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Cold Agglutinin Disease: Pathophysiology, Clinical Management, and Emerging Therapeutic Approaches Including Plant-Derived Compounds

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ABSTRACT

Cold Agglutinin Disease (CAD) is a rare form of autoimmune haemolytic anaemia characterized by the binding of cold-reactive antibodies (cold agglutinins) to red blood cells at low temperatures, leading to clumping and haemolysis. Predominantly affecting older adults, CAD can be either primary (idiopathic) or secondary to underlying conditions such as infections, malignancies, or autoimmune disorders. The disease mechanism involves IgM antibodies binding to red blood cells in cold environments, activating the classical complement pathway, and causing haemolysis. Patients typically present with anaemia symptoms, including fatigue and jaundice, as well as cold-induced circulatory issues like acrocyanosis. Diagnosis is confirmed through clinical evaluation, positive direct antiglobulin test, and elevated cold agglutinin titers. Treatment strategies include avoiding cold exposure, supportive care, and pharmacologic interventions such as corticosteroids, rituximab, and emerging complement inhibitors like eculizumab. Recent advances in understanding CAD's molecular mechanisms have led to more targeted therapies. While plant-derived chemicals like curcumin and resveratrol are not yet established treatments, they are under investigation for their potential benefits in autoimmune and haematological disorders, potentially providing future therapeutic options for CAD. This review offers a comprehensive overview of CAD's causes and treatments, emphasizing recent research and future directions.

Keywords: *Cold Agglutinin Disease, haemolysis, autoimmune disorders, corticosteroids, curcumin*

1. INTRODUCTION

Cold agglutinin disease (CAD) is an uncommon form of autoimmune hemolytic anemia (AIHA) marked by the presence of cold-reactive immunoglobulin M (IgM) autoantibodies that target red blood cells (RBCs) at temperatures below physiological norms (1). These autoantibodies initiate RBC agglutination and complement-mediated haemolysis, resulting in both intravascular and extravascular red cell destruction. CAD accounts for approximately 15% of all AIHA cases and exhibits an estimated incidence of 1 case per million individuals annually (2). It predominantly affects older adults, with a peak onset after the age of 50 and a slight female predominance. Clinically, CAD is characterized by features of chronic hemolytic anemia—such as fatigue, pallor, and jaundice—as well as cold-induced manifestations, including acrocyanosis and Raynaud's phenomenon, caused by agglutination-induced microvascular obstruction (3,4).

The pathophysiology of CAD is distinct from other AIHA subtypes and involves activation of the classical complement pathway through IgM binding to the I/i carbohydrate antigens on RBC surfaces in cooler peripheral body regions. This triggers complement fixation and C3d deposition, ultimately leading to the formation of the membrane attack complex.

(MAC) and haemolysis (5,6). Hepatic macrophages play a central role in the clearance of opsonized erythrocytes. In nearly 90% of CAD cases, monoclonal IgM antibodies—typically encoded by the IGHV 4-34 gene segment—are responsible for disease activity. CAD may arise as a primary (idiopathic) condition or may occur secondarily in association with infections such as Mycoplasma pneumoniae or Epstein-Barr virus, lymphoproliferative malignancies like non-Hodgkin lymphoma, or autoimmune diseases (7-9).

Diagnosis relies on the integration of clinical presentation with serologic findings, particularly a positive direct antiglobulin test (DAT) for C3d and elevated cold agglutinin titers. Given the distinct pathogenic mechanism of CAD, treatment strategies must diverge from those used for warm antibody AIHA (10-12). Supportive measures such as avoidance of cold exposure and RBC transfusions with warmed blood remain foundational. However, corticosteroids, which are commonly effective in warm AIHA, show limited utility in CAD due to the IgM-complement-mediated pathology. Less than 20% of patients respond favourably to steroids, and their long-term use is associated with adverse effects including osteoporosis, glucose intolerance, and increased infection risk (13-16).

Rituximab, an anti-CD20 monoclonal antibody, has emerged as the most effective first-line pharmacological agent for CAD (Table 1). By selectively depleting B-lymphocytes, rituximab reduces the production of pathogenic cold agglutinins. Clinical studies report response rates between 45–60%, with onset of effect typically observed within 1–3 months. Despite its favourable safety profile in elderly patients, the therapeutic benefit is often transient, with a median response duration of approximately 11 months and incomplete control of complement activation in some cases (17,18). Advances in therapeutic strategies have introduced complement inhibitors such as eculizumab, which target components of the complement cascade to prevent MAC formation and reduce haemolysis. Although promising, these agents are still undergoing clinical evaluation, and challenges remain in terms of accessibility, cost, and long-term safety (19)

For patients with inadequate response to rituximab or frequent relapses, more potent immunosuppressive agents may be considered (20). Alkylating agents like cyclophosphamide and purine analogs such as fludarabine can target the clonal B-cell populations responsible for cold agglutinin production (21). Bendamustine, with its dual alkylating and antimetabolite properties, has shown particular promise with response rates exceeding 70% in some series. However, these agents carry significant risks including myelosuppression, increased infection risk, and potential for secondary malignancies, necessitating careful patient selection and monitoring (22).

The development of complement inhibitors has revolutionized CAD treatment by directly addressing the terminal effector mechanism of haemolysis. Eculizumab, a C5 inhibitor, prevents formation of the membrane attack complex, with clinical trials demonstrating rapid reduction in haemolysis and transfusion requirements (23,24). Novel agents targeting upstream components of the complement cascade (e.g., sutimlimab, a C1s inhibitor) have shown even greater promise in early studies, with some achieving complete inhibition of complement-mediated haemolysis. These therapies may be particularly valuable for patients with ongoing haemolysis despite B-cell targeted therapy (25-27).

Recently, natural plant-derived compounds have garnered interest as potential adjunctive or alternative therapies for CAD. Bioactive molecules including flavonoids (e.g., quercetin), polyphenols (e.g., curcumin and resveratrol), and catechins (e.g., epigallocatechin gallate) possess immunomodulatory, anti-inflammatory, and complement-inhibitory properties. Curcumin has demonstrated the ability to suppress IgM production and inhibit complement activation in vitro, while quercetin may help stabilize RBC membranes against immune-mediated damage. Although these findings are preliminary, they suggest a promising avenue for novel interventions pending further preclinical validation and clinical research (28-33).

This manuscript aims to provide a comprehensive overview of CAD with emphasis on its immunopathogenesis, clinical characteristics, and current treatment modalities, while also exploring emerging therapies, particularly the therapeutic potential of plant-derived compounds

Table 1. Drugs Used in the Treatment of Cold Agglutinin Disease (CAD)

Drug	Mechanism of Action	References
Rituximab	Monoclonal antibody targeting CD20 on B cells, leading to B cell depletion and reduced cold agglutinin titers.	(17,34)
Corticosteroids	Anti-inflammatory and immunosuppressive effects; generally less effective in CAD compared to other AIHA types.	(35)
Cyclophosphamide	Alkylating agent that targets proliferating B cells, reducing the production of cold agglutinins.	(36,37)
Fludarabine	Purine analogue that inhibits DNA synthesis, leading to reduced B cell proliferation and cold agglutinin production.	(38)

Bendamustine	Chemotherapy agent with alkylating properties; reduces B cell proliferation and cold agglutinin production.	(39)
Eculizumab	Monoclonal antibody that inhibits C5, preventing the formation of the membrane attack complex and reducing haemolysis.	(40)
Sutimlimab	Monoclonal antibody that inhibits C1s, an early component of the classical complement pathway, reduces haemolysis.	(41)

Exploration of Plant-Derived Compounds for Cold Agglutinin Disease Treatment

Plant-derived chemicals are not yet established as standard treatments for Cold Agglutinin Disease (CAD), but some compounds from natural sources are under investigation for their potential therapeutic benefits. Here are a few plant-derived chemicals that have been explored in the context of autoimmune and haematological disorders, which might offer insights into future CAD treatments:

Curcumin

Curcumin, a bioactive diarylheptanoid and the primary curcuminoid derived from the rhizome of *Curcuma longa* (turmeric), has demonstrated significant potential due to its multifaceted pharmacological properties. Curcumin exhibits potent anti-inflammatory, antioxidant, and immunomodulatory effects, which may be particularly relevant in managing CAD. Its anti-inflammatory action is mediated through the inhibition of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6, as well as the suppression of NF-κB activation, a key regulator of inflammatory responses (42-44). Additionally, curcumin functions as a powerful antioxidant, scavenging free radicals and upregulating endogenous antioxidant enzymes, thereby mitigating oxidative stress—a contributing factor in autoimmune hemolysis (45). Beyond its anti-inflammatory and antioxidant roles, curcumin modulates immune function by influencing T cell and B cell activity, promoting regulatory T cell (Treg) differentiation, and inhibiting macrophage-mediated inflammation (46). These mechanisms suggest that curcumin could help attenuate the pathogenic immune responses driving CAD, including the production of cold agglutinins and complement activation. While preclinical studies support its potential efficacy, further research, including clinical trials, is necessary to evaluate its safety, optimal dosing, and therapeutic impact in CAD specifically. The exploration of curcumin and other plant-derived compounds highlights a growing interest in natural products as adjunctive or alternative treatments for autoimmune hematologic disorders like CAD (47,48).

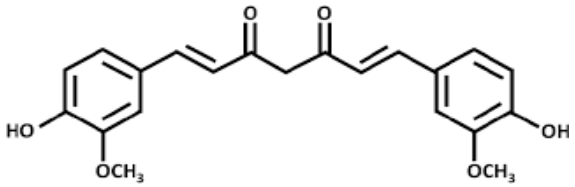

Figure 1. Curcumin

Resveratrol

Resveratrol, a naturally occurring stilbenoid polyphenol and phytoalexin, represents another promising plant-derived compound for potential application in CAD treatment (49). This bioactive compound is synthesized by various plants, including *Vitis vinifera* (grapes), *Vaccinium koreanum* (blueberries), *Rubus idaeus* (raspberries), *Morus rubra* (mulberries), and *Arachis hypogaea* (peanuts), particularly in response to pathogenic stress or injury (50). Resveratrol has garnered significant scientific interest due to its potent anti-inflammatory, antioxidant, and immunomodulatory properties, which may offer therapeutic benefits in autoimmune conditions like CAD (51).

The compound exerts its anti-inflammatory effects primarily through the inhibition of key pro-inflammatory cytokines, including TNF-α, IL-6, and IL-1β, while simultaneously modulating critical signaling pathways such as NF-κB that play central roles in autoimmune pathogenesis (52). These mechanisms could potentially attenuate the inflammatory cascade associated with CAD-mediated haemolysis. Furthermore, resveratrol demonstrates robust antioxidant activity by effectively neutralizing reactive oxygen species and enhancing cellular antioxidant defenses, thereby reducing oxidative stress - a significant contributor to erythrocyte damage in CAD (53).

Beyond these properties, resveratrol exhibits notable immunomodulatory capabilities that may be particularly relevant for CAD treatment. It has been shown to regulate various immune cell functions, including T-cell differentiation and macrophage polarization, which could help restore immune homeostasis in autoimmune disorders (54). These multifaceted actions

suggest that resveratrol might interfere with multiple pathological processes in CAD, from reducing cold agglutinin production to protecting erythrocytes from complement-mediated damage. While these pharmacological properties make resveratrol an attractive candidate for CAD therapy, rigorous clinical studies are needed to evaluate its efficacy, optimal dosing, and safety profile specifically in CAD patients. The compound's natural origin and generally favourable safety profile further enhance its potential as a complementary therapeutic approach for this challenging hematologic disorder.

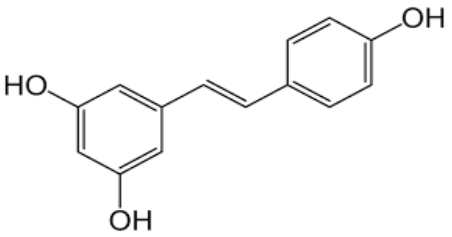

Figure 2. Resveratrol

Gingerol:

Gingerol, the primary bioactive phenolic compound found in fresh ginger (*Zingiber officinale*), has emerged as a promising plant-derived therapeutic candidate for CAD due to its significant pharmacological properties (55). This pungent yellow oil, responsible for ginger's characteristic flavour, exhibits dual anti-inflammatory and antioxidant mechanisms that may be particularly beneficial in autoimmune conditions like CAD. As a potent anti-inflammatory agent, gingerol effectively suppresses key inflammatory mediators involved in autoimmune pathogenesis, including pro-inflammatory cytokines (TNF-α, IL-1β) and enzymes (COX-2), potentially modulating the inflammatory cascade associated with CAD-mediated haemolysis (56,57). Simultaneously, its robust antioxidant activity helps scavenge reactive oxygen species and enhance cellular antioxidant defenses (58), offering protection to erythrocytes against oxidative damage during complement-mediated destruction. The compound's unique ability to target both inflammatory pathways and oxidative stress is especially relevant for CAD treatment, as these processes significantly contribute to disease pathology (59). Gingerol multimodal action suggests it may simultaneously address multiple aspects of CAD pathogenesis by reducing inflammation-mediated tissue damage, protecting red blood cells from oxidative injury, and potentially modulating immune cell activation (60). While these pharmacological properties make gingerol an attractive natural therapeutic option, further research is specifically needed to evaluate its efficacy in CAD models and establish optimal dosing regimens for clinical application. The compound's well-documented safety profile and widespread availability further strengthen its potential as a valuable adjunctive therapy in comprehensive CAD management strategies.

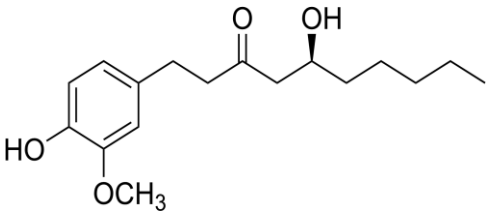

Figure 3. Gingerol

Quercetin:

Quercetin, a naturally occurring flavonol belonging to the polyphenol group, is widely distributed in various fruits and vegetables, including apples (*Malus domestica*), onions (*Allium cepa*), berries, and leafy greens like kale (61). Known for its bitter taste, this bioactive compound has gained attention for its potential therapeutic applications in autoimmune diseases, including CAD (62).

Quercetin exhibits a dual mechanism of action, combining potent antioxidant and anti-inflammatory properties that may be particularly beneficial in CAD. As an antioxidant, quercetin effectively scavenges free radicals and reduces oxidative stress, a key contributor to red blood cell damage in CAD. Its anti-inflammatory effects are mediated through the inhibition of pro-inflammatory cytokines such as TNF-α, IL-1β, and IL-6 (63,64), which play crucial roles in the inflammatory cascade associated with autoimmune haemolysis.

Beyond these properties, quercetin demonstrates significant immunomodulatory activity by regulating the function of key immune cells, including T cells and macrophages (65,66). This modulation of immune cell activity may help restore immune homeostasis in CAD, potentially reducing the production of pathogenic cold agglutinins and complement activation. While preclinical studies highlight quercetin promising effects on oxidative stress reduction and immune regulation, further clinical

research is necessary to evaluate its efficacy, optimal dosing, and safety profile specifically in CAD patients. The compound's natural origin, combined with its multi-targeted mechanism of action, positions it as a potential adjunctive therapy for CAD, either alone or in combination with existing treatments. However, more robust clinical evidence is required to fully establish its therapeutic role in this challenging hematologic disorder.

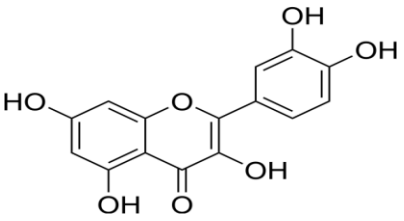

Figure 4. Quercetin

Epigallocatechin Gallate (EGCG):

Epigallocatechin gallate (EGCG), the most abundant and biologically active catechin in green tea (*Camellia sinensis*), represents a promising polyphenolic compound for the management of autoimmune disorders, including CAD. As a potent antioxidant, EGCG effectively scavenges free radicals and mitigates oxidative stress (67,68), a critical factor in the complement-mediated haemolysis characteristic of CAD.

EGCG therapeutic potential extends beyond its antioxidant capacity, encompassing significant anti-inflammatory and immunomodulatory properties. The compound inhibits key pro-inflammatory cytokines, including TNF-α and IL-1β, which are implicated in the inflammatory cascade driving RBC destruction in CAD. Furthermore, EGCG modulates immune cell function, potentially reducing aberrant B-cell activity and autoantibody production while promoting regulatory T-cell responses (69,70).

Emerging evidence suggests EGCG may be particularly beneficial in autoimmune conditions such as rheumatoid arthritis and lupus (71), highlighting its potential applicability to CAD. By simultaneously targeting oxidative stress, inflammation, and immune dysregulation, EGCG addresses multiple pathological mechanisms involved in CAD progression.

Despite these promising preclinical findings, clinical studies are necessary to evaluate EGCG efficacy, optimal dosing, and safety profile specifically in CAD patients. The compound natural origin, combined with its multimodal mechanism of action, positions it as a potential adjunctive therapy, either alone or in combination with existing treatments. However, further research is required to establish its therapeutic role and clinical utility in CAD management.

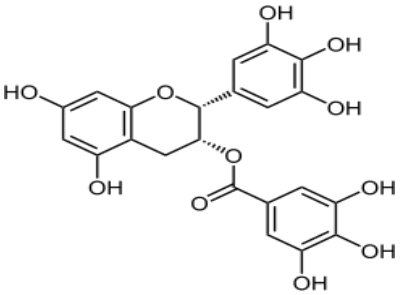

Figure 5. Epigallocatechin gallate

2. CONCLUSION

Cold Agglutinin Disease (CAD) presents complex treatment challenges, but recent advancements offer promising options. Rituximab, targeting CD20 on B cells, has proven effective in reducing cold agglutinin titers and managing symptoms. Complement inhibitors like eculizumab and sutimlimab show significant promise, particularly in severe cases where traditional treatments fall short. Although plant-derived chemicals are not yet established as standard treatments for CAD, ongoing research into natural compounds may provide new insights and potential therapies for autoimmune and haematological disorders. While these plant-derived chemicals show potential, they are not yet approved or validated as primary treatments for CAD. Their use remains exploratory, and further research is necessary to confirm their efficacy and safety in this context. Continued clinical trials and studies are crucial to refining these therapies and improving patient outcomes.

Ethical Considerations

Compliance with ethical guidelines

This manuscript is a review that does not involve any human or animal subjects.

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Authors' contributions

Conceptualization and Supervision: Ashok Kumar BS; Searching article, data collection and writing-original draft: Dhruthi Narayan BA, Disha NS, Writing the legal section: Ashok Kumar BS; Writing-review & editing: All authors.

Conflict of interest

The authors declare that there are no conflicts of interest.

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