Acupuncture and Herbal Medicine

Multi-layered effects of Codonopsis Radix on the immune system

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Abstract

Recent research has highlighted the potential of Codonopsis Radix to modulate the immune system, making it a promising candidate for treating chronic inflammatory and cardiovascular diseases, tumors, and aging. However, because of the complex immune activities of its various components, a comprehensive understanding of Codonopsis Radix immune-regulating properties is still lacking. This knowledge gap hinders its widespread utilization in clinical practice. Therefore, this review aimed to assess the impact of Codonopsis Radix on the immune system and elucidate its underlying mechanisms. Additionally, we compared the immunomodulatory effects of different active ingredients derived from Codonopsis Radix to provide a theoretical basis for future investigations on immunomodulation.

Keywords: Active ingredients, Codonopsis Radix, Immune system, Immunomodulation herbal medicine, Traditional Chinese medicine

Graphical abstract: http://links.lww.com/AHM/A136.

Introduction

Codonopsis Radix (CR) belongs to the Campanulaceae family, genus *Codonopsis*, and is the dried root of the plants *Codonopsis pilosula* (Franch.) Nannf. (*C. pilosula*), *Codonopsis pilosula* Nannf. var. modesta (Nannf.) L. T. Shen (*C. pilosula* var. modesta), or *Codonopsis pilosula* tangshen Oliv. (*C. pilosula* tangshen). CR is primarily produced in Gansu, Sichuan, Shanxi, Shaanxi, Hubei, Qinghai, Henan, and other regions of China. The Chinese name for CR is Dangshen, as listed in the Chinese Pharmacopoeia Commission (2020).

CR, the dried root of *Codonopsis pilosula* (Franch.) Nannf. (*C. pilosula*), is distributed worldwide[1]. CR has great medicinal and nutritional values. Its usage extends beyond being a traditional remedy and also serves as a dietary supplement across Asian countries, including China, Japan, Korea, and Singapore. It can be incorporated into various preparations such as tea, alcoholic beverages, soups, and porridge[1,2].

CR is a representative traditional Chinese medicine (TCM) that serves both medicinal and dietary purposes. It possesses the traditional functions of strengthening the spleen and tonifying the lungs, nourishing blood and engendering liquids. Since the Qing dynasty, it has been used in TCM for treating conditions such as *qi* deficiency of the spleen and lungs, deficiency of *qi* and blood, body fluid deficiency, and thirst[3]. As natural products derived from animals and plants, tonic Chinese medicine exhibits characteristics of homology, homogeneity, and common usage. They can regulate immune functions within the body. Their mechanism does not target specific disease pathways but rather modulates certain disease resistance mechanisms in the body, particularly in maintaining a dynamic balance within the neuroendocrine-immune system network[4,5].

According to the principles of ancient Chinese herbal medicine, CR is frequently employed as a cost-effective substitute for the more expensive ginseng because of its comparable therapeutic effects[3,6]. Modern research has substantiated that CR is abundant in alkaloids, alkynes, terpenoids, flavonoids, lignins, steroids, and sugars[7]. These compounds exhibit diverse properties, including anti-oxidative activity, anti-aging potential, anti-tumor efficacy, enhancement of learning ability, and immune regulation[8–12]. Notably, the capacity of CR and its active components to modulate the immune responses is particularly significant[13]. As a fundamental factor in maintaining homeostasis within the internal environment of the body, immune function plays an integral role in the onset and progression of various diseases. Literature review revealed that a variety of components of Radix Codonopsis can play immunomodulatory roles, including polysaccharides, flavonoids, terpenoids, phenolic, organic acids, lignins, steroids, and other compounds.

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Table 1

Characteristics of the major polysaccharides in CR

No.	Polysaccharide names	Monosaccharide compositions (quantity ratio of matter)	Molecular weight (Da)	References
1	CPP	Galactose-rhamnose-arabinose (1.12:1.00:1.00)	1.01×10^4	[14]
2	CPP1a	Rhamnose-arabinose-glucose-galactose-galacturonic acid (1.34:12.30:3.49:10.44:1.18)	1.01×10^5–1.03×10^5	[15]
3	CPP1b	Rhamnose-arabinose-galactose-galacturonic acid (0.25:0.12:0.13:2.51)	1.45×10^5	
4	CPP1c	Rhamnose-arabinose-galactose-galacturonic acid (2.99:1.15:1.94:33.29)	1.26×10^5–1.49×10^5	[9]
5	CERP1	Arabinose-glucose-galactose (2.99:1.15:1.94:33.29)	4.84×10^3	[16,17]
6	WCP-I	Arabinose-rhamnose-mannose-galactose-glucose-galacturonic acid (5.50:6.40: 0.70:17.60:0.20:69.60)	–	[18]
7	S-CPPA1	Glucose-galactose-arabinose (10.50:3.40:1.70)	1.33×10^5	[19]
8	CPPN	Glucose-fructose (4.70:95.30)	2.29×10^3	[20]
9	COP-W1	Mannose-rhamnose-glucose-galactose (20.32:1:00:1.27:36.13)	2.34×10^4	
10	CTPN	Glucose-fructose (6.00:94.00)	3.95×10^3	[19]
11	CPO	Glucose-fructose (1.21:1.00)	3.18×10^2	[21]
12	CPSP-1	Arabinose-rhamnose-galactose-galacturonic acid (8.90:9.30:11.00:70.10)	1.31×10^4	[22]
13	CTSP-1	Arabinose-rhamnose-galactose-galacturonic acid (8.20:11.20:18.90:61.30)	2.30×10^4	[20]
14	CPPS3	Galactose-arabinose-rhamnose (1.13:1.12:1.00)	7.40×10^4	[23]
15	RCNP	Arabinose-galactose (75.20:24.80)	1.14×10^4	[6]
16	RCAP-1	Rhamnose-arabinose-galacturonic acid (5.70:3.50:90.80)	5.09×10^4	[6]
17	RCAP-2	Rhamnose-arabinos-galacturonic acid (3.30:3.00:93.70)	2.58×10^5	[6]

CERP1: *Codonopsis pilosula* extractum residue polysaccharide 1; COP-W1: A polysaccharide extracted from the root of *Codonopsis tangshen* Oliv; CPO: Chitosan oligosaccharide; CPP: Carboxypropylated chitosan; CPPN: *C. pilosula* Nannf polysaccharides; CPPS3: *C. pilosula* polysaccharides; CPSP-1: The acidic polysaccharide from stems of *C. pilosula*; CTPN: *C. tangshen* polysaccharide; CTSP-1: The acidic polysaccharide from stems of *C. tangshen*; RCAP-1: Radix Codonopsis (Dangshen) 0.5 M NaCl-eluted fraction polysaccharidest; RCAP-2: Radix Codonopsis (Dangshen) 0.5 M NaCl-eluted fraction polysaccharidest; RCNP: Radix Codonopsis (Dangshen) the water-eluted fraction polysaccharidest; S-CPPA1: The acidic polysaccharide from stems of *C. pilosula*; WCP-I: *C. pilosula* acidic polysaccharide.

Therefore, the objective of this review was to provide a comprehensive overview of the immunomodulatory effects of various components of CR on diverse immune cells, elucidate the mechanisms involved, and explore the potential of CR to promote the immune microenvironment under different pathological conditions. This study aimed to establish a theoretical foundation for future research on immune regulation and offer novel references and insights for further investigation of CR. Additionally, we discussed the prospective applications of CR in chronic inflammation, regulation of cardiovascular function, anti-tumor therapy, and anti-aging interventions.

Immune active components in CR

Various active substances have been found in CR including saccharides, alkaloids, alkynes, polyacetylenes, flavonoids, lignans, steroids, terpenoids, organic acids, and volatile oils. Detailed structural information regarding these components has been presented in previously published reviews[1,7]. It is worth noting that saccharides, saponins, flavonoids, and alkaloids are the main immunoactive substances in CR.

Saccharides

CR is rich in saccharides including polysaccharides, monosaccharides (primarily glucose, galactose, and fructose), and oligosaccharides. Its chemical composition consists mainly of heteropolysaccharides, particularly polysaccharides. A variety of polysaccharides, primarily heteropolysaccharides, have been isolated from different parts of CR. The polysaccharides identified so far include carboxypropylated chitosan (CPP), CPP1a, CPP1b, carboxymethyl propionyl chitosan (CPP1c), *Codonopsis pilosula* extractum residue polysaccharide 1 (CERP1), *C. pilosula* acidic polysaccharide (WCP-I), the acidic polysaccharide from stems of *C. pilosula* (S-CPPA1), *C. pilosula* Nannf polysaccharides (CPPN), a polysaccharide extracted from the root of *Codonopsis tangshen* Oliv (COP-W1), *C. tangshen* polysaccharide (CTPN), chitosan oligosaccharide (CPO), the acidic polysaccharide from stems of C. pilosula (CPSP-1), the acidic polysaccharide from stems of *C. tangshen* (CTSP-1), sulfated carboxymethyl propionyl chitosan (CPPS)3, Radix Codonopsis (Dangshen) the water-eluted fraction polysaccharidest (RCNP), Radix Codonopsis (Dangshen) 0.5 M NaCl-eluted fraction polysaccharidest (RCAP-1), and RCAP-2 (57–73) (Table 1).

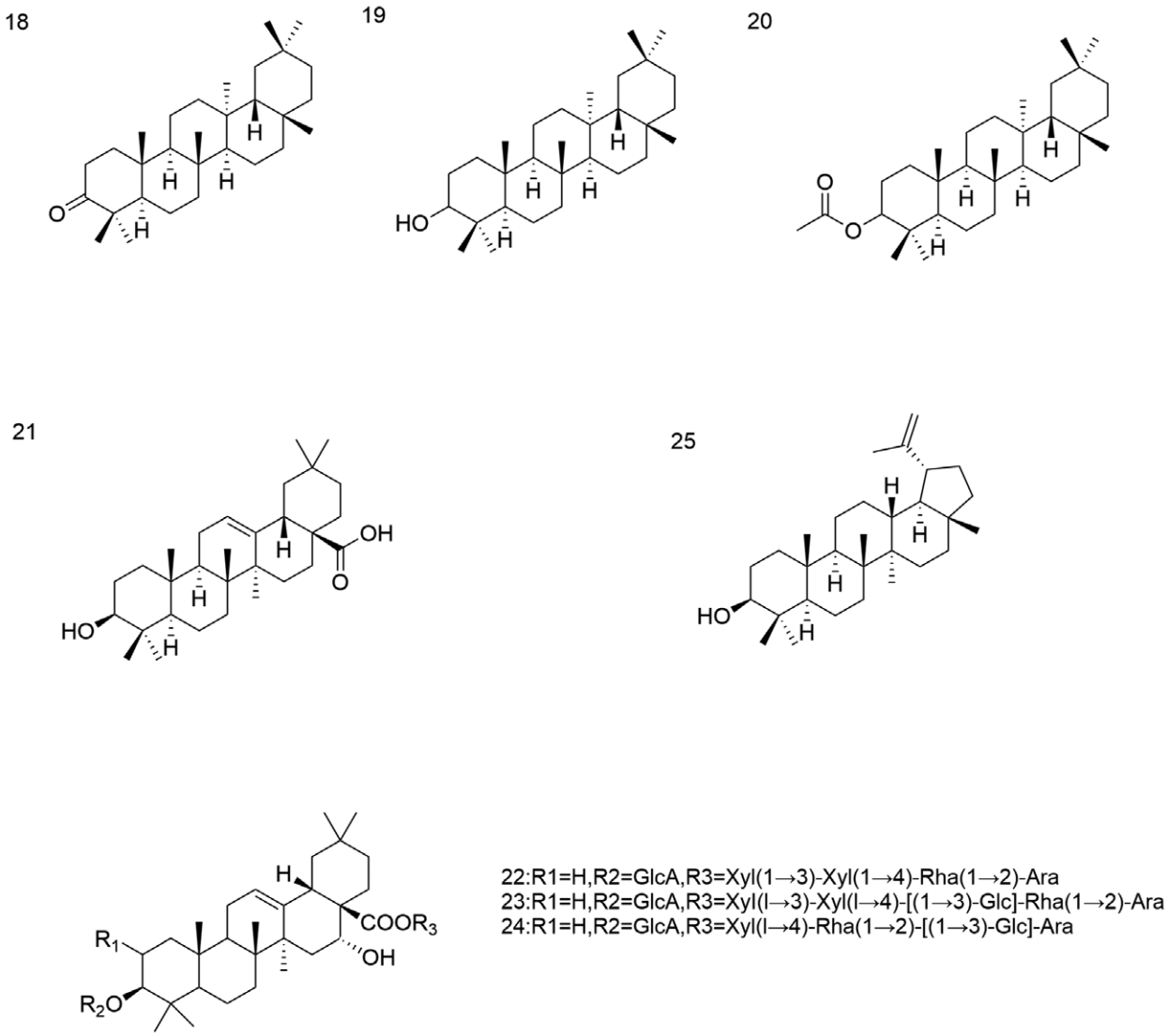


Figure 1. Saponins (18–25) from CR. CR: Codonopsis Radix.

Numerous studies have focused on the immunological effects of polysaccharides extracted from CR, specifically their ability to enhance lymphocyte proliferation and modulate immune responses[9,14,24]. CPPs and their derivatives, such as selenized CPPS (sCPPS5), have shown dose-dependent stimulation of lymphocyte proliferation and immune-enhancing activities, such as improved phagocytic activity, nitric oxide (NO) production, and cytokine secretion[25].

The immunomodulatory effects of specific polysaccharides, such as RCAP-1, RCAP-2, and purified oligosaccharides from CR have also been extensively investigated because of their significant impact on the immune system through various mechanisms[6]. Chemically sulfated polysaccharide derivatives of CR, such as sCPPStp and sCPPS50c, also exhibit enhanced immunomodulatory activity[26].

Furthermore, research indicates that complex blends of herbal polysaccharides exhibit synergistic effects on immunostimulation in various mouse models. Additionally, CPPs and their derivatives show potential as immunoregulatory agents; however, further studies are required to fully understand the precise mechanisms underlying these immunoregulatory effects associated with CPP-based products[27,28].

Saponins

The main saponins in CR are terpenoids such as taraxerone, taraxerol, taraxeryl acetate, oleanolic acid (OA), lancemaside A, B, and C, and lupeol (Figure 1)[29–31].

Atractylodes lactone, a crucial sesquiterpenoid, exhibits anti-inflammatory, antioxidant, and anti-tumor properties, and regulates the immune system[32]. Another significant component, 5-Hydroxymethylfurfural (5-HMF) (12 mg/kg/day), modulates immune function by inhibiting the elevation of IgE levels, reducing interleukin (IL)-4 and interferon (IFN)-γ concentrations while enhancing macrophage response[33–35]. OA, a pentacyclic triterpenoid, enhances immunity by maintaining the balance among immunomodulatory cytokines and improving intestinal defense mechanisms[36,37]. Cycloxylanenol, a terpenoid modulates the immune system by suppressing IL-10 expression[38]. β-sitosterol and stigmasterol are representative steroid compounds with immunomodulatory effects[39,40]; they stimulate the Th1 response while

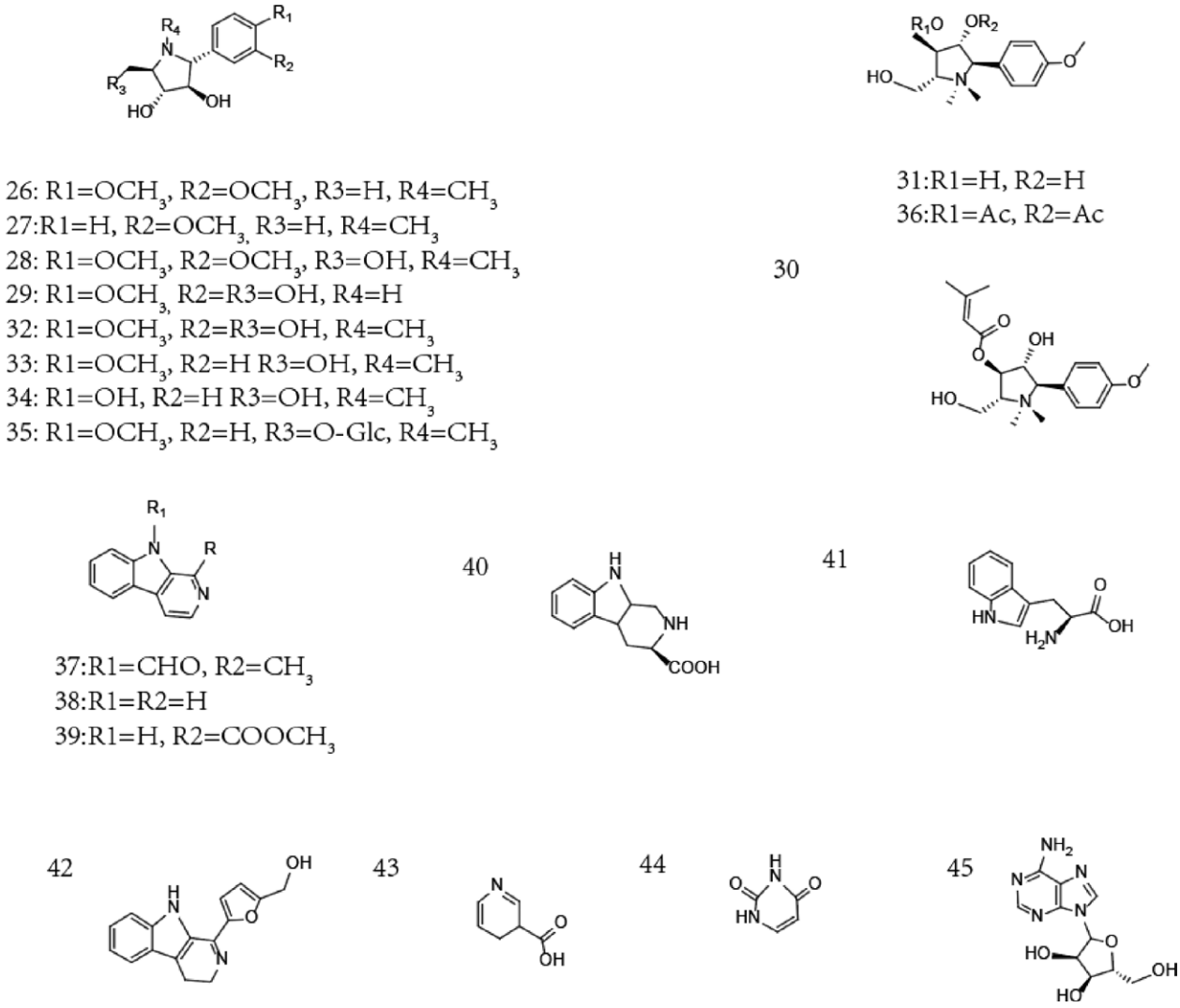


Figure 2. Alkaloids (26–45) from CR. Alkaloids codonopsine (26), codonop sinine (27), codonopsinol (28) and radicamine A (29), codono pyrrolidiums A (30), and codonopyrrolidiums B (31) were isolated from the roots of *Codonopsis pilosula* and *C. tangshen*. *C. pilosula* served as a rich source of pyrrolidine alkaloids as codonopsinols A (32), codonopsinols B (33), codonopsinols C (34) along with glycoside, codonopiloside A (35) were isolated from its roots section. Roots of *C. tubulosa* resulted in the isolation of codotubulosine B (36). Compounds, *n*-9-formyl harman (37), norharman (38), 1-carbomethyl carboline (39), 1,2,3,4-tetrahydro-bcarboline-3-carboxylic acid (40), and tryptophan(41), were obtained from the roots of *C. lanceolata*. Tryptophan (41), perlolyrine (42), and nicotinic acid (43) were isolated from the roots of *C. pilosula*. The uracil (44) and adenosine (45) were obtained from the root parts of *C. pilosula* and *C. tangshen*, respectively. Adenosine (45) had been also isolated from the roots of *C. lanceolata*. Two bioactive alkaloids, namely, codonopsine (26) and codonopsinine (27), had been isolated from the *C. ovata*. CR: Codonopsis Radix.

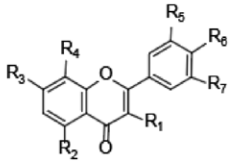
regulating immune cell infiltration and differentiation to maintain homeostasis within the immune system[41].

Alkaloids

The alkaloids present in CR exhibit significant immunomodulatory effects that are responsible for their traditional medicinal applications (Figure 2). These alkaloids enhance immune function by promoting the proliferation and activation of immune cells, thereby bolstering body's defenses against pathogens[42,43]. Additionally, their anti-inflammatory properties mitigate the detrimental effects of inflammation on immune cells and safeguard the integrity of the immune system. Notably, alkaloids contribute to fine-tuning immune balance, particularly in autoimmune disorders, by modulating the delicate equilibrium between T helper (Th)1 and Th2 immune responses and mitigating excessive immune activation, which may otherwise harm the host[44–46].

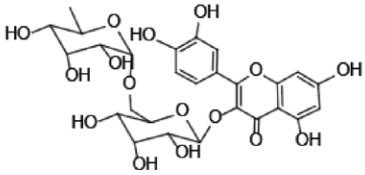
Flavonoids

Flavonoids present in CR are a crucial group of compounds known for their immunomodulatory properties (Figure 3). These potent antioxidants effectively counteract the harmful effects of free radicals and reduce oxidative stress, which could potentially compromise immune cell function and maintain the vitality of the immune system[47]. Furthermore, flavonoids enhance immune strength by promoting the proliferation and differentiation of immune cells, thereby strengthening the body's resilience to infections[48,49]. Additionally, their anti-inflammatory and anti-bacterial properties impede the inflammatory processes and inhibit microbial growth, thereby alleviating the burden of inflammation on the immune system. These flavonoids interact synergistically with other bioactive constituents to target multiple aspects of the immune system, orchestrating a comprehensive immunomodulatory response, reinforcing the overall health and immunological well-being[50–52].



46: R1=R4=R5=R7=H, R2=R3=R=OH
47:R1=R4=R5=H, R2=R3=R6=R7=OH
48: R4=R5=R7=H, R1=R2=R3=R6=OH
50: R1=R4=R5=R7=H, R2=R3=R6=OH
51: R1=R4=R7=H, R2=O-Glc, R3=R5=R6=OH
52: R1=R4=H, R2=R3=R6=OH, R5=R7= OCH_3
53:R1=R4=R7=H, R2=R3=R6=OH, R5= OCH_3
54:R1=R5=R6=R7=H, R2=R3=OH, R4=OCH_3
55: R1=R1=R4=R7=H, R2=OH, R3=O-Glc (6-1)-Glc, R5=R6=OH

49



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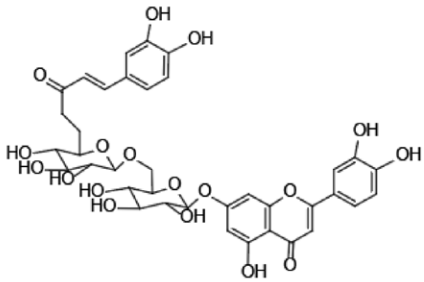

Figure 3. Flavonoids (46–56) from CR. Apigenin (46), luteolin (47), Kaempferol (48), Rutin (49), apigenin-7-O-β-D-glucopyranoside (50), and luteolin-7-O-β-D-glucopyranoside (51) had been isolated from the whole plant of *C. ovata*. 1,2 Tricin (52), chrysoeriol (53), luteolin (54), and wogonin (55) were isolated from the roots of *C. xundianensis*. Luteolin (56), kaempferol (57), luteolin-7-O-β-D-glucopyranoside (51), luteolin-7-O-β-D-gentiobioside (55), apigenin-7-O-β-D-glucopyranoside (50), and luteolin-7-O-β-D-glucopyranosyl (1!6)-[(6000-O-caffeoyl)]-β-D-glucopyranoside (56) were obtained from *C. nervosa*. Luteolin (47), luteolin-7-O-β-D-glucopyranoside (51), and luteolin-7-O-β-D-gentiobioside (55) were also obtained from the aerial parts of *C. thalictrifolia*. Besides these, luteolin (47) and luteolin-7-Oβ-D-glucopyranosyl (1!6)-[(6000-O-caffeoyl)]-β-D-glucopyranoside (56) were identified from the aerial parts of *C. clematidea*. Luteolin (47) had been isolated from the roots of *C. pilosula*.

Role of CR in regulating adaptive immunity

Although the involvement of CR in the innate immune system provides a key mechanism for the rapid sensing and elimination of pathogens, its effects on innate immunity indirectly regulate the adaptive immune system. Evidence shows that CR affects adaptive immunity by promoting the proliferation and differentiation of immune cells, stimulating the number of lymphocytes, especially T and B lymphocytes, and enhancing cellular and humoral immune functions in animals. These processes occur in various lymphoid organs that comprise the lymphatic system[53].

The regulation of lymphoid cell proliferation and programmed cell death

Water-soluble polysaccharides such as CPP, CPO, CPP1c, CPPS, and sulfated carboxymethyl propionyl chitosan (sCPPS) have shown significant potential in stimulating lymphocyte proliferation and enhancing immune response. The notably, CPP1c, CPPS, and sCPPS exhibit superior effectiveness in increasing the $CD4^+/CD8^+$ T cells ratio. Moreover, CPP1c promotes lymphocyte proliferation while modulating the proportion of $CD28^+$ and $CD152^+$ T cells. It also enhances the production of IL-2, tumor necrosis factor (TNF)-α, and IFN-γ, exhibiting promising immunoregulatory properties[9,14,25,54]. However, the effect of quercetin on normal human T cells is non-specific[55].

Additionally, quercetin induces hemeoxygenase-1 (HO-1) expression in T cells and inhibits T-cell function by activating HO-1. It also activates the Notch pathway to regulate the proliferation of (Th2) cells and group 3 congenital lymphocytes (ILC3s), and reshape the inflammatory microenvironment[56,57]. Among them, the compounds in CR are also involved in the regulation of programmed cell death in T cells. Treatment with CPP-A-1 inhibited Toll-like receptor 4/nuclear factor kappa B (TLR4/NF-κB) and transforming growth factor-β1/small mother against decapentaplegic 3 (TGF-β1/Smad3) signaling while inducing apoptosis, suggesting a potential pro-apoptosis effect on normal T cells[58]. Luteolin promotes IL-10 expression and alleviates caspase-11-dependent pyroptosis by activating regulatory T cell (Tregs) function[59]. Apigenin can inhibit the programmed death ligand 1 (PD-L1) expression, thereby affecting the proliferation and IL-2 synthesis of Jurkat T cells[49]. However, it remains unclear how distinct efficiencies can be generated for the lifespan of specific T cells.

Lymphoid T cells

Various extracts and components derived from CR exhibit significant immunomodulatory effects. Rich selenium-banqiao-*C. pilosula* (BCPA) enhances delayed-type hypersensitivity, improves response to antigen, increases the number of $CD3^+$, $CD4^+$, and $CD44^+$ T cells, thereby promoting immune response. It demonstrates the ability to regulate the activity of various lymphocyte subtypes and T cells concurrently influencing IL-2 and IL-6 levels[60,61]. CR extract inhibits Th2 cell activation and reduces chemokine levels, as evidenced by decreased GATA3 expression. CR induces the expression of mitochondrial reactive oxygen species (ROS) dismutase (SOD2) and FoxP3, activates Treg cells, and mediates the activation of Th2 cells by inhibiting mitochondrial reactive oxygen species (mROS) production[62]. Hydroethanolic extract of CR and its active component, naringenin (NRG), which promotes the shift from a Th2 immune response to a

Th1 type and simultaneously induces $CD4^+$ and $CD8^+$ T cells. Additionally, NRG restores immune status by activating NF-κB and inducible nitricoxide synthase (iNOS) expression, which increases NO and ROS production[63].

The Codonopsis polysaccharide is a key immunomodulatory component of CR that effectively stimulates the proliferation and activation of T cells. By engaging the receptors on the surface of T cells and initiating signal transduction pathways, the immune function of these cells is significantly enhanced. CPPs can partly inhibit excessive Tregs cells through TLR4 signal transduction on Tregs cells, inhibit the expression of Foxp3 on Tregs cells, and activate $CD4^+$ T cells, thereby triggering the transition from Th2 to Th1[12]. CPPs can balance $CD4^+$/$CD8^+$ T cells, Th1/Th2 cells, Tregs/Th17 cells, IL-10/TNF-α, and IL-10/IL-1β to participate in the regulation of the activity of different subtypes of lymphocytes and T cells[64]. Selenizing CPPs (sCPPs) are more effective than CPPs in promoting lymphocyte proliferation and increasing the $CD4^+$/$CD8^+$ T cells ratio. The levels of IFN-γ, IL-2, and IL-4 were significantly increased. These results suggested that selenylation enhances the immunomodulatory activity of CPPs. sCPPs can be used as constituent drugs in new immunopotentiators[25]. CR can also inhibit the expression of pro-inflammatory cytokines and promote the expression of anti-inflammatory cytokines by affecting short-chain fatty acids, thereby indirectly reducing damage to the colonic epithelial mucosa and restoring the balance of Th17/Treg cells in ulcerative colitis (UC) mice[65]. CPP1c has the ability to enhance lymphocyte proliferation, promote the activation of T cells through T cell antigen receptor (TCR)/CD28 signaling pathway, regulate the percentage of $CD4^+$, $CD8^+$, $CD28^+$, and $CD152^+$ T cells, and enhance the production of IL-2, TNF-α, and IFN-γ. The expression of CD28, PI3K, and p38 [mitogen-activated protein kinase (MAPK) mRNA] was enhanced to exert the immunostimulatory effect[9]. Codon ginseng polysaccharide (CPPW1) has a dual co-stimulatory effect on B or T lymphocyte proliferation in splenocytes, enhancing both T cell and B cell response to mitogens[66]. CR oligosaccharides (CPO) can enhance the protein expression of p-p38, p-JNK, and p-ERK1/2, which may play an immunoregulatory role by up-regulating a variety of transcription factors in the MAPK signaling pathway. Induction of Treg differentiation affects IL-2 and IFN-γ production[54]. CPP-A-1 also improved the expression of inflammatory factors (TNF-α and IL-6) and inflammatory factor genes (TNF-α and IL-11 mRNA) by regulating TLR4/NF-κB and TGF-β1/Smad3 signaling pathways[58]. Additionally, WCP-Ia, an acidic polysaccharide derived from CR increases the ratio of CD4/CD8 T cells and enhances the secretion of immunoglobulin A (sIgA)[67] in Peyer patch lymphocytes. These findings suggest that the gastrointestinal immune system is a potential primary site of action of WCP-Ia[17].

The active monomers present in CR also play a crucial role in regulating the activation and differentiation of T cells by modulating the molecular expression on their surfaces, thereby enhancing the functionality of T cells during immune responses. Luteolin can improve T cell infiltration and inhibit $CD4^+$ T cell proliferation and Th cell differentiation[68], while increasing the proportion of Tregs, which is the key to its immunosuppressive effect. Luteolin can also balance Treg/Th17 ratio, thus affecting Th17/ Treg markers IL-17A[69], retinoic acid receptor-related orphan nuclear receptor γt (RORγt)/IL-10, forkhead box P3 (Foxp3) level, and TLR4/NF-κB pathway to improve inflammation and Th1/Th2 imbalance[48]. Quercetin can induce HO-1 in T cells and inhibit its function through HO-1, thereby affecting the expression of IL-2 and the inflammatory response by improving the imbalance of Th1/Th2 and Treg/Th17. Quercetin regulates the down-regulation of AKT and PDK1 phosphorylation in T-cell lymphoma, which is consistent with the decrease in phosphorylation of downstream survival factors such as bcl2-associcated agonist of cell death (BAD), glycogen synthase kinase 3β (GSK-3β), mammalian target of rapamycin (mTOR), and inhibitor kappa B alpha (IκBα), and increase in levels of phosphatase PTEN affecting T-cell lymphoma[50,51,56]. The induction of Treg cells inhibited by Wogonin, which results in the reduction in the frequencies of $CD4^+$, $CD25^+$, $CD127^+$ and $CD4^+$, $CD25^+$, $Foxp3^+$ cells in the colon and spleen[47]. Wogonin stimulates the activation of NF-κB and Erk but down-regulates the phosphorylation of STAT3 in $CD4^+$ T cells. Wogonin down-regulates ERK and STAT3-Y705 phosphorylation but promotes NF-κB and STAT3-S727 activation in regulatory T cells. Wogonin enhances immune activity by stimulating effector T cells and down-regulating regulatory T cells. Wogonin preferentially kills malignant lymphocytes and suppresses T cell tumor growth by inducing PLC gamma1$^-$ and Ca_2^+-dependent apoptosis[70]. Wogonin inhibites Smad3, GSK-3β, and ERK1/2 signaling pathways in Treg cells, while the phosphorylation of P38 MAPK enhances significantly, which can inhibit the T-cell response to TGF-β1 by regulating the Smad and non-Smad signaling pathways[71]. OA activates T-cell phase through the GATA-3/Foxp3 pathway, exhibits a stronginhibitory effect on Th2 cells, and mildly inhibits Th17 activation *via* the RORγt pathway[72].

Lymphocyte B cells

According to the literature, CR and its chemical components can regulate immunoglobulins in serum and inflammatory tissues and have been proven to directly affect the immunoglobulin producering B lymphocytes.

Hydroethanolic extracts of *Codonopsis clematidea* and NRG were found to reduce $CD19^+$ B cells[63]. Quercetin inhibits the STAT3 pathway and down-regulates the expression of survival genes, affecting the growth of diffuse large B-cell lymphoma (DLBCL)[73]. Quercetin disrupts the crosstalk between IL-6 and STAT3, reduces ROS levels, and promotes autophagy to counteract the accumulation of chelator 1/p62 (SQSTM1/p62), leading to the prevention of B cell immortalization[52].

The canonical Wnt pathway acts directly on B-1 cells by inducing the expression of c-Myc and cyclin, thereby stimulating cell proliferation. Wnt/β-catenin signaling also interferes with the production of IL-6, a cytokine that contributes to the survival and proliferation of B-1 cells *in vitro*. Thus, the blockade of Wnt/β-catenin signaling by quercetin plays a role in reducing the survival and proliferation of B-1 cells *in vitro*[74]. Quercetin down-regulates Mcl-1 by inhibiting the PI3K/Akt signaling pathway, leading to the instability of Mcl-1 and affecting

the apoptosis of B cell[75]. Furthermore, the inhibition of STAT3 and ERK phosphorylation by wogonin demonstrates that wogonin suppressed the potential IL-10 production in B cells through STAT3 and ERK signaling pathways and by inhibiting the mRNA and protein levels of Hif-1α, a transcription factor involved in IL-10 signaling transduction[76].

B-cell development and humoral immune responses are controlled by signal transduction thresholds differentially regulated by $CD22^+$ and $CD19^+$ cell surface receptors *in vivo*. The differential regulation of tyrosine phosphorylation by $CD19^+$ and $CD22^+$ cells may provide a molecular mechanism for modulating the B-cell receptor (BCR) signal transduction threshold. Wogonin increases the population of $CD19^+$ cells, thereby regulating B cells[77]. OA inhibits B cell–dependent production of OVA-specific IgE[72].

Regulation of the immunoglobulin and complement systems

The components of CPPs have the potential to prevent immune damage, enhance humoral immunity and increases the concentration of IgA, IgG, and IgM antibodies in the blood[78]. CPPs is administered to intervene in the CTX-induced immunosuppression model and restore serum IgG and ileum sIgA levels[79,80]. IgG neutralizes toxins and promotes pathogen clearance[81]. However, IgA protects the body surface from invading pathogens[82]. Different doses of sCPPS significantly increase the levels of IgG and IgM in the serum, and sCPPS improves the $CD4^+/CD8^+$ ratio more effectively, indicating that selenium modification can enhance the immunomodulatory activity of CPPS[25]. IgM is a primary antibody that responds rapidly to invading pathogens and marks the initial phase of the immune response[83].

Cleavage of complement component 3 (C3) is central to the complement cascade, while C4 cleavage in the classical pathway and early in other pathways also activates the complement cascade[84]. CPPs can promote the production of C3, C4, IgG, IgM, IgA, growth hormone, insulin-like growth factor 1 (IGF-1), triiodothyronine (T3), thyroxine (T4), and insulin (to varying degrees, and inhibit immunodeficiency)[25]. Lu *C. pilosula* (LCPP) antagonizes the TNF-α-induced increase in complement C3 levels within 24 hours. It also inhibits complement-mediated hemolysis, suggesting CR may act as a complement inhibitor[61].

CR regulates the activation of C3, C4, and immunoglobulins. It remains unclear whether this modulation occurs directly or indirectly by influencing antibodies and cytokines, which, in turn, activates the complement pathway. Thus, the extent of the regulatory influence of CR on other complement components requires further investigation[85].

Inhibition of immune checkpoints

Immune checkpoints link the adaptive immune cell response as one of the innate control mechanisms of adaptive immunity, and their function in guiding T-cell function has been studied. Stimulation of immune checkpoints can transmit positive signals, leading to T-cell activation, differentiation, and immune memory[86]. Although this mechanism is highly activated in tumor tissues to protect tumor cells from adaptive immunity, blocking immune checkpoints is an important strategy for cancer immunotherapy[87]. CPPs can inhibit the expression of CDK1/PDK1/β-catenin signaling axis by inhibiting CDK1 and affecting the expression of PDK1/β-catenin signaling axis factors, inhibit cell proliferation, reduce cell migration ability, affect Epithelial-Mesenchymal Transition (EMT) process, and reduce cell stemness[88]. Quercetin dihydrate attenuates the inhibitory effect of PD-L1 on T cells by inhibiting the PD-1/PD-L1 interaction[89,90]. Additionally, quercetin has been shown to be effective in blocking PD-1/PD-L1 and CTLA-4/CD80 interactions[91]. Quercetin treatment decreases kynorenine concentrations and indoleamine 2, 3-dioxygenase (IDO)/tryptophan-2,3-dioxygenase (TDO) activity and enhances white blood cells, $CD4^+$ T cells, and other hematologic measures of the immune response[92]. CR can increase the mRNA and protein expression of IDO, promotes IDO activity, and causes the balance of Th cytokines to deviate from type 1[93].

In conclusion, the active components in CR bolster immune function by modulating innate immunity (*via* macrophages, dendritic cells, granulocytes), activating lymphocytes in adaptive immunity, and managing the complement system (Figure 4). They regulate T-cell balance, sustaining cellular immune homeostasis, specifically enhancing $CD4^+$ T-cell proliferation, facilitating Th2 to Th1 shift, augmenting Treg circulation, and markedly decreasing TLR4 levels. While $CD8^+$ T-cell proliferation remained unaffected, Treg and Th17 cells decreased, contributing to CD4/CD8, Th1/Th2, and Treg/Th17 balance. This fosters overall immune health. Furthermore, these components enhance macrophage phagocytosis, modulate granulocyte-macrophage colony-stimulating factor (GM-CSF) release to optimize NK cell function, stimulate lymphocyte proliferation, induce apoptosis, and influence cytokine (IL-2, IL-4, IFN-γ) release, thereby strengthening humoral immunity and elevating IgA, IgG, and IgM antibody levels.

Application of immunomodulatory efficacy

Current applications and clinical clues

Traditional application of CR

The traditional medicinal uses of CR have been documented in the Chinese Pharmacopeia since 1963. This highlights the plant's significant medicinal value, specifically in various TCM prescriptions, such as the Sijunzi decoction for treating *qi* deficiency and digestive issues, Buzhong Yiqi decoction for spleen deficiency and related ailments, and Bufei decoction for lung reinforcement. CR can sometimes substitute Radix et Rhizoma Ginseng in treating conditions such as fatigue and anemia, although, higher dosages may be necessary because of its relatively weaker effects. CR is also utilized in other countries, including South Korea and Japan, where it is recognized in their respective pharmacopoeias and employed to address various health issues, such as dyspepsia and respiratory problems[2,94–96].

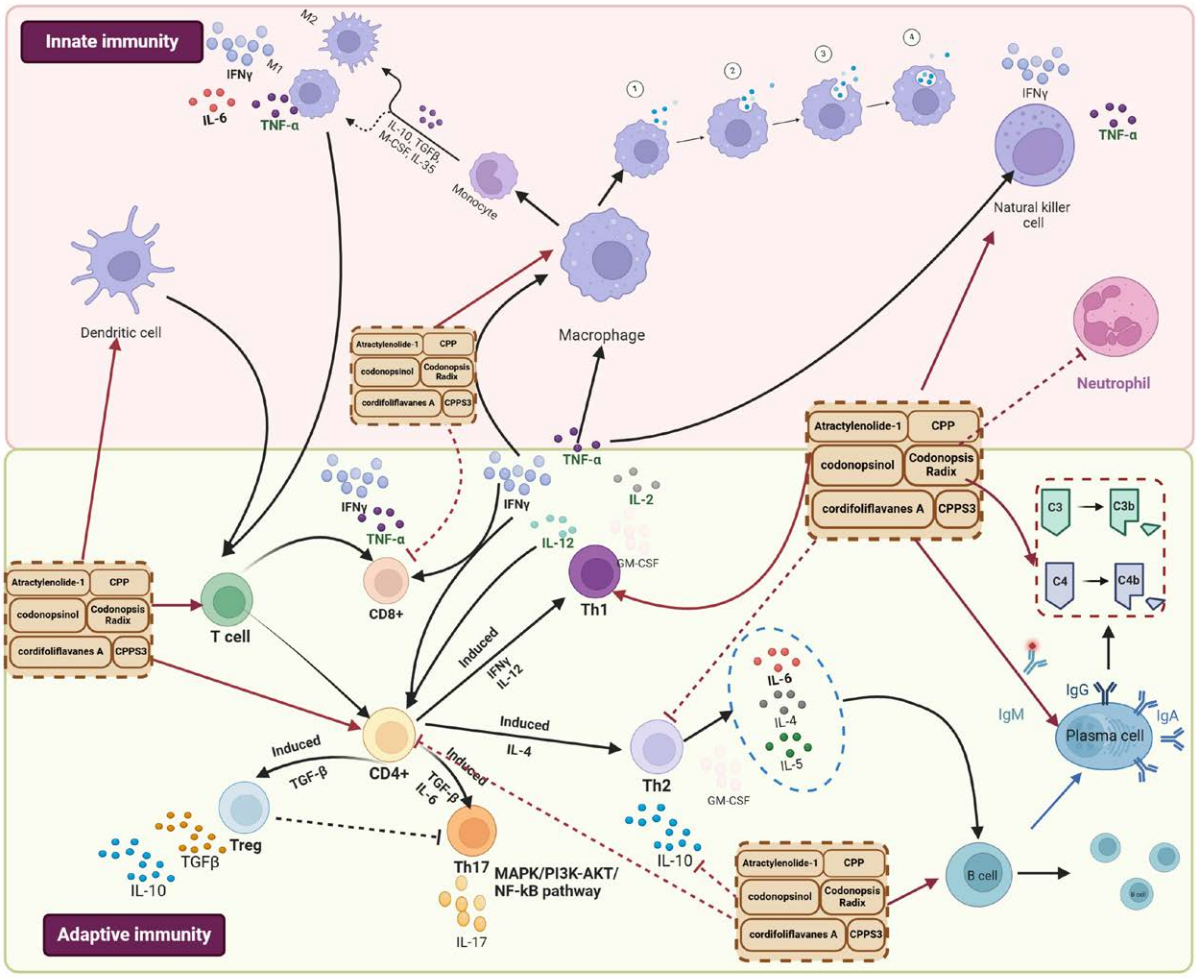

Figure 4. Immunoregulatory mechanisms of CR and its active ingredients. It is mainly achieved by regulating macrophages, dendritic cells, and granulocytes to strengthen the regulation of innate immunity, activate lymphocytes in adaptive immunity, and manage the complement system, so as to enhance immune function and improve immune status. CR: Codonopsis Radix.

Healthcare food

CR extract comes from *Depei Bencao* (得配本草). It is the earliest prescription to use CR as dietary therapy. It is composed of CR, Radix Salviae, and longan meat. Additionally, there are codonopsis-medicated food therapies, such as Codonopsis poria porridge and warm spleen invigorating effects, which are suitable for people with a weak spleen and stomach. CR and lily porridge moisten lung cough, spleen, and *qi* effect; CR and jujube stewed with sea cucumber are beneficial for filling the pulp, nourishing *qi* and blood; CR stewing pig heart has the effect of activating blood circulation, removing blood stasis, and nourishing *qi* blood.

Presently, CR is also used as a raw material to produce CR low-sugar preserved fruit, CR beverage, CR rice, and other nutritious leisure foods and beverages invigorate the spleen and stomach, strengthen the body, and offer various beneficial effects. The preparation process is simple, paving the way for the development and utilization of *C. pilosula*[97–100].

Additionally, in our country, there are various health products in the market that utilizes CR as raw materials, such as Ejiao Wolfberry Codonshen Dihuang oral liquid (G20150633), Ejiao Huangqi Codonshen tablets (G20140294), Codonshen Huangqi and Wolfberry oral liquid (G20160256), Codonshen Bird's nest Huangqi oral liquid (G20080250), etc, its main role is to improve anemia and enhance immunity. It is suitable for patients with nutritional anemia and patients with immunocompromised conditions.

Drugs

CR is a commonly used traditional herbal medicine in China and one of the most valuable herbs. Common clinical prescriptions include Shengmai *yin* (Dangshen decoction), compound Dangshen tablets, Dangshen oral liquids, and Dangshen Lizhong pills. Among them, Shengmai decoction is widely used in clinical practice and has the functions of beneficial *qi*, nourishing *yin*, and promoting fluid. Common forms of CR include decoctions, pills, tablets, granules, capsules, and syrups. The commonly used clinical CR adjuvant prescriptions summarized in ancient Chinese medicine books and the Chinese Pharmacopeia can be applied to different processing methods and adjuvants of TCM to adjust the therapeutic effect, adjust the nature, and reduce side effects. Among these, Bazhen Yimu decoction can replenish *qi* and blood, regulate menstruation, and

treat irregular menstruation. Ginseng and Schisandrin decoctions can invigorate the spleen and *qi* and treat asthenia of the temper and timidity of the middle *qi*. Additionally, there are some local standards, including the codonginseng formula, such as Baosheng pills, that can treat mental weakness, waist and knee soft limbs, and other diseases[101,102].

The application of CR in livestock production

Studies in China have explored the potential use of CR as an animal feed source because of its nutritional value and low cost. Liu et al.[103]. Feed crayfish with CPPs for 8 weeks; the specific growth rate, feed conversion rate, immunity, antioxidant, and disease resistance of crayfish improve significantly, and the effect of adding 0.15–0.20% CPPs is better; the combination of *Codonopsis* sulfate polysaccharide and Angelica sinensis polysaccharide (9:1) has been used to inhibit Newcastle disease virus (NDV) in chickens. The results have showed that the combination of the *codonopsis* sulfate polysaccharide and Angelica sinensis polysaccharides (9:1) inhibits NDV by 66.12%. The structure of the NDV virus fragments within 2 h, and the expression of the viral antigen inhibits effectively[104]. Studies have shown that the addition of *Codonopsis* stems and leaves to chicken feed can significantly improve the growth performance and immunity of broilers[105,106]. Adding CR leaves and stems to the daily feed of laying hens can effectively improve egg quality and production rates, and the addition of *Bacillus trichinus* stems and leaves to pig feed has been shown to significantly improve the growth performance of pigs[107]. Additionally, researchers have reported that the protein content of lamb meat can be greatly improved by adding extracted *Codonopsis* residue to the daily diet of sheep[108]. It has also been observed that growth performance and resistance to flow-mediated dilation (FMD) in growing finishing pigs are enhanced by the addition of a combination of *Aspergillus membranacea* and *Clostridium trichiura* extracts called HEM dietary supplements[107,109].

The above-ground parts of CR are nutrient-rich and have great potential for use as animal feed.

Prospects for immunomodulatory effects

Chronic inflammation

CR and its active components have anti-inflammatory effects mainly by blocking NF-κB and MAPK, and can reduce the release of inflammatory factors[54,58,110–112]. CPPs showed a strong anti-inflammatory effect in an lipopolysaccharide (LPS)-induced RAW264.7 cell inflammation model, and its mechanism was related to the inhibition of macrophage TLR4/NF-κB pathway[113]. Using an LPS-induced peritoneal macrophage model, we found that Lancemaside A extracted from CR exerted anti-inflammatory effects by regulating the binding of LPS to TLR4 on macrophages[114]. CR polysaccharides have a protective effect on dextran sodium sulfate (DSS)-induced colitis in mice, and their mechanism includes up-regulating the expression of anti-inflammatory cytokines and downregulating the secretion of pro-inflammatory cytokines related to the Th17/Tregs balance[65]. Triterpenoids contribute to the anti-inflammatory activity of CRethanol extract[43]. Lee et al.[115] showed that the methanol extract of CR blocked the production of TNF-α and NO, the expression of IL-3 and IL-6, and the uptake of phagocytes in RAW264.7 cells activated by LPS, suggesting that the therapeutic activity of CR on inflammation-mediated symptoms may be mediated by the regulation of macrophage function. Lancemaside A (15 and 30 μM), a triterpenoid isolated from CR, inhibits NO production, expression of NO producing enzyme inducible NO synthase, up-regulation of co-stimulatory molecule CD80, and morphological changes induced by LPS exposure, significantly inhibiting the inflammatory function of LPS-treated RAW264.7 cells. The anti-inflammatory mechanism of lancemaside A involves inhibition of cellular responses in macrophages and monocytes by blocking REDOX activation and the IKK/NF-κB pathway[116].

Regulation of cardiovascular function

To study the effect of Shenqi Fuzheng injection (SQ) on myocardial ischemia-reperfusion, it was found that SQ could activate Sirtuin1 (Sirt1)/Peroxisome proliferator-activated receptor (Peroxisome) proliferators-activated receptors (PPAR)y coactivator 1a/PPAR pathway can increase the expression of PPARa, PPARy, and Sirt1, improve the metabolic function of injured myocardium, and play a protective role in the heart[117]. Wang et al.[118] found that CR water extract can significantly improve cardiac function in rats with myocardial infarction induced by left anterior descending branch ligation, and Kun et al.[119] found that CR can inhibit apoptosis of H9c2 cardiomyocytes induced by angiotensin 1 and human insulin-like growth factor 1. The mechanism may be related to the inhibition of the insulin-like growth factor 2 receptor signaling pathway, reduction of calcium ion influx, decreased mitochondrial membrane permeability, and inhibition of apoptosis.

Tumor immunotherapy

Studies have shown that CR and its chemical components can play anti-tumor roles. Inhibition of tumor cell proliferation. *pilosula* polysaccharide and CR total saponins can activate caspases, regulate Bcl-2/Bax expression, and promote tumor cell apoptosis through endogenous or exogenous pathways[15,120,121]. Xu et al.[66] extracted a CPPW1 from codon ginseng and studied the differences between CPPW1 and its side chain (CPPW1B) in anti-tumor and immune regulation in mice *in vitro* and *in vivo*[18]. Moreover, it stimulates the proliferation of splenic cells and enhances phagocytosis by macrophages. NO production by peritoneal macrophages was induced in mice, thereby inhibiting tumor growth, and crude CR polysaccharide (CPCP) reduced the number of $CD68^+$ macrophages in tumor tissues. Cpcp-purified Codonginseng polysaccharide (dCPP), which is composed of mannose, arabinose, rhamnose, xylose, galactose, and glucose, can inhibit lL-4-induced M2-like tumour-associated macrophages (TAMs), promote the proliferation of M1-like

TAMs, increased IL-1 m RNA, IL-6 mRNA, iNOS mRNA and TNF-α mRNA were detected RNA expression levels, promote the repolarization of M2-like TAMs to M1-like phenotype, and reduce tumor volume in melanoma mice[122]. The study showed that both wen *codonopsis pilosula* polysaccharide (WCPP) and baitiao codonopsis pilosula polysaccharide (BTCPP) can increase the serum levels of IL-2, IL-1B, and IL-6 in tumor-bearing mice. The contents of TNF-α and INF-γ decreased the level of IL-4 in serum, enhanced the activity of NK cells and the proliferation of lymphocytes in tumor-bearing mice, and significantly inhibited the transplanted tumor in mice[123,124].

Aging

To investigate the protective effects of CR on aging-related oxidative stress and apoptosis. It was found that CR enhances defense mechanisms by reducing lipid peroxidation, increasing superoxide dismutase (SOD) activity, and lowering malondialdehyde (MDA) levels in aging tissues, specifically in D-gal-aged mice[125]. codonopsis radix polysaccharide (CRP) treatment significantly improves the expression of antioxidant enzymes in various organs, indicating its role in promoting cellular health[125]. Additionally, CR has been shown to elevate Bcl-2 gene expression in neurons and reduce apoptosis and neurodegeneration, thus exhibiting strong anti-aging effects[126]. Furthermore, CR potential to combat photoaging was evidenced by its ability to decrease apoptosis markers in the skin cells of UV-induced photoaging mice[127].

Additionally, a 15 g/kg dose positively influenced spleen tissue integrity by decreasing pro-apoptotic Bax levels, increasing vascular endothelial growth factor, and enhancing spleen morphology[128]. SAMP8 mouse, a model for studying aging-related immune senescence, were used to investigate the effects of CPP1c on the immune response. Immunosenescence results in a decline in innate and adaptive immunity, which hinders the responses to pathogens and vaccines. The results showed that CPP1c significantly promotes splenic cell proliferation, suggesting its potential as an immunopotentiator. The roles of key molecules in T-cell activation[129] such as CD28, PI3K, and p38 MAPK, essential for T-cell proliferation and survival, were further explored. CPP1c upregulates the mRNA and protein levels of these molecules, thereby promoting T-cell activation through the TCR/CD28 signaling pathway and ultimately improving the immune function of aged mice[9].

Therefore, this study suggests that CRWE has potential protective effects against aging in various organs, including the immune system and reproductive organs.

In conclusion, CR stands as a promising therapeutic candidate for addressing chronic inflammation, cardiovascular diseases, tumors, and the aging process. Its profound pharmacological effects stem from an abundance of active components that adeptly modulate immune function, fortify blood circulation, and combat oxidative stress by scavenging free radicals (Figure 5).

Application of CR in TCM theory

Upon investigating the medicinal attributes of CR, we discerned its gentle, sweet nature, and its affiliation with the spleen and lung meridians in TCM. TCM highlights its capacity to fortify these organs and replenish fluids and blood. It is commonly prescribed for conditions related to spleen and lung *qi* deficiency, including dyspepsia, fatigue, palpitations, dyspnea, pallor, thirst, and overall *qi* and blood insufficiency.

While Western medicine primarily views the spleen as an immune organ, TCM embraces a broader concept rooted in the spleen-stomach theory, which encompasses multiple organs and systems. This holistic approach underscores the spleen's involvement in digestion, absorption, water metabolism, immune defense, and endocrine balance, thereby transcending its anatomical limitations[130,131]. The ancient text by *Ben Cao Cong Xin* (本草从新) attests to the virtues of *C. pilosula*, emphasizing its sweetness, mildness, and efficacy in nourishing the middle, enriching *qi*, and harmonizing the spleen-stomach complex. Contemporary literature reinforces its therapeutic value in strengthening the spleen-stomach system and augmenting the middle *qi*[65].

In TCM, *qi*, a fundamental energy-sustaining life, is paramount for the maintenance of health and disease prevention[132,133]. Derived from innate sources, food, and nature, *qi* governs organ functions, immune defense, and nutrient transportation. Imbalances, or "evil," disrupt qi's harmony, necessitating interventions like codon ginseng to replenish *qi*, particularly for those with diminished original *qi*[134,135]. "*qi* deficiency," a precursor to illness, manifests as fatigue, weakness, and anorexia, with patients suffering from stroke, diabetes, and hypertension being particularly prone[136]. Given the vital role of *qi* in immunity, organ health, and vitality, its restoration is crucial[137].

Contemporary research underscores Yiqi's (a *qi*-tonifying approach) ability to restore homeostasis through mechanisms such as bolstering T-cell activity, elevating immunoglobulin levels, modulating immune cell balance, mitigating inflammation, normalizing gut flora, and inhibiting tumor growth[138–140]. During *qi* deficiency, the spleen and lungs are vulnerable, and CR, known for its *qi*-tonifying, blood-nourishing, and balancing properties, is beneficial. It acts as an immunomodulator, restoring homeostasis through multiple pathways[25,141,142].

Suggested dosage and toxicity

Comprehensive toxicological investigations were conducted on diverse extracts of CR, meticulously observing and documenting minimal instances of notable toxicity or adverse effects. Adhering to the national food safety benchmarks stipulated in GB 15193.3-2014, GB 15193.4-2014, GB 15193.5-2014, GB 15193.8-2014, and GB 15193.13-2015, Wen Radix Codonopsis underwent rigorous testing, encompassing acute oral toxicity assessment, three distinct genotoxicity tests (encompassing bacterial reverse mutation, mammalian erythrocyte micronucleus, and mouse spermatocyte chromosome aberration), and a subchronic toxicity evaluation. The 90-day oral toxicity study, administered at doses of 2, 4, and 8 g/kg/day, revealed excellent overall growth patterns across all animal groups, with no statistically significant divergence from the negative control group. All

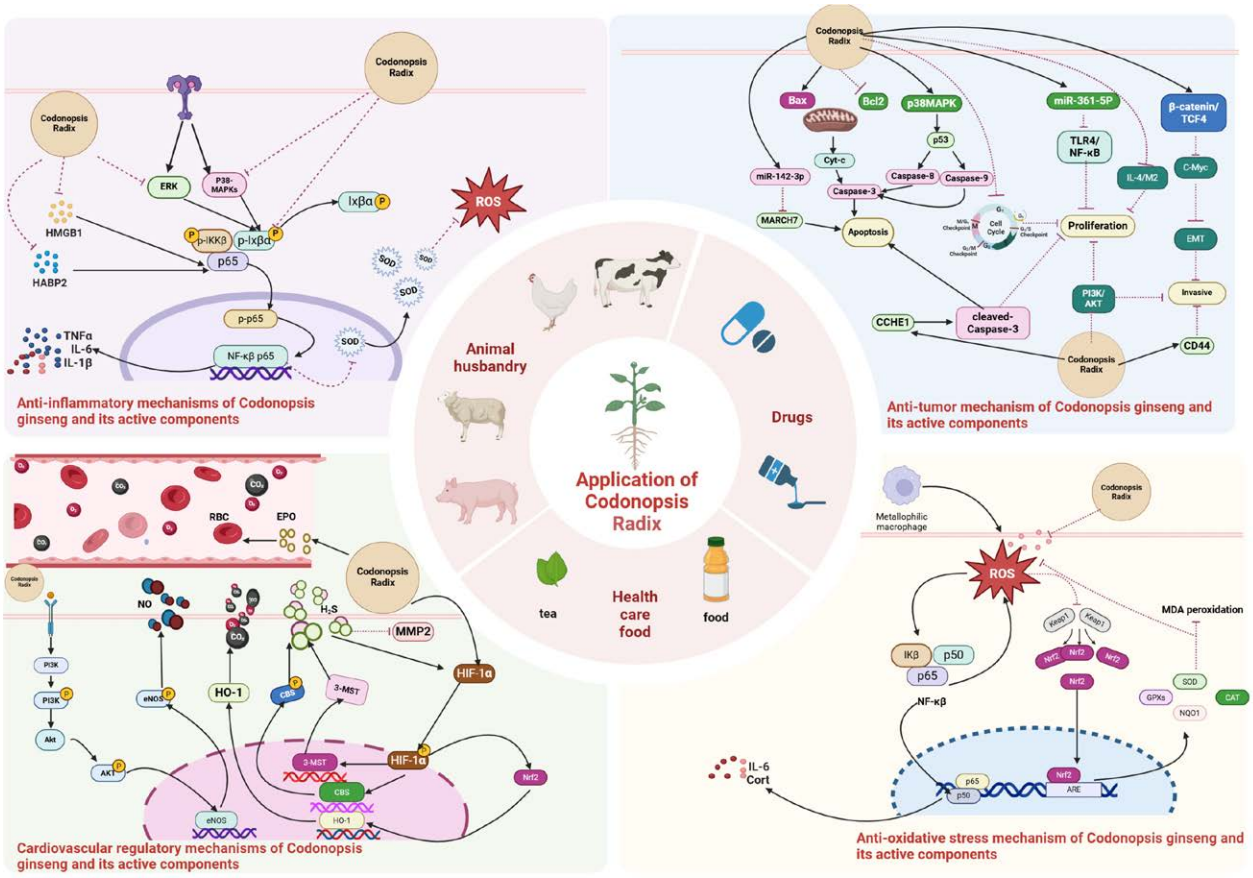

Figure 5. Daily application and regulation mechanism of CR and its active ingredients. CR is used in livestock production, health food, and medicine in daily life. The potential of CR to modulate the immune system makes it a promising candidate for the treatment of chronic inflammation and disease, cardiovascular disease, cancer, and aging. And may regulate the corresponding diseases through related mechanisms. CR: Codonopsis Radix.

findings fell within our laboratory's normative range, underscoring the safety profile. Gross anatomical examinations remained unremarkable, and no histopathological alterations or specific test material-related injuries were detected. In conclusion, under these conditions, Wen Radix Codonopsis demonstrates an absence of discernible acute oral toxicity, genotoxicity, or subchronic toxicity, thereby affirming its safety profile.

The acute toxicity test of CPPs administered at 20 g/kg three times daily for seven consecutive days, revealed no aberrant changes in the animals, with all mice surviving the trial period. Furthermore, the long-term toxicity assessment indicated that the oral solution of CPPs (2 g crude drug per mL, administered at 1 mL/100 g body weight daily) did not exhibit notable toxicity when compared to an equivalent dose of normal saline. The subchronic toxicity test of the water extract of CR, administered at doses ranging from 0.18 to 7.20 g/kg daily over 13 weeks, identified 1.80 g/kg as the minimum effective dose and 0.18 g/kg as the threshold ineffective dose. Additionally, the teratogenicity test confirmed that the water extract of CR did not elicit teratogenic effects within the tested concentration range of 0.18–9.00 g/kg. Regarding the aqueous extract of CR, toxicity studies were conducted, which demonstrated that repeated oral administration of the aqueous extracts at concentrations of 1,250, 2,500, and 5,000 mg/kg for 4 weeks did not induce acute or subchronic toxicity in rats. These findings further validate the safety profile of CR and its derivatives.

Summary and prospect

TCM, particularly CR, offers unique benefits over synthetic drugs owing to its natural origin. As both medicinal and food herb, it enhances immunity. The immunomodulatory effect of CR is characterized by its gentle and prolonged nature, distinguishing it from other potent immune stimulants. This unique attribute allows CR to regulate immune function without inducing immune disorders or adverse reactions associated with excessive stimulation. Chemical modification, combination, and formulation can boost the immunomodulatory potential. Based on clinical and preclinical findings, health products such as drinks, vinegar, granules, and oral liquids have been developed. Additionally, CR modulates the gut flora, enhances animal feed for livestock sustainability, and offers insight into the diversification of TCM immune enhancers. Its immunomodulatory effects hold promise in managing inflammation, wounds, tumors, vaccines, infections, and cardiovascular diseases. However, discrepancies in efficacy stem from variability in the extract parts, processing, and mechanisms, which are unclear at the multi-omics level. Future research must delve into active ingredient interactions, their diverse immunological pathways, and the link between TCM's "*qi*" theory and modern immunity.

This integrated approach is crucial for the advancement of *C. pilosula*-based immune enhancers, quality control, and TCM modernization.

Conflict of interest statement

The authors declare no conflict of interest.

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Author contributions

Xiyu Chen and Rui Shao wrote the manuscript. Yu Wang and Rui Shao revised the manuscript. All the authors have read and approved the final version of the manuscript.

Ethical approval of studies and informed consent

Not applicable.

Acknowledgments

None.

Data availability

All data generated or analyzed during this study are included in this published article.

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