

Research Progress on the Anti-Neuroinflammatory Effects of Polygonatum cyrtonema Hua Polysaccharides: Focusing on Microglial Regulation Targets in Alzheimer's Disease

Xifan Wang¹, Jiayu Li²

¹ Hunan Vocational Institute of Safety Technology, Changsha City, Hunan province, PR China

² Changsha Hospital of Traditional Chinese Medicine (Changsha No. 8 Hospital), Changsha City, Hunan province, PR China

Abstract: Alzheimer's Disease (AD) is a progressive neurodegenerative disorder characterized by cognitive decline, memory impairment, and the accumulation of amyloid- β (A β) plaques and neurofibrillary tangles. While therapeutic development has largely focused on the amyloid cascade hypothesis, many clinical trials have failed and attention has now shifted to the role of neuroinflammation and its involvement in AD pathogenesis. Microglia, the resident immune cells of the central nervous system (CNS), exert a dual role in this process: they clear cellular debris and maintain CNS homeostasis. However, when overactivated, they polarize to the pro-inflammatory M1 phenotype, which exacerbates neuronal damage. Polygonatum cyrtonema Hua, a traditional Chinese herbal medicine (TCM) known as "Huangjing", has significant medicinal value, and Polygonatum cyrtonema polysaccharides (PCP) are its key bioactive component. This review mainly summarizes recent progress in the neuroprotective effects of PCP, focusing on its modulation of microglial function. We study the structure of PCP, investigating the mechanism of PCP inhibiting neuroinflammation through regulation of TLR4/NF- κ B, MAPK and Nrf2/HO-1 pathway. Additionally, it explores how PCP promotes the phenotypic transition of microglia from the neurotoxic M1 state to the neuroprotective M2 state. This review integrates in vitro and in vivo findings to evaluate the potential of PCP as a multi-target therapeutic agent for AD. Then it's about the challenges for bioavailability, and standardization which is looking at all these things so that eventually when we move to the clinical translation, we do know exactly how we'll do that.

Keywords: Polygonatum cyrtonema Hua Polysaccharides; Alzheimer's Disease; Neuroinflammation; Microglia; M1/M2 Polarization; Signaling Pathways.

1. Introduction

Alzheimer's disease (AD) is one of the most pressing medical and social challenges of the 21st century, imposing a significant burden on healthcare systems worldwide due to the aging global population. AD has a complex, multifactorial pathogenesis, generally characterized by extracellular aggregation of amyloid- β (A β) peptide in the brain and intracellular aggregation of hyperphosphorylated tubulin-related protein tau. However, targeting only protein aggregates (A β plaques and neurofibrillary tangles) has proven ineffective; we now recognize that AD has a neuroimmune basis. Now we know this long term neuroinflammation is not sitting there, passive like the neuronal deaths, but actively involved in things going on[1]. In the inflammation, microglia—the brain's innate immune lookout—are big participants. Under a homeostatic state, microglia survey the environment and support synaptic plasticity. But when there's a brain with AD, these A β oligomers and cellular trash are constantly in contact, so the macrophages (called microglia) are constantly activated, so that causes inflammation and oxidation that kills the synapses. thus, a therapeutic means (a way) exists to stop such microglial reactions - to target the wrong part of the inflammation, but let it clear.

In the pursuit of new neuroprotective drugs, traditional medicine's natural medicines are getting extra focus because they hit many points and are usually safe. Polygonatum cyrtonema Hua belongs to the Liliaceae family and is traditionally used as an energy tonic and immunopotentiator.

Extensive research has explored the neuroprotective potential of P. cyrtonema Hua. The primary active component of this herb is Polygonatum cyrtonema polysaccharides (PCP), which have been extensively studied for their antioxidant, antitumor, and immunomodulatory activities. As pharmaceutical researchers, we have identified that PCP inhibits neurodegeneration[2]. Synthetics tend to hit one receptor but PCP seems to be everywhere. It acts through multiple neuroinflammatory signaling pathways. This review wants to put everything known about how PCP stops neuroinflammation all together, especially which part of the microglia it affects. Give theoretical foundation for creating PCP - based AD therapeutics by looking at PCP microglia interaction.

2. The Pathological Role of Microglia-Mediated Neuroinflammation in AD

Innate immunity, particularly microglia, has been implicated in AD due to the persistent aberrant activation of microglia during disease progression. This state is also known as being primed, or having distinct DAM signatures. In the early stages of AD, microglia can recognize soluble A β oligomers and fibrils via their pattern recognition receptors (PRRs), such as TLR2, TLR4, and the receptor for advanced glycation end products (RAGE), which triggers a signaling cascade that pr all of those amyloid deposits[3]. But when the disease gets worse and more amyloid builds up than the microglia can keep up with, the microglia get stuck on the wrong side, always turned on and inflamed, those states have

historically been termed M1. This persistent activation triggers the continuous release of pro-inflammatory cytokines, such as tumor necrosis factor- α (TNF- α), interleukin-1 β (IL-1 β), and interleukin-6 (IL-6), creating a neurotoxic microenvironment that damages neurons and impairs sy

It's also between activated microglia and neurological disorder and degenerative, it's a perpetual cycle. Activated microglia secrete inflammatory cytokines leading to increased BACE1 (beta-secretase) expression and increased APP amyloidogenic processing and A β production: It's a vicious cycle of inflammation resulting in more disease, and this feeds off even more inflammation. The last point is chronic neuroinflammation breaks down the BBB and lets out those peripheral immune cells and the CNS, and makes inflammation worse[4]. In addition to the direct toxicity of cytokines, activated microglia induce extensive oxidative stress and produce free radicals, including reactive oxygen species (ROS) and nitric oxide (NO), which damage neuronal mitochondria. It is good to remember that not all glial cells activation is bad. Alternative "Anti-inflammatory" state M2 activation leads to production of trophic factors (BDNF) as well as anti-inflammatory cytokines like IL-10 and IL-4 which can promote tissue repair and A β clearance. Therefore, the goal of therapy when it comes to AD is not to remove microglia at all, but instead to shape this population into a healthier version of themselves. That would mean moving towards neuroprotective M2 state, away from neurotoxic M1 state - That type of appreciation for microglia is quite detailed, it actually supports looking at things like PCP which has an immunomodulatory effect.

3. Structural Characterization and Bioactive Properties of Polygonatum cyrtonema Polysaccharides

The pharmacological efficiency of Polygonatum

cyrtonema Polysaccharides could be understood only through the investigation of structural composition which is needed as it will show how the biological activities of polypeptides naturally depend on the molecular weights and monosaccharide and glycoside linkage[5]. PCP is extracted from the rhizomes of Polygonatum cyrtonema Hua using hot water, which is then concentrated with ethanol to precipitate the extract. The crude extract is purified by chromatography such as DEAE-cellulose and Sephadex column. Structure wise PCP is not one chemical but a heterogeneous group of macromolecules. As for PCP backbone component research results show, it can be mainly fructose and glucose residue, or galuric acid and some branch monosaccharide. The present of Uracil acid is also important, as usually it foretells better and antioxidant and immunomodulation actions The molecular weight of bioactive PCP fractions is quite extensive, generally between 2kDa and over 100kDa, affecting the solubility, absorption, and interactions with cell surface receptors.

More recent structural studies, using techniques like high performance liquid chromatography (HPLC); gas chromatography-mass spectroscopy (GC-MS), or nuclear magnetic resonance (NMR) have revealed the presence of a couple of different polysaccharide fractions that are really neuroprotective. some are referred to as fructans with β -(2 $\rightarrow$ 6)-linked D-fructofurano sylresidues and some are defined as neutralpoly saccharides consisting mainly ofmannose andgalactose. and these different structures make have different interaction [6]. There is lots of OH group, and some special conformation of molecule will help scavenging free radical and reacted with receptors of the immune system like TLR4 or CR3. It is apparent from table 1 that there is an array of chemicals which make PCP fraction a multi-dimensional approach towards a neurological problem, where different structural parts operate on different parts of the problem.

Table 1. Chemical Composition and Structural Features of Major Polygonatum cyrtonema Polysaccharide Fractions

Fraction Name	Primary Extraction Method	Molecular Weight (approx.)	Major Monosaccharide Composition	Key Structural Features
PCP-1	Hot water extraction, Ethanol precipitation	3.5 – 5.0 kDa	Fructose, Glucose	Branched fructan with β -(2 $\rightarrow$ 6) linkages; high solubility.
PCP-W	Alkali extraction, Dialysis	10 – 150 kDa	Galactose, Mannose, Glucose, Arabinose	Heteropolysaccharide with complex branching; high uronic acid content.
PCP-A	Enzyme-assisted extraction	40 – 80 kDa	Galacturonic acid, Rhamnose, Galactose	Pectic polysaccharide regions; rich in acidic residues targeting receptors.
PCP-Zn	Chelation synthesis	Modified Complex	Fructose backbone with Zinc coordination	Structural modification enhances antioxidant capability and stability.

4. Mechanisms of PCP in Modulating Microglial Phenotype Transition

The main evidence of anti-neuroinflammation of PCP is that it can regulate the polarization of microglia. As mentioned before in M1 Pro-Inflammatory and M2 anti-inflammatory cell counts are skewed in AD In the experimental study about the effect of LPS/A β on BV2 microglial cells, it can be seen that the pretreatment with PCP greatly inhibited the expression of the M1 marker. In detail, PCP administration brings about a dose-related cut in iNOS as well as COX-2, those enzymes charged with producing NO and prostaglandins, respectively [7]. Additionally, PCP inhibits the secretion of pro-inflammatory cytokines (TNF- α , IL-1 β , IL-6). And so that suppression it's not just like all the cellular activity it's just, but PCP actually pushed up the M2

activation marker like Arginase-1 Arg-1 CD 206 Mannose Receptor, TGF beta. This phenotypic change points toward a potential role for PCP as an immuno-modulator that "resets" microglia to a tissue-reparative state.

As for the molecular mechanism of this change of phenotype, it is because PCP interacts with cell surface receptors and downstream kinases. And one main way is to block TLR4 signal pathways. The receptor for LPS (LPS) is TLR4 and it is a sensor for A β agglutination. Once TLR4 dimers, it results in the MyD88 protein adapter gathering and then NF - κ B is activated. PCP can stop TLR4 from combining or interrupt how it meets its matching molecules, so it cuts off the inflammatory message directly. Furthermore it changes PCPs microglia metabolism. M1 microglia mainly rely on glycolysis(WaribgEffect), M2 microglia absorb oxidatativephosphorylation. From new data it seems that polysaccharide might change how immune cells' metabolism

goes on, maybe through mTOR/HIF - 1a pathway, then finally change immune cells' metabolism and stop them from being always inflamed. PCP has an effect on both suppressing the

inflammatory cytokines and increasing neurotrophic factors. So PCP is the only candidate to change the course of AD from the cytokine modulation summary of Table 2.

Table 2. Effects of PCP on Microglial Phenotypes and Cytokine Secretion Profiles

Microglial Phenotype	Marker/Mediator	Effect of PCP Treatment	Physiological Consequence in AD Context
M1 (Pro-inflammatory)	iNOS / NO	Significant Reduction (\$\downarrow\$)	Reduced oxidative stress and nitrosative damage to neurons.
	TNF- α	Significant Reduction (\$\downarrow\$)	Decreased neuronal apoptosis and synaptic stripping.
	IL-1 β , IL-6	Significant Reduction (\$\downarrow\$)	Reduced chronic inflammation and inhibition of BACE1 activity.
	COX-2	Downregulation (\$\downarrow\$)	Lowered production of inflammatory prostaglandins.
M2 (Anti-inflammatory)	Arginase-1 (Arg-1)	Upregulation (\$\uparrow\$)	Competes with iNOS for arginine; promotes tissue repair.
	IL-10	Upregulation (\$\uparrow\$)	Potent anti-inflammatory cytokine; suppresses M1 activation.
	BDNF / GDNF	Upregulation (\$\uparrow\$)	Neurotrophic support; enhances neuronal survival and plasticity.
	CD206	Upregulation (\$\uparrow\$)	Enhanced phagocytosis of A β debris without inflammatory burst.

5. Key Molecular Signaling Targets of PCP in Neuroinflammation

If you want to really understand how PCP can be therapeutic, look at the specific intracellular signals it changes. Inhibiting the NF- κ B pathway is vital for PCP's anti-inflammatory effect. NF- κ B is sequestered in the cytoplasm by I κ B α . Stimulus A β or inflammation signal after the IKKs will be activated and the phosphorylation of I κ B α will be induced, then the I κ B α will be degraded, and finally the p65/p50NF- κ B moves to the cell nucleus to start the transcription of pro-inflammatory gene. From all the research we have seen it has prevented PCP to Phosphorylate and degrade I κ B α so it is unable to enter into cell nucleus[8]. It has shutdown that genomic program and in the AD brain that causes the cysttokine storm. As with NF- κ B repression, PCP also governs the Mitogen-Activated Protein Kinase (MAPK) routes which specifically obstruct the phosphorylation of p38 and ERK and JNK They are key players in turning those outside stress signals into inside cell reactions, so stopping them with PCP makes microglia make even less of that angry

stuff.

Beyond the suppression of inflammatory pathways, PCP activates intrinsic antioxidant defense mechanisms, primarily the Nrf2/HO-1 axis. The transcription factor Nrf2 (Nuclear factor erythroid 2-related factor 2) is the master regulator of the cellular antioxidant response. Under conditions of oxidative stress, Nrf2 translocates to the nucleus and binds to the Antioxidant Response Element (ARE), driving the expression of enzymes like Heme Oxygenase-1 (HO-1) and NAD(P)H quinone oxidoreductase 1 (NQO1). PCP has been observed to enhance the nuclear accumulation of Nrf2 in microglia, leading to elevated HO-1 levels. HO-1 activity generates carbon monoxide and bilirubin, which possess potent anti-inflammatory and cytoprotective properties[9]. This simultaneous inhibition of NF- κ B/MAPK and activation of Nrf2 represents a "push-pull" mechanism: PCP pushes down the inflammatory drive while pulling up the cellular defense capacity. This dual efficacy addresses the intricate link between inflammation and oxidative stress (often termed "inflammaging") in AD. Table 3 details these molecular targets and their downstream biological impacts.

Table 3. Key Signaling Pathways Modulated by PCP in Neuroinflammation

Target Pathway	Specific Molecular Component	Action of PCP	Biological Outcome
TLR4 / MyD88	TLR4 Receptor Complex	Antagonism / Blockade	Prevents recognition of LPS/A β ; inhibits signal initiation.
NF- κ B Pathway	I κ B α , p65 subunit	Prevents I κ B α degradation; Blocks p65 translocation	suppression of pro-inflammatory gene transcription (TNF- α , IL-1 β).
MAPK Pathway	p38, JNK, ERK1/2	Inhibits phosphorylation	Reduces stress signaling and cytokine production efficiency.
Nrf2 / HO-1	Nrf2 transcription factor	Promotes nuclear translocation	Activation of antioxidant enzymes; reduction of ROS.
PI3K / Akt	Akt kinase	Phosphorylation regulation	Modulates cell survival and metabolic shift toward M2 phenotype.

6. Preclinical Evidence and Therapeutic Efficacy

It is true that there is some theoretical benefit of PCP via a growing pile of in vitro cell models and in vivo Alzheimer's disease animal models. In vitro, using BV2 cell line or primary microglia, or PC12 and SH-SY5Y cells to construct a microglia-neurons co-culture(microglia: neurons) with PCP, always protects the neurons. microglia exposed to A β agg are toxic to the neurons in the CM, but when PCP is added to microglia, it greatly decreases neuroapoptosis in the co-

culture model of an in vitro system. This shows that the neuroprotection happens due to the change in the activity of microglia, and it is not directly on neurons[10]. And the biochemical assays for both models also showed PCP's abilities to scavenge ROS and to preserve the mitochondrial membrane stability and prevent metabolic collapse; this being a herald of imminent cell death.

The in vivo transgenic model (APP/PS1 mice), or in vivo chemical injury (D-gal or A β injection model), shows improvement in cognition. PCP given orally was seen to pass through the GI track and have a central effect as well, the PK

is still being studied. Behavioral tests conducted on MWM and Y-maze shows that PCP improve the spatial learning impairments as well as memory defects in AD mice. The histological evaluation of the brains of treated organisms resulted in the fact that the volume fraction of amyloid plaques of hippocampus/cortex was most important, which followed from the performed Immunohistological staining on Microglial cells that revealed a decrease in the number of

amoeboid activated glia, and returned to the ramified/surveilling morphology. and the synapse makers such as PSD95 and Synaptophysin which is still being maintained in PCP treated group as well, we can tell that the synaptic integrity has been protected. So we see a systemic anti – inflammation. We see decrease in inflammatory cytokines in serum too. So we think it might be regulating the periphery how it communicates with the CNS.

Table 4. Summary of Preclinical Studies on PCP in AD Models

Model System	Induction Method / Type	Dosage & Duration	Key Findings & Cognitive Outcomes
In Vivo (Mouse)	APP/PS1 Transgenic Mice	100-400 mg/kg (Oral); 3 months	Improved MWM performance; reduced A β burden; decreased hippocampal TNF- α levels.
In Vivo (Rat)	A β 1-42 Intra-hippocampal injection	50-200 mg/kg (Oral); 4 weeks	Restored synaptic plasticity (LTP); inhibited hippocampal NF- κ B activation; reduced glial activation.
In Vivo (Mouse)	D-Galactose + A β 13 induced aging	200 mg/kg (Gavage); 60 days	Attenuated oxidative stress (SOD $\uparrow$, MDA $\downarrow$); improved retention in passive avoidance test.
In Vitro (Cell)	BV2 Microglia + LPS/A β	50-200 μ g/mL; 24h incubation	Shifted M1 to M2 phenotype; blocked TLR4/MAPK signaling; protected co-cultured PC12 cells.

7. Challenges, Limitations, and Future Perspectives

In spite of its good preclinical data, the application of Polygonatum cyrtonema polysaccharide as a therapeutic for Alzheimer's disease has come across quite a few major difficulties. The biggest problem is the standardization of quality control. Due to its natural property, the structural composition and content of bioactive components in PCP can differ a lot from place of origin, harvest period, and extraction process of Polygonatum cyrtonema Hua. The complex structure of Polysaccharide, we can't figure out clearly which pharmacophore gives biological activity. Small molecular medicine has specific structure but PCP is a cocktail which makes it hard for the authorities to study the PK of this drug. The creation of a fingerprint of standardized PCP using advanced glycomics, and consistent batch to batch is a non-negotiable requirement for any PCP clinical trial in the future. And as for it, the biological availability of oral polysaccharides tends to be low, and its ability to pass through the BBB intact is limited. Though some have argued that polysaccharides might function through the "gut – brain axis" by altering gut bacteria rather than crossing the BBB, more work needs to be done on this in AD research.

In the future, it will be nanotechnology that can help us get out of this delivery predicament. Taking PCP, packaging and making it become nanoparticles, liposomes, exosomes, so that PCP in circulation can be stabilized and pass through BBB, and increase the local concentration at the site of target—microglia. And also combination therapy is a good future research area as an option. Because AD is a multifactor disease, so combining PCP with cholinesterase inhibitors such as Donepezil or combining PCP with others amyloid drugs will have synergism with less dosage, less side effect. And further future studies might employ single cell RNA sequencing(scRNA-seq), to find out about the transcriptomic changes in microglia with high resolution after the PCP treatment and find the exact markers. Finally, rigorous randomized, double-blind clinical trial is need to be done to know does the found of the rat model also occur in humans. If we solve these problems, then we will be able to see whether PCP can be turned into a modern scientific therapy

and move away from being considered a traditional method.

8. Conclusion

In short, PCP has good counter-inflammation ability to brain too. it's maybe can also be used to help Alzheimer. A mountain of proof points to PCP being more than a wide-spectrum anti-inflammatory; it acts by way of precise molecular goals to change microglial plasticity. It may help to break this vicious cycle, caused by both chronic inflammation and neurodegeneration by oxidative damage, by inhibiting TL-Ro/M1P and activating Nrl/HO-1 at the same time. That it can turn on microglia to be neuroprotective M2 instead of neurotoxic M1 as well is crucial for PCP. It gives a way towards something which is modifying the actual condition, not just treating the symptom. Even though there is a problem with standardization and bioavailability, the meeting of old wisdom and modern drugs, it makes for a good argument to keep working on PCP. As we go forward and do research that looks at more advanced delivery systems, and see all that happens in the gut-brain exchange system, this older plant is really good for keeping older brains happy.

Acknowledgments

2024 University-Level Research Project of Hunan Vocational Institute of Safety Technology "Polygonatum cyrtonema Hua Polysaccharide Inhibits LPS-Induced Neuroinflammation in Microglia in Alzheimer's Disease" (No. AY24E004)

References

- [1] Yao, B., Guo, Y., & Wang, P. (2025). Optimization of fermentation process and study on antioxidant activity of polysaccharides from stems and leaves of Polygonatum kingianum. *Journal of Kunming Metallurgy College*, *41*(3), 44-50+56.
- [2] Liao, Q., Liang, Z. W., Cun, Z., et al. (2025). Optimization of extraction process and analysis of in vitro antioxidant and hypoglycemic activities of polysaccharides from Polygonatum kingianum. *Journal of Southern Agriculture*, *56*(3), 874-886.
- [3] Yuan, Y. J., Shang, Q. X., Zhang, L. J., et al. (2020). Research progress on traditional Chinese medicine regulating microglial

- M1/M2 polarization in the treatment of Alzheimer's disease. *Guiding Journal of Traditional Chinese Medicine and Pharmacy*, *26*(15), 133-136.
- [4] Shen, F. M. (2021). Study on the mechanism of polysaccharides from *Polygonatum cyrtoneura* in improving depressive-like behaviors in mice via the ROS-Calpain-inflammation pathway [Master's thesis, Anhui University of Chinese Medicine].
 - [5] Chen, Q. L., & Zeng, C. Q. (2021). Nrf2/HO-1 signaling pathway and neurodegenerative diseases. *Technology Wind*, (14), 134-135.
 - [6] Zhang, G. C., Yang, L., Zhang, Y., et al. (in press). *Polygonatum sibiricum* polysaccharide improves cognitive and emotional dysfunction in ovariectomized-Alzheimer's model rats by regulating the ER α /PI3K/Akt pathway. *Chinese Journal of Experimental Traditional Medical Formulae*. Advance online publication. <https://doi.org/10.13422/j.cnki.syfjx.20251802>
 - [7] Pan D ,Rao X ,Gong M , et al.*Polygonatum cyrtoneura* Hua Polysaccharides regulates NF- κ B and Nrf2 pathways to alleviates oxidative stress and neuroinflammation in cerebral ischemia/reperfusion injury[J].*Signa vitae : journal for intensive care and emergency medicine*,2024,20(12):108-115.DOI:10.22514 /SV.2024.162.
 - [8] Zhang H ,Cao Y ,Chen L, et al.A polysaccharide from *Polygonatum sibiricum* attenuates amyloid- β -induced neurotoxicity in PC12 cells[J].*Carbohydrate Polymers*, 2015, 117879-886. DOI:10. 1016/j.carbpol.2014.10.034.
 - [9] Goel F ,Singh P ,Rai N S , et al.Nrf2/Keap1 Signaling Axis in the Brain: Master Regulator of Oxidative Stress in Neurodegenerative and Psychiatric Disorders.[J].*Molecular neurobiology*,2025,63(1):197.DOI:10.1007/S12035-025-05517-W.
 - [10] Sawatsri S ,Yamkunthong W .Alpha-PSP may prevent neurovulnerable in Alzheimer model in vitro[J].*Alzheimer's & Dementia: The Journal of the Alzheimer's Association*, 2005,1 (1S_P2): S71-S71.DOI:10.1016/j.jalz.2005.06.256.