

Exploring the Application Prospects of Aboveground Parts of *Codonopsis pilosula* in Agri-Food and Other Industries Based on Chemical Composition and Pharmacological Effects: A Review

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Abstract Due to the tradition of using the root as medicine and the lack of in-depth research, more than thousands of tonnes of above-ground parts of *Codonopsis* are still discarded every year, resulting in unimaginable waste of resources and environmental damage. In order to maximally utilize the nutrients in medicinal resources, we systematically reviewed the published literature on chemical composition, pharmacological experiments and exploitation, and summarized the amino acids, polysaccharides, saponins, terpenoids and flavonoids contained in the stems, leaves, flowers and seeds of *Codonopsis pilosula* into more than 130 kinds of 15 categories, and explained its anti-fatigue, anti-hepatic fibrosis, antioxidant, lipid regulating, immune enhancing, antibacterial and anticancer effects. It also summarises the new trends of its application in health food, edible mushroom cultivation, chemical medicine manufacturing and feed additives based on the amount of chemical enrichment from the perspectives of toxicity test, nutritional value and ecological benefits. The in-depth study will help to establish a more sustainable food system, improve the nutritional status of consumers, address the unmet needs in clinical, scientific research, and daily health care, and have a positive practical significance for the conservation, development and utilisation of medicinal plant resources.

Keywords: Above ground part of *Codonopsis pilosula*, *Codonopsis pilosula* pollen, *Codonopsis pilosula* stem and leaves, Chemical Composition, Pharmacological effects, Nutrient components

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1. Introduction

Codonopsis pilosula is the dried root of *Codonopsis pilosula* (Franch.) Anna, C.penisula Anna.var.modes ta (Anna.) L.T. Chen or C. tangshen Oliv, family Platycodonaceae [1], and is a traditional bulk tonic herbal medicine. [2] It is a perennial herb with twining stems [3], long cylindrical in shape with a greyish-yellow surface [1,4], with a special odour and a slightly sweet taste [1] (Figure 1); Chinese Pharmacopoeia records that *Codonopsis pilosula*, which is sweet in flavor and neutral in nature, is useful for tonifying the middle-jiao, augments Qi and generating fluids and blood. [1] Modern pharmacological studies have also shown that *Codonopsis*

pilosula has a variety of tonic effects such as antiulcer [5], stomach protection [6-7], regulating blood sugar [6], anti-fatigue [8], anti-inflammatory [9-10], immune regulation, anti-oxidation, anti-aging, liver protection and improvement of memory disorders. [2,5,6]

The *Codonopsis pilosula* is cold resistant, which grows in mountains, forest margins and thickets at 1560-3100m. [4,11] China is rich in medicinal *Codonopsis pilosula* resources, with many species. There are more than 40 species of *Codonopsis pilosula* plants in the genus *Codonopsis pilosula* worldwide, 39 species in China. [2]

With economic development, the utilization value of *Codonopsis pilosula* has gradually been fully recognized, and in 2018, it was officially included in the management of food and drug substances by the Health Commission. [12] The market for *Codonopsis pilosula* is large in East

and South Asia [13], and clinical use and health care needs have led to increased demand.[3,14] Literature on the investigation of wild *Codonopsis pilosula* resources in different regions have shown that with the reclamation of mountainous areas and uncontrolled harvesting [14], the wild *Codonopsis pilosula* communities are declining rapidly and wild resources are facing depletion, and are now mostly planted in captivity.[3,15-18]

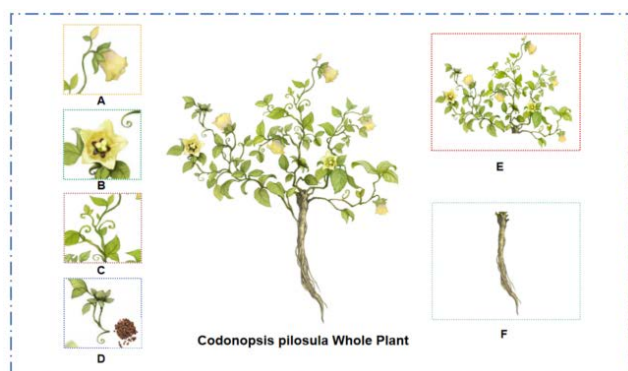


Figure 1. Whole plant diagram of *Codonopsis pilosula*. (A) *Codonopsis pilosula* flowers (side view). (B) *Codonopsis pilosula* flowers (front view). (C) *Codonopsis pilosula* Stem and Leaf. (D) *Codonopsis pilosula* seeds. (E) Above-ground parts of *Codonopsis pilosula*. (F) *Codonopsis pilosula* root

However, *Codonopsis pilosula* has the dilemma of allelopathy in artificial cultivation. It is the main cause of crop failure. A study in 2010 confirmed that there is a strong self-disease (i.e., inhibition of self-growth) in cultivated *Codonopsis*, which is an important factor affecting the yield of ginseng in artificial cultivation. [19] Xie, M. also provided relevant evidence for the study of the barrier caused by the allelopathy of *Codonopsis pilosula* on artificial cultivation. [20]

The roots of *Codonopsis pilosula* have been used as medicine for hundreds of years. [13] Practice and research have shown [21-25] that in the current artificial cultivation of *Codonopsis pilosula*, stem and vine cutting treatments of *Codonopsis pilosula* at flowering stage can effectively increase herb yield and seed yield. [22,24,25] This is related to the inhibition of nutrient consumption by aboveground stems, reduction of leaf layer thickness, improvement of photosynthetic efficiency [21] and increase of soil temperature for root development. [22,23,25] In addition, cutting stems during the growth period of *Codonopsis* facilitates the conversion of the underground part of the leachate formation, increasing yield, root length, root weight and root diameter [24]. Therefore, the aboveground part discarded by pruning during the cultivation of *Codonopsis pilosula* becomes waste, and its exploitation not only does not affect the yield of the traditional medicinal roots of *Codonopsis pilosula*, but also serves to increase yield and improve quality. [22-25] This feature provides the most basic theoretical and practical basis for us to develop and utilise aboveground resources.

Previous studies have extracted, purified and analysed the chemical substances in the above-ground part of

Codonopsis pilosula by UPLC-MS analysis [13], ethanol reflux extraction [15], phenol-sulphuric acid colourimetry [27,28], Dual-enzyme synergistic ultrasound [29], HPLC [28,29], LSCM [30] and GC-MS [31], etc. And it has been proved that above-ground part of the *Codonopsis pilosula* contains a large number of chemicals similar to the roots, such as amino acids [27,28], polysaccharides [27] [32,33], sterols [13,34], alkynes [13], and organic acids[13], etc, and the content of some of the substances is far more than that in the roots of the *Codonopsis pilosula* [11,13,29] [27,28].

Based on the chemical composition and content, the extracts and derivatives of the aboveground part of *Codonopsis pilosula* have corresponding pharmacological effects and high development value, such as antioxidant [35], anti-inflammatory [9,36], immunomodulatory [35-37], anti-cognitive decline [35,38], promoting the recovery of haematopoietic dysfunction [39], replenishes nutrients [40,41] and so on. which provides a sufficient theoretical basis for us to research and develop the above-ground part of *Codonopsis*.

However, the above-ground part of the *Codonopsis pilosula* has not been reasonably exploited. [11] *Codonopsis pilosula* has a wide planting area, and the annual output of roots reaches 5000 tons. [13] According to the data in 2021, the annual planting area of *Codonopsis pilosula* is 33 thousand hm². [29] Xu Zeng et al. noted that thousands of tons of above-ground parts are discarded directly after harvest each year [13], and that the biological production of above-ground parts is large. The huge cultivation area and the tradition of using the roots as medicine make the above-ground part of the resources wasteful. For the purpose of protecting the wild herbal resources and maximizing the utilization of the resources under artificial cultivation, there is an urgent need and positive practical significance for the rational exploitation of the above-ground part of *Codonopsis pilosula*.

2. Chemical Composition of the Above-Ground Parts of *Codonopsis Pilosula*

As a common clinical Chinese medicine, *Codonopsis pilosula* has a wide range of pharmacological effects such as immune modulation, anti-oxidation and anti-aging, anti-bacterial and anti-cancer. A review concluded that the material basis for its action is mainly polysaccharides, alkynyl glycosides, alkaloids and other components. [42] A number of scholars have analyzed the composition and content differences between the above-ground and root parts of *Codonopsis pilosula*, and the results all indicated that the compounds contained in the above-ground and underground parts of different species of *Codonopsis pilosula* were basically the same. [2,12]

In terms of the total content of amino acids, [27] trace elements, [27] coumarin, [29] vitamins, [43] the content of the aboveground part is basically greater than that of the medicinal rhizome. This means that the above-ground parts of *Codonopsis pilosula* have great potential for use, and the author summarises the chemical constituents reported in the available literature as follows (Table 1).

Table 1. The table of chemical constituents and biological activity of aerial parts of *Codonopsis pilosula*

no	chemical composition		measurement methods
	large categories	subcategories	
1	amino acids	Asp, Thr, Ser, Glu, Gly, Ala, Cys, Val, Met, Ile, Leu, Tyr, Phe, Lys, His, Arg, Pro	hitachi 835-50 automatic amino acid analyzer [27]
		glutamic acid	fully automatic amino acid analyser [28]
2	trace elements	Al,Fe,Ca,Mg,K,Na,Ti,Mn,P,Ba,Co,Cr,Cu,Li,Ni,Pb,Sr,V,Zn,Y,Mo,Zr	jarrell-ash 1160 plasma spectrometer [27]
		Fe, Si, Al, Se, Mn, Zn, B, Cu, Ni, Co, Mo, Cr, As	atomic absorption spectrophotometer [28]
3	vitamins	A,E,C,B1,B2,B6, β -carotene, K1	LC-6A high performance liquid chromatograph [43]
4	alkaloid	Choline	thin-layer chromatography [27,44]
		codotubulosine A,codonopsinine, adenosine, hypoxanthine, Codonopsinol C, Codonopiloside A, Codonopsinol A, radicamine A, 6-methoxy-4-formyl quinoline/6-methoxyquinoline-4-carbaldehyde, N-9-formyl harman, Codonopsine 2	UPLC-MS analysis [13]
5	sugars	D-Glucuronic acid, rhamnose, galactose, glucose, D-fructose	phenol-sulphuric acid method [27]
		codonopsis polysaccharide	gel chromatography & electrophoresis [32]
6	saponins	Codonopsis pilosula total saponin	ethanol reflux method [15]
		Ginsenoside Rg1, Ginsenoside Re, Ginsenoside Rb1	column chromatography, thin layer preparation and other methods [20]
7	volatile oil	palmitic acid, 9,12,15-octadecatrienal, linoleic acid, myristic acid, olive oil, trans-sec-butylpropyl disulphide, etc.	GS-MS [47]
8	glycerides, glycerol esters	Stearic acid; linolenoylglycerol 1-O-[α -D-galactopyranosyl-(1 \rightarrow 6)-O- β -D-galactopyranoside; 3- α -linolenoylglycerol 1-O- β -D-galactopyranoside and 3-(7,10,13-hexadecatrienoylglycerol)1-O- β -D-galactopyranoside mixture	silica gel column chromatography, MCI column chromatography, thin layer preparation and other methods [34]
		luteolin, luteolin-5-O-glucoside	column chromatography, thin layer preparation and other methods [20]
9	flavonoids	total flavonoids of codonopsis	double enzyme synergistic ultrasound [29]
		apigenin, tricrin, chrysoerio, 5-hydroxy-4',6,7-trimethoxy flavone, 5-hydroxy-4',7-dimethoxy flavone, apigenin-7-O- β -D-glucopyranoside, luteolin-7-O- β -D-glucopyranoside/9 luteolin-5-O- β -D-glucopyranoside/ luteolin-7-galactoside/ cynaroside, luteolin-7-rutinoside, tectoridin, uteolin-7-O-D-gentibioside, neokurarinol	UPLC-MS analysis[13]
10	steroids	Δ 7- stigmastenol	shimadzu CS-930 thin layer scanner [44]
		α -spinasterol, (22)-5 α ,8 α -epidioxy-ergosta-6,22-dien-3 β -ol	silica gel column chromatography, MCI column chromatography, thin layer preparation and other methods [34]
11	terpenoids	Δ 7-stigmasterol and Δ 5,22-stigmasterol	UPLC-MS analysis [13]
		taraxerol acetate, taraxerol	shimadzu CS-930 thin layer scanner [44]
12	Coumarins	atractylenolide III, oleanolic acid, echinocystic acid, 8 β -hydroxyasterolid/atractylenolide, albigenic acid, rubiprasin, hopane-6 α ,22-diol	UPLC-MS analysis [13]
13	alkynes, alkenes compounds	coralline lactone, 5-hydroxy-8-methoxy-psoralen	LSCM, HPLC [29-30]
		lobetyolin	column chromatography, thin layer preparation, etc. [20]
14	lignans	Lobetyol, Lobetyolinin, Pilosulyne A, Pilosulyne C, Pilosulyne F, Pilosulyne G, 9-(tetrahydropyran-2-yl)-non-trans-8-ene-4,6-yn-1-ol, tetradeca-4E,8E,12Etriene-10-yne-1,6,7-triol	UPLC-MS analysis [13]
		tangshenoside I, tangshenoside III, tangshenoside IV, codonoside A, codonopiloneolignanin A, ethyl-syringin, syringaresinol, lanceolune A, lanceolune B	UPLC-MS analysis [13]
15	organic acids	lauric acid, 2,4-non-adlenic acid, caffeic acid, chlorogenic acid/ neochlorogenic acid/ 3-O-Caffeoylquinic acid, 8-O-4' diferulic acid, syringic acid	UPLC-MS analysis [13]

2.1. Amino Acids, Trace Elements and Vitamins

As early as 1992, it has been reported that the stems, leaves, flowers and roots of *Codonopsis pilosula* contain 17 amino acids (Asp, Thr, Ser, Glu, Gly, Gla, Cys, Val, Met, Ile, Leu, Tyr, Phe, Lys, His, Arg, Pro). [27] Zheng et al. detected 17 amino acids in the aerial parts and roots of *Codonopsis pilosula* in Miaoyu Town, Wushan County, Chongqing. [28] The results were consistent and pointed out the following conclusions:

Compared to the roots, the composition of essential amino acids in the above-ground parts of *Codonopsis* is closer to the FAO/WHO standard model in the amino acid pattern spectrum, suggesting higher nutritional value;

The total gustatory amino acids in the above-ground parts were 2.35 times higher than those in the roots, suggesting that the above-ground parts of *Codonopsis pilosula* would have good flavour when developed as food;

The total amount of medicinal amino acids is 1.76 times that of the root, suggesting that the medicinal value of the aerial part of *Codonopsis* is worth exploring.

The amino acid content in the roots of *Codonopsis pilosula* were determined by Wang Yan et al. in five major producing areas in China, and the results were still 17. [8] They also suggested that the content of Arg, Glu, Asp and other medicinal amino acids in the roots could be used as indicators for the nutritional evaluation of *Codonopsis pilosula*, and outlined that these amino acids are the material basis for the immune regulation, liver protection, gastric mucosa protection and fatigue prevention of *Codonopsis pilosula*. [8] According to the test results of study, the content of the aboveground part is 1.3-5.3 times that of the root. [27]

Vitamins, including A, E, C, B1, B2, B6, β -carotene, K1, were detected in the roots, stems and leaves of *Codonopsis pilosula* by piao et al, and the total vitamin content in stems and leaves was higher than that in roots. [43] There are 22 kinds of trace elements (Al, Fe, Ca, Mg, K, Na, Ti, Mn, P, Ba, Co, Cr, Cu, Li, Ni, Pb, Sr, V, Zn, Y, Mo, Zr) in stems, leaves, flowers, fruits and roots, and the content of each part on the ground is 2.27-3.57 times higher than that of roots, which is higher than that of roots. [27]

Fe, Si, Al, Se, Mn, Zn, B, Cu, Ni, Co, Mo, Cr and As in both the roots and the above-ground parts of the Wushan *Codonopsis pilosula* were found by Zheng et al., with the above-ground part containing 88.83% of the essential trace elements in the roots. [28] They also noted that the above-ground parts contained 1.24, 2.10, 2.51 and 1.04 times more silicon, selenium, manganese and zinc essential trace elements than the roots [28], respectively, except for iron, which was less than the root content.

This alone suggests that the above-ground parts of *Codonopsis pilosula* contain great value for exploitation.

2.2. Alkaloids

The above-ground stems and leaves of *Codonopsis pilosula* have the same alkaloid components (choline) with different content as the roots. [27,44] According to the study, the total alkaloids of *Codonopsis* can enhance NGF-induced PC12 cell prominence by causing a certain upstream step in the signaling pathway of a large number

of mitogenic protein kinases, [45] and Choline enhances memory. [44] Xu Zeng et al. determined 11 substances with significantly different contents in the stems and leaves and roots of *Codonopsis pilosula* [13]: codotubulosine A, codonopsinine, adenosine, hypoxanthine, Codonopsinol C, Codonopiloside A, Codonopsinol A, radicamine A, 6-methoxy-4-formyl quinoline/ 6-methoxyquinoline-4- carbaldehyde, N-9-formyl Harman, Codonopsine 2. Codotubulosine A and codonopsinine were more abundant in the stem and leaves, while codonopsinol A and C, codonopiloside A, radicamine A, and codonopsine 2 were more abundant in the roots. The overall distribution of different types of alkaloids in stems, leaves and roots is different.

2.3. Sugars

D-glucuronide, rhamnose, galactose, glucose and D-fructose were extracted from both the stems and roots of *Codonopsis pilosula*, and the total content of the roots was higher than that of the above-ground parts. [27] Five polysaccharides were extracted from the pollen of *Codonopsis pilosula* by Liu et al, [27] which is one of the main active parts of *Codonopsis pilosula*. The total content of sugars in the roots was found to be higher than that in the above-ground parts by Zhang Yan Yun. [33] While, their results showed that the polysaccharides in the stems and leaves of *Codonopsis pilosula* were the same as those in the roots, and had higher antioxidant stress activity.

2.4. Saponins

The total saponins of *Codonopsis pilosula* have immunomodulatory, anti-tumor, antibacterial, hypoglycemic and lipid-lowering effects. [15] The total saponin content of the roots was determined to be seven times higher than that of the above-ground parts, [44] and Xie Min et al. isolated ginsenoside Rg1, ginsenoside Re, ginsenoside Rb1 from the above-ground parts. [20] The total saponins extracted from the stems and leaves of *Codonopsis pilosula* by ethanol reflux extraction have higher DPPH free radical, hydroxyl radical and superoxide anion radical scavenging ability, and the maximum scavenging rates of each free radical in the experimental concentration range are 86.92 %, 55.37 % and 82.21 %, respectively. [20]

2.5. Volatile Oil

In the volatile oil of roots and stems and leaves, there are a lot of fatty acids, palmitic acid content is the most, [46] mainly fatty acids, aldehydes, alcohols, olefins, alkanes and a small amount of esters and ketones. The main compounds in the volatile oil were palmitic acid (32.75 %), 9,12,15-octadecatrienal (10.42 %), linoleic acid (6.48 %), myristic acid (4.05 %), olive alcohol (2.71 %), trans-sec-butylpropenyl disulfide (2.23 %) and so on. [47]

9,12,15-octadecatrienal (the second most abundant chemical in the volatile oil) is one of the two main components of the sex pheromone of *Hyphantria cunea*, which can be used for the synthetic lure of *Hyphantria cunea* [47] to reduce its harm to crops.

2.6. Glycerides and Glycerol Esters

Stearic acid, 3- α -linolenic acid glyceride 1-O-[α -D-galactosyl- (1 \rightarrow 6) -O- β -D-galactoside], 3- α -linolenic acid glyceride 1-O- β -D-galactoside and 3-(7,10,13-hexadectrienoic acid) glyceride 1-O- β -D-galactoside mixture were extracted from the aerial part of *Codonopsis pilosula* by Xie Min et al., and the latter two had hypolipidemic effect. [34]

2.7. Flavonoids

Flavonoids have anti-oxidation, anti-aging, anti-cancer, liver protection, anti-inflammatory and other effects. [31] Flavonoids in stems and leaves of *Codonopsis pilosula* were found more abundant than those in roots. [13] Luteolin, luteolin-5-O-glucoside were isolated from above ground part of *Codonopsis pilosula* by Xie Min et al. [20] The total flavonoids with strong antioxidant activity from *Codonopsis pilosula* stems and leaves was found by double enzyme synergistic ultrasonic extraction. [29] Apigenin, tricetin, chrysoeriol, 5-hydroxy-4', 6, 7-trimethoxy flavone, 5-hydroxy-4', 7-dimethoxy flavones, apigenin-7-O- β -D-glucopyranoside, luteolin-7-O- β -D-glucopyranoside, luteolin-7-rutinoside, tectoridin, luteolin-7-O-D-gentibioside, neokurarinol and other flavonoids were measured in the stems, leaves and roots of *Codonopsis pilosula* by Xu Zeng et al. [13] Among them, apigenin, tricetin, chrysoeriol, tectoridin, and luteolin-glucopyranoside were higher in the stems and leaves of *Codonopsis pilosula*, while quercetin, kaempferol, angelicin, and psoralen were not significantly different in stems and leaves and roots.

2.8. Steroids

Steroids, including α -spinasterol, (22E)-5 α , 8 α -bridging ergosta-6,22-diene-3 β -ol, were also found in the stems and leaves of *Codonopsis pilosula* by silica gel column chromatography, MCI column chromatography and thin layer preparation, [34] which also clearly stated that both can inhibit pancreatic lipase and have a hypolipidemic effect. Meanwhile, the content of Δ 7-leguminol in the above-ground parts of *Codonopsis pilosula* was found to be 1.5 times that of its roots by Yan. [44] Studies suggest that, steroids are more common in the stems and leaves of *Codonopsis pilosula*. Δ 7-stigmasterol and Δ 5,22-stigmasterol are more enriched in stems and leaves. [13]

2.9. Terpenoids

The study showed that The aerial parts of *Codonopsis pilosula* contained Taraxerol acetate, taraxerol, and the content of aerial parts was 78.4 times and 4.6 times that of its roots, respectively. [44] Atractylenolide III, oleanolic acid, echinocystic acid, 8 β -hydroxyasteroid/atractylenolide, albigenic acid, rubiprasin, hopane-6 α ,22-diol were found in the stems and leaves and roots of *Codonopsis pilosula* by Xu Zeng et al. [13] According to studies, Atractylenolide III, oleanolic acid and echinocystic acid have anti-inflammatory, stomach-protective, antibacterial and anti-cancer effects, [13,48] and they are more enriched in the stems and leaves, [13]

suggesting that the stems and leaves of *Codonopsis pilosula* have good prospects for exploitation.

2.10. Coumarins

Coralline lactone and 5-hydroxy-8-methoxypsoralen were found in the scape, stem and root of *Codonopsis pilosula* by HPLC by Zhang et al. In terms of content, these two substances are enriched in seeds. [29] Zhang et al. also obtained consistent results by LSCM method. [30]

2.11. Alkynes, Alkenes Compounds

Alkenes were found to accumulate more in stems and leaves by Xu Zeng et al. [13] Lobetyol; Pilosulyne A; Pilosulyne C; Pilosulyne F; Pilosulyne; 9-(tetrahydropyran-2-yl)-non-trans-8-ene-4,6-dien-1-ol; Codonopilodiyne (D/E/F/G); tetradeca-4E,8E,12E-triene-10-yne-1,6,7-triol, etc. were detected in roots, stems and leaves, and their expression levels were different. Of these, Lobetyol, pilosulyne and codonopilodiyne D were enriched in the stems and leaves. Lobetyol and lobetyolin (polyacetyl compounds) in roots and the above ground part of *Codonopsis pilosula* (stems and leaves) were showed no significant difference by metabolomics analysis results. Xie Min et al. also isolated lobetyolin from the stems and leaves of *Codonopsis pilosula*. [20]

2.12. Lignans

Lignin is widely distributed in plants, including antioxidant, antibacterial, antiviral, anti-tumor and anti-asthma activities. [13,48] Tangshenoside I, tangshenoside III, tangshenoside IV, codonoside A, codonopiloneolignanin A, ethyl-syringin, syringaresinol, lanceolone A, lanceolone B were detected in the stems, leaves and roots of *Codonopsis pilosula*, while ethylsyringin and syringaresinol accumulated more in the stems and leaves of *Codonopsis pilosula*. [13]

2.13. Organic Acids

The content of organic acids in stems and leaves is much higher than that in roots. [13] There are lauric acid, 2,4-nonadecenoic acid, caffeic acid, chlorogenic acid / neochlorogenic acid / 3-O-Caffeoylquinic acid, 8-O-4-diferulic acid, syringic acid, etc. Among them, the relative content of lauric acid, caffeic acid, and chlorogenic acid, was higher in stems and leaves than in roots, while the relative content of syringic acid was lower in stems and leaves than in roots.

3. Pharmacological Effects of the Above-Ground Parts of *Codonopsis pilosula*

3.1. Antioxidation

The antioxidant activity is generally related to polyphenols, flavonoids and saponins. [11] Flavonoids have antioxidant and anti-aging effects, [31] while flavonoids in the stems and leaves of *Codonopsis pilosula* are more

abundant than those in the roots, and the above-ground part extracts have a more pronounced free radical scavenging capacity, [13] Atractylenolide III also has an effect on reducing oxidative stress, while Atractylenolide III is more abundant in the stem and leaves. [13] According to research, the total flavonoids and total saponins in the stem and leaves of *Codonopsis pilosula* have strong antioxidant activity. [15,29] This implies that the stem and leaves of *Codonopsis pilosula* have good utilization value and development prospects.

3.2. Anti-bacterial

Some studies have indicated that the relevant extracts from the leaves of *Codonopsis pilosula* have inhibitory effects on common pathogenic bacteria such as *Escherichia coli*, *Bacillus subtilis* and *Staphylococcus aureus*. [49-50] Bhardwaj et al. also found that the extract of the leaves of *Codonopsis pilosula* had an inhibitory effect on bacteria, moulds and yeasts. [49] The polysaccharides in the stem and leaves of *Codonopsis pilosula* can promote the growth of probiotics such as *Bifidobacterium* and *Lactobacillus*, and inhibit the growth of *Salmonella* and *Enterococcus* [51], as well as inhibit the colonization of pathogenic bacteria. [52] The conclusions of these modern pharmacological studies are mutually confirmed with the traditional effects of *Codonopsis pilosula*, which can tonify the middle-jiao and augment Qi, whose meridian affinity is Spleen meridians.

3.3. Blood Lipid Regulation

Xie Min et al. detected α -spinasterol; (22E)-5 α ,8 α -epidioxy-ergosta-6,22-dien-3 β -ol; 9,12-linoleic acid; 3- α -linolenylglycerol 1-O-[α -D-galactopyranosyl-(1 \rightarrow 6)-O- β -D-galactopyranoside in the stems and leaves of *Codonopsis pilosula*, and found that they had inhibitory effect on pancreatic lipase activity. [34] Meanwhile, one study found that *Codonopsis* pollen seems to have the effect of reducing hepatic TG by accelerating lipid transport. [53] Phellopterin, which are contained in the scapes, stems, leaves and roots of *Codonopsis*, promote lipolysis and inhibit lipid synthesis. [13]

3.4. Regulating Immunity

Codonopsis pilosula polysaccharides have strong immunomodulatory effects in both humans and animals, and the above-ground parts of *Codonopsis pilosula* contain high levels of polysaccharides. [31,54] A study was shown that *Codonopsis pilosula* polysaccharides could modulate immunity by improving intestinal flora dysbiosis and enhancing mucosal immunity against immunosuppression caused by cyclophosphamide in mice. [52] At the same time, more literature has reported the good effect of adding the stems and leaves of *Codonopsis pilosula* to animal feed to improve the immunity and disease resistance of animals, and pointed out that the stems and leaves of *Codonopsis pilosula* can be used as

immunomodulators. [56-59] Related studies have also shown that *Codonopsis pilosula* pollen can correct the immunosuppressive state and significantly enhance humoral immunity and non-specific immunity. [60-61]

3.5. Other Possible Pharmacological Effects

Xu Zeng et al. measured polysaccharides, lobetyolin, lobetyolinin, lauric acid, caffeic acid and chlorogenic acid and other substances in both stems and leaves and roots of *Codonopsis pilosula*. [13] The content of lauric acid, caffeic acid, chlorogenic acid, atractylenolide III, oleanolic acid and echinocystic acid in stems and leaves was higher than that in roots, while lobetyolin and lobetyolinin had no significant difference in stems and leaves and roots, [13] suggesting that the aboveground parts of *Codonopsis pilosula* may also contain higher related activities.

3.5.1. Stomach Protection

Atractylenolide III, *Codonopsis* polysaccharide and lobetyolin has the effect of protecting stomach. He et al. found that *Codonopsis pilosula* polysaccharide had a mild effect on normal gastric epithelial cells. [62] *Codonopsis pilosula* polysaccharide may maintain the function of digestive system flora by stimulating the growth of *Lactobacillus* was found by Fu et al. [48], which has a protective effect on the destruction of gastric mucosal immune barrier and low inflammatory risk.

3.5.2. Against Cancer

Codonopsis pilosula polysaccharide, lobetyolin, luteolinic acid, oleanolic acid have anti-cancer effect. [13] *Codonopsis pilosula* polysaccharide can selectively inhibit gastric cancer cells and inhibit cancer cell proliferation by regulating energy metabolism. [62] Lobetyolin and Lobetyolinin inhibit drug-induced apoptosis and tumor growth, and their anticancer activity is dependent on amino acid transporter ASCT2 -mediated glutamine metabolism inhibition. [63] Yu et al. verified that luteolin can exert anti-hepatocellular carcinoma effect through AKT or MAPK-JNK signal-mediated ESR1. [64]

3.5.3. Anti-inflammatory

Atractylenolide III, echinococcus acid, caffeic acid, chlorogenic acid and syringic acid all have anti-inflammatory activity and are found in higher amounts in the stem and leaves of *Codonopsis pilosula*. [13]

3.5.4. Cognitive Improvement

A study by Lu Wan et al. indicated that *Codonopsis pilosula* polysaccharide may alleviate the associated memory impairment and cognitive deficits by restoring the altered synaptic protein PSD95 and synaptic aggregation protein, downregulating BACE1 activity, [65] while protecting primary neurons from A β 1-42-induced cytotoxicity had a mitigating and ameliorating effect on Alzheimer's disease in APP/PS1 mice, significantly reducing cognitive deficits.

Table 2. Pharmacological effects of Codonopsis pollen

System	Object of observation	Model / Situation	Effect and function	
Liver system	mice	CCL4-induced liver injury	Improves hepatic lipid deposition and reduces hepatocyte degeneration and necrosis; Inhibits active fibroblast proliferation ; Fight against liver fibrosis. [53,55]	
		Immunosuppression due to cyclophosphamide	Increased lymphocyte transformation rate and E wreath production rate [60-61,66]	
Immune system	mice	Immunosuppression due to glucocorticoids	Enhanced production of vacuole-forming cells and IgM Viability of mouse peritoneal macrophages [60-61,66]	
		normal	No significant effect on immune organs, lymphocyte conversion rate and E wreath formation [60-61,66]	
		normal	Enhanced production of vacuole-forming cells and IgM and viability of murine peritoneal macrophages [60-61,66]	
Hematopoietic system	rat	Cyclophosphamide impairs bone marrow hematopoietic function	Elevated white blood cell and granulocyte levels [67]	
		normal	No significant effect on peripheral blood [67]	
	mice	Anti-mitomycin inhibits hematopoietic system	Resistance to inhibition of the haematopoietic system caused by mitomycin [68]	
		Patients with clinical hematopoietic dysfunction	aplastic anemia patients	Bone marrow karyoerythrocyte division index increased dramatically; Good recovery from bone marrow review [69]
		Hematopoietic dysfunction caused by tumor radiotherapy and chemotherapy		Protecting the haematopoietic system [70]
Smooth muscle	rabbit	isolated aortic	(Codonopsis pilosula pollen with protein fraction) activate [71]	
	rat	isolated uterine muscle	Strong inhibition [71]	
	guinea pig	isolated intestine	Excitate jejunum, increase ileum tension [72]	
	guinea pig	isolated biliary tract	Activate [72]	
Other pharmacological effect	-	-	Antifatigue [73]	
	-	-	Antioxidation [32]	
	-	-	Boosting immunity [8,27,31]	
	-	-	Anti-cancer [60]	
	-	-	Regulation of glucose and lipid metabolism [53]	

4. Pharmacological Effects and Related Research of Codonopsis Pollen

We describe the existing pharmacological studies on Codonopsis pilosula pollen as follows, which are briefly summarized in Table 2.

4.1. Effects on the Liver

According to Xiao et al, the ingestion of a diet containing 6.8% codonopsis pollen significantly enhanced the recovery rate of mice with liver injury and liver necrosis already caused by CCl₄, [53] significantly improved hepatic steatosis, [54] inhibited the active proliferation of fibroblasts, and served to slow down the process of fighting liver fibrosis. [53] Li et al. also found that in the early stages of chronic liver injury, the pollen of Codonopsis pilosula could play a preventive role by reducing the degenerative necrosis and inflammatory response of hepatocytes and promoting the regeneration of hepatocytes, protecting liver metabolism and preventing the development of liver fibrosis. [53,55]

4.2. Effects on Immune Function

The root of Codonopsis pilosula has the effect of enhancing immunity, which is related to its amino acids, total saponins, polysaccharides and other substances. As mentioned above, these substances also exist in the

aboveground part of Codonopsis pilosula. The results of the study on the pollen part of the aerial part of Codonopsis pilosula showed that the pollen of Codonopsis pilosula also had strong pharmacological effects of regulating immunity, which may also be related to these substances.

4.2.1. Correction of Immunocompromised States

Li's team found that the pollen had no significant effect on the immune organs (spleen, thymus) of normal mice, [61] no significant effect on lymphocyte conversion rate and E wreath formation, and a significant counteracting effect on these two indices inhibited by cyclophosphamide, which may have less normal effect on the organism's cellular immunity, [60,61] also expanding the scope of action of the pollen from the side.

4.2.2. Enhance Humoral Immunity and Nonspecific Immunity

Li's team found that codonopsis pollen significantly enhanced the production of vacuole-forming cells and IgM in normal and glucocorticoid-inhibited mice. [61] It also increased the viability of mouse peritoneal macrophages, and both this activation and antagonism of glucocorticoid effects were mediated by the polysaccharides in Codonopsis pollen. [66]

4.3. Effects on the Haematopoietic System

4.3.1. Against Amelioration of Chemically Induced Hematopoietic Damage in Bone Marrow (Animal Experiment)

The pollen of *Codonopsis pilosula* significantly reduced the hematopoietic damage of bone marrow in rats caused by cyclophosphamide, increased the level of leukocytes and granulocytes, [67] and counteracted the inhibitory effect of mitomycin-induced hematopoietic system in mice, [68] while it had no significant effect on the peripheral blood picture of normal rats and had no adverse effects [67] on long-term administration.

4.3.2. Significantly Improve Hematopoietic Dysfunction (Clinical Examples)

Yin summarized seven cases of aplastic anemia patients who did not respond to cell-raising drugs and hormones. The bone marrow nuclear erythrocyte division index increased dramatically after long-term administration of *Codonopsis pilosula* pollen, and the bone marrow recovered well on review with no specific adverse effects, [69] obtaining remarkable therapeutic effects. Cai's team administered *Codonopsis pilosula* pollen to 26 patients who had various types of haematopoietic disorders and who also had poor results with anti-radiotherapy drugs after receiving radiotherapy, The results showed that 25 patients had increased white blood cells, suggesting that *Codonopsis pilosula* pollen has a protective effect on the haematopoietic system of such patients. [70]

4.4. Effects on Smooth Muscle

4.4.1. Exciting Isolated Aorta

Both *Codonopsis* pollen suspension and centrifugal fluid can activate (protein-containing part) activates the isolated aorta of rabbits and has a synergistic effect with NE, but after deproteinization treatment can not. [71]

4.4.2. Potent Inhibition of Rat Isolated Uterine Muscle

Both *Codonopsis* pollen and centrifugal solution inhibited isolated rat uterine muscle (pregnant and non-pregnant) and antagonized pituitary agonism in a concentration-dependent manner. [71]

4.4.3. There Were Species Differences for Isolated Intestinal Tubes

- (1). Jejunum : Excited jejunum. [71]
- (2). Ileum : Generally speaking, excites the ileum, increasing contraction force and frequency. It can also produce a small concentration to increase the ileum tension of guinea pig isolated intestine, and cooperate with Ach. [71]
- (3). Colon : no significant effect. [71]

4.4.4. Exciting Isolated Biliary Tract and Biliary Sphincter

Codonopsis pilosula pollen (protein-containing or deproteinized part) can activate the isolated biliary tract of guinea pigs in a dose-dependent manner.[72]*Codonopsis* pollen (protein-containing part) can activate sphincter, increase contraction frequency, and promote bile emptying effect. [72]

4.5. Antifatigue

According to the research of Shu et al., *Codonopsis pilosula* pollen has the effect of anti-fatigue, anti-high temperature and low temperature. [73] It is clear that *Codonopsis* pollen contains a large number of amino acids, trace elements, [8,27] fatty acids, [74] polysaccharides [32] and other substances, so it has anti-fatigue, anti-oxidation, improve immunity and so on.

4.6. Other Pharmacological Effect

4.6.1. Anticancer

The combination of *Codonopsis pilosula* pollen and cyclophosphamide prolongs the survival time of experimental animals and increases the anticancer effect. [60]

4.6.2. The Regulation of Glucose and Lipid Metabolism

The administration of *codonopsis* pollen seems to have the effect of protecting sugar metabolism, accelerating lipid transport and reducing liver TG. [53]

5. Extension of the Industrial Chain of the Aboveground Part of *Codonopsis pilosula*

To maximise the reader's convenience in understanding exactly where and what substances are present in the above-ground parts of *Codonopsis pilosula*, we have plotted the most enriched chemical components of each part of *Codonopsis pilosula* with the industries from which they may be derived, see Figure 2.

5.1. Animal Husbandry

As mentioned above, the stems and leaves of *Codonopsis pilosula* contain amino acids, trace elements, carbohydrates such as polysaccharides and other bioactive components, and have rich nutrition. A considerable amount of literature has been published on the effects of feeding the stems and leaves of *Codonopsis pilosula* to chickens and pigs, with the animals showing increased appetite and intake, [75,76] increased body mass, [56,59,77] increased immunity, [56,59,77] improved meat quality, [59] [75-77] and improved egg quality in laying hens. [78-80] This method of feeding can also reduce the meat-to-feed ratio, further increasing economic returns and reusing resources. It also has natural advantages over hormones and chemical drugs, such as being natural, less toxic [81] and less resistant, [58] and has good prospects for application in animal husbandry.

The use of the above-ground parts of *Codonopsis pilosula* in animal husbandry can be summarized in the following three points :

- (1). As a feed additive to reduce the meat-to-feed ratio; [58,59] [76,80]

- (2). Chinese medicine, veterinary medicine immune enhancers to improve immunity and disease resistance; [12] [56-59]
- (3). As nutritional supplement [56,75,79] and growth performance regulator to improve growth rate and production performance. [51,59,75,80]

5.2. Health Food

The chemical composition of the above-ground part of *Codonopsis pilosula* contains a large number of bioactive substances similar to those in the root, which can produce similar tonic effects on the human body as the root, while the total saponins and flavonoids in the stem and leaves have strong antioxidant capacity. [15,29] The above-ground parts also have lipid-regulating [34], anti-aging [29,47] and hypoglycaemic effects and can be used to make health products. In terms of food safety, several scholars have conducted [56] [81-82] acute and chronic tests on the above-ground parts, all of which showed that the above-ground stems and leaves and pollen of *Codonopsis pilosula* have a wide range of safety and are safe to use. There is a growing body of literature on theoretical research and successful practice of using the above-ground parts of *Codonopsis pilosula* as raw material for food preparation, which is summarized below:

5.2.1. Tea & Beverage

There has been a gradual increase in research related to the use of the stem leaves of *Codonopsis pilosula* in the tea industry and health drinks. It has been suggested that higher levels of lobetyol can be obtained by processing into tea [63], and there are now a series of patents and successful practices using the stem leaves of *Codonopsis pilosula* as raw material, such as the highly aromatic *Codonopsis Pilosula* Green Leaf Tea, [83] *Codonopsis Pilosula* Health Drink [84], *Codonopsis Pilosula* Leaf Tea, [85] etc.

5.2.2. Prebiotic Related Industries

It has been noted in the literature that *Codonopsis Pilosula* polysaccharides can promote the growth of probiotics such as *Bifidobacterium*, *Lactobacillus* and inhibit the growth of *Salmonella* and *Enterococcus*[51-52,76,86,-87] and are suitable as prebiotics. Lingya Cao et al. showed that *Codonopsis Pilosula* polysaccharides can play a role in regulating the intestinal microbiota by affecting energy conversion such as amino acid metabolism, tricarboxylic acid cycle and nitrogen metabolism, which can help restore homeostasis in the intestine.[51,86] It is promising in the improvement of the intestinal microecological environment. It is promising to extract polysaccharide components from the above-ground parts as raw materials for related production.













Parts on the ground		Industry chain & Application	
		Bioactive substances with prominent content	Action & Effect
 <p>1.pollen</p>	Fatty acids, Vitamins, Amino acids, etc.		Correction of haematopoietic dysfunction, Immune enhancement, Anti-ageing, Antioxidant, Anti-fatigue
	Polysaccharides		Promotes probiotic growth; Maintains gastrointestinal homeostasis
 <p>2.stems and leaves</p>	Amino acids, vitamins, saponins, polysaccharides, trace elements, etc.		Lipid-regulating, health benefits
	High levels of fibre and trace elements		Improves quality, enhances immunity and increases yield
			Improve chicken quality and egg quality, increase broiler weight
—	—		Improves overall nutritional value and quality; Increases yield
 <p>3.seeds</p>	Flavonoids		A substance for the control of avian influenza (after fermentation)
	Saponins, polysaccharides, etc.		Antioxidant; Anti-ageing
	Coumarins, etc.		Raw materials for pharmaceutical fine chemicals

Figure 2. Diagram of the extension of some of the industrial chains on the ground of *Codonopsis pilosula*

5.2.3. Codonopsis Nectar

Pollen honey is rich in nutrition, and the flowers of *Codonopsis Pilosula* have a long history of being used as a nectar source. Ding et al. identified eight fatty acids and vitamin C (especially unsaturated fatty acids) in *Codonopsis Pilosula* pollen, thus having anti-ageing, antioxidant and immune boosting effects. [74] Other studies have reported that the nectar of *Codonopsis Pilosula* has the effect of promoting the recovery of haematopoietic function and raising white blood cells, [69,72] making it an excellent tonic for tumour patients during radiotherapy. According to Tian et al., the pollen of *Codonopsis Pilosula* is safe and non-toxic to humans, without chronic accumulation of toxicity, and can be safely consumed. [73,82]

5.3. Pharmaceutical Industry

The main active ingredients of *Codonopsis*, *Codonopsis* saponins and polysaccharides, Cheng et al. pointed out that the content of related substances in stems and leaves is high, and the utilization space is large. [88] Some studies have also pointed out that there are abundant polysaccharides in the callus induced by the leaves of *Codonopsis pilosula*, and the content of polysaccharides is positively correlated with the callus. [86,89] It is expected to carry out quantitative production through a new way of inducing callus [2] and expand the source of raw materials. The above-ground part of *Codonopsis*, especially the fruit (*Codonopsis* seeds), is rich in coumarin. [29,30] It is expected to be used as raw materials and intermediates for drugs and refined chemical products by extracting such compounds from the above-ground part of *Codonopsis*, and derived into pharmaceutical related products. [90]

5.4. Agriculture: Edible Fungi Cultivation

At present, there have been successful practices in the cultivation of *Coprinus comatus* using cellulose-rich *Astragalus membranaceus* and licorice stems and leaves as raw materials. [91] The content of crude fiber components in stems and leaves of *Astragalus* and *Codonopsis* is higher, [58] The study also show that the crude fiber content in the stems and leaves of *Codonopsis pilosula* (42.46 %) was significantly higher than that in the roots (8.08 %). The contents of cellulose, hemicellulose, K, Ca, Mg, S, Fe, Zn, Mo and other trace elements in the stem and leaf culture matrix of *Codonopsis pilosula* are high, [40] which can meet the needs of edible fungi cultivation.

In 2019, Guo et al. produced a mainstream edible fungus cultivation matrix with the stems and leaves of *Codonopsis pilosula* as the main components and applied for a patent, and pointed out that such technologies have many advantages such as health benefits, economic benefits, and resource reuse. [92] Zeng et al. found that after adding the stems and leaves of *Codonopsis pilosula* to the culture matrix, the cultivated *Pleurotus ostreatus* contained the active substances of the stems and leaves of *Codonopsis pilosula*, [93] which had the effects of quality improvement and yield increase. And they also found that adding *Codonopsis pilosula* stems and leaves to the culture matrix can greatly promote the overall nutritional

value, amino acid content and trace element concentration of *Pleurotus Eryngii*, which is consistent with the research results of Guo et al. [92]

Li et al. showed that the safety evaluation of the cultivation of edible mushrooms on the stems and leaves of *Codonopsis pilosula* showed that the cultivated mushrooms met the national standards, [94] which has shown that the cultivation of edible mushrooms on the stems and leaves of *Codonopsis pilosula* as a substrate is practical and feasible.

5.5. Skincare and Related Industries

Free radicals are considered to be the main cause of human aging, and antioxidants can scavenge free radicals. [29] According to research, the total flavonoids extracted from the stem and leaves of *Codonopsis pilosula* have strong antioxidant activity, [29] and Cai et al. showed that the total saponins extracted from the stem and leaves of *Codonopsis pilosula* had a maximum scavenging capacity of 86.92%, 55.37% and 82.21% for DPPH radicals, hydroxyl radicals and superoxide anion radicals, respectively. [15] This suggests that the stem and leaves of *Codonopsis pilosula* can be used as raw materials for the extraction of natural antioxidants for the production of skin care products.

5.6. Other Domains

Guo et al. used fermentation technology to ferment and extract the stems and leaves of *Codonopsis pilosula*, and obtained a substance that effectively prevents avian influenza, [95] which provides a new idea for us to develop and utilize the aboveground parts of *Codonopsis pilosula*.

6. Conclusion and Perspective

In summary, there is a huge market demand for *Codonopsis pilosula*, [3,14] while wild *Codonopsis pilosula* resources are decreasing drastically [3] [15-18] and *Codonopsis pilosula* resources are facing a serious contradiction between supply and demand, while the above-ground part of *Codonopsis pilosula* is still being discarded. [40]

Studies has confirmed that the aboveground parts (stem, leaf, flower, seed) and derivatives (nectar) of *Codonopsis* contain a large number of amino acids [27,28,96], flavonoids [13,29], terpenoids [44], organic acids [13] and other bioactive substances, which have similar or even better than the root of the antioxidant [13,15,29], immunomodulation [31,96], lipid regulation [34], antibacterial [49-52] and other pharmacological effects and utilisation value. *Codonopsis* pollen also has important biological benefits such as anti-hepatic fibrosis [53], promoting haematopoiesis [54] [69-70], and anti-fatigue [27,73].

The industrial chain can be expanded to include agricultural production [92-94], food [83-85], pharmaceutical and chemical manufacturing [90,95], animal husbandry [56-59] [76,81], hygienic food, cosmetics [15,29] and other industries, with the advantages of low cost [92], safety [82], high value and promising development [88]. Its rational development and utilisation will help expand food sources

and create a more sustainable food system. The abundant amino acids, trace elements, polysaccharides and many other nutrients similar to roots detected in its agricultural by-products (e.g., nectar of *Codonopsis pilosula*, cultivated mushrooms from the stem and leaves of *Codonopsis pilosula*, etc.) will improve the nutritional status of consumers [92-93], and at the same time may be beneficial to health, enhance resistance and possibly reduce the incidence of related diseases. The rich content of flavonoids [15], polysaccharides [29], coumarins [29,30] and other components in the above-ground part with high biological effects can expand the source of raw materials in the production of medicinal chemistry and provide low-cost raw materials for the chemical research industry or pharmaceutical and health industry [90]. Applied to poultry and livestock to regulate immunity, increase the quality of the effect will provide a sustainable development of agriculture is worth the depth of the development of ideas. [56-59] It also provides new ideas and new references for solving the lack of resources of Chinese herbal medicine. Reasonable shearing of the above ground part of *Codonopsis pilosula* can increase the quality of the root of the medicinal part, and the derivation and development of the industry can protect the environment and increase the income of the growers at the same time, which can realise the win-win situation of the economic and ecological benefits.

Our systematic review showed that the distribution of the different types of chemical components in the above-ground parts of the plant differed significantly. For example, amino acids, [27] steroids, atractylenolide III, oleanolic acid, and echinocystic acid [13] being more abundant in the stems and leaves, while coralline lactone and 5-hydroxy-8-methoxypsoralen were enriched in the seeds. [29] These results provide focused guidance for subsequent research, utilisation and development.

At present, studies related to *Codonopsis pilosula* above ground are still in the primary stage. [11] The chemical compositions of the aboveground parts have not been fully elucidated, and there are obvious differences in the chemical compositions, content differences and degree of enrichment of different parts of *Codonopsis pilosula* from different species and sources [2,8], as well as the molecular mechanisms of certain related pharmacological effects are not yet well understood, and more validation studies are needed to systematically elucidate this point. [14].

Above all, the above-ground parts of *Codonopsis pilosula* have shown their great advantages and development value [11,12] [27,96]. We sincerely hope that, with the progress of research, people will recognise the developmental value of the aboveground parts of *Codonopsis pilosula* and gradually make rational use of it, which is of positive practical significance for the rational utilisation and innovative development of herbal resources, expanding the sources of food and chemical raw materials, and improving the socio-economic benefits and environmental protection.

Author Contributions

Zhu Hui-feng and Liu Qian-zhen conceived the review. Liu Qian-zhen collected the literatures and wrote the manuscript. Huihui Zheng and Ruhong Jiang helped to

provide and revise the paper. Zhu Hui-feng and Wan Dong is corresponding authors and revise the paper. All authors gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

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Conflict of Interest

None.

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Abbreviations Used

WHO, World Health Organization; FAO, Food and Agriculture Organization of the United Nations; TG, triglycerides; ASCT2, alanine-serine-cysteine transporter 2; AKT, protein kinase B; MAPK, Mitogen-activated Protein Kinase; JNK, stress-activated protein kinase; ESR1, estrogen receptor 1; PSD95, postsynaptic density protein 95; BACE1, Beta-site APP(amyloid precursor protein) cleaving enzyme 1; A β 1-42, Amyloid β Peptide 1-42; CCl₄, carbon tetrachloride; IgM, Immunoglobulin M; NE, norepinephrine; Ach, acetylcholine; DPPH, 1,1-diphenyl-2-picryl-hydrazyl

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