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Immunomodulatory Effects of Plant Polysaccharides in Chronic Inflammatory Diseases: From Innate to Adaptive Immunity

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ABSTRACT: Chronic inflammatory and autoimmune diseases—including inflammatory bowel disease, rheumatoid arthritis, asthma and metabolic inflammation—arise from a failure of immune homeostasis in which innate over-activation and dysregulated adaptive responses reinforce one another. Plant polysaccharides, structurally complex biomacromolecules from herbs, fruits and fungi, have emerged as broad-spectrum immunomodulators that act, uniquely, along the entire innate-to-adaptive continuum. Recognised as pathogen-associated-molecular-pattern (PAMP)-like ligands by pattern-recognition receptors (PRRs)—chiefly Toll-like receptor 4 (TLR4), Dectin-1, the mannose receptor and complement receptor 3—they engage MyD88–NF-κB, Syk–Card9 and MAPK signalling to shape macrophage polarisation, dendritic-cell maturation and natural-killer-cell activity. Through dendritic-cell bridging they then direct the adaptive response, rebalancing the Th1/Th2, Th17/Treg and effector/regulatory axes whose distortion drives chronic inflammation. A third, indirect route operates through the gut microbiota: non-digestible polysaccharides are fermented to short-chain fatty acids that promote regulatory T-cell differentiation and epithelial-barrier integrity.

This review synthesises these mechanisms, emphasising the structure–activity relationships—molecular weight, backbone linkage, branching and conformation—that govern potency, and the context-dependent, bidirectional nature of polysaccharide

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immunomodulation. Compiled preclinical data show 45–88% shifts in pro- versus anti-inflammatory mediators, restoration of Th17/Treg balance, and 45–62% reductions in disease-severity markers across models of chronic inflammation. The review concludes that plant polysaccharides are versatile homeostatic immunomodulators whose translation now depends on structural standardisation, resolution of oral-bioavailability limitations, and rigorous clinical validation.

1. INTRODUCTION

The immune system defends the host through two integrated arms: a rapid, non-specific innate response and a slower, antigen-specific adaptive response, coupled by antigen-presenting cells. When this coupling is well regulated it resolves threats and returns to homeostasis; when it is not, the result is chronic inflammation—the shared pathological substrate of inflammatory bowel disease (IBD), rheumatoid arthritis (RA), asthma, psoriasis and the low-grade "inflammaging" of metabolic disease. [1,2] In these conditions innate over-activation (persistently M1-polarised macrophages, excess pro-inflammatory cytokines) and adaptive dysregulation (a distorted Th17/Treg balance, loss of tolerance) sustain one another in a self-amplifying loop. [2,3] Current biologic therapies that neutralise single cytokines are effective but costly, immunosuppressive and prone to loss of response, motivating interest in agents that restore balance rather than blanket-suppress immunity.

Plant polysaccharides are among the most promising such agents. These high-molecular-weight carbohydrate polymers—β-glucans, pectins, arabinogalactans, fucoidans and heteroglycans from medicinal herbs, fruits and fungi—have a long ethnomedical history and a rapidly expanding evidence base as immunomodulators with low toxicity. [3,4] Their defining feature is breadth: rather than hitting a single target, they act across the innate-to-adaptive continuum, engaging pattern-recognition receptors on innate cells, reprogramming macrophage and dendritic-cell behaviour, and thereby steering the adaptive T-cell response, with an additional indirect route through the gut microbiota. [4,5,6] Critically, their action is often bidirectional and context-dependent—stimulating an under-active immune system yet damping an over-active one—which is precisely the property required to treat chronic inflammation. [5,7]

This review is organised along the innate-to-adaptive axis that gives the field its logic (Figure 1). We first consider how the structure of a polysaccharide determines its activity; then how PRRs recognise these molecules and transduce signals in innate cells; how dendritic cells bridge to the adaptive compartment and rebalance T-cell subsets; how the microbiota provides a parallel indirect pathway; and finally how these mechanisms translate into efficacy across chronic inflammatory diseases. Throughout, we emphasise the structure–activity relationships and context-dependence that a rigorous, translational account of the field requires.

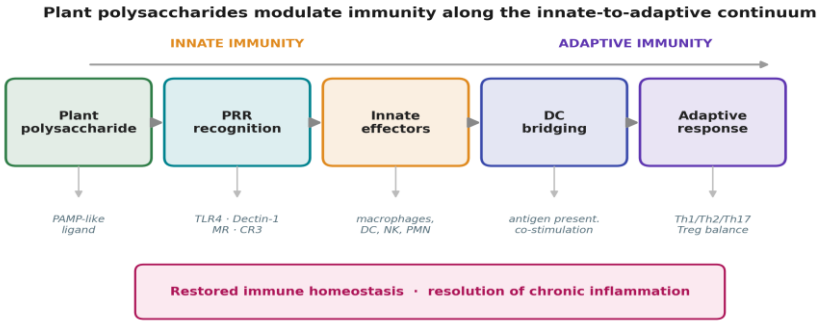

Figure 1. Plant polysaccharides act along the innate-to-adaptive continuum. Recognised as PAMP-like ligands by pattern-recognition receptors, they activate innate effectors (macrophages, dendritic cells, NK cells, neutrophils); dendritic cells then bridge to the adaptive compartment, where the Th1/Th2 and Th17/Treg axes are rebalanced—restoring immune homeostasis and promoting resolution of chronic inflammation.

2. SOURCES, STRUCTURE AND STRUCTURE–ACTIVITY RELATIONSHIPS

Immunomodulatory polysaccharides are chemically diverse (Table 1), ranging from the (1→3)-β-glucans of fungi and yeast to the pectic polysaccharides and arabinogalactans of higher plants. Their biological activity is not incidental to structure but is dictated by it, and understanding these structure–activity relationships (SARs) is essential for both interpretation and standardisation. [4,8] Figure 2 summarises the two most important determinants. First, molecular weight exerts a bell-shaped influence: oligosaccharides are usually too small to cross-link receptors effectively, very high-molecular-weight polymers aggregate and lose solubility, and intermediate species (roughly 10^4–10^5 Da) are typically most active. [8] Second, backbone linkage and branching are decisive—the (1→3)-β-glucan backbone is far more immunostimulatory than a (1→4)-linked one, and the introduction of (1→6)-β side branches further enhances activity, as does a preserved triple-helical conformation; debranching or chain degradation attenuates it. [8,9,10] Charge (sulfation, uronic-acid content), monosaccharide composition (notably arabinose and galacturonic acid) and solubility complete the picture (Table 2 summarises these determinants).

Polysaccharide	Botanical / fungal source	Structural class	Approx. MW	Signature activity
β-Glucan (lentinan, curdlan)	Shiitake / microbial	(1→3)-β-glucan ± (1→6) branches	10^5–10^6 Da	Dectin-1 activation; M1 polarisation
Astragalus polysaccharide (APS)	*Astragalus membranaceus*	Heteroglycan (Glc, Gal, Ara)	8–160 kDa	Th17/Treg balance; TLR4 modulation
Lycium barbarum polysaccharide	*Lycium barbarum* (goji)	Arabinogalactan-protein	10–150 kDa	Macrophage & NK activation
Ganoderma polysaccharide	*Ganoderma lucidum*	β-glucan / heteroglycan	10^5 Da	DC maturation; cytokine modulation
Pectic polysaccharide	Apple, citrus, herbs	Homogalacturonan / RG-I	5–100 kDa	TLR4 signalling; barrier support
Arabinogalactan	Larch, many herbs	Type-II arabinogalactan	10–120 kDa	Complement & macrophage activation

Table 1. Representative immunomodulatory plant and fungal polysaccharides, their sources, structural classes, approximate molecular weights and signature activities. Structural heterogeneity underlies the breadth of their immunomodulatory action.

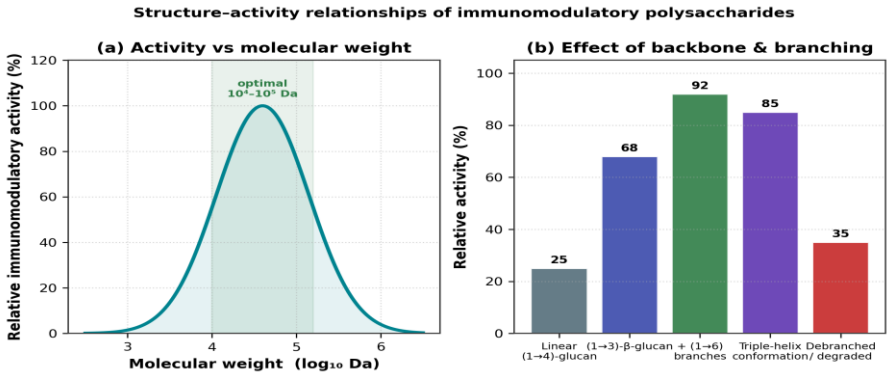

Figure 2. Structure–activity relationships. (a) Molecular weight exerts a bell-shaped effect, with intermediate species (≈10^4–10^5 Da) most active. (b) Backbone and branching are decisive: the (1→3)-β-glucan backbone with (1→6) branches and a preserved triple-helix conformation is far more active than linear (1→4) glucan or debranched/degraded chains. Values are representative trends synthesised from the cited SAR literature.

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Structural determinant	Direction of effect on immunomodulatory activity
Molecular weight	Bell-shaped; optimal at intermediate MW (~10^4–10^5 Da)
Backbone linkage	(1→3)-β ≫ (1→4); β- generally > α-linkages
Branching	(1→6)-β branches enhance activity; over-debranching reduces it
Conformation	Triple-helix / ordered chains more active than random coil
Charge / substitution	Sulfation, uronic acids can enhance or redirect activity
Monosaccharide composition	Arabinose, galacturonic acid associated with anti-inflammatory action
Solubility	Adequate solubility required for receptor engagement

Table 2. Structural determinants of the immunomodulatory activity of plant polysaccharides. These parameters must be characterised and reported for results to be comparable and reproducible.

3. INNATE IMMUNITY: PATTERN RECOGNITION AND SIGNALLING

The innate arm is the entry point. Plant polysaccharides are recognised as PAMP-like ligands by a defined set of pattern-recognition receptors on macrophages and dendritic cells—principally Toll-like receptors 4 and 2, the β-glucan receptor Dectin-1, the mannose receptor and complement receptor 3 (CR3)—which may act singly or assemble into signalling complexes (Table 3). [6,11] Receptor engagement triggers convergent intracellular cascades: TLR ligation signals through MyD88 to activate NF-κB and the p38/ERK MAPK pathways, while Dectin-1 signals through the Syk–Card9 axis; both culminate in NF-κB/AP-1-driven transcription of immune mediators (Figure 3). [11,12,13] The functional output is cytokine secretion (TNF-α, IL-6, IL-1β, IL-10, IL-12), production of nitric oxide and reactive oxygen species, enhanced phagocytosis, and—centrally—the direction of macrophage polarisation.

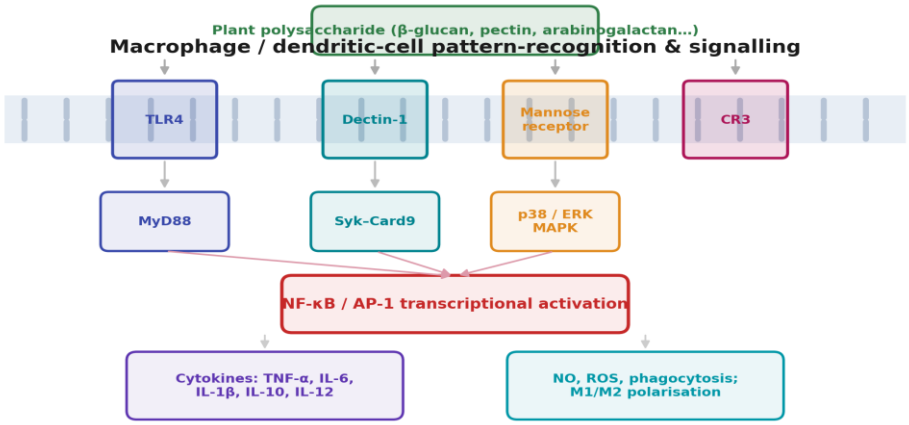

Figure 3. Pattern-recognition and signalling in innate cells. Plant polysaccharides engage TLR4, Dectin-1, the mannose receptor and CR3; downstream MyD88, Syk–Card9 and MAPK adaptors converge on NF-κB/AP-1 activation, driving cytokine output, nitric-oxide/ROS production, phagocytosis and macrophage M1/M2 polarisation.

Receptor	Recognised feature	Signalling	Principal outcome
TLR4 (± TLR2)	Diverse polysaccharide motifs	MyD88 → NF-κB, p38 MAPK	Cytokine induction; M1 polarisation
Dectin-1	(1→3)-β-glucan	Syk → Card9 → NF-κB/ERK	Phagocytosis; Th17-skewing; M1

Receptor	Recognised feature	Signalling	Principal outcome
Mannose receptor	Mannose / fucose termini	Endocytic; co-signalling	Antigen uptake; DC handling
Complement receptor 3	β-glucan (iC3b-opsonised)	Integrin signalling	Phagocytosis; priming

Table 3. Pattern-recognition receptors that recognise plant polysaccharides, the structural features they sense, their downstream signalling and principal functional outcomes. Co-operative, multi-receptor engagement is common.

3.1 Macrophage polarisation and its context-dependence

Macrophage polarisation is the pivotal innate readout. Depending on context, plant polysaccharides can drive classical (M1, pro-inflammatory, microbicidal, tumoricidal) or alternative (M2, reparative, resolving) programmes, governed by transcriptional switches—NF-κB, STAT1, IRF5 and AP-1 for M1 versus STAT6, IRF4 and PPARγ for M2. [11,12] Yeast and mushroom β-glucans, for example, drive M1 polarisation and can even reconvert immunosuppressive M2/tumour-associated macrophages to an M1 phenotype through Dectin-1, a property exploited in oncology. [9,10] In chronic inflammation, however, the therapeutic need is the opposite—to damp an M1-dominant, cytokine-rich milieu—and here many plant polysaccharides promote resolution by shifting the balance toward M2 and inducing anti-inflammatory mediators. Figure 4 depicts this rebalancing. This bidirectionality is not a contradiction but the essence of homeostatic immunomodulation: the same molecule nudges a dysregulated system back toward equilibrium, its net effect depending on the starting state, dose and structure. [5,7,12]

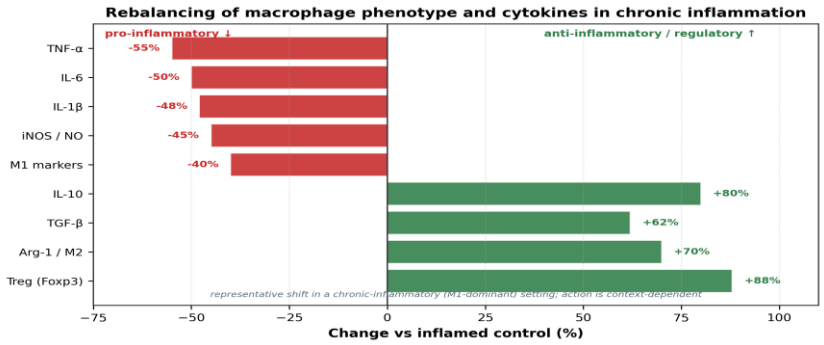

Figure 4. Rebalancing of macrophage phenotype and cytokines by plant polysaccharides in a chronic-inflammatory (M1-dominant) setting: suppression of pro-inflammatory mediators (TNF-α, IL-6, IL-1β, iNOS/NO, M1 markers) and induction of anti-inflammatory and regulatory mediators (IL-10, TGF-β, Arg-1/M2 markers, Foxp3$^+$ Treg). The direction of effect is context-dependent; in immunosuppressed settings the same agents can instead promote M1 activation. Values are representative.

4. BRIDGING TO ADAPTIVE IMMUNITY: DENDRITIC CELLS AND T-CELL BALANCE

Dendritic cells are the essential link between the two arms. On sensing polysaccharides through the same PRRs, they mature—up-regulating MHC and co-stimulatory molecules and migrating to lymphoid tissue—and, through the cytokine milieu they create, instruct the differentiation of naive CD4$^+$ T cells. [6,14] The therapeutic target in chronic inflammation is the balance among effector and regulatory subsets, above all the Th17/Treg axis, whose distortion toward pro-inflammatory Th17 cells (with loss of Foxp3$^+$ regulatory T cells) is central to IBD, RA and other autoimmune conditions. [2,15] Plant polysaccharides characteristically restore this balance. Astragalus polysaccharide (APS), for instance, alleviates dextran-sulfate-sodium (DSS)-induced ulcerative colitis by down-regulating Th17 (and memory-Th17) populations while expanding regulatory T cells, in part through TIGIT/CD155 signalling and inhibition of NF-κB. [15,16] Figure 6a illustrates this rebalancing. Beyond Th17/Treg, polysaccharides can correct Th1/Th2 skewing (relevant to allergy and asthma) and enhance the cytotoxic and antibody arms when host defence is the goal, again reflecting context-dependent restoration rather than uniform stimulation. [3,6]

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5. THE GUT MICROBIOTA–SCFA AXIS: AN INDIRECT ROUTE

A third mechanism, increasingly recognised as central for orally administered polysaccharides, is indirect and operates through the intestinal microbiota. Most plant polysaccharides are not digested by human enzymes; instead they reach the colon intact and are fermented by the resident microbiota, functioning as prebiotics that reshape community composition and yield short-chain fatty acids (SCFAs)—butyrate, propionate and acetate (Figure 5). [5,17] SCFAs are potent immunometabolic signals: through inhibition of histone deacetylases and engagement of the receptors GPR43/GPR41, they promote the differentiation and function of colonic regulatory T cells, reinforce the epithelial barrier and suppress NF-κB-driven inflammation. This route is not incidental. In DSS colitis, APS restores SCFA production and rebalances Th17/Treg homeostasis in a strictly microbiota-dependent manner—its benefit is abolished in antibiotic-treated mice and transferable by faecal microbiota transplantation from APS-treated donors—demonstrating that the microbiota is a necessary intermediary rather than a bystander. [17] This mechanism also helps reconcile the paradox that large, poorly absorbed polysaccharides exert systemic immune effects despite negligible direct bioavailability.

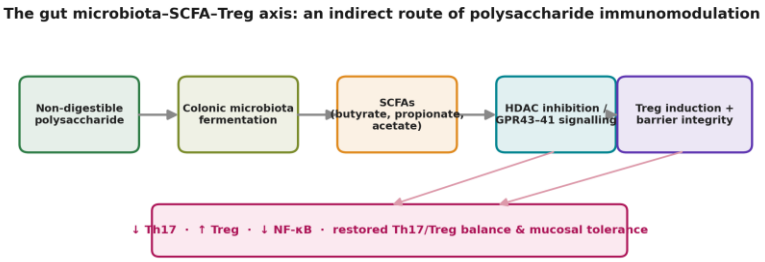

Figure 5. The gut microbiota–SCFA–Treg axis. Non-digestible plant polysaccharides are fermented by the colonic microbiota to short-chain fatty acids, which—via HDAC inhibition and GPR43/41 signalling—induce regulatory T cells, strengthen barrier integrity and suppress NF-κB, restoring Th17/Treg balance and mucosal tolerance. This indirect route is essential for many orally administered polysaccharides.

6. APPLICATIONS IN CHRONIC INFLAMMATORY DISEASES

The convergence of these mechanisms—innate rebalancing, adaptive Th17/Treg correction and microbiota-mediated tolerance—translates into efficacy across a spectrum of chronic inflammatory diseases (Table 4). In IBD, polysaccharides such as APS reduce colitis severity, restore SCFAs and normalise Th17/Treg ratios; in RA, they exert anti-inflammatory, antioxidant and cartilage-protective effects while modulating immune-cell function and the gut–joint axis; in allergic asthma they correct Th2 skewing; and in metabolic inflammation they attenuate macrophage-driven low-grade inflammation. [1,15,18,19] Figure 6b summarises representative reductions in disease-severity markers across these models, which typically fall in the 45–62% range.

Disease	Representative polysaccharide	Model	Principal mechanism / outcome
Ulcerative colitis / IBD	Astragalus polysaccharide	DSS colitis (mouse)	↑ SCFA; ↓ NF-κB; Th17/Treg rebalanced; barrier repair
Rheumatoid arthritis	Multiple (e.g. Astragalus, Lycium)	CIA / adjuvant arthritis	↓ pro-inflammatory cytokines; cartilage/bone protection
Allergic asthma	Herbal heteroglycans	OVA-induced asthma	Th2 → Th1/Treg shift; ↓ airway inflammation
Psoriasis-like inflammation	β-glucans, pectins	Imiquimod model	↓ IL-17 axis; keratinocyte inflammation
Metabolic / inflammaging	Arabinose-rich polysaccharides	High-fat / aged models	↓ macrophage inflammation; antioxidant support

Table 4. Representative applications of plant polysaccharides across chronic inflammatory diseases, with models and principal mechanisms. Across conditions, the unifying theme is restoration of immune balance rather than blanket suppression.

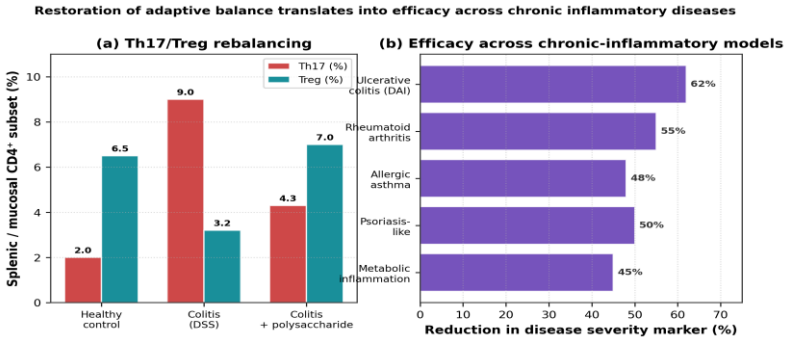

Figure 6. From adaptive rebalancing to clinical benefit. (a) Restoration of the Th17/Treg balance: colitis elevates Th17 and depletes Treg, and polysaccharide treatment reverses both. (b) Representative reductions in disease-severity markers across chronic-inflammatory models. Values are representative figures compiled from the cited preclinical literature.

7. CHALLENGES AND FUTURE PERSPECTIVES

Several obstacles must be resolved for the field to mature. Structural standardisation: polysaccharides are heterogeneous, batch-variable natural products, and because activity is exquisitely structure-dependent, reproducibility demands full physicochemical characterisation (molecular weight, linkage, branching, purity) and standardised, well-defined preparations—a requirement too often unmet. [4,8] Bioavailability and delivery: most polysaccharides are large and poorly absorbed, so systemic effects rely partly on the microbiota route; for targets beyond the gut, delivery strategies (nanoparticles, structural tailoring, fragments of optimal molecular weight) are needed. Context-dependence and safety: the bidirectional nature of immunomodulation is therapeutically valuable but demands careful dose- and disease-specific characterisation to ensure a polysaccharide resolves rather than aggravates inflammation. Mechanistic and clinical gaps: much evidence is preclinical, receptor engagement is often inferred rather than demonstrated, and rigorous randomised trials with immunological biomarkers are scarce. [1,3,7] Promising directions include microbiota-informed "precision-prebiotic" design, structure-guided fragmentation to isolate the active pharmacophore, combination with conventional therapy to lower immunosuppressive drug doses, and multi-omics dissection of the polysaccharide–microbiota–immune network.

8. CONCLUSION

Plant polysaccharides occupy an unusual and valuable niche in immunopharmacology: rather than blocking a single mediator, they act as homeostatic immunomodulators across the entire innate-to-adaptive continuum. Recognised by pattern-recognition receptors on macrophages and dendritic cells, they reprogramme innate signalling and macrophage polarisation; through dendritic-cell bridging they rebalance the Th1/Th2 and Th17/Treg axes that drive chronic inflammation; and, for orally delivered agents, they act indirectly through microbiota-derived short-chain fatty acids that induce regulatory T cells and restore mucosal tolerance. Their activity is governed by well-defined structure–activity relationships and is characteristically bidirectional and context-dependent—stimulating when immunity is deficient and restraining when it is excessive—which is exactly the profile required to treat chronic inflammatory disease. Across preclinical models this translates into rebalanced immune cell populations and 45–62% reductions in disease severity. Realising this promise clinically now depends less on discovering new activities than on structural standardisation, rational delivery, and biomarker-guided clinical validation.

Declarations

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Author contributions: Conceptualisation, A.O.; investigation and writing—original draft, A.O. and A.T.; visualisation, A.T.; writing—review and editing, A.T.; supervision, A.O. All authors approved the final manuscript.

Data availability: No new primary data were generated; all data discussed are available in the cited references.

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