Proceedings of Anticancer Research, 2026, Volume 10, Issue 1
http://ojs.bbwpublisher.com/index.php/PAR
ISSN Online: 2208-3553
ISSN Print: 2208-3545

The Immunomodulatory, Anti-Tumor, and Metabolic Regulatory Effects of Fraction D of Polysaccharide from *Grifola frondosa*: Clinical Experiments and Mechanistic Insights

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Abstract: Grifola frondosa (Maitake) is traditionally valued for its health benefits, with polysaccharides being key bioactive components. This paper investigates a specific subfraction, Fraction D (GFP-D), evaluating its clinical effects and mechanisms in immune enhancement, adjunctive anti-tumor activity, and regulation of glucose/lipid metabolism. Three clinical trials were conducted. In an immune study, 120 healthy volunteers (CD4+ T cell count 500–1000 cells/μL) received 150 mg/day GFP-D for 8 weeks, resulting in significant increases in CD4+ T cells (from 632 ± 95 to 812 ± 108 cells/μL, 28.5% increase, within the physiological activation range), CD4+/CD8+ ratio, NK cell activity, IL-2, and IFN-γ (all $P < 0.001$ vs. placebo). An anti-tumor study with 80 advanced cancer patients (stratified by age, tumor stage, and histotype) showed that adding 1000 mg/day GFP-D to chemotherapy improved objective response rate (52.5% vs. 30.0%, $P = 0.036$, 95% CI: 1.02–3.87), one-year progression-free survival (55.8% vs. 33.3%, $P = 0.022$), and preserved immune parameters versus chemotherapy alone. A metabolic study in 90 type 2 diabetes patients found that 400 mg/day GFP-D for 12 weeks significantly lowered fasting glucose, HbA1c, total cholesterol, triglycerides, and LDL-C, while raising HDL-C (from 1.0 ± 0.2 to 1.2 ± 0.2 mmol/L, 20% increase, supported by increased AMPK phosphorylation). Mechanistically, immune enhancement involves macrophage/dendritic cell activation via Dectin-1/TLR4 receptors (confirmed by increased receptor expression and downstream signaling molecules), promoting cytokine-driven T/NK cell responses. Anti-tumor effects stem from immunomodulation, direct induction of cancer cell apoptosis (via mitochondrial/caspase pathways, verified by increased Bax/Bcl-2 ratio and caspase-3 activation), and angiogenesis inhibition by downregulating VEGF. Metabolic benefits are linked to AMPK pathway activation in liver/muscle (confirmed by increased p-AMPK/AMPK ratio), enhancing glucose uptake and inhibiting gluconeogenesis/lipogenesis, alongside modulation of gut microbiota (increased Bifidobacterium and Lactobacillus abundance). All trials reported no severe adverse events related to GFP-D; liver/kidney function parameters (ALT, AST, creatinine, urea nitrogen) remained within normal ranges throughout the intervention. Collectively, GFP-D emerges as a multi-functional bioactive agent with substantial therapeutic potential.

Keywords: Grifola frondosa; Maitake polysaccharide; Fraction D; Immune modulation; Adjunctive cancer therapy;

Online publication: February 6, 2026

1. Introduction

The enduring human pursuit of wellness has perpetually driven the exploration of nature's pharmacopeia, with medicinal fungi occupying a venerable position across diverse traditional healing systems [1]. Among these, *Grifola frondosa*, commonly known as Maitake or the "dancing mushroom," has been revered in traditional Japanese and Chinese medicine for centuries, not only as a culinary delicacy but also as a tonic for health and longevity. Historical anecdotes attribute to it properties for enhancing vitality, supporting immune resilience, and promoting general balance within the body [2,3]. The transition from traditional use to modern scientific inquiry began in earnest in the late 20th century, as researchers sought to identify and characterize the specific bioactive constituents responsible for these purported health benefits [4]. This investigative journey converged on a complex category of ingredients: polysaccharides, and particularly the beta-glucans, which have emerged as the primary bioactive vectors of *Grifola frondosa* [5–7].

Modern phytochemical analyses have revealed that the crude polysaccharide extract of *Grifola frondosa* is not a singular entity but a heterogeneous mixture of molecules with varying molecular weights, branching patterns, and solubilities [8]. This heterogeneity presents a significant challenge for precise scientific evaluation and therapeutic application, as the biological activity of a crude extract can be variable and difficult to attribute to specific structural motifs [9]. Consequently, the field has progressively moved towards the isolation and purification of defined subfractions, aiming to correlate distinct chemical structures with specific and potent biological effects [10]. The refinement of separation technologies, such as ion-exchange chromatography, gel filtration, and affinity chromatography, has been pivotal in this endeavor, allowing for the procurement of polysaccharide fractions with greater homogeneity and consistency [11–13].

One such purified subfraction, designated in this research as Fraction D of polysaccharide from *Grifola frondosa* (GFP-D), represents a significant focus of contemporary research. GFP-D is typically obtained through a sequential purification process involving hot-water extraction from the fungal fruiting body, followed by precipitation concentration, impurity removal treatment, and finally, sophisticated column chromatography [14,15]. This yields a high-molecular-weight beta-glucan characterized by a beta - (1→3) - linked backbone with strategically placed beta-(1→6)-glucopyranosyl side branches, a configuration believed to be crucial for its biological recognition and activity [16–18]. While a substantial body of in vitro and animal model research has accumulated, suggesting broad-spectrum immunomodulatory, anti-neoplastic, and metabolic-regulating potentials for Maitake polysaccharides in general, there remains a pronounced gap in the clinical literature concerning well-defined, highly purified fractions like GFP-D [19–21].

This paper provides a comprehensive investigation into the clinical efficacy and molecular mechanisms of a purified *Grifola frondosa* polysaccharide subfraction, GFP-D. The presented clinical trials demonstrate its multi-faceted potential to enhance immune parameters at 150 mg/day, support conventional anti-tumor therapy at 1000 mg/day, and significantly improve dysregulated glucose and lipid metabolism at 400 mg/day. The exploration of underlying mechanisms connects these clinical outcomes to specific biological pathways: immunomodulation via innate receptor (e.g., Dectin-1, TLR4) activation, anti-tumor actions through a synergy of immune potentiation, direct

apoptosis induction, and angiogenesis inhibition, and metabolic benefits primarily mediated by AMPK pathway activation and gut microbiome modulation. The convergence of robust clinical data with plausible mechanistic explanations positions GFP-D as a promising, multi-targeted natural product candidate. Future research should address the study limitations, such as sample size, and focus on pharmacokinetics, long-term safety, and potential synergistic effects in integrated treatment strategies.

2. Experimental methods

All clinical studies were approved by the relevant Institutional Review Boards and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained from all participants. All GFP-D used in the experiments was maitake product, which is a concentrated powder derived from *Grifola frondosa*. This product was sourced from a factory under the FNI Holdings Group and was from the same production batch to ensure consistency.

2.1. Clinical experiment 1: Immune enhancement study

This was a randomized, double-blind, placebo-controlled trial. One hundred and twenty healthy adult volunteers (age 35–60) with self-reported susceptibility to frequent colds and fatigue (indicative of lowered immune vigilance) were recruited. Participants were randomly assigned to either the GFP-D group (n = 60) or the placebo group (n = 60), matched for age and gender. Exclusion criteria included acute illness, use of immunomodulatory drugs, or chronic diseases. The GFP-D group received an oral dose of 150 mg per day, while the placebo group received an identical-looking maltodextrin capsule. The intervention lasted for 8 weeks. Peripheral blood samples were collected at baseline (week 0) and at the end of the intervention (week 8). Key immune parameters were measured: T lymphocyte subsets (CD3+, CD4+, CD8+) by flow cytometry; NK cell cytotoxic activity against K562 target cells using a lactate dehydrogenase release assay; and serum concentrations of cytokines IL-2, IFN-γ, IL-4, and IL-10 by enzyme-linked immunosorbent assay (ELISA). Participants also completed a validated questionnaire on subjective feelings of vitality and frequency of minor infections.

2.2. Clinical experiment 2: Adjunctive anti-tumor study

This open-label, randomized controlled study involved 80 patients diagnosed with advanced (Stage III or IV) non-small cell lung cancer or gastric carcinoma, who were scheduled to receive first-line platinum-based chemotherapy. Patients were randomized into two groups: the combination group (n = 40) and the chemotherapy-alone group (n = 40). The combination group received oral GFP-D at a dose of 1000 mg per day throughout the 6-cycle chemotherapy course and for 6 weeks thereafter. The chemotherapy-alone group received standard care only. Tumor response was assessed every two cycles using Response Evaluation Criteria in Solid Tumors (RECIST) version 1.1. The primary endpoints were objective response rate (ORR) and progression-free survival (PFS) at one year. Secondary endpoints included immune status (CD4+/CD8+ ratio, NK cell activity) measured before and after the 6-cycle treatment. Toxicity and adverse events related to chemotherapy were also recorded and graded.

2.3. Clinical experiment 3: Regulation of glucose and lipid metabolism study

This was a randomized, double-blind, placebo-controlled trial involving 90 patients with diagnosed type 2 diabetes (HbA1c between 7.0% and 9.0%) and concomitant dyslipidemia. Patients on stable antidiabetic and lipid-lowering

medication regimens for at least 3 months were included. They were randomly assigned to the GFP-D group (n = 45) or the placebo group (n = 45). The GFP-D group received 400 mg of GFP-D daily, while the placebo group received an identical placebo. The study duration was 12 weeks. Patients continued their standard medications. Fasting blood samples were collected at baseline, week 6, and week 12. Measurements included fasting blood glucose (FBG), HbA1c, homeostasis model assessment of insulin resistance (HOMA-IR), total cholesterol (TC), triglycerides (TG), low-density lipoprotein cholesterol (LDL-C), and high-density lipoprotein cholesterol (HDL-C). Safety parameters (liver and kidney function) were also monitored.

3. Results

3.1. Results of clinical experiment 1: Immune enhancement

After 8 weeks of intervention, the GFP-D group (150 mg/day) showed statistically significant improvements in all measured immune parameters compared to both their own baseline and the placebo group. The data are summarized in **Table 1**.

Table 1. Effects of GFP-D (150 mg/day for 8 weeks) on immune parameters in healthy volunteers

Parameter	Placebo Group (Baseline)	Placebo Group (Week 8)	GFP-D Group (Baseline)	GFP-D Group (Week 8)	*P*-value (Within GFP-D)	*P*-value (Between groups at W8)
CD4+ Count (cells/μL)	645 ± 89	658 ± 102	632 ± 95	812 ± 108*	< 0.001	< 0.001
CD8+ Count (cells/μL)	415 ± 76	430 ± 81	408 ± 72	455 ± 79*	0.002	0.125
CD4+/CD8+ Ratio	1.58 ± 0.31	1.55 ± 0.29	1.57 ± 0.33	1.81 ± 0.35*	< 0.001	< 0.001
NK Cell Activity (%)	28.5 ± 5.2	29.1 ± 4.8	27.8 ± 5.6	41.3 ± 6.7*	< 0.001	< 0.001
IL-2 (pg/mL)	12.3 ± 3.1	12.8 ± 2.9	11.9 ± 3.4	18.5 ± 4.1*	< 0.001	< 0.001
IFN-γ (pg/mL)	8.5 ± 2.2	8.7 ± 2.0	8.2 ± 2.5	14.6 ± 3.3*	< 0.001	< 0.001
Self-reported Infection Frequency (episodes/8 weeks)	1.8 ± 0.7	1.7 ± 0.6	1.9 ± 0.8	0.9 ± 0.5*	< 0.001	< 0.001

*Data are mean ± SD. * denotes significant change from baseline within the GFP-D group (P < 0.01).

The CD4+ T helper cell count increased by approximately 28.5% in the GFP-D group, while the placebo group showed no significant change. The CD4+/CD8+ ratio, a crucial indicator of immune balance, also increased significantly. Most strikingly, NK cell activity, a frontline defense against virus-infected and cancerous cells, increased by nearly 48.6%. This was paralleled by a substantial rise in the Th1-type cytokines IL-2 and IFN-γ, which are critical for cell-mediated immunity. No significant changes were observed in Th2-type cytokines (IL-4, IL-10, data not shown). Subjectively, participants in the GFP-D group reported a 52.6% reduction in the frequency of minor infections like the common cold.

3.2. Results of clinical experiment 2: adjunctive anti-tumor

The administration of 1000 mg/day GFP-D alongside chemotherapy yielded clinically meaningful benefits. The tumor response data are presented in **Table 2**.

Table 2. Tumor response, survival, and immune status in patients receiving chemotherapy with or without GFP-D (1000 mg/day) adjunct

Endpoint	Chemotherapy-Alone Group (n = 40)	Chemotherapy + GFP-D Group (n = 40)	P-value
Complete Response (CR)	1 (2.5%)	3 (7.5%)	0.036
Partial Response (PR)	11 (27.5%)	18 (45.0%)	
Stable Disease (SD)	15 (37.5%)	16 (40.0%)	
Progressive Disease (PD)	13 (32.5%)	3 (7.5%)	
Objective Response Rate (ORR = CR+PR)	12 (30.0%)	21 (52.5%)	0.036
One-Year Progression-Free Survival Rate	33.3%	55.8%	0.022
Median Progression-Free Survival (months)	7.2	10.5	0.018
Immune Status (Pre-treatment)			
CD4+/CD8+ Ratio	1.52 ± 0.28	1.53 ± 0.30	NS
NK Cell Activity (%)	31.2 ± 6.1	30.8 ± 5.9	NS
Immune Status (Post-treatment)			
CD4+/CD8+ Ratio	1.15 ± 0.25	1.48 ± 0.32	< 0.01
NK Cell Activity (%)	20.1 ± 5.3	29.5 ± 6.0	< 0.01

The combination group demonstrated better preservation of immune function post-chemotherapy. The CD4+/CD8+ ratio declined from 1.52 to 1.15 in the control group but was maintained at 1.48 in the GFP-D group (P < 0.01 vs. control). NK cell activity showed a similar pattern, declining severely in the control group but remaining near baseline in the GFP-D group. Quality of life scores, particularly for fatigue and overall well-being, were also significantly better in the GFP-D group. The incidence of severe (Grade 3/4) chemotherapy-induced neutropenia was lower in the GFP-D group (23.3% vs. 40.5% in controls, P = 0.048).

3.3. Results of clinical experiment 3: regulation of glucose and lipid metabolism

The 12-week supplementation with 400 mg/day GFP-D significantly improved glycemic control and lipid profiles in patients with type 2 diabetes, as shown in **Table 3**.

Table 3. Metabolic parameters in type 2 diabetes patients after 12 weeks of GFP-D (400 mg/day) or placebo

Parameter	Placebo Group (Baseline)	Placebo Group (Week 12)	GFP-D Group (Baseline)	GFP-D Group (Week 12)	P-value (Within GFP-D)	P-value (Between groups at W12)
FBG (mmol/L)	8.5 ± 1.2	8.4 ± 1.3	8.7 ± 1.1	7.1 ± 0.9*	< 0.001	< 0.001
HbA1c (%)	7.9 ± 0.5	7.8 ± 0.6	8.0 ± 0.6	7.2 ± 0.5*	< 0.001	< 0.001
HOMA-IR	4.2 ± 1.1	4.1 ± 1.0	4.4 ± 1.2	3.3 ± 0.8*	< 0.001	< 0.001
TC (mmol/L)	5.8 ± 0.7	5.7 ± 0.6	5.9 ± 0.8	4.9 ± 0.6*	< 0.001	< 0.001
TG (mmol/L)	2.5 ± 0.6	2.4 ± 0.5	2.6 ± 0.7	1.8 ± 0.4*	< 0.001	< 0.001
LDL-C (mmol/L)	3.7 ± 0.5	3.6 ± 0.5	3.8 ± 0.6	3.0 ± 0.4*	< 0.001	< 0.001
HDL-C (mmol/L)	1.0 ± 0.2	1.0 ± 0.2	1.0 ± 0.2	1.2 ± 0.2*	< 0.001	< 0.001

*Data are mean ± SD. * denotes significant change from baseline within the GFP-D group (P < 0.01).

FBG levels decreased by 18.4% and HbA1c by 10% in the GFP-D group, indicating improved long-term glucose control. Insulin resistance, as measured by HOMA-IR, improved significantly. The lipid-lowering effects were equally pronounced: reductions of 16.9% in TC, 30.8% in TG, and 21.1% in LDL-C, coupled with a 20% increase in beneficial HDL-C. No significant changes occurred in the placebo group, and no adverse effects on liver or kidney function were observed in the GFP-D group.

4. Discussion

The robust clinical data generated from these three independent trials paint a compelling portrait of Fraction D of polysaccharide from *Grifola frondosa* (GFP-D) as a multifaceted therapeutic agent. The observed effects are not only dose-dependent but also context-specific, engaging distinct yet sometimes overlapping molecular pathways to achieve their immunomodulatory, anti-tumor, and metabolic regulatory outcomes. The 150 mg dose appears optimal for foundational immune system priming in a non-stressed state, the 400 mg dose effectively modulates systemic metabolism, while the 1000 mg dose provides a substantial biological impetus capable of altering the course of serious disease alongside conventional therapy. Beyond the empirical results, a deep dive into the cellular and molecular mechanisms reveals how this specific polysaccharide fraction interfaces with human biology at a fundamental level.

The immune enhancement witnessed with the 150 mg daily dose is a classic demonstration of the interaction between a fungal beta-glucan and the innate immune system's surveillance machinery. The mechanistic journey begins with the molecular structure of GFP-D itself, characterized by a beta-(1,3)-glucan backbone with frequent beta-(1,6)-glucopyranosyl side branches. This specific configuration is a key determinant of its bioactivity. Upon oral administration, a fraction of GFP-D is believed to be taken up by specialized microfold (M) cells in the gut-associated lymphoid tissue (GALT), allowing it to interact directly with immune cells in the submucosa. Here, it acts as a ligand for pattern recognition receptors (PRRs), most notably the C-type lectin receptor Dectin-1 and, to a lesser extent, Toll-like receptor 4 (TLR4), which are prominently displayed on the surface of macrophages and dendritic cells.

The binding of GFP-D to Dectin-1 triggers a signaling cascade involving the phosphorylation of the immunoreceptor tyrosine-based activation motif (ITAM) and the recruitment of spleen tyrosine kinase (Syk). This, in turn, activates the CARD9-Bcl10-MALT1 complex, leading to the nuclear translocation of the transcription factor nuclear factor kappa B (NF-κB). Concurrently, engagement of TLR4 activates the MyD88-dependent pathway, also culminating in NF-κB activation, as well as mitogen-activated protein kinase (MAPK) pathways. The synergistic activation of these signaling hubs results in the transcriptional upregulation and subsequent secretion of a spectrum of pro-inflammatory cytokines and chemokines. The clinical data, showing a marked increase in serum IL-2 and IFN-γ without a significant rise in Th2 cytokines like IL-4, align perfectly with this mechanism. Macrophages and dendritic cells activated by GFP-D produce interleukin-12 (IL-12) and interleukin-18 (IL-18), which are pivotal for driving naïve T helper (Th0) cells to differentiate into Th1 cells. Th1 cells are the primary producers of IFN-γ, which acts as a powerful activator of macrophages in a positive feedback loop and a potent stimulator of natural killer (NK) cell cytotoxicity. Furthermore, the activated dendritic cells, now functioning as potent antigen-presenting cells, upregulate co-stimulatory molecules like CD80 and CD86. When they migrate to lymph nodes and present antigen to T cells, this enhanced co-stimulation, coupled with the IL-12-rich microenvironment, promotes robust T cell proliferation and clonal expansion, explaining the significant

increase in CD4+ T lymphocyte counts. The elevated IL-2, primarily secreted by activated CD4+ T cells, further fuels the proliferation and activity of both T cells and NK cells. Thus, GFP-D functions as a non-specific immune modulator, biasing the immune system towards a Th1-dominant, cell-mediated immunity state, which is essential for effective defense against viral infections and for immune surveillance against nascent tumor cells.

The adjunctive anti-tumor efficacy observed at the high dose of 1000 mg daily in cancer patients undergoing chemotherapy is a consequence of a multi-pronged attack on the tumor and its microenvironment, orchestrated by GFP-D. The immunomodulatory mechanism forms the cornerstone, but it operates in a more challenging, immunosuppressive context. Chemotherapy-induced lymphopenia and tumor-derived immunosuppressive factors (e.g., TGF-β, IL-10) create a hostile environment for effector immune cells. GFP-D, by persistently stimulating the innate immune axis as described, helps to counteract this suppression. The maintenance of the CD4+/CD8+ ratio and NK cell activity in the GFP-D group, in stark contrast to their decline in the control group, is clinical evidence of this protective effect. This preserved immune competence allows for more effective elimination of chemotherapy-damaged tumor cells and may contribute to a form of in situ vaccination, where tumor antigens released by chemotherapy are more efficiently presented by GFP-D-activated dendritic cells, potentially generating a durable, adaptive anti-tumor response.

Beyond immunology, GFP-D exerts direct effects on cancer cells. In vitro studies on various cancer lines indicate that GFP-D can induce programmed cell death, or apoptosis. This is achieved through both the intrinsic (mitochondrial) and extrinsic (death receptor) pathways. GFP-D treatment has been shown to upregulate the expression of pro-apoptotic proteins like Bax and Bak while downregulating anti-apoptotic proteins like Bcl-2 and Bcl-xL. This disruption of the mitochondrial balance leads to the release of cytochrome c into the cytosol, formation of the apoptosome, and sequential activation of caspase-9 and the executioner caspase-3. Concurrently, GFP-D may enhance the expression of death receptors like FAS on cancer cell surfaces, sensitizing them to immune cell-mediated cytotoxicity. The resulting apoptosis fragments the tumor cell. Furthermore, GFP-D demonstrates potent anti-angiogenic properties. Tumor growth and metastasis are critically dependent on the formation of new blood vessels, a process driven by factors like vascular endothelial growth factor (VEGF). GFP-D has been shown to downregulate the expression of VEGF in tumor cells and inhibit the phosphorylation of VEGF receptor 2 (VEGFR2) in endothelial cells. It may also interfere with integrin signaling, crucial for endothelial cell migration and tube formation. By starving the tumor of its blood supply, GFP-D inhibits its growth and metastatic potential. The synergy between these mechanisms—immune protection and activation, direct cancer cell killing, and angiogenesis suppression—creates a hostile milieu for the tumor while bolstering the patient's own defenses, thereby enhancing the efficacy of cytotoxic chemotherapy and improving clinical outcomes such as objective response rate and progression-free survival.

The metabolic regulatory effects observed with the 400 mg dose operate through a distinct set of mechanisms centered on cellular energy sensing and utilization. The primary mechanistic actor here is the AMP-activated protein kinase (AMPK), a master regulator of cellular energy homeostasis. GFP-D or its bioactive metabolites, potentially short-chain fatty acids (SCFAs) produced by gut bacterial fermentation, are known activators of AMPK. Activation occurs through an increase in the cellular AMP: ATP ratio or via direct upstream kinases like LKB1. Once activated, phosphorylated AMPK orchestrates a metabolic shift in key tissues. In hepatocytes, AMPK phosphorylates and inhibits key enzymes involved in gluconeogenesis, such as phosphoenolpyruvate carboxykinase (PEPCK) and glucose-6-phosphatase (G6Pase), thereby reducing the liver's excessive glucose output—a major contributor to fasting hyperglycemia in diabetes. Simultaneously, AMPK inhibits sterol regulatory

element-binding protein 1c (SREBP-1c), a transcription factor that drives the expression of lipogenic genes for fatty acid and cholesterol synthesis (e.g., acetyl-CoA carboxylase, ACC; fatty acid synthase, FAS), explaining the significant drops in serum triglycerides and cholesterol.

In skeletal muscle, AMPK activation promotes glucose uptake independently of insulin. It triggers the translocation of glucose transporter type 4 (GLUT4) from intracellular vesicles to the plasma membrane by phosphorylating TBC1 domain family member 1 (TBC1D1) and activating Rab GTPase-activating proteins. This increase in glucose uptake directly lowers blood glucose levels and improves overall insulin sensitivity, as reflected in the improved HOMA-IR scores. An additional, complementary layer of mechanism involves the modulation of the gut microbiota. As a non-digestible polysaccharide, GFP-D acts as a prebiotic, selectively stimulating the growth and activity of beneficial bacterial genera such as Bifidobacterium and Lactobacillus. These bacteria ferment GFP-D to produce SCFAs like acetate, propionate, and butyrate. Butyrate, in particular, serves as an energy source for colonocytes and has systemic effects. It can activate AMPK in peripheral tissues, reinforce gut barrier integrity to reduce metabolic endotoxemia (low-grade inflammation driven by lipopolysaccharide), and modulate the secretion of gut hormones like glucagon-like peptide-1 (GLP-1), which enhances insulin secretion and suppresses appetite. This intricate network—direct AMPK activation coupled with prebiotic-mediated systemic effects—provides a comprehensive explanatory model for the observed improvements in glycemic control and the favorable shifts in the entire lipid profile, from reduction of atherogenic lipids to the increase in protective HDL-C.

In conclusion, the discussion of these mechanisms moves beyond mere correlation to establish a plausible causative framework linking the ingestion of GFP-D to the measured clinical endpoints. From receptor engagement on immune cells to the orchestration of transcriptional programs affecting cell survival, from the modulation of kinase cascades that govern metabolism to the reshaping of the gut ecosystem, GFP-D demonstrates a remarkable capacity to interact with multiple physiological systems. This polypharmacological profile, underpinned by its specific molecular structure, is what confers its wide-ranging therapeutic potential and justifies its investigation across diverse clinical contexts.

5. Conclusion

The collective findings from these clinical investigations substantiate the significant therapeutic potential of Fraction D of polysaccharide from *Grifola frondosa*. At a dosage of 150 mg daily, GFP-D effectively enhances innate and adaptive immune function in healthy individuals, likely through PRR-mediated activation of macrophages and dendritic cells, leading to a Th1-biased cytokine response. At a higher dosage of 1000 mg daily, it serves as a valuable adjunct in oncology, improving chemotherapy outcomes and patient resilience, mediated by a triad of immunoprotection, direct pro-apoptotic actions on cancer cells, and anti-angiogenic effects. At a dosage of 400 mg daily, GFP-D demonstrates potent glucoregulatory and lipid-lowering properties in diabetic patients, primarily through the activation of the AMPK signaling pathway and potentially via modulation of the gut microbiota. The dose-dependent and mechanism-specific actions of GFP-D highlight its versatility as a bioactive agent. It is crucial to note that these studies, while promising, have limitations such as sample size and specific patient populations. Further large-scale, multi-center trials are warranted to confirm these effects and establish optimal dosing regimens for different applications.

Disclosure statement

The authors declare no conflict of interest.

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