroterpene A		Antidiabetic [128,129], neuroprotective effect [130], anti-tumor [129], cataract inhibition [131], and angiogenesis inhibition [131].
	Dendroterpene B		
	Dendroterpene C		
	Dendroterpene D		
	Dendroterpene E		
	Dendroaduoid A		

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Table 1 (*continued*)

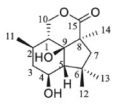
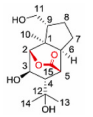
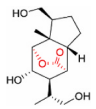
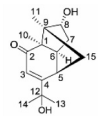
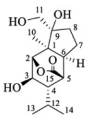
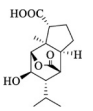
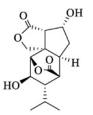
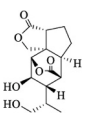
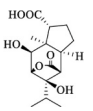
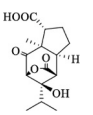
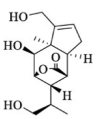
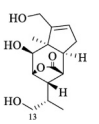
Compound type	Compound name	Compound structure	Pharmacological effects
	Dendroaduol		
	(+)-(1R,2S,3R,4S,5R,6S,9R)-3,11,12-trihydroxypicrotoxane-2(15)-lactone		
	(−)-(1S,2R,3S,4R,5S,6R,9S,12R)-3,11,13-trihydroxypicrotoxane-2(15)-lactone		
	(+)-(1R,5R,6S,8R,9R)-8,12-dihydroxy-copacamphan-3-en-2-one		
	Dendrowardin A		
	Dendrowardin B		
	Dendrowardin C		
	Dendrowardin D		
	Dendrowardin E		
	Dendrowardin F		
	Dendrowardin G		
	Dendrowardin H		

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Table 1 (*continued*)

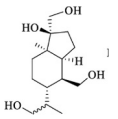
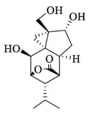
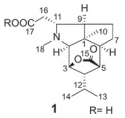
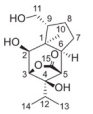
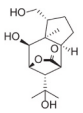
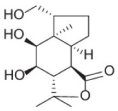
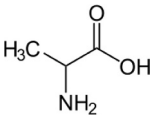
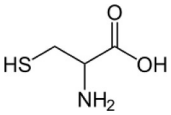
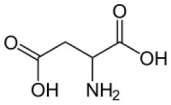
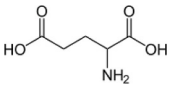
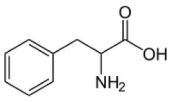
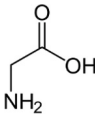
Compound type	Compound name	Compound structure	Pharmacological effects
	Dendrowardin I		
	Dendrowardin J		
	(−)-(1R,2S,3R,4S,5R,6S,9S,11R)-11-Carboxymethyldendrobine		
	(+)-(1R,2S,3S,4R,5R,6S,9R)-2,4,11-Trihydroxypicrotoxane-3(15) lactone		
	(+)-(1R,2S,3R,4S,5R,6S,9R)-2,11,12-Trihydroxypicrotoxane-3(15) lactone		
	Findlayanin		
Amino acids	Alanine		By affecting genes related to bacterial membrane transport and amino acid metabolism pathways, it has an anti-Escherichia coli, *Pseudomonas aeruginosa* and Candida albicans effect [132,133].
	Cysteine		
	Aspartate		
	Glutamate		
	Phenylalanine		
	Glycine		

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Table 1 (*continued*)

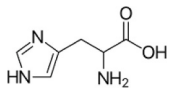
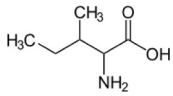
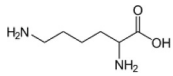
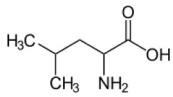
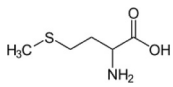
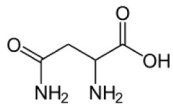
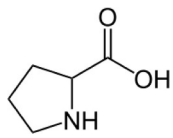
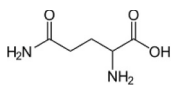
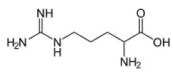
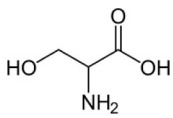
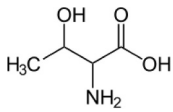
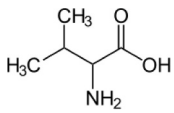
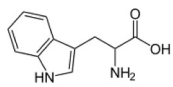
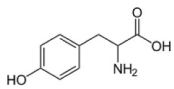
Compound type	Compound name	Compound structure	Pharmacological effects
	Histidine		
	Isoleucine		
	Lysine		
	Leucine		
	Methionine		
	Asparagine		
	Proline		
	Glutamine		
	Arginine		
	Serine		
	Threonine		
	Valine		
	Tryptophan		
	Tyrosine		

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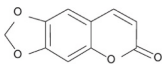
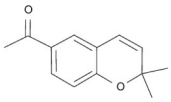
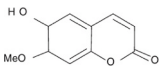
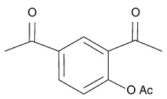
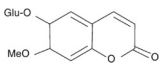
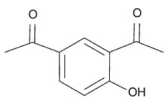
Table 1 (*continued*)

Compound type	Compound name	Compound structure	Pharmacological effects
Coumarins	Ayapin		Antibacterial [134], anti-cancer, anti-diabetic, anti-inflammatory [135], cardiac, hepatic and neuroprotective effects [136,137].
	Scopoletin		
	Scopolin		
	Demethoxyencecalin		
	3-acetyl-4-acetoxyacetophenone		
	3-acetyl-4-hydroxyacetophenone		

others. There are various strains of Dendrobium. According to statistics, there are more than 1,000 species worldwide, among which as many as 80 species of Dendrobium have been recorded in China [1,2]. Chinese Pharmacopoeia 2020 Edition (Part One) defines Dendrobium as the newly harvested or dehydrated stems of cultivated products of *Dendrobium huoshanense C.Z.Tang et S.J.Cheng*, *Dendrobium nobile Lindl.*, *Dendrobium fimbriatum Hook* or. *Dendrobium chrysotoxum Lindl.*, and similar botanical herbs of the same origin. It is widely used because of its high ornamental, edible, and medicinal value. Among them, Dendrobium officinale has been included in the list of both medicine and food by the National Health and Family Planning Commission of China [3]. In China, Dendrobium has a medicinal history of thousands of years, which can be dated back to *ShenNongBenCaoJing*. It is known as the first of the nine herbs with miraculous effects and is known as soft gold. Among the many strains of *Dendrobium chrysotoxum Lindl.*, the strains with medicinal value account for about 65% [4].

Studies have shown that main chemical parent structural in Dendrobium include polysaccharides, flavonoids, bibenzyls, polyphenols, alkaloids, and sesquiterpenes. However, the chemical composition and structure of different strains of Dendrobium are also different [5]. In recent decades, Dendrobium and its extracts have been used to treat tumors, hyperglycemia, hyperlipidemia, decreased immunity, and neurological diseases caused by aging, etc [6]. In order to fully understand the regulation mechanism of this precious Chinese medicinal material on the human body and the main regulation pathways of various compounds, this review summarizes the chemical composition of Dendrobium and its pathways *in vivo* and *in vitro* reported in existing studies. In addition, we also focus on the clinical transformation of dendrobium. Therefore, in this review, we have made statistics and sorted out the dendrobium preparations currently on the pharmaceutical market in China.

2. Materials and methodology

A search strategy was used to extract available literature from the PubMed database and China National Knowledge Infrastructure (CNKI). The term "Dendrobium" was used to search in the database. After carefully screening the titles and abstracts of all identified literature to confirm that they contained extracts from Dendrobium and their pharmacological effects to ensure that they met the inclusion criteria, nearly 200 articles that met these criteria were included. In addition, we searched the PubMed and CNKI databases using the compound names in Table 1 as search terms to screen literature related to pharmacological effects and structural analysis. We searched literature in CNKI using the search terms "Shihu Yeguang Wan", "Shihu Mingmu Wan", "Shihu Yeguang Keli", "Fufang Xianshihu Keli", "Fufang Xianshihu Jiaonang" and "Fufang Shihu Pian", the one which unrelated to disease or pharmacological effects was excluded. A total of 20 articles meeting these criteria were included. Original studies, including prospective and retrospective studies and review papers, were included and cross-referenced. The ingredients and indications of Chinese patent medicines were queried through the China Medical Information Platform (https://www.dayi.org.cn/), and the Latin names of herbal medicines were confirmed through the China Species Library· Flora (https://species.sciencereading.cn/biology/v/biologicalIndex/122.html), and database of systems pharmacology for drug discovery from herbal medicines (TCMSP) (https://old.tcmsp-e.com/index.php).

3. The overall regulation of Dendrobium to human health

It is recorded in the Chinese Pharmacopoeia that the effects of Dendrobium candidum are benefiting the stomach and promoting

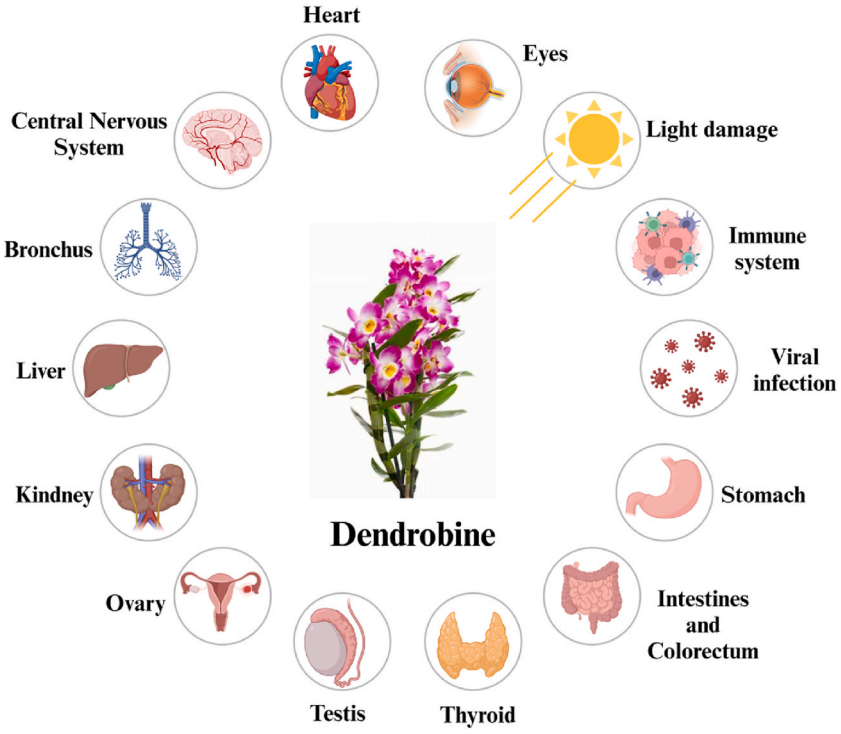


Fig. 1. Schematic diagram of the effect of the traditional Chinese medicine Dendrobium on the human body (created with BioRender).

body fluid, nourishing yin and clearing away heat. It is used to treat symptoms such as dry mouth and polydipsia, fluid injuries in febrile diseases, insufficient stomach yin, loss of appetite, lingering heat after illness, hyperactivity of fire due to yin deficiency, bone steaming fever, blurred vision, and weakness or flaccidity of the muscles and bones [138]. Modern pharmacological studies proved that Dendrobium can regulate the immune system and affect multiple organs in the human body (Fig. 1).

3.1. *Immune and nervous system modulatory effects*

Dendrobium and its bioactive compounds have the ability to regulate the immune system through immune cells and cytokines. Dendrobium polysaccharides (DP) stimulate immune activity by activating the extracellular signal-regulated kinase 1/2 (ERK 1/2) and nuclear factor-kappa B (NF-κB) signaling pathways in human leukemic monocytic cell line THP-1 cells [139]. Additionally, some subfractions of DP exhibit immunomodulatory activities *in vivo* and enhance immune responses by increasing proliferation of immune cells, the secretion of cytokines such as TNF-α, the production of nitric oxide (NO), and phagocytosis [140]. Among these compounds, 2,3-O-acetylated-1,4-β-D-glucomannan can target chemokines such as chemokine CC motif ligand 4 (CCL 4) and interferon gamma-inducible protein 10 (IP-10) to trigger immune responses in human leukemia monocytic cell line THP-1 cells. These effects are primarily related to the activation of NF-κB, which is regulated by the Toll-like receptor 4 (TLR 4) signaling pathway [141]. Another major regulatory system influenced by Dendrobium is the central nervous system. Dendrobine has protective effects against amyloid-β $(Aβ)_{(25-35)}$-induced neuronal damage [142]. Further research into the mechanism found that the effect is to inhibit $Aβ_{(25-35)}$-induced axonal degeneration by activating the autophagy process, which may be the pharmacological basis of dendrobium in preventing Alzheimer's disease (AD) [143]. Other reported anti-AD mechanisms include the regulation of hyperphosphorylation of microtubule-associated tau protein, reduction of extracellular amyloid plaques, activation of autophagy, enhancement of synaptic connections, suppression of neuroinflammation and inhibition of neuronal apoptosis, etc [30,35,144–148]. In addition, Dendrobium extract can also alleviate symptoms of chronic unpredictable mild stress depression [149–151], and improve the health of sub-healthy mice caused by neuroendocrine and immune system disorders [152].

3.2. *Antioxidant and photodamage effects*

It is well known that ultraviolet (UV) A irradiation can damage the proliferative capacity and lifespan of cells. Research has shown that DP can effectively increase the activity of antioxidant enzymes, while inhibiting the activation of JNK pathway and the expression of matrix metalloproteinase (MMPs), thereby protecting human foreskin fibroblasts (HFF-1) from UVA-induced damage and preventing cell aging [4]. Acute exposure to large amounts of UV radiation and overproduction of reactive oxygen species (ROS) are major causes of ocular pathologies. Dendrobium extract protects ARPE-19 cells from oxidative stress induced by UV through

mitogen-activated protein kinase (MAPK) and Nrf2/HO-1 signaling pathways [153]. Another aspect of photodamage is damage to the epidermis of the skin caused by acute UVB exposure. Studies have shown that DP mitigates oxidative damage and apoptosis in human immortal keratinocyte line HaCaT cells induced by UVB mediated by MAPK [154]. Another possible regulatory mechanism is to reduce the release of inflammatory factors by inhibiting the transcriptional activity of NF-κB (p65), and then alleviation occurrence of inflammatory reaction and oxidative stress irradiated by UVB [155]. At the animal level, DP can protect hairless mouse skin from photodamage by regulating the process of oxidative stress, mainly manifested as significantly reducing erythema and preventing skin dryness [156].

3.3. Visual protection

Dendrobium has beneficial effects on eye health. Dry eye disease is a common clinical condition characterized by eye irritation, dryness, vision loss, and corneal damage, often caused by abnormalities in the tear film and ocular surface. Studies have shown that Dendrobium officinale extract can make gland secretion function better in patients with dry eye syndrome. The specific mechanism may involve the upregulation of AQP5 and mucin 5ac proteins in the lacrimal gland by Dendrobium water extract, which subsequently inhibits the activation of the MAPK and NF-κB pathway. Thus, the effect of inhibiting eye inflammation is exerted [27]. This effect was also verified in mouse models [51]. Diabetic retinopathy is a microvascular complication associated with diabetes. Erianin, an active ingredient in Dendrobium nodules, inhibits retinal inflammation induced by microglia by reducing cellular glucose uptake and activation of ERK1/2-NF-κB pathway, accordingly attenuating diabetic retinal inflammation, and blood-retinal barrier disruption during disease progression [90]. In vivo experiments have shown that Dendrobium extracts can inhibit the expression of inflammation-related factors and overexpressing tight junction proteins occludin and claudin-1 to relieve diabetic retinopathy [157]. Regarding ocular damage caused by excessive UV exposure, as mentioned previously, dendrobium extract can protect ARPE-19 from UV-induced visual damage through related pathways [153]. In addition to retinal epithelial cells, DP inhibits H_2O_2-induced apoptosis in human lens epithelial (HLE) cells by inhibiting MAPK signaling pathway [158]. In a diabetic cataract model simulated by glucose-induced HLE cells, Dendrobium extract not only inhibited aldose reductase, but also inhibited aldose reductase gene expression. It was also proved in the rat model that gigantol can inhibit the formation of cataract induced by galactose by inhibiting the expression and activity of aldose reductase and inducible NO synthase (iNOS) gene [103]. In addition, Moscatilin, a bibenzyl compound of Dendrobium, also inhibited the progression of developmental retinal vascular diseases caused by insistent ischemia/hypoxia [159].

Some dendrobium Chinese patent medicines currently used in China are also mainly developed for dry eye disease, such as Shihu Yeguang Wan. Based on their good effects during clinical use, the future development of dendrobium preparations more suitable for topical use in the eyes may have important clinical significance and economic value.

3.4. Improving lung function

Dendrobium extract also showed excellent effects in improving lung function. Studies have shown that the effect of DP on improving airway inflammation in chronic obstructive pulmonary disease (COPD) model mice can be achieved by inhibiting oxidative stress and inflammatory responses in mice [160]. Ferroptosis is a groundbreaking discovery for a form of programmed cell death, one of its manifestations is iron-dependent lipid peroxidation. Ferroptosis has been shown to be closely connected with a variety of diseases, such as tumorigenesis, arthritis, heart disease, etc. Erianin inhibits liver cancer cell activity by inducing ferroptosis and cell migration. This process may be dependent on Ca^{2+}/CaM pathway [88]. *In vivo*, Dendrobium officinale has a strong tumor-inhibitory effect on lung cancer xenograft tumor models in nude mice [161]. The mechanism of dendrobium anti-lung tumors revealed by existing studies mainly involves cycle regulation [162,163], inhibition of proliferation [164], promotion of apoptosis [165,166], inhibition of migration and invasion [167,168], inhibition of epithelial-mesenchymal transformation [169,170], inhibition of angiogenesis [91], and improvement of chemosensitivity [171,172]. In addition, Dendrobium extracts also showed the potential in targeting lung cancer stem cells [173–176]. Among them, 4,5,4′-trihydroxy-3,3′-dimethoxybibenzyl and Lusianthridin inhibit the cell phenotype of human lung cancer stem cells via the Akt/GSK3β/β-catenin and Src-STAT3-c-Myc signaling pathways, and improve the ability of tumor cells to drug sensitivity [174,175].

At present, researchers have conducted more extensive and in-depth research on the gastrointestinal regulation and anti-gastrointestinal tumors of dendrobium polysaccharides than other types of compounds. However, compared with monomeric compounds, the structural units of polysaccharides are more complex and variable. Therefore, we may need to do more work in the future to study the anti-gastric cancer characteristics and mechanisms of polysaccharides under specific structures.

3.5. Regulate gastrointestinal function

In terms of regulating gastrointestinal function, DP can prevent the accumulation of inflammatory factors caused by excessive activity of intestinal macrophages, restore the homeostasis of the intestinal microenvironment, and thus alleviate inflammatory bowel disease [177]. For malignant colonic lesions, DP can inhibit colorectal cancer by inhibiting autophagy and enhancing immune response [12,178]. In a rat model of chronic atrophic gastritis, Dendrobium candidum can improve the histopathology of gastric mucosa in rats, reverse gastric atrophy and intestinal metaplasia, and relieve gastritis symptoms [179]. Polysaccharides of *Dendrobium huoshanense C.Z.Tang et S.J.Cheng* also have protective effects on gastric mucosa [180]. As the disease progresses, in the malignant lesions of the digestive tract, Dendrobium polysaccharides can not only inhibit the precancerous lesions of gastric cancer [181–183],

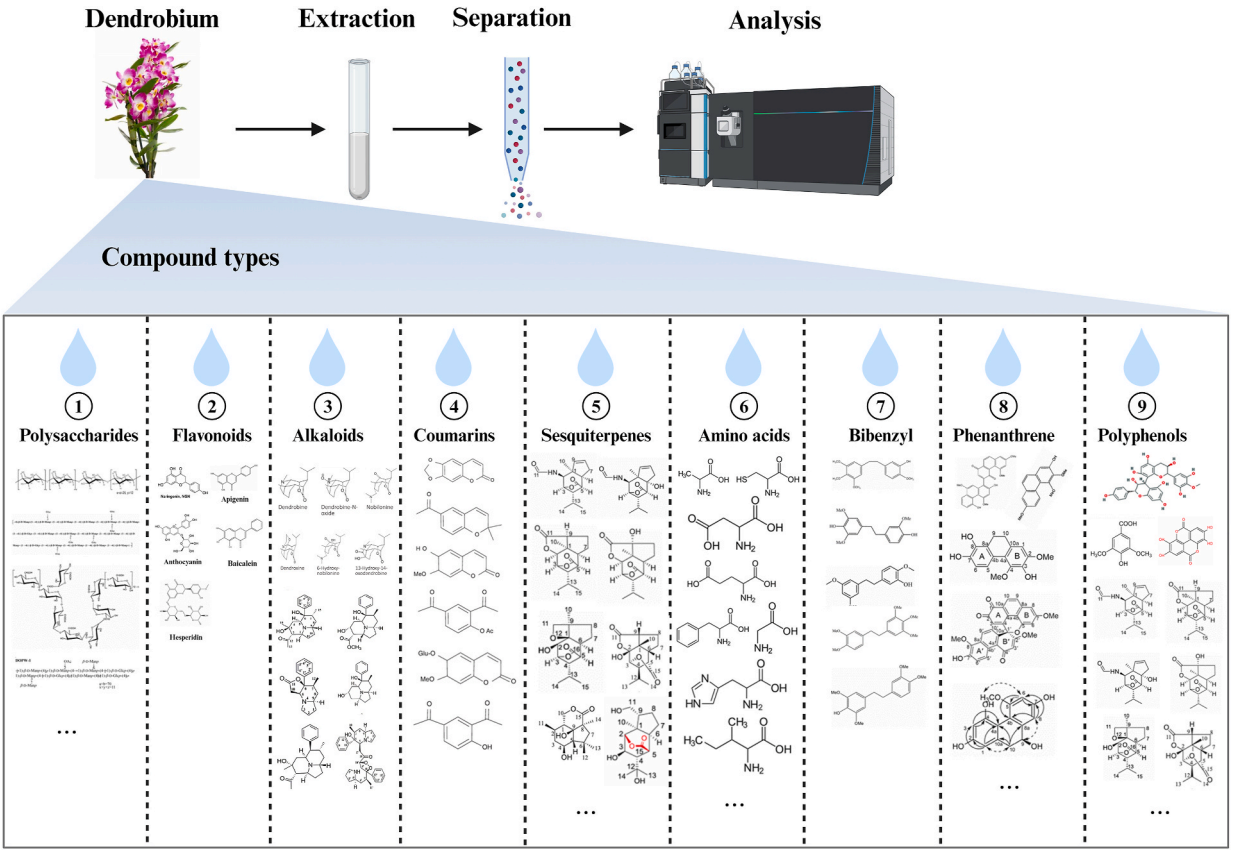


Fig. 2. The main compound types obtained by separation and extraction of Dendrobium (created with BioRender).

but also enhance T cell-mediated immune response, inhibit tumor angiogenesis and induce tumor cell apoptosis to play an anti-gastric cancer role [184,185]. Dendrobium officinale extract can prevent gastric cancer by regulating DNA damage, oxidative stress and cytokines related to canceration and inducing apoptosis [186].

3.6. Antiviral, reproductive system protection and anti-tumor effects

In addition to the regulation of Dendrobium on different human systems listed above, Dendrobium extracts also have antiviral effects, such as H1N1 influenza virus [17], influenza A virus [187] and herpes simplex virus [188]. It is interesting to note that the water extract of Dendrobium officinale has the potential to prevent, treat and recover from adverse reactions of COVID-19 at the moment when the new coronavirus epidemic is fully open. However, its anti-inflammatory activity can affect antibody production, possibly reducing the body's production of antibody levels [189]. Therefore, it should be used with caution in practical applications. For the reproductive system, DP has protective effects on diabetes-induced testicular damage by increasing the proliferation of testicular germ cells, inhibiting apoptosis and activating the glycolytic pathway in testis [190,191]. On the other hand, DP can also improve polycystic ovary syndrome [192,193], and premature ovarian failure in naturally aging mice [194]. Dendrobium has a broad anti-tumor spectrum. In addition to the tumor types listed above, Dendrobium is also effective against human liver cancer [195,196], breast cancer [183,197,198], bladder cancer [199–201], prostate cancer [109], kidney cancer [202], pancreatic cancer [203], leukemia [204], and melanoma [205], ect.

4. Composition of compounds in Dendrobium and their regulatory mechanisms

Phytochemical research data have shown that Dendrobium officinale is an excellent source of biologically active substances such as alkaloids, bibenzyls, flavonoids, and polysaccharides [206,207]. The pharmacological effects of different types of compounds are also different. The main compound categories in Dendrobium are listed in Fig. 2.

4.1. Dendrobium polysaccharide

Polysaccharides refer to chemical polymers composed of more than 10 types of monosaccharides assemble, which are important

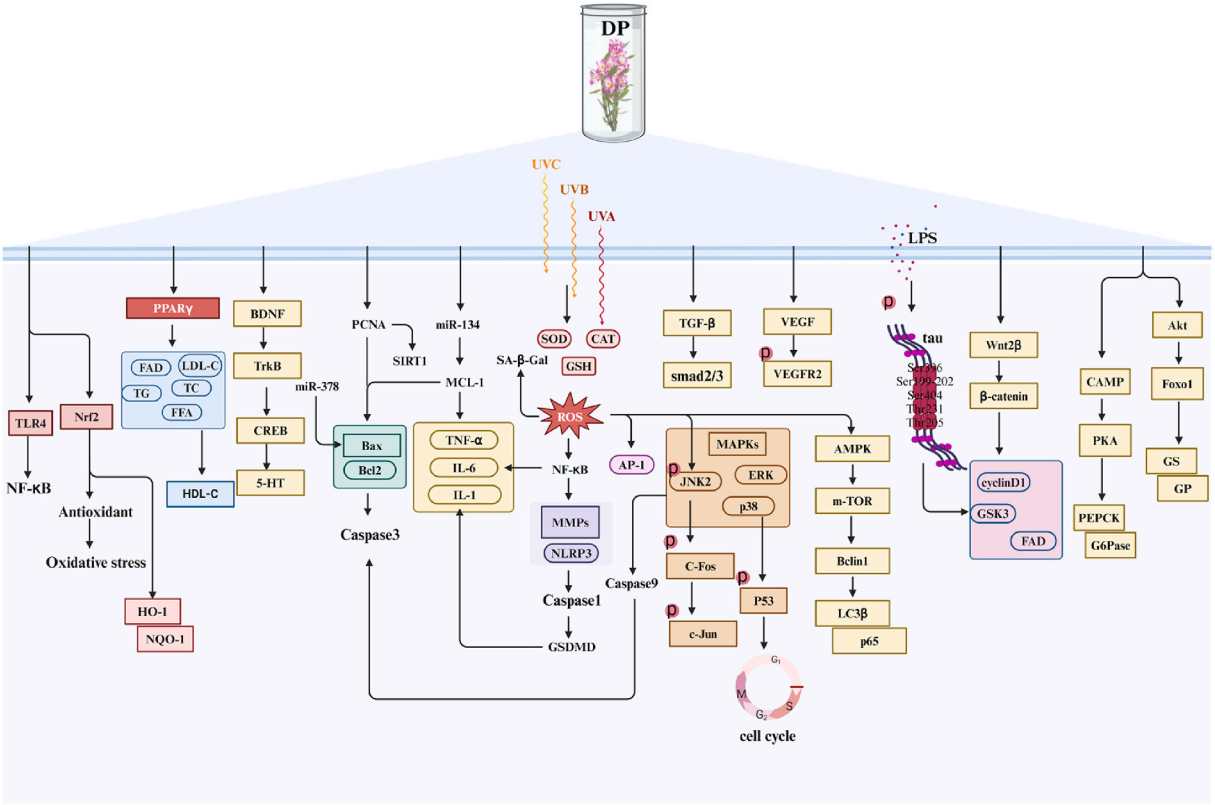


Fig. 3. Related pathways of Dendrobium polysaccharides regulating cellular biological processes (created with BioRender).

active ingredients in most Chinese herbal extracts and have significant pharmacological activity. DP are mainly enriched in flowers, stems, leaves and roots of Dendrobium. Among them, the polysaccharide content in the stem is significantly higher than other parts [208]. The molecular weight, different chemical structures and molecular conformations of polysaccharides have a significant impact on their pharmacological effects and activities *in vivo* and *in vitro*. DP is mainly composed of mannose, glucose and galactose, with small amounts of rhamnose, arabinose and xylitol [209]. DP has positive effects of anti-tumor, promotion of immune response, anti-oxidation and anti-inflammation (Fig. 3). DP can inhibit the accumulation of ROS due to UV irradiation. ROS can affect and regulate a variety of cellular enzymes, such as AP-1 and NF-κB. Once activated, AP-1 and NF-κB further regulate the transcription of matrix metalloproteinases (MMPs), thereby exerting the biological effect of degrading collagen and elastin. On the other hand, as far as NF-κB itself is concerned, it is a major activator of inflammatory cell infiltration. Studies have shown that it stimulates the further expression of MMPs by inducing the release of pro-inflammatory cytokines such as TNF-α and IL [210,10]. ROS can also participate in autophagy by activating the AMPK-mTOR signaling pathway, which further activates the Bclin1 and LC3β-p65 complex [211], and DP has a blocking effect on this process [12]. In another study, UVA can rapidly activate the phosphorylation of JNK/c-Fos/c-Jun protein and up-regulate the expression of MMPs by acting on fibroblasts to generate ROS. DP can block this process [4]. In addition, DP reduced the generation of apoptotic bodies in epidermal cells, up-regulated the expression levels of cleaved-caspase9 and cleaved-caspase3, and down-regulated the activation of MAPK pathway and p53, indicating that DP has an strong protective effect against UVB-induced acute photodamage [154]. In terms of ovarian protection in female animals, DP treatment increased the levels of PCNA mRNA and protein in polycystic ovary syndrome (PCOS) ovarian tissues, and inhibited PCOS ovaries by regulating the expression and ratio of apoptosis-related proteins Bax, Bcl-2 and caspase-3 [193]. Similarly, in male animals, after DP intervention, the pathological changes of seminiferous tubules were significantly improved with the upregulation of PCNA and SIRT1 and the inhibition of apoptosis [190]. In the central nervous system, DP markedly down-regulated the expression of miR-134 *in vivo* and *in vitro* after ischemic injury, and affected the release of inflammatory factors and the expression of apoptotic proteins by changing the level of MCL-1 protein, thereby alleviating ischemic brain injury [212]. In the treatment of AD, inhibiting the hyperphosphorylation of tau protein is an important strategy, and DP has certain advantages in the treatment of AD. Studies have shown that in the lipopolysaccharide (LPS)-induced AD rat model, the phosphorylation of tau protein Ser396, Ser199-202, Ser404, Thr231, and Thr205 sites were overexpressed, along with increased GSK-3β expression, which inducd neuronal apoptosis. DP significantly improved these changes. Dendrobium nobile polysaccharide, in combination with vascular endothelial growth factor (VEGF) and vascular endothelial growth factor receptor 2 (VEGFR2), can inhibit the phosphorylation of VEGFR2 and reduce the expression of VEGF and its transcription factor Activator protein-1 (AP-1) [213]. This effect blocks angiogenesis, suggesting that DP may be a potential anti-angiogenic drug. DP has also been shown to mitigate macrophage injury induced by uropathogenic *Escherichia coli* (UPEC) by

inhibiting the activation of the NLRP3 inflammasome, reducing the induction and activation of caspase-1/GSDMD, and decreasing the secretion of pro-inflammatory cytokines, such as IL-1β [214]. In addition, the pathways regulated by DP include TLR4 signaling pathway [215], Nrf2/HO-1 signaling pathway [216], BDNF-TrkB-CREB pathway [217], fat metabolism-related pathways [19], cAMP-PKA and Akt/FoxO1 liver metabolism-related pathway [218], tumor-related Wnt/β-catenin signaling pathway [219], etc. In a gastric cancer model exposed to 1-methyl-3-nitro-1-nitrosoguanidine (MNNG), DP can regulate the NRF2 signaling pathway. The Nrf2/HO-1 signaling pathway serves as a double-edged sword, which can not only prevent normal cells from progressing into tumor cells, but also protect tumor cells from excessive oxidative stress, thereby improving the growth rate of tumor cells. In this study, the effect of DP on this pathway was specifically manifested by inhibiting NRF2 downstream heme oxygenase-1 (HO-1) and NADPH quinone oxidoreductase-1 (NQO-1), thereby preventing the progression of gastric cancer [185].

4.2. Alkaloids

Alkaloids are a class of natural products with broad pharmacological activity, including anti-inflammatory, cardiovascular protective, anti-tumor and anti-viral. In addition to its medicinal activity, it is also a class of toxic plant active ingredients that can be used to kill insects. Up to now, dozens of alkaloids with different structures have been separated and extracted from Dendrobium [220], mainly enriched in the rhizome of Dendrobium [221]. The content of alkaloids is not only related to the species of Dendrobium, but also to the growth age and distribution parts of the plants [222]. Studies have shown that the total alkaloids in Dendrobium regulate hepatic lipids and gluconeogenesis, reduce high blood pressure and exhibit effects on the nervous system, as well as anti-inflammatory, anti-diabetic, anti-tumor and anti-viral properties [223]. Dendrobium alkaloids play a prominent role in neuroprotection. They can repair synaptic and mitochondrial damage mediated by Aβ protein, inhibit amyloidosis, and protect integral synapses by activating the Wnt/β-catenin pathway *in vitro* and *in vivo* [30]. Dendrobine can inhibit neurotoxic Mn-induced cytotoxicity by regulating autophagic flux and improving mitochondrial function mediated by PINK1/parkin. Dendrobium alkaloids can also prevent nerve cell damage caused by oxidative stress [31,32], apoptosis or pyroptosis [145,33], and DNA methylation [34]. They can alleviate cognitive dysfunction caused by the formation of extracellular amyloid plaques, regulate tau protein hyperphosphorylation, activate autophagy, enhance synaptic connections, and inhibit neuroinflammation and neuronal apoptosis [143,35,146]. In terms of hepatic lipid metabolism, Dendrobium alkaloids ameliorate abnormal lipid metabolism in the liver through two ways: strengthening the strong hydrophilic taurine-coupled bile acid to promote the elimination of cholesterol to stabilize metabolic balance, and reducing the ratio of cholic acid/chenodeoxycholic acid to regulate intestinal metabolic function [36]. In addition, Dendrobium alkaloids can promote the expression of genes related to liver glucose and lipid metabolism, and can increase the expression of Nrf2-antioxidant pathway genes, comprehensively regulating disordered body metabolism [37]. Studies have shown that Dendrobium alkaloids can attenuate acute liver injury induced by CCl_4 [38–40], improve hepatocyte degeneration and steatosis, and normalize alcohol-induced abnormal gene expression patterns [41]. In the respiratory system, Dendrobium alkaloids restrain the emancipation of NO in macrophages induced by LPS and protect against acute lung injury caused by LPS stimulation in mice by downgrading the MyD88/MAPK signaling pathway [42]. In terms of bone protection, Dendrobine inhibited the formation of osteoclasts by inhibiting p38-c-Fos, ROS and NFATc1-MMP9 *in vitro*, thereby alleviating inflammatory bone ablation *in vivo* [43].

In general, similar to the pharmacological effects of most alkaloids, the alkaloid compounds in dendrobium have shown good medicinal activity in different disease models and are a class of compounds with development value.

4.3. Flavonoids

Flavonoids are one of the remarkable abundant groups of chemical products of natural plant origin. Across all dendrobium parts, studies have shown that the flavonoid content in leaves is significantly higher than in stems [224]. In dendrobium leaves, flavonoids and polysaccharides are the most important active substances. Naringenin is a flavonoid compound found only in the stems of Dendrobium officinale [225]. In addition, apigenin, anthocyanin, baicalein, and hesperidin are also important components of Dendrobium flavonoids [226]. Studies have shown that naringenin has a broad anti-cancer spectrum, whether it is naringenin alone, embedded and loaded in drug delivery systems, or used in combination with chemotherapy drugs [44]. They can be used to treat tumors at various sites, such as brain cancer, oral squamous cell carcinoma, colon cancer, lung cancer, breast cancer, pancreatic cancer, liver cancer [45], brain cancer, skin cancer, prostate cancer, cervical cancer, ovarian cancer, bladder cancer, gastric cancer and osteosarcoma. Its effect in controlling tumor progression may involve the regulation of multiple mechanisms [44], such as inducing apoptosis, arresting cell cycle, inhibiting angiogenesis, modifying Wnt/β-catenin, NLRP3/NF-κB [45], PI3K/Akt, TGF- β and other signaling pathways. In addition, naringenin also exhibits immunomodulatory and cardiovascular protective effects [46,47], and also has certain research and development value in the treatment of aging-related neurodegeneration such as AD and Parkinson's disease [48]. Besides, it has confirmed pharmacological effects in antiviral and anti-inflammatory [49], antidiabetic [50], and bone protection [51]. Apigenin is an important flavonoid widely found in herbs and vegetables. Studies have shown that it has significant effects in anti-cancer [52,53], anti-diabetic [54,55], anti-inflammatory [56], anti-viral [57], anti-depressant [58], anti-neurodegenerative diseases [59], cardioprotective [60], bone-protective [51], immune modulation [61], and treatment of skin diseases [62,63]. Anthocyanin inhibits oxidative stress and reactive astrogliosis, inhibits nerve cell apoptosis and tau protein hyperphosphorylation, resists neuroinflammation, restores cholinergic and amyloidosis pathway dysfunction, and regulates membrane potential abnormalities to achieve the anti-neurodegenerative results [64,65]. In addition, it inhibits inflammation and obesity by regulating the release of inflammatory mediators and the activation of Toll-like receptor signaling pathways, as well as immune activation and the connection between transcription factors in adipose tissue [67,68]. Unsurprisingly, anthocyanin also exhibits excellent pharmacological activity in some

serious human diseases, such as cancer. It has shown significant anti-cancer activity against lung cancer, breast cancer, prostate cancer, gastric cancer, liver cancer and colorectal cancer by exhibiting antioxidant, anti-inflammatory, anti-tumor cell proliferation, interfering with tumor cell cycle, inhibiting metastasis, and modulating immune responses [69,70]. In addition, anthocyanin has powerful antioxidant and free radical scavenging activities [71]. Baicalein is an emerging anti-cancer natural compound. Studies have shown that Baicalein resensitizes lung adenocarcinoma cells to cisplatin by inhibiting the EMT properties of tumor cells through the PI3K/Akt/NF-κB pathway [227]. It induces apoptosis and autophagy of tumor cells, inhibits angiogenesis, regulates signal transduction and transcriptional activators, blocks normal cell cycle, and activates PI3K/Akt and other pathways to achieve a wide range of anti-cancer purposes. Baicalein improves ulcerative colitis through the AhR/IL-22 pathway [228]. Baicalein exerts neuroprotective effects by inhibiting oxidative stress and the activity of the ERK pathway [73,74]. In addition, Baicalein also exhibits excellent antibacterial [76,77], anti-acute liver and kidney injury [78,79], joint protection [80], and anti-inflammatory effects [81]. As a bioflavonoid, hesperidin is present in high concentrations in citrus fruits in addition to its presence in dendrobium. Hesperidin has shown effectiveness in anti-pulmonary fibrosis [82], neuroprotection [83], anti-osteoporosis [84], anti-inflammatory and anti-oxidative stress [85,86], and anti-cancer [87].

4.4. Bibenzyl

Bibenzyl compounds are a class of compounds composed of two benzyl units. The benzyl groups are connected to the methyl groups through a single C-C bond. Bibenzyl compounds are widely found in a variety of plants in nature, including ferns, mosses and angiosperms. As a biologically active compound, they are abundant in Dendrobium, mainly in the stems [229]. These compounds have shown excellent antioxidant and anticancer activities, and has become an important compound type in the current study of Dendrobium extract. For example, three new bibenzyl compounds isolated from Dendrobium nobile showed good activity in the free radical scavenging experiment *in vitro* [230]. In addition, Moscatilin [205], Gigantol [164,201], Erianin [231,89], Chrysotobibenzyl [232,233] and Chrysotoxine [176] in Dendrobium are the star anticancer compounds of Dendrobium bibenzyl compounds in recent years. Among them, Erianin is more prominent in antitumor activity than other bibenzyl compounds. Erianin is effective against lung cancer [88,165], bladder cancer [199,200], breast cancer [234], gastric cancer [181], liver cancer [196], kidney cancer [202], cervical cancer [235], prostate cancer [236], oral squamous cell carcinoma [237], nasopharyngeal carcinoma [163], esophageal squamous cell carcinoma [238], osteosarcoma [239], melanoma and colorectal cancer [240]. The currently revealed anti-tumor mechanisms include promoting ferroptosis of tumor cells, inhibiting tumor cell migration [88,202], inducing oxidative stress [199], inhibiting tumor cell proliferation [165], promoting cell apoptosis [234], causing cell cycle arrest [181,200], inducing DNA damage and abnormal mitosis [241], promoting mitochondrial apoptosis [235], promoting autophagy [242], inhibiting angiogenesis [91], and regulating immunity [96]. With the gradual deepening of research, scientists discovered the huge medicinal value of Erianin. Currently, pharmacological research on Erianin is continuing. Moreover, in view of the poor water solubility of this compound, researchers are still exploring ways to make up for this shortcoming of Erianin, such as using nanomaterials to encapsulate it to build a drug delivery system, or loading it on functional materials to give it additional Functional characteristics [243].

4.5. Phenanthrenes

Phenanthrene compounds are structurally polycyclic aromatic hydrocarbons composed of three benzene rings. Phenanthrene has a wide variety of biological activities, and Orchidaceae is the most important source of natural phenanthrene [244]. The phenanthrene compounds extracted from Dendrobium have effects of antitumor [245,246], anti-inflammatory [108,247], immune regulation [106], antibacterial [107], and antioxidant [105]. Studies have shown that Dendropalpebrone significantly reduces ROS in H_2O_2-stimulated macrophages, and increases the activeness of superoxide dismutase (SOD), glutathione peroxidase and catalase (CAT) enzymes, thereby playing a role in scavenging free radicals [105]. Two Dendrocrumenol compounds have forceful immune regulation effect on $CD3^+$ T cells and $CD14^+$ monocytes. It is shown to reduce the production of IL-2 and TNF in T cells and monocytes treated with PMA/Iono, and reduce the activation of T cells [106]. In *in vitro* antibacterial experiments, dendroscabrol B showed strong α-glucosidase inhibitory activity [107]. Phenanthrene compounds extracted from Dendrobium candidum can inhibit the production of NO by LPS-activated mouse macrophage RAW264.7. The underlying mechanism may involve inhibiting the expression of iNOS induced by LPS, as well as the phosphorylation of p38, JNK, MAPK, and IκBα [108]. In terms of antitumor activity, Dendrobium extract Nudol exhibited antiproliferative effects against osteosarcoma cells, with the mechanism likely involving cell cycle arrest and apoptosis through caspase-dependent pathways [110]. In the reproductive system, Denbinobin can prevent CXCL12-induced migration of prostate cancer cells by inhibiting the activity of Rac1 [109]. In terms of digestion and metabolism, Dendrobium phenanthrene compounds exhibited inhibitory effects on pancreatic lipase activity. In addition, Denbinobin inhibits the proliferation activity and invasion ability of gastric cancer cells through MAPK-related pathways [111].

4.6. Polyphenols

By analyzing the content and tendency analysis of current research reports on Dendrobium extracts, that while most studies focus on common bioactive components (such as polysaccharides and alkaloids) in Dendrobium orchid, another important secondary metabolite polyphenols have been overlooked [248–250]. The biological activities of polyphenols can be awakened with the help of microbial fermentation, such as the anti-inflammatory and antioxidant stress effects of polyphenols [251]. It is clear that the gut microbiota plays a key role in regulating the production of polyphenols in the body, increasing their bioavailability and bioactivity

[252]. Conversely, polyphenols can also modulate the composition or activity of colonic microbiome [120,121]. Previous studies have also reported several polyphenolic compounds in Dendrobium, such as rutin, hyperoside, and quercetin. But they were later classified as flavonoids. In addition, Dendrobium also contains phenolic acids and their derivatives, including syringic acid, ellagic acid, and gallotannins. These polyphenolic compounds have been shown to possess various biological activities, such as hypoglycemic, antioxidant, antimicrobial, anticancer, and immunity-boosting potential [253,127]. Due to the lack of research on the mechanism of Dendrobium polyphenols, their deep regulation mechanism on the body remains to be elucidated.

4.7. Sesquiterpenes

Dendrobium contains many sesquiterpenes, including picridane, isovanillin, cyclodiocamphenes, codiocamphores, and juniperane sesquiterpenes [254]. These compounds are reported to have the effects of neuroprotection, immune regulation, anti-diabetes, anti-tumor and improvement of acute cerebral ischemia. Terpenoids extracted from Dendrobium showed the inhibitory activity of α-glucosidase, suggesting that they may be potential drugs for diabetes treatment [128,129]. (+)-(1R,2S,3R,4S,5R,6S,9R)-3,11,12-trihydroxypicrotoxane-2(15)-lactone, (+)-(1R,5R,6S,8R,9R)-8,12-dihydroxy-copacamphan-3-en -2-one, and (−)-(1S,2R,3S,4R,5S,6R,9S,12R)-3,11,13-trihydroxypicrotoxane-2(15)-lactone have obvious protective effect on neural damage caused by H_2O_2-induced oxidative damage in pheochromocytoma cells [130]. In terms of anti-tumor, terpenoids extracted from Dendrobium have shown inhibitory effects on multiple tumor cell lines such as colorectal cancer, lung cancer, pancreatic cancer and gastric cancer [129]. Sesquiterpenoids extracted from Dendrobium stems are inhibitory to D-galactose-induced proliferation of HLECs cells, providing new candidate compounds for cataract therapy [131]. In addition, in the zebrafish model, the terpenoid extract of Dendrobium nobile also showed an influence on the generation of injured blood vessels [255]. Recently, it also showed preliminary antioxidative [256], and immunomodulatory activities [257–259].

4.8. Amino acids

After extraction and analysis, it is found that there are more than 20 kinds of basic amino acids in Dendrobium [260,261]. The amino acid content in leaves of Dendrobium was substantially higher than that in stems. There are also substantial differences in the amount of amino acids contained in different parts of a plant. In Dendrobium officinale, the total amino acid content in leaves was 6.76–7.97 g/100 g, and that in stems was 1.61–2.44 g/100 g [262]. The free amino acids and trace elements in Dendrobium officinale are one of the necessary nutritional elements for the human body, including a variety of essential and non-essential amino acids [263]. This is an important material basis for its pharmacological effects. For example, 12 trace elements and 20 amino acids were detected in Shihu Yeguang Pills [264]. Due to the complex regulatory mechanism of amino acids, the pathways of amino acids in Dendrobium have not yet been elucidated.

4.9. Others

In addition to the above main types of compounds, Dendrobium also contains tannin compounds. Tannins are a unique class of phenolic metabolites, with a molecular weight between 500 and 30,000 Da. The content of tannins in Dendrobium is related to the species of Dendrobium [116]. There is literature indicating that among different strains of Dendrobium, *Dendrobium nobile Lindl.* has the highest tannin content, about 14.28%, followed by *Dendrobium chrysotoxum Lindl.*, about 3.61% [265]. The content of tannins in Dendrobium candidum is only less than 0.4% [266]. Modern pharmacological studies have shown that tannins have various biological activities such as regulating gastrointestinal motility [267], antitumor [268], antioxidation [116], antibacterial [269], and antiviral [270]. However, the specific pharmacological mechanism of tannins in Dendrobium has not been reported so far, and further exploration is needed.

In addition, Dendrobium extract also contains coumarins, Ayapin, scopoletin, marsartene, and 6,7-dimethoxycoumarin [271]. Studies have shown that Ayapin has antibacterial, anti-infectious and anti-inflammatory activity [134,272]. Scopolamine has protective effects on various chronic diseases, such as anti-cancer, anti-diabetic, anti-inflammatory, neuroprotective, cardioprotective and hepatoprotective effects [136,137]. Scopoletin modulates multiple tumor molecular signals, including EGFR, AMPK, NF-κB, MAPK/ERK, STAT3and PI3K/Akt/mTOR. In addition, it is also involved in the regulation of key markers of metabolic diseases aspartate aminotransferase (AST), alanine aminotransferase (ALT), total cholesterol (TC) and triglyceride (TG) levels. In neurological diseases, it participates in the regulation of inflammatory factors, such as ILs and TNF, thereby reducing the symptoms and severity of these diseases [135]. The reported compound types, representative compound structures, and their pharmacological effects in dendrobium are shown in Table 1.

Since researchers continue to optimize the extraction and separation process of the compounds in Dendrobium, we are gradually unraveling the mystery of this ancient Chinese herbal medicine. Both ancient medical records and modern pharmacological research have revealed its extensive pharmacological activities. Whether it is *in vivo* or *in vitro* studies, or the study of metabolic characteristics, it is an important step to achieve the transformation of dendrobium extracts. This is the key bottleneck that we urgently need to solve.

5. Dendrobium preparations in China

In order to understand the marketing and application of dendrobium products in China, we have reviewed the approved dendrobium-related domestic drugs, imported drugs and traditional Chinese medicine formulas information on the website of the

Table 2
The composition, indications and pharmacological research progress of the dendrobium proprietary Chinese medicine compound approved by NMPA.

Drug Name	Compatibility (Latin name)	Indications supported by drug inserts	Indications supported by literature
Shihu Yeguang Wan	Asparagus cochinchinensis, Ophiopogon japonicus, Rehmannia glutinosa, Rehmanniae Radix Praeparata, Panax Ginseng C. A. Mey., Poria Cocos(Schw.) Wolf., Rhizoma Dioscoreae, Lycii Fructus, Achyranthis Bidentatae Radix, Dendrobium nobile, Cassia mimosoides, Dendranthema lavandulifolium, Amygdalus Communis Vas, Cuscutae Semen, Antelope Horn, Cistanches Herba, Schisandra chinensis, Saposhnikoviae Radix, Glycyrrhiza uralensis, Astragalus complanatus, Coptis chinensis, Citrus aurantium L., Chuanxiong Rhizoma, Gleditsia sinensis Lam., Celosia argentea.	It is suitable for liver and kidney deficiency, yin deficiency and fire exuberance, cataracts, dark eyes, and dim vision.	Relieve dry eye syndrome [273–276], vitreous opacity [277, 278], central serous chorioretinopathy [279,280], glaucoma [281], visual fatigue [282], cataract [283], and low intraocular pressure [284].
Shihu Mingmu Wan	Dendrobium nobile, Celosia argentea, Cassia mimosoides, Tribulus terrester, Rehmannia glutinosa, Rehmanniae Radix Praeparata, Lycium chinense, Cuscuta chinensis, Cistanche deserticola, Panax ginseng, Rhizoma Dioscoreae, Poria Cocos(Schw.) Wolf., Asparagi Radix, Ophiopogon japonicus, Schisandra chinensis, licorice, Aurantii Fructus, Chrysanthemi Flos, Saposhnikoviae Radix, Coptidis Rhizoma, Achyranthis Bidentatae Radix, Chuanxiong Rhizoma, Amygdalus Communis Vas, Gypsum Fibrosum, Magnetitum, Bubali Cornu.	It is suitable for patients with liver and kidney deficiency, dilated pupils, night blindness, blurred vision, cataract pain, dizziness, and mental fatigue caused by rising deficiency fire.	Effective against diabetic retinopathy [285,286], macular degeneration [287], and dry eye syndrome [288].
Shihu Yeguang Keli	Dendrobium nobile, Rehmanniae Radix Praeparata, Lycii Fructus, Cuscutae Semen, Achyranthis Bidentatae Radix, Chrysanthemi Flos, Tribulifructus, Celosiae Semen, Cassiae Semen, Bubali Cornu, Antelope Horn, licorice, Panax Ginseng C. A. Mey., Rhizoma Dioscoreae, Poria Cocos(Schw.) Wolf., Cistanches Herba, Rehmannia glutinosa, Schisandra chinensis, Asparagi Radix, Ophiopogon japonicus, Amygdalus Communis Vas, Saposhnikoviae Radix, Chuanxiong Rhizoma, Aurantii Fructus, Coptidis Rhizoma.	It is suitable for liver and kidney deficiency, yin deficiency and fire exuberance, cataracts, dark eyes, and dim vision.	Effective against cataract [289,290].
Fufang Xianshihu Keli	Dendrobium nobile, Radix Puerariae, Panax Notoginseng (Burk.) F. H. Chen Ex C. Chow.	It is suitable for dry mouth and throat, hunger, inability to eat, and polydipsia caused by insufficient stomach yin.	Treat alcoholic liver disease [291], and enhance immunity [292].
Fufang Xianshihu Jiaonang	Dendrobium nobile, Radix Puerariae, Panax Notoginseng (Burk.) F. H. Chen Ex C. Chow.	It is suitable for symptoms such as insufficient stomach yin, dry mouth and throat, hunger and inability to eat, red tongue and lack of fluid, dryness and deficiency of fluid after drinking, and polydipsia after drinking.	NA
Fufang Shihu Pian	Panax Ginseng C. A. Mey., Antelope Horn, Schisandra chinensis, Lycii Fructus, Chuanxiong Rhizoma, Rhizoma Dioscoreae, Rehmannia glutinosa, Angelicae Sinensis Radix, Bubali Cornu, Scutellariae Radix, Gardeniae Fructus, Saposhnikoviae Radix, Dendrobium nobile, Aurantii Fructus, Ophiopogon japonicus, Eucommiae Cortex, Cassiae Semen, licorice, Asparagi Radix, Achyranthis Bidentatae Radix, Cuscutae Semen, Rehmanniae Radix Praeparata, Poria Cocos(Schw.) Wolf., Amygdalus Communis Vas, Tribulifructus, Chrysanthemi Flos, Celosiae Semen, Anemarrhenae Rhizoma.	It is suitable for symptoms such as dizziness and cataracts, vision loss, mydriasis, round nebula and cataracts, blurred vision caused by clouds and fog, and tears in the wind.	NA

National Medical Products Administration (NMPA) (https://www.nmpa.gov.cn/). It was found that there were a total of 178 approval information, among which Dendrobium preparations were divided into 6 types, including Shihu Yeguang Wan, Shihu Mingmu Wan, Shihu Yeguang Keli, Fufang Xianshihu Keli, Fufang Xianshihu Jiaonang, and Fufang Shihu Pian. Their compatibility composition and functional indication information are shown in Table 2.

6. Summary and outlook

Dendrobium has been extensively employed as a functional food and herbal medicine for the prevention and treatment of many diseases. Dendrobium has a long history of folk application, but in-depth and multi-center clinical research is still needed to confirm its pharmacological effects and mechanism of action in the human body. This review summarizes the conditioning and therapeutic effects of Dendrobium on different organs of the human body, and classifies and describes the pharmacological effects of different types of compounds in Dendrobium. We found that there are many studies on the polysaccharides and alkaloids in Dendrobium extracts. These studies have verified the pharmacological effects of Dendrobium from different mechanisms, but there are still great limitations in promoting the transformation and medicinal use of Dendrobium. In addition, more investigation evidence is still needed for the development of the medicinal potential of Dendrobium. By combining modern technology, better control of the quality and safety of Dendrobium, and research and development of the series of products of Dendrobium, the development of traditional Chinese medicine Dendrobium can be promoted.

Ethics approval and consent to participate

Not applicable.

Data availability statement

No data was used for the research described in the article.

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CRediT authorship contribution statement

Xin Wei: Writing – original draft, Methodology, Investigation. **Dan Wang:** Writing – original draft, Investigation. **Ziming Xu:** Investigation. **Jiajia Liu:** Formal analysis. **Qizhi Zhu:** Formal analysis. **Qi Chen:** Investigation. **Heng Tang:** Writing – review & editing, Methodology. **Weiping Xu:** Writing – original draft, Supervision, Methodology, Funding acquisition, Conceptualization.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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