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Dendrobium, survey on a natural medicine with multidimensional uses and pharmacological characteristics

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Abstract: Genus *Dendrobium* consisting of nearly 1000 species which is basically found in tropical and subtropical areas. The genus *Dendrobium* have been utilized in traditional Chinese medicine for around 2000 years. The systematic review of manuscripts and articles dedicated to traditional medicine in China has been carried out. The surveys of interest were indexed in "SciFinder", "PubMed", "Web of Science", and "Scopus". Relevant literature has been obtained using the keywords "Traditional Chinese Medicine", "*Dendrobium*", "Anti-cancer activity", "Antioxidant activity", "Polysaccharides", "Alkaloids", "Antibacterial activity", "Anti-fungal activity", "Bibenzyls", and "Glycosides". This review aims to promote utilization of *Dendrobium* which is an important part of traditional Chinese medicine because of its different pharmaceutical and medicinal properties, lastly, future challenges and research directions are discussed. Furthermore, clinical trials studies promote researches to highlight and focus on the scope of application of traditional Chinese medicine in growing system of medicine.

Keywords: *Dendrobium*; anti-cancer activity; alkaloids; polysaccharides; antioxidant activity.

INTRODUCTION

Dendrobium is an epiphytic herb, polymorphic, most are lithophytic, and a few are terrestrial (Marmitt, Shahrajabian, 2021; Sun et al., 2021c; Shahrajabian, Sun, 2023a,b). Genus name originates from the Greek words *dendron* meaning a tree and *bios* meaning life (Shahrajabian, Sun, 2023a,b). *Dendrobium* is one of the largest genera among Orchidaceae family plants about 1500 species spread all over the world, and *Dendrobium*, as the traditional Chinese medicine (TCM) (Shahrajabian et al., 2022a,b; Li et al., 2023), makes wonderful contributions to public healthcare and promotes the development of TCM (Wu et al., 2016a,b; Wang et al., 2019). Their stems can be: 1: erecting with a knobby rhizome, 2: rhizomatous, 3: knobby new stems arise from the base of old stems (Shahrajabian et al., 2021a,b,c,d). They have an extensive distribution and great alterations in floral structure and growth characteristics, and they may be deciduous or evergreen (Shahrajabian et al., 2020a,b,c), and both types may need a dormant rest phase in winter (Sun et al., 2021a,b). Traditional application of the leaves of 16 *Dendrobium* species by native people in Bangladesh, Australia, India, Korea, Indonesia, Myanmar, Liberia, Nepal, and Malaysia were reported (Sun et al., 2022a,b; Wu et al., 2023). In China, shi hu and tie pi shit hu are well-known traditional medicines and are recorded in the Chinese Pharmacopoeia (Zhang et al., 2018; Wang, 2021; Shahrajabian et al., 2023). *Dendrobium nobile* Lindl. is a famous medicinal food that is advantageous for human health, and modern pharmacological research indicates that *Dendrobium nobile* polysaccharides and alkaloids are regarded to be the chief active constituents

(Yang et al., 2014; Cakova et al., 2017; Zheng et al., 2020), which have the main roles of regulating immunomodulatory activities, and anti-tumor, anti-hyperglycemic, neuroprotective, and antiviral impacts (Li et al., 2017a,b; Zhang et al., 2019a,b,c). Modern pharmacological researches have proved that *Dendrobium* has anti-tumor, anti-aging, anti-fatigue, gastrointestinal protective, antioxidant, liver protection, antibacterial, anti-inflammatory, anti-diabetic, antihypertensive, cardioprotective, immunomodulatory, neuroprotective, anti-platelet aggregation, antifungal, anti-osteoporosis, etc. activity (Nie et al., 2020; Shahrajabian, 2021; Fu et al., 2023; Sun, Shahrajabian, 2023a,b). Many review articles, academic papers and manuscripts have been discussed and complied in this manuscript using the following online databases such as Pubmed, Scopus, Science Direct, Web of Science and Google Scholar. The literature was scanned using the following keywords such as *Dendrobium*, antioxidant activity, anti-microbial activity, anti-bacterial activity, anti-cancer activity, anti-tumor activity, traditional Chinese medicine, pharmaceutical benefits, anti-inflammatory activities. The most important species of *Dendrobium* are *D. nobile* Lindl., *D. kingianum* Bidwill ex Lindl., *D. catenatum* Lindl., *D. lindleyi* Steud., *D. anosmum* Lindl., *D. speciosum* Sm., *D. moniliforme* (L.) Sw., *D. aphyllum* (Roxb.) C.E.C.Fisch., *D. densiflorum* Schltr., *D. thyrsiflorum* B.S.Williams, *D. loddigesii* Rolfe, *D. farmeri* Paxton, *D. chrysotoxum* Lindl., *D. fimbriatum* Hook., *D. moschatum* (Buch.-Ham.) Sw., *D. parishii* H.Low, *D. amabile* (Lour.) O'Brien, *D. antenuatum* Lindl., *D. cuthbertsonii* F.Muell., *D. sulcatum* Lindl., *D. macrophyllum* A.Rich., *D. tetragonum* A.Cunn. ex Lindl., *D. bellatulum* Rolfe, *D. taurinum* Lindl., *D. linguiforme* Sw., *D. chrysanthum* Wall. ex Lindl., *D. unicum* Seidenf., *D. formosum* Roxb. ex Lindl., *D. bracteosum* Rchb.f., *D. hekouense* Z.J.Liu & L.J.Chen, *D. crepidatum* Lindl. & Paxton, *D. senile* C.S.P.Parish & Rchb.f., *D. infundibulum* Lindl., *D. heterocarpum* Wall. ex Lindl., *D. lituiflorum* Lindl., *D. pulchellum* Roxb. ex Lindl., *D. devonianum* Paxton, *D. findlayanum* C.S.P.Parish & Rchb.f., *D. tortile* Lindl., *D. atroviolaceum* Rolfe, *D. williamsonii* Day & Rchb.f., *D. falconeri* Hook., and *D. aduncum* Lindl.

The aim of this review manuscript is a survey of chemical compounds, and pharmaceutical benefits of *Dendrobium*, especially by considering traditional medicinal sciences in both *in vitro* and *in vivo* experiments.

CHEMICAL CONSTITUENTS AND ACTIVE INGREDIENTS OF *DENDROBIUM*

In the past decades, several constituents have been extracted and isolated from the *Dendrobium* species, especially phenanthrenes, polysaccharides, phenolics, alkaloids, and bibenzyls, whose biological functions and beneficial health impacts have been extensively explored (Hwang et al., 2010; Chaotham et al., 2014; Li et al., 2014; Klongkumnuankarn et al., 2015; Huang et al., 2016, 2019; Zhang et al., 2019b,c). Zhang et al. (2022) isolated nineteen compounds from *Dendrobium chrysanthum*, including four phenol, three monoterpenes, three alkaloid, three lignans and six phenanthrenes. In their experiments compounds carbofuran and (6*R*,7a*R*)-7a-hydroxy-3,6-dimethyl-5,6,7,7a-tetrahydrobenzofuran-2(4*H*)-one were reported from the Kingdom Plantae for the first time (Chaves et al., 2016). The most notable functions of *Dendrobium*'s chemical components are presented in Table 1.

ANTI-INFLAMMATORY ACTIVITY

Dendrobium and its active components show hepatoprotective effect, and the hepatoprotective impact of *Dendrobium* is associated to its oxidative and inflammatory regulation. Stimulation of mitochondrial homeostasis is active in *Dendrobium*-mediated hepatoprotection, it shows antitumor activity in liver cancer, and it has a therapeutic potential for liver disorders (Zhang et al., 2008b). Kongkatitham et al. (2018) and Lin et al. (2011) proved that (-)-Dendroparishiol indicated potent anti-inflammatory and antioxidant effects, and it increased SOD, CAT and GPx activities in hydrogen peroxide (H_2O_2) treated RAW264.7 cells, decreased TNF-α and NO secretion in lipopolysaccharide (LPS) treated RAW264.7 cells, and decreased iNOS and COX-2 expression in LPS treated RAW264.7 cells. Hu et al. (2020) and Shang et al. (2021) reported that six pairs of octahydroindolizine-type alkaloid enantiomers were separated from *Dendrobium crepidatum*, enantiomers revealed important enantioselectivity in anti-inflammatory activity, and dimeric alkaloid significantly reduced LPS-induced acute lung injury in mice. Lin et al. (2013) and Li et al. (2019b) concluded that *Dendrobium huoshanense* stems ethanol extract could significantly inhibit LPS-induced production of NO, IL-1β, and TNF-α which proposed that *D. huoshanense* stems ethanol extract and bibenzyls 1-4 might be well progressed as therapeutic agent to prevent inflammatory diseases. Liang et al. (2019a) concluded that *Dendrobium officinale* polysaccharides (DOPS) have the considerable therapeutic impacts on learning and memory disabilities and its mechanism may be associated to activate Nrf2/HO-1 pathway to decrease oxidative stress and neuro-inflammation. Zeng et al. (2018) also supported the fact that *Dendrobium* as folk medicine, exerted its medicinal function relatively by its inhibitory impacts on inflammation by significantly reducing TNF-α, IL-6 and MCP-1 production. The treatment of *Dendrobium* polysaccharides notably decreased hepatic damage in APAP-treated mice and db/db mice through antioxidant and anti-inflammatory functions (Yang et al., 2006; Li et al., 2018; Liang et al., 2018; Wang et al., 2020; Wu et al., 2020). *Dendrobium* polysaccharides also reduced ethanol-induced acute hepatic injury and lessened AST levels in serum and hepatic tissue, and concurrently inhibited the production of inflam-

Table 1. The most important functions of *Dendrobium*'s chemical components.

Chemical components	Important functions	Reference
Alkaloids	Alkaloids are the first ingredients extracted and purified from *Dendrobium*, which are also main active components.	Chaves et al. (2016)
	Alkaloids have an extensive range of pharmacological activities including anti-inflammatory, antioxidant, anti-anxiety, and anti-depressant characteristics, as well as neuroprotective impacts.	Li et al. (2019a,b)
	Recent studies have shown that *Dendrobium* alkaloids also has an important function in protecting the liver.	Wang et al. (2012) Wang et al. (2016) Zhou et al. (2020)
Polysaccharides	Polysaccharides have been discovered to be one of the chief active components in *Dendrobium* plants, indicating immunomodulatory, antiviral, antitumor activities, and hepatoprotective.	Wang et al. (2010) Tian et al. (2013) Pan et al. (2014) Liu et al. (2019) Fan et al. (2020)
	Dendrobium also contains the following glycosides that have been demonstrated to have biological activities: dendroside C, dendroside A, dendroside A, dendronobiloside B, dendroside E, narcissin, 4-methoxy-2,5,9R-trihydroxy-9,10-dihydrophenan-threne-2-O-β-D-glucopyranoside and 4-hydroxy-3,5-dimethoxyphenyl-β-D-glucopyranoside.	Zhao et al. (2001) Ye and Zhao (2002) Yang et al. (2007)
Phenanthrenes	The phenanthrene compounds identified from *Dendrobium* up to now include 2,8-dihydroxy-3,4,7-trimethoxyphenanthrene, 2,3,5-trihydroxy-4,9-dimethoxyphenanthrene, flavanthrinin, 2,5-dihydroxy-4,9-dimethoxyphenanthrene, 3,7-dihydroxy-2,4-dimethoxyphenanthrene, moscatin, lusianthridin, flavantridin, condusarin, phochinenin, 4,5-dihydroxy-2-methoxy-9,10-dihydrophenanthrene, 6,7-dihydroxy-2-methoxy-1,4-phenanthrene-dione, ephemeranthol, hircinol, nudol, and epheneranthol-C, coelonin, 2,4,5-triol-7-methoxy-9,10-dihydrophenanthrene, denbinobin, eriantridin, 2,5-diol-3,4,8-tri-methoxyphenanthrene, and 4,7-dihydroxy-2-methoxy-9,10-dihydrophenanthrene.	Lee et al. (1995) Zhang et al. (2008a,b) Song et al. (2012) Kim et al. (2015) Zhou et al. (2016) De Natale et al. (2020)
Dibenzyls	Bioactivity-directed fractionation of 60% ethanolic extract of *Dendrobium* stems using the 2,2-diphenyl-1-picrylhydrazyl (DPPH) assay cause the isolation of 3-hydroxy-5-methoxy bibenzyl, batatasin, 4,5,4'-trihy-droxy-3,3'-dimethoxybibenzyl, tristin, moscatilin, 3-methylgigantol, as well as nobilin B, nobilin A, nobilin E, nobilin C, nobilin D, chrysotobibenzyl, chrysotoxin, erianin, and crepidatin.	Zhang et al. (2007) Zhang et al. (2008a,b)

matory cytokines such as IL-1β and TNF-α, and inhibited NF-κB phosphorylation (Yang et al., 2020a,b). Lipidomics analysis in various studies revealed that *Dendrobium* polysaccharides could improve oxidative stress, inflammation, and signs of lipid accumulation in the liver by decreasing the disorders of fatty acids, glycerolipids and glycerides (Zheng et al., 2017; Zhang et al., 2020).

ANTIVIRAL ACTIVITY

Polysaccharides from *Dendrobium nobile* Lindl. have been proved to have antiviral activities (Li et al., 2020; Huang et al., 2020). Several components in *Dendrobium* sp. had been considered to exert pharmacological activities to treat common COVID-19-related sings, and on the basis of the binding mode, DB36 bound with the spike protein at the host receptor, angiotensin-converting enzyme 2 (ACE2) binding motif, leading to antiviral activity (Jiaranaikulwanitch et al., 2020). Dendrobine indicates potential to be developed as the promising factors to treat influenza virus infection, and it could bind to the highly conserved region of viral nucleoprotein (NP), subsequently restraining nuclear export of viral NP and its oligomerization (Li et al., 2017b).

PROTECTIVE EFFECTS OF *DENDROBIUM* ON THE LIVER (HEPATOPROTECTIVE EFFECTS)

The therapeutic benefits of *Dendrobium* for liver diseases include drug-induced liver injury, acute hepatic injury, alcoholic liver injury, liver fibrosis, non-alcoholic fatty liver disease and liver tumors (Pan et al., 2012; Lin et al., 2018; Li et al., 2019a,b; Zhou et al., 2020). Research has also found that *Dendrobium* polysaccharides show strong radical scavenging properties, playing a direct antioxidant function in the process of liver protection. *Dendrobium* polysaccharides can also significantly prevent alcoholic liver injury in mice, and the process may be associated to

Dendrobium's participation in ethanol metabolism pathway (Wang et al., 2014, 2015). In non-alcoholic fatty liver disease (NAFLD) model, *Dendrobium* extract was considered to improve lipid droplet accumulation and stimulate mitochondrial function, so reducing liver injury (Lei et al., 2020). Furthermore, *Dendrobium* polysaccharides can relieve lipid accumulation in the liver of type II diabetic rats (Yang et al., 2020a,b). Another study has also indicated that *Dendrobium* has significantly inhibitory impacts on liver tumors or hepatocellular cancer cells (Xing et al., 2018).

BRAIN PATHOLOGY AND *DENDROBIUM* SPECIES

The effects of *Dendrobium* species on brain pathology are on neuronal injury, brain hypoxia-ischemia, brain inflammation, Hungtington's disease, epileptic seizures, depression anxiety, Parkinson's disease, diabetic neuropathy and Alzheimer's disease (Hu et al., 2008; Wu et al., 2016a; Wang et al., 2023). Rutin, a flavonoid glycoside usually found in *Dendrobium* species, and it was discovered that rutin inhibited neuroinflammation and suppressed NLRP3 inflammasome activation to decrease IL-18, IL-1β, and TNF-α in rat spinal cord injured model (Wu et al., 2016b,c). Erianin derived from the extract of *D. chrysotoxum* (Xiang et al., 2021; Zhang et al., 2021) directly suppressed NLRP3 inflammasome activation, indicating that erianin may serve as the potential novel therapeutic factor against NLRP3-driven brain inflammation (Li, Hong, 2020; Liu et al., 2020).

Dendrobium species have been proved for their hypoglycemic and lipid-lowering impacts (Kuang et al., 2020; Qu et al. 2021). Among active ingredients discovered in *Dendrobium* species, moscatilin has demonstrated potential neuroprotective and anti-diabetes effects (Yoon et al., 2011). *Dendrobium* alkaloids could increase learning and memory function in elderly normal mice (Nie et al., 2016; Kesh et al., 2021). A monoterpenoid lactone loliolide is found in *D. huoshanense* stems, and it improved cell viability, protected mitochondrial function, decreased oxidative stress and apoptosis in 6-OHDA-exposed SH-SY5Y cells (Jiang et al., 2017; Silva et al., 2021). *D. officinale* flos had antidepressant-like impacts, and its ethanol extract alleviated depression-like behaviors in CUMS-exposed mice (Zhu et al., 2021). *D. officinale* polysaccharide reduced TNF-α and IL-1β expression, and inhibited p-ERK1/2, p-JNK, and p38 in hippocampus (Chen et al., 2017).

ANTIBACTERIAL ACTIVITY

Dendrobium has great capability as antimicrobial agent against selected pathogenic microorganisms because of the presence of selected flavonoid and alkaloid compounds (Sandrasagaran et al., 2014). Polysaccharide is the characteristics bioactive ingredient of *Dendrobium*, which indicates antibacterial activity (Wang et al., 2022a,b; Shahrajabian, Sun, 2023a,b,c,d,e). Methanol extract from *Dendrobium* showed antimicrobial impacts (Paudel et al., 2020; Shahrajabian et al., 2021a,b,c,d; Sun, Shahrajabian, 2023a,b; Zhang et al., 2024). Chua et al. (2022) reported that antimicrobial activities may be related to constituents like alkaloids, phenols, flavonoids, saponins, terpenoids and tannins.

ANTI-TUMOR ACTIVITY

Two main polysaccharides present in *Dendrobium* namely (1→4)-*β*-d-Glc*p* and *O*-acetylated (1→4)-*β*-d-Man*p*, has shown anti-tumor characteristics and they have potential to be a functional agent for lung cancer prevention (Ye et al., 2021). *Dendrobium officinale* polysaccharides can modulate immune responses and inflammation to decrease experimental colitis, and they can improve the metabolic ability of tumor infiltrated $CD8^+$ cytotoxic T lymphocytes (CTLs) and decreased the expression of PD-1 on CTLs to enhance the anti-tumor immune response in the tumor microenvironments (TME) (Liang et al., 2019a,b,c; Wang et al., 2022a,b). It has been reported that cultivated *Dendrobium huoshanense* stem polysaccharide (cDHPS) inhibits tumor growth of murine forestomach carcinoma (MFC) tumor-bearing mice, and induces tumor cell apoptosis, inhibits tumor angiogenesis, and increases T cell immune response of MFC tumor-bearing mice (Liu et al., 2021a,b). *Dendrobium officinale* includes of D-mannose, D-glucose, and D-galactose in a mole ration of 3:2:1, and it possesses antitumor and immunomodulation activity, and could inhibit the growth of S180 tumors by improving the tumor immune microenvironment (Sun et al., 2022a,b).

ANTIOXIDANT ACTIVITY

Antioxidant activity plays an important role in the pharmacological potential of *Dendrobium*, which can inhibit the damage of reactive oxygen species (Li et al., 2008; Liang et al., 2019a,b; Paul, Kumaria, 2020; Cui et al., 2023). It has a definite antioxidant capacity, especially associated to its polysaccharide content and relative high molecular mass, and the rich antioxidant activity can meaningfully influence their effectiveness as functional food supplements and medicines (Fan et al., 2009; Luo et al., 2009, 2010; Moretti et al., 2013; Liu et al., 2021a,b; Shahrajabian, Sun, 2022; Rahamtulla et al., 2023). The leaves of *Dendrobium* may be developed as antioxidant sources for health food and medicinal resources, and the major flavonoid ingredient of the leaves was rutin (Rahamtulla et al., 2023). Tian et al. (2013) reported the antioxidant activities of a polysaccharide fraction (DHP1A) extracted from *Dendrobium*, and it extensively consisted of mannose (Man), glucose (Glc), and a trace of galactose (Gal) with a molecular weight of 6700 Da. Luo et al. (2016) also showed

that glucose and mannose are the main constituent of *Dendrobium officinale* polysaccharide, and the polysaccharide has antioxidant property. Zhang et al. (2019a) indicated that flowers of *Dendrobium* are new food component and exhibit potential antioxidant characteristics, 1-O-caffeoyl-β-D-glucoside, isoquercitrin and rutin were the dominant antioxidants in the flowers. *Dendrobium* extracts showed high inhibition of monophenolase activity in melanin synthesis, and exhibited higher tyrosinase inhibitory activity than kojic acid (Fang et al., 2015; Wu et al., 2016a,b,c; Li et al., 2017a,b; Athipornchai, Jullapo, 2018; Nie et al., 2018; Zhang et al., 2017, 2019b,c; Kim et al., 2020). The methanol leaf extract showed good anticancer and antioxidant activity against the cell lines tested when compared to ethyl acetate extract, and there is a positive connection between the anticancer and antioxidant activity of leaf extracts (Kim et al., 2020).

CONCLUSION

Traditional herbal medicine (THM) has a long history, making them accepted and trusted by a significant number of people in the world. *Dendrobium* is a large and diverse genus of orchids with different cultivation needs. *Dendrobium* orchids are primarily epiphytic, growing in nature on the branches and trunks of trees. It is the second largest genus of Orchidaceae, which is a perennial herbaceous plant, and there are more than 1500 species of *Dendrobium* in the world, mainly distributed in tropical Southeast Asia and Oceania. The most important chemical constituents of *Dendrobium* are alkaloids, phenolics, polysaccharides, bibenzyls, glycosides and phenanthrenes. Alkaloids have an extensive range of pharmacological activities including anti-inflammatory, antioxidant, anti-anxiety, and antidepressant characteristics, as well as neuroprotective impacts. Polysaccharides have been discovered to be one of the chief active components in *Dendrobium* plants, indicating antitumor, antiviral, immunomodulatory and hepatoprotective activities. The most notable pharmacological benefits of *Dendrobium* are anti-tumor, antioxidant and anti-hypertensive, neuroprotective impacts, anti-inflammatory, anti-bacterial, anti-fungal effects, liver protection and anti-platelet aggregation activity. It is suggested that *Dendrobium* cultivation has a great potency to connect between organic life and traditional Chinese medicine. Future studies should address the methodologic parameters are warranted to evaluate the therapeutic advantages of *Dendrobium* as Chinese herbal medicine for different diseases.

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