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Review Article

Ganoderma applanatum Polysaccharides in Obesity-Associated Dysglycaemia and Liver Injury: Gut–Liver Mechanisms and Translational Gaps

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Abstract

Obesity-associated dysglycaemia and metabolic dysfunction-associated steatotic liver disease (MASLD) arise from interacting inflammatory, oxidative, lipotoxic, and gut-liver mechanisms. *Ganoderma applanatum* polysaccharides are an under-characterized candidate adjunct, but their translational relevance remains uncertain. The study aims to narratively review mechanistic and preclinical evidence linking *G. applanatum* polysaccharides with obesity-associated dysglycaemia and liver injury and to identify key translational gaps.

A structured narrative review of PubMed/MEDLINE and Google Scholar literature, complemented by backward citation screening, was undertaken. Evidence on preparation chemistry, structural features, metabolic and hepatic outcomes, gut-liver mechanisms, and clinical translation was synthesized qualitatively.

Available evidence is limited and predominantly preclinical, with MACAPOS-2 obese rat studies providing the main *G. applanatum* data. Defined water-soluble preparations have been associated with improved glucose tolerance, insulin responsiveness, dyslipidaemia, oxidative stress markers, aminotransferases, and histologic liver injury. A biologically coherent explanation is gut-centered modulation involving microbiota remodelling, microbial metabolite signalling, barrier reinforcement, and downstream attenuation of endotoxemia-linked hepatic inflammatory and oxidative stress. However, the evidence base is constrained by preparation heterogeneity, incomplete structural characterization, modest sample sizes, limited direct measurement of gut-liver pathway engagement, and heavy reliance on a single research network.

G. applanatum polysaccharides should currently be viewed as preparation-specific, biologically plausible immunometabolic modulators rather than clinically ready therapies. Progress requires structurally defined preparations, independent replication, mechanism-anchored biomarkers, and adequately powered human studies in carefully phenotyped populations.

Keywords: *Ganoderma applanatum*; polysaccharides; obesity; insulin resistance; MASLD; gut-liver axis

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Introduction

Obesity has become a dominant driver of global morbidity, with sustained population-level increases in body-mass index documented across regions (1). Beyond epidemiologic scale, obesity imposes substantial direct and indirect economic costs through chronic disease complications and health-system utilization (2). A clinically important feature of obesity is the frequent co-evolution of dysglycaemia and liver injury, reflecting shared upstream mechanisms in adipose tissue, liver, and the intestinal ecosystem. Obesity is increasingly conceptualized as a chronic, low-grade inflammatory state that alters immune and adipokine signalling and contributes to insulin resistance (3). Oxidative stress provides an additional bridge linking adipose expansion, insulin resistance, and end-organ vulnerability (4). In parallel, hepatic lipid accumulation and lipotoxic signalling can amplify hepatic insulin resistance and sensitise the liver to injury, progressing from simple steatosis toward inflammatory phenotypes (5, 6). The gut-liver axis further integrates these processes, as altered microbiome function, barrier integrity, and microbial metabolites can modulate both hepatic inflammation and systemic glucose handling (7). Because several cited mechanistic and clinical studies predate the 2023 nomenclature consensus, the terms NAFLD and NASH are retained when reproducing original study language, but are interpreted here within the contemporary MASLD and MASH framework unless diagnostic differences are specifically relevant (8).

Despite major advances in obesity and diabetes therapeutics, residual cardiometabolic and hepatic risk remains common, and long-term management can be limited by tolerability, adherence, and access. These constraints motivate interest in adjunct approaches capable of engaging multiple pathogenic layers. Polysaccharides from edible and medicinal mushrooms are candidates of interest because they may act as complex biological modifiers, often through fermentative and immunomodulatory effects that reshape microbiome-derived metabolites and inflammatory tone. Interpretation, however, is complicated by the fact that ‘polysaccharides’ in the literature frequently represent heterogeneous, preparation-dependent mixtures whose biological effects depend on molecular structure and co-extracted constituents (9, 10).

Within *Ganoderma* research, *G. lucidum* has the largest evidence base, yet clinical translation has been inconsistent. A randomized, double-blind, placebo-controlled trial in adults with type 2 diabetes and metabolic syndrome found no meaningful improvement in hyperglycaemia or cardiovascular risk factors after 16 weeks of *G. lucidum* (11). Against this backdrop, *G. applanatum* represents an understudied species with emerging preclinical evidence. In the MACAPOS-2 diet-induced obese rat model, water-soluble *G. applanatum* polysaccharides have been associated with improvements in metabolic and hepatic injury markers (12, 13). This review integrates mechanistic frameworks relevant to obesity-linked dysglycaemia and liver injury and evaluates the currently available evidence for *G. applanatum* polysaccharides, while recognizing that the obesity-linked preclinical literature is presently centered on two MACAPOS-2 reports from the same research network and lacks independent replication (12, 13).

Methods

Review design and rationale

This review was conducted as a narrative review. A narrative design was selected because the literature specifically addressing *G. applanatum* polysaccharides in obesity-associated dysglycaemia and MASLD is sparse, predominantly preclinical, and heterogeneous with respect to preparation chemistry, experimental models, doses, and outcome definitions. Under these conditions, qualitative narrative synthesis was considered more appropriate than formal meta-analysis. The reporting quality of the review was checked against the SANRA criteria (14). Protocol registration was not undertaken because this article was not designed as a systematic review or meta-analysis, and a PRISMA flow diagram was therefore not pursued.

Search strategy

PubMed/MEDLINE and Google Scholar were searched from database inception through 28 February 2026, and reference lists of relevant articles were manually screened to identify additional studies. The search combined organism/exposure terms (“Ganoderma applanatum”, “Ganoderma lucidum”, “Ganoderma polysaccharide*”, “beta-glucan*”, “mushroom polysaccharide*”) with phenotype/mechanism terms (“obesity”, “insulin resistance”, “dysglycaemia”, “MASLD”, “NAFLD”, “MASH”, “NASH”, “gut-liver axis”, “oxidative stress”, “endotoxemia”, “microbiota”, and “liver injury”). Search strings were adapted to database syntax. Backward citation screening of eligible articles and authoritative reviews was also performed to identify foundational mechanistic papers and earlier MACAPOS-2 reports.

Eligibility criteria and study selection

Eligibility was guided by a modified PICOS framework. The population/model domain included humans or experimental models relevant to obesity, insulin resistance, dysglycaemia, hepatic steatosis/injury, or gut-liver dysfunction. The intervention/exposure domain included *G. applanatum* polysaccharides and, when needed for a mechanistic or translational context, other *Ganoderma* polysaccharide preparations. Comparators included untreated or obese controls, placebo groups, or other experimental comparators where applicable. Outcomes of interest included glycaemic, lipid, hepatic, oxidative, inflammatory, microbiome, barrier, or histologic endpoints. Study designs eligible for inclusion comprised primary preclinical studies, clinical trials, mechanistic studies, and authoritative reviews directly relevant to the review question. Studies were excluded if they were clearly unrelated to *Ganoderma* polysaccharides, did not address metabolic or hepatic outcomes/mechanisms of interest, or lacked sufficient methodological description to identify the tested preparation. Search results were screened by title and abstract, followed by full-text review of potentially relevant papers. Final inclusion and emphasis were determined by discussion within the author group. Because several source studies predate the current nomenclature, NAFLD/NASH terms are reported as originally published but interpreted within the contemporary MASLD/MASH framework where appropriate (8).

Data extraction, critical appraisal, and synthesis

For key primary studies, data were extracted on species/preparation, extraction approach, structural characterization, experimental model or population, dose and duration, metabolic endpoints, hepatic endpoints, and mechanistic readouts. No meta-analysis was attempted because the evidence base is small and heterogeneous, with substantial between-study differences in preparation definition, dose range, model design, and outcome measurement. Instead, findings were synthesized narratively with explicit attention to preparation specificity and translational relevance. The methodological quality of the principal preclinical studies was appraised qualitatively using domains emphasized in animal-research guidance, including randomization, blinding, completeness of outcome reporting, sample-size justification, and standardization of histologic assessment (15, 16).

Pathobiology: why dysglycaemia and liver injury travel together in obesity

Obesity-associated dysglycaemia is not adequately explained as a simple imbalance between caloric intake and expenditure. Rather, it represents an **immunometabolic state** in which nutrient excess, adipose tissue expansion, and ectopic lipid deposition activate coordinated inflammatory and stress-response programs that disrupt insulin signalling across multiple organs. In this framework, adipose tissue is not merely a storage depot but an active endocrine and immune organ that can amplify systemic metabolic risk. Adipose inflammation—characterized by altered immune cell composition, increased pro-inflammatory cytokine tone, and impaired adipokine signalling—has been positioned as a key contributor to obesity-related insulin resistance, with downstream effects on glycaemic control and cardiometabolic risk (3).

A central biological bridge between obesity and multisystem metabolic injury is **oxidative stress**, which both reflects and reinforces immunometabolic dysfunction. Seminal mechanistic work demonstrated that oxidative stress rises early in obesity, is prominent within accumulated fat, and is linked to dysregulated adipocytokine profiles and metabolic syndrome phenotypes, including glucose intolerance and hepatic steatosis (4). This oxidative milieu promotes insulin resistance through multiple mechanisms—impairing insulin receptor signalling cascades, disrupting mitochondrial function, and sustaining inflammatory transcription programs—thereby creating a self-reinforcing loop in which metabolic stress and immune activation become mutually amplifying.

The liver is uniquely positioned at the center of these processes, which explains why dysglycaemia and liver injury frequently co-evolve. In obesity, increased delivery of free fatty acids to the liver, coupled with altered *de novo* lipogenesis and impaired fatty-acid oxidation, promotes hepatic lipid accumulation and metabolic inflexibility. These changes are not metabolically neutral: hepatic steatosis is tightly connected to hepatic insulin resistance and to increased hepatic glucose production, thereby worsening fasting hyperglycaemia and postprandial dysglycaemia. Integrative models of insulin resistance emphasize that ectopic lipid accumulation, lipid-derived signalling intermediates, endoplasmic reticulum stress pathways, and innate immune activation form interacting "common threads" that jointly drive insulin resistance phenotypes (6). Complementing this, molecular syntheses of NAFLD pathogenesis highlight that multiple hepatic lipid-handling pathways converge to produce steatosis and to increase vulnerability to inflammatory injury and progression beyond simple fat accumulation (5).

A further mechanistic layer is the **gut-liver axis**, increasingly recognized as a biologically plausible route by which obesity shapes both hepatic inflammation and systemic glucose regulation. Obesity-related shifts in gut microbial composition and function can alter bile-acid signalling, modify short-chain fatty acid availability, and influence intestinal barrier integrity. When permeability increases, translocation of microbial products into the portal circulation can provoke hepatic innate immune activation and systemic inflammation. The "metabolic endotoxemia" paradigm—originally demonstrated in experimental models showing that low-grade endotoxin exposure can initiate or aggravate obesity and insulin resistance—provides one mechanistic template linking gut-derived inflammatory signalling to metabolic disease expression (17). Contemporary reviews further conceptualize the gut-liver axis as a bidirectional regulatory system in which host metabolites, microbial metabolites, and immune mediators jointly shape both hepatic health and systemic metabolic trajectories (7).

Taken together, these convergent pathways—**adipose inflammation, oxidative stress, hepatic lipid overload and stress signalling, and gut-liver immune-metabolic crosstalk**—explain why dysglycaemia and liver injury frequently travel together in obesity, and why interventions that address only a single node may fail to fully modify risk. This biology also clarifies the rationale for agents with **multi-layer effects**, particularly those capable of modulating inflammatory tone, oxidative injury, and gut-derived metabolic signalling in parallel. These considerations motivate the next section, which examines why *Ganoderma* polysaccharides must be interpreted as **preparation-specific biological entities**, with structural and extraction determinants that directly govern their plausibility as immunometabolic modulators.

Ganoderma polysaccharides: composition, extraction, and why structure matters

Mushroom-derived polysaccharides are attractive as multi-pathway immunometabolic modulators, but "*Ganoderma* polysaccharides" do not represent a uniform exposure class. Across *Ganoderma* species, beta-glucans and heteropolysaccharides are usually recovered from hot-water extracts, then enriched by ethanol precipitation and subsequent fractionation. Reported molecular weights span a broad range - approximately 10^3 to 10^6 Da across *Ganoderma* beta-glucans (9) - while *G. applanatum*-specific fractions purified by gradient alcohol precipitation have been reported at average molecular weights of 77.75, 9.25, and 1.03 kDa, with glucose as the dominant monosaccharide (18). Common structural motifs include beta-(1→3), beta-(1→4), and beta-(1→6) linkages with variable beta-(1→6) branching, but heteroglycans containing galactose, mannose, rhamnose, and other residues also occur (10). These characteristics are not trivial compositional details; they influence solubility, fermentability, receptor engagement, conformation, and ultimately biological activity (9, 10).

What are we calling "polysaccharides" in *Ganoderma* studies?

Across the literature, the term may refer to crude water-soluble fractions, semi-purified beta-glucan-rich preparations, heteropolysaccharides, or polysaccharide-protein conjugates. Similar nominal doses can therefore represent materially different molecular exposures. This is particularly relevant for translation, because mechanistic inference is only credible when linked to a defined preparation. Classic structural studies in *G. lucidum* identified both highly branched beta-glucans and heteroglycans by linkage analysis, NMR, and mass spectrometry (10), whereas more recent syntheses emphasize that molecular size, branching density, monosaccharide composition, and higher-order conformation all modulate bioactivity (9). Accordingly, the term "polysaccharide effect" should be interpreted as preparation-specific unless reproducible characterization and manufacturing conditions are demonstrated.

Extraction and process variables drive bioactivity.

Extraction conditions function as structural determinants. Temperature, extraction time, solvent ratio, precipitation conditions, and downstream purification can enrich different molecular-weight fractions and alter branching or co-extracted protein content. In the MACAPOS-2 studies, the tested *G. applanatum* material was a native water-soluble hot-water extract precipitated with ethanol and described mainly procedurally, with limited reporting of molecular-weight distribution, linkage mapping, or batch reproducibility (12, 13). By contrast, chemically modified preparations are not equivalent exposures. (sulphated?) Residue polysaccharides have altered charge density and substitution patterns and may differ in conformation, solubility, and receptor interactions; their hepatoprotective signal in CCl_4 injury therefore supports biologic plausibility but should not be interpreted as directly interchangeable with the native water-soluble preparations used in diet-induced obesity (9, 19). Because structural characteristics strongly influence the biological activity of fungal polysaccharides (9, 10), future studies should routinely report extraction yield, purity, molecular-weight distribution, monosaccharide composition, linkage analysis, and degree of substitution for derivatives. When immune readouts are emphasized, endotoxin testing should also be reported as a methodological safeguard.

Mechanistic pathways by which *Ganoderma* polysaccharides may improve glucose homeostasis and liver integrity

For polymeric polysaccharides, systemic effects are plausibly driven largely through the intestinal ecosystem rather than through intact absorption. Fermentation and mucosal interactions can reshape microbial composition and function, alter short-chain fatty acid and bile-acid profiles, and strengthen barrier integrity, thereby reducing portal inflammatory signalling—pathways central to gut-liver axis biology (7). Consistent with this framework, metabolic endotoxemia models support the concept that reducing gut-derived inflammatory inputs can improve obesity-linked metabolic dysfunction (17).

Gut microbiota and metabolite signalling as a central hub

A key mechanistic premise is that high-molecular-weight polysaccharides are typically not absorbed intact in quantities sufficient to explain systemic effects through direct pharmacologic exposure. Instead, they interact with the gut lumen and mucosa, functioning as fermentable substrates and immunomodulatory ligands that can reshape microbial ecology and host signalling. This is biologically important because the gut-liver axis provides a direct route by which intestinal events influence hepatic inflammation and metabolism via portal circulation, bile-acid signalling, and immune crosstalk. The broader gut-liver axis framework emphasizes that microbial metabolites and barrier function are not secondary correlates but active determinants of hepatic and systemic metabolic phenotypes (7).

Within this paradigm, polysaccharide-driven changes in microbial fermentation can alter short-chain fatty acid availability, which in turn can influence glucose regulation, satiety-related signalling, and inflammatory tone. Parallel microbial effects on bile-acid composition and receptor signalling provide another plausible route linking intestinal fermentation to hepatic lipid and glucose metabolism. Perhaps most critically for obesity-associated hepatic vulnerability, improvements in barrier integrity can reduce translocation of microbial products, thereby attenuating low-grade portal inflammatory signalling and downstream hepatic innate immune activation. This logic resonates with foundational experimental evidence supporting "metabolic endotoxemia" as a mechanistic contributor to obesity and insulin resistance, in which modest increases in circulating endotoxin derived from gut microbial products promote inflammatory activation and metabolic dysfunction (17).

A mechanistic exemplar within the *Ganoderma* field is the observation that *G. lucidum* polysaccharides can remodel disrupted gut microbiota and associated metabolomic signatures in experimental type 2 diabetes models, supporting a microbiome-mediated route to improved glycaemic regulation (20). While species-specific and preparation-specific differences remain important, this work provides proof-of-concept that *Ganoderma* polysaccharides can alter intestinal ecology in ways that align with improved metabolic phenotypes, thereby offering a plausible explanatory layer for systemic outcomes observed in diet-induced obesity models. Although not an obesity model, species-specific support for a gut-centered mechanism also comes from DSS-colitis work showing that *G. applanatum* polysaccharides promoted intestinal barrier recovery and exerted microbiota-dependent protection (21).

Insulin signalling and hepatic lipid handling

Downstream of gut-centered effects, several mechanistic routes converge on improved insulin sensitivity and hepatic lipid handling. One commonly cited pathway involves modulation of AMPK-linked metabolic programs, which would be expected to favour improved lipid oxidation and reduced de novo lipogenesis, thereby reducing ectopic lipid burden and improving insulin responsiveness. Although mechanistic details vary across studies, preclinical data from mushroom-derived polysaccharides and *Ganoderma*-based preparations frequently suggest shifts in hepatic lipid handling and inflammatory tone consistent with improved metabolic flexibility. This conceptual framing is supported by integrative models of insulin resistance that emphasize the interaction of lipid-derived signalling intermediates, endoplasmic reticulum stress, and innate immune activation as shared drivers of systemic insulin resistance (6). In practical terms, any intervention that reduces hepatic lipid stress or inflammatory activation has a plausible path to improve fasting glycaemia by reducing inappropriate hepatic glucose production and improving insulin-mediated suppression of gluconeogenesis.

Inflammatory transcription programs provide another mechanistic bridge. When polysaccharide preparations reduce pro-inflammatory cytokine tone, whether through gut-driven immune calibration or through direct interaction with pattern-recognition receptors, the downstream expectation is partial relief of inflammation-mediated insulin receptor signalling interference. In obesity, metabolic inflammation has been positioned as a core mechanism connecting nutrient excess and immune activation to insulin resistance, underscoring why interventions that attenuate inflammatory tone can have disproportionate effects on glucose regulation even without major weight loss (3). For the liver specifically, the same inflammatory attenuation may reduce susceptibility to injury in the setting of steatosis by lowering cytokine-driven oxidative and mitochondrial stress.

Oxidative stress and hepatoprotection: markers and meaning

Oxidative stress is both a mechanistic driver and a measurable signature of obesity-associated metabolic injury. Seminal work demonstrated that oxidative stress rises early in obesity and contributes to insulin resistance and metabolic syndrome phenotypes (4). In this context, claims of hepatoprotection by *Ganoderma* polysaccharides are frequently supported by reductions in lipid peroxidation products such as malondialdehyde and hydroperoxides, together with improvements in endogenous antioxidant enzyme activities and reductions in serum aminotransferases. These outcomes are coherent with reduced hepatocellular injury and diminished oxidative burden, and they align conceptually with the "multiple-hit" model of fatty liver injury in which oxidative stress and inflammatory activation amplify vulnerability beyond simple steatosis.

At the same time, a rigorous translational interpretation requires clarity about what these biomarkers do and do not establish. Reductions in malondialdehyde, hydroperoxides, or aminotransferases provide supportive evidence for decreased oxidative injury and hepatocyte stress, but they are not sufficient surrogates for disease-modifying effects in metabolic-associated fatty liver disease when considered in isolation. For translation to human settings, biomarker improvements are most persuasive when they align with histologic features (ballooning injury, lobular inflammation, fibrosis stage) or with validated noninvasive endpoints such as MRI-proton density fat fraction and elastography-derived measures of liver stiffness, alongside clinically relevant glycaemic outcomes (19). This distinction is important when interpreting preclinical findings from MACAPOS-2 and related models, where biochemical improvements may precede—or sometimes occur without—structural reversal of liver disease.

Taken together, these mechanistic considerations suggest a coherent multi-pathway hypothesis: defined *Ganoderma* polysaccharide preparations may improve glucose homeostasis and hepatic integrity through gut-centered remodelling of microbial ecology and metabolites, reinforcement of barrier function with reduced inflammatory translocation, attenuation of metabolic inflammation, and downstream improvements in hepatic lipid stress and oxidative injury. The next section evaluates how these pathways map onto the measured outcomes in the MACAPOS-2 model and related preclinical evidence for *G. applanatum* polysaccharides, while highlighting the preparation-definition requirements needed for credible translation (13). Figure 1 presents an evidence-graded conceptual framework that separates established obesity–gut–liver biology from hypothesized gut-mediated actions of defined *G. applanatum* polysaccharide preparations and measured preclinical outcomes (3, 4, 7, 17, 20).

Evidence base for *Ganoderma applanatum* polysaccharides in obesity-linked metabolic and hepatic outcomes

The preclinical evidence for *G. applanatum* is anchored in the MACAPOS-2 diet-induced obesity model, a locally formulated high-energy/high-fat regimen designed to induce integrated metabolic disturbance. In the 2021 MACAPOS-2 report, the diet was described as maize-, cassava-, palm oil-, and sugar-based, with sucrose, palm oil, and steeped cassava contributing to an estimated energy density of ~4730 kcal/kg (12). The model's strength is its diet-driven, multi-organ phenotype that allows simultaneous assessment of glucose tolerance, lipids, and liver injury pathways, but reproducibility can be influenced by local formulation variability and rodent-specific metabolism.

The 2026 MACAPOS-2 study: glucose homeostasis and hepatoprotective endpoints

After 16 weeks of diet-induced obesity, animals received *G. applanatum* polysaccharides (50-150 mg/kg) for two months, with assessment of oral glucose tolerance, insulin tolerance, fasting glycaemia, hepatic lipid peroxidation markers, antioxidant enzyme activities, aminotransferases, and liver histology (13). Reported outcomes included improved glycaemic indices and insulin responsiveness, reductions in lipid peroxidation markers, lower aminotransferases, and histologic improvement compared with obese controls (13). The study is promising, but interpretive limits include modest sample sizes typical of the model and limited structural characterization of the tested fraction beyond procedural extraction description.

The 2021 MACAPOS-2 study: lipid effects and physiologic complexity

Water-soluble *G. applanatum* polysaccharides improved circulating lipid parameters (lower total cholesterol, triglycerides, and LDL-cholesterol with higher HDL-cholesterol) after two months of administration (12). The reported increases in food intake and body weight in treated obese animals underscore the need for deeper phenotyping (body composition, energy expenditure, satiety hormones, and gut-derived biomarkers) to clarify how biochemical improvements relate to whole-body energy balance.

Beyond MACAPOS-2: supportive injury and fibrosis models

Chemical injury models provide supportive plausibility that *G. applanatum* polysaccharides scaffolds can modulate hepatic oxidative and inflammatory injury cascades. Sulfated residue polysaccharides have shown hepatoprotective signals in CCl4-induced injury settings (22). While etiology differs from MASLD, these data reinforce the principle that preparation chemistry can be tuned and must be explicitly defined when interpreting hepatoprotection and planning translation. The key experimental studies and the principal clinical benchmark informing interpretation of the evidence base are summarized in Table 1.

Table 1. Key studies informing the evidence base for *Ganoderma* polysaccharides in obesity-linked dysglycaemia and liver injury.

Species / preparation	**Model / population**	**Dose & duration**	**Key endpoints**	**Main findings (direction)**	**Key caveats**	Key reference (citation no.)
G. applanatum water-soluble polysaccharides (hot-water extract; ethanol precipitation)	MACAPOS-2 diet-induced obese rats (after 16 weeks induction)	50, 100, 150 mg/kg; 2 months	OGTT, ITT, fasting glucose; MDA/OOH; SOD/CAT/GPx; ALT/AST; liver histology	Improved glycaemic indices and insulin responsiveness; reduced lipid peroxidation and aminotransferases; improved histology	Preparation defined procedurally more than structurally (limited MW/linkage data); modest group sizes typical of model	13
G. applanatum water-soluble polysaccharides	MACAPOS-2 diet-induced obese rats	50–150 mg/kg; 2 months	Lipids (TC, TG, LDL-C, HDL-C); food intake; body weight	Improved lipid profile (↓TC/TG/LDL-C; ↑HDL-C)	Reported increases in food intake and body weight highlight need for body composition, energy expenditure and gut biomarkers	12
G. applanatum sulfated residue polysaccharides (structurally modified)	CCl_4-induced hepatotoxicity model (preclinical injury paradigm)	As reported in study	Liver injury enzymes; oxidative/inflammatory readouts (model-dependent)	Hepatoprotective signal in toxin-injury setting (supports plausibility of injury-pathway modulation)	Different etiology from MASLD; sulfation yields non-equivalent exposure vs native hot-water extracts	22
G. lucidum clinical preparation (powder/capsules)	Adults with type 2 diabetes and metabolic syndrome (randomized, placebo-controlled trial)	3 g/day; 16 weeks	Hyperglycaemia and cardiovascular risk factors	No meaningful improvement vs placebo	Highlights need for preparation standardization, phenotype selection, and mechanism-anchored endpoints in humans	11

Footnote: Most obesity-linked *G. applanatum* evidence currently derives from one research network using the MACAPOS-2 platform.

Critical appraisal of the preclinical evidence

The preclinical signal is biologically intriguing but remains methodologically limited. Most of the obesity-linked evidence comes from two MACAPOS-2 studies originating from the same research network (12, 13), raising concerns about external validity and model-specific bias. The 2026 report extends the phenotype to glucose homeostasis and liver injury but does not yet resolve reproducibility across independent laboratories (13). Across these studies, treatment allocation, concealment of group assignment, blinding of biochemical or histologic assessment, and a priori sample-size justification are not described in sufficient detail to permit confident assessment of internal validity using domains emphasized by SYRCLE and ARRIVE (15, 16). The reports also provide limited information on prespecified primary outcomes, attrition handling, and whether histologic scoring was standardized or performed by a blinded observer. These limitations do not invalidate the observed biologic signal, but they reduce confidence in effect size, increase the risk of overinterpretation, and underscore the need for independent replication in separate laboratories using blinded outcome assessment, clearer protocol transparency, and more granular liver phenotyping. Because the evidence base remains small and preparation-specific, the present review interprets these animal data as hypothesis-generating rather than definitive proof of efficacy.

What the broader *Ganoderma lucidum* literature adds and why it matters for translation

Because human data for *G. applanatum* are limited, the larger *G. lucidum* literature provides both mechanistic scaffolding and a cautionary translational benchmark. Foundational work identified hypoglycaemic glycans (“ganoderans”) from *G. lucidum* with glucose-lowering activity in experimental models (23), supporting genus-level plausibility for glycaemic modulation. More recent systems biology studies report that *G. lucidum* polysaccharides can reshape gut microbiota and systemic metabolomic profiles in rodent type 2 diabetes models, consistent with microbiome-mediated improvements in glycaemic phenotypes (20). Contemporary syntheses also describe multi-pathway hepatoprotective mechanisms for *G. lucidum* across liver disease contexts, including antioxidative, anti-inflammatory, immunomodulatory, and gut-liver axis pathways (24).

However, rigorous human evidence is mixed. A randomized, double-blind, placebo-controlled trial in adults with type 2 diabetes and metabolic syndrome reported no meaningful benefit of *G. lucidum* (3 g/day for 16 weeks) on hyperglycaemia or cardiovascular risk factors (11). For *G. applanatum*, this underscores that preclinical plausibility is insufficient without standardized and bioactive preparations in humans, careful phenotype selection (e.g., early insulin resistance with MASLD rather than advanced multi-comorbidity), and endpoints aligned to a likely gut-centered mechanism.

Clinical and research translation: what “good next studies” should look like

Translation of *G. applanatum* polysaccharides requires study designs that make both positive and neutral results interpretable. In the current clinical landscape, lifestyle intervention with weight reduction, dietary change, physical activity, and optimal management of cardiometabolic comorbidities remains the foundation of care for obesity and MASLD/MASH (19). Contemporary guidelines also recognize incretin-based therapies such as semaglutide and tirzepatide for appropriately selected patients with obesity or type 2 diabetes and, where locally approved, resmetirom for non-cirrhotic MASH with significant fibrosis (19). Importantly, the evidentiary basis supporting these interventions is qualitatively different from the *Ganoderma* literature: semaglutide has demonstrated histologic benefit in a large phase 3 randomized trial (25), and tirzepatide has shown encouraging biopsy-based efficacy in phase 2 randomized data (26). Accordingly, *G. applanatum* should be positioned as a hypothesis-generating adjunct candidate within a crowded therapeutic landscape, not as an alternative to interventions already supported by human randomized evidence.

Standardization and characterization as a prerequisite for credibility

Studies intended to support clinical progression should report extraction parameters, yield, and batch reproducibility, molecular-weight distribution, compositional and linkage features, and protein content when relevant, with endotoxin testing when immune readouts are used. This is essential because *Ganoderma* bioactivity is strongly structure-dependent (9).

Mechanism-anchored endpoints that are persuasive beyond surrogate biochemistry

Glycaemic endpoints should extend beyond fasting glucose to include fasting insulin with derived indices, dynamic testing (OGTT-based indices; clamp studies in mechanistic trials), and HbA1c in longer-duration studies. For hepatic outcomes, validated noninvasive measures of liver fat and fibrosis risk should be prioritized, with biopsy reserved for appropriately justified settings (19). Given the likely gut-centered mechanism, gut-liver pathway engagement should be assessed using microbiome functional profiling and targeted metabolite panels (e.g., bile acids and short-chain fatty acids) (7).

Dose and formulation logic that respects limited intact absorption

Human studies should justify dose using allometric reasoning, specify whether the intervention is a whole extract or an enriched fraction, and incorporate adherence/exposure checks using measurable downstream signatures consistent with fermentability or pathway engagement.

Safety, interactions, and real-world feasibility in cardiometabolic populations

Prospective safety monitoring should be tailored to cardiometabolic populations and should include gastrointestinal tolerability and serial liver enzyme assessment; additional vigilance is reasonable in participants receiving antiplatelet or anticoagulant therapy or in those with immune compromise. A minimum reporting and endpoint framework to strengthen reproducibility and translational interpretability is presented in Table 2.

Table 2. Minimum reporting and endpoint framework for translational studies of *Ganoderma applanatum* polysaccharides.

Domain	**Minimum elements (reporting or measurement)**	**Rationale (why it matters)**
Preparation definition	Extraction parameters (time, temperature, solvent ratios, cycles); yield; batch reproducibility; MW distribution (SEC); monosaccharide composition and linkages; protein content (if polysaccharide–peptide); endotoxin testing when immune readouts are used	Bioactivity is structure-dependent; without reproducible characterization, cross-study comparability and dose translation are unreliable.
Mechanism engagement (gut–liver axis)	Microbiome functional profiling; targeted metabolites (bile acids, SCFAs); permeability/Barrier markers; inflammatory tone markers aligned to hypothesis	Large polysaccharides are often gut-active; mechanism confirmation increases the interpretability of neutral or positive clinical results.
Efficacy endpoints (glucose)	HbA1c (longer studies); fasting glucose/insulin with derived indices; OGTT-based indices; clamp studies in mechanistic trials	Dynamic phenotyping improves sensitivity to insulin resistance changes and reduces reliance on single-point glucose measures.

Efficacy endpoints (liver)	MRI-PDFF for liver fat; elastography for stiffness; validated serum fibrosis scores; biopsy only when justified	Aminotransferases and oxidative markers are supportive but insufficient surrogates for disease modification.
Safety and interactions	GI tolerability; serial liver enzymes; bleeding-risk surveillance in antiplatelet/anticoagulant users; prespecified approach for immunocompromised participants	Cardiometabolic populations frequently use concomitant therapies and may have baseline hepatic vulnerability.

Conclusions

Preclinical studies support a coherent signal that defined *Ganoderma applanatum* polysaccharide preparations can improve integrated metabolic phenotypes in diet-induced obesity models, including glucose tolerance, insulin responsiveness, circulating lipids, hepatic oxidative stress markers, aminotransferases, and histologic injury in the MACAPOS-2 framework (12, 13). These findings are biologically plausible within established models of immunometabolic dysfunction and gut–liver axis regulation.

However, the current evidence base remains pre-translational. Preparations are frequently defined procedurally rather than structurally, mechanistic pathway engagement—particularly within the gut–liver axis—is often inferred rather than directly measured, and sample sizes are modest. Moreover, much of the obesity-linked signal currently derives from a single research network using the MACAPOS-2 platform, so reproducibility across independent laboratories remains unproven. In addition, no human trials have evaluated *G. applanatum* polysaccharides in obesity-associated dysglycaemia or MASLD. Experience from the broader *Ganoderma* literature, including neutral findings in randomized controlled trials of *G. lucidum*, underscores that preclinical efficacy does not ensure clinical benefit (11).

Future studies should prioritize rigorous structural characterization, reproducible manufacturing parameters, and mechanism-anchored biomarkers alongside clinically meaningful metabolic and hepatic endpoints. Until such data are available, *G. applanatum* polysaccharides should be regarded as a biologically plausible but experimentally defined exposure requiring further validation rather than as a therapeutic intervention ready for clinical application.

Figure 1. Evidence-graded obesity–gut–liver framework and proposed points of action of defined *Ganoderma applanatum* polysaccharide preparations. Obesity and nutrient excess promote adipose inflammation, oxidative stress, hepatic lipid overload, and gut dysbiosis, which converge on insulin resistance and hepatic vulnerability leading to dysglycaemia and liver injury. Solid black arrows denote established obesity–MASLD biology. Dashed gray arrows denote biologically plausible but not directly demonstrated *G. applanatum* mechanisms, including microbiome remodelling, short-chain fatty acid signalling, bile acid signalling, and barrier reinforcement. Solid blue arrows and the blue outcome box denote measured preclinical effects in MACAPOS-2 obese rats, including improved OGTT/ITT, aminotransferases, oxidative stress markers, and histology. No element implies demonstrated clinical efficacy because human trials are not available. Arrow interpretation: Solid arrows - established disease biology or demonstrated preclinical outcomes. Dashed arrows - biologically plausible mechanisms not yet directly demonstrated

Abbreviations: ALT, alanine aminotransferase; AST, aspartate aminotransferase; ITT, insulin tolerance test; OGTT, oral glucose tolerance test.

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