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Synergistic Effects of Grape Polyphenols and Polysaccharides on Glucose and Lipid Metabolism: Research Progress from Mechanistic Interactions to Functional Food Applications

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Abstract: Disorders in glucose and lipid metabolism are one of the main global problems of chronic diseases, requiring urgent safe and effective dietary intervention methods. Polyphenols and polysaccharides, found in large amounts in grapes, have improving effects on metabolism through host signalling pathways and the gut microflora respectively; Furthermore, as they exist in complex forms within natural food systems, they may show synergistic effects. This paper summarizes the clinical data, molecular mechanisms and synergistic studies about grape polyphenols and polysaccharides during the last five years, suggests a 'three-dimensional synergistic assessment model' including polyphenols, polysaccharides and the gut microflora, and investigates three application methods: functional wine, grape pomace dietary supplements and functional ingredients derived from complexes of polyphenols and polysaccharides. It is found that the synergistic action has been confirmed at the molecular level; however, the unclear optimal ratios and the shortage of clinical evidence still limit the application process.

Keywords: Grape Polyphenols; Grape Polysaccharides; Glucose and Lipid Metabolism; Synergistic Effects; Gut Microbiota.

1. Introduction

Disorders of glucose and lipid metabolism, including type 2 diabetes (affecting over 500 million people worldwide), obesity and non-alcoholic fatty liver disease (NAFLD, with a prevalence of approximately 25 per cent), have become major global public health challenges. Current clinical interventions are primarily based on drugs such as metformin, GLP-1 receptor agonists and SGLT2 inhibitors; however, the gastrointestinal side effects and financial burden associated with long-term medication have driven in-depth exploration of non-pharmacological dietary intervention strategies [1,2] .Grapes and wine processing by-products are rich in two major natural bioactive components: polyphenols (resveratrol, proanthocyanidins, anthocyanins, quercetin, etc.) and polysaccharides (primarily HG-type and RG-I-type pectins), which exert metabolic-improving effects via the AMPK/SIRT1/PPAR signalling pathway and gut microbiota fermentation, respectively [3,4] .

In terms of clinical evidence, human trials on grape polyphenols mainly focus on resveratrol. A meta-analysis of 17 randomized controlled trials showed that resveratrol supplements (100 mg to 1 gram per day, lasting 4 to 24 weeks) can moderately reduce fasting blood glucose levels in patients with type 2 diabetes (WMD is about -0.3 mmol/L) [1] Another meta-analysis focusing on metabolic syndrome shows that resveratrol has a more significant effect on improving lipid metabolism. The WMD value of its triglycerides is about −0.3 mmol/L, and the level of HDL-C is significantly improved [2] However, its effect is greater than that of metformin or GLP-1 receptor agonists are less effective; therefore, polyphenols are more suitable as an auxiliary intervention. Subgroup analysis showed that patients with high baseline BMI had a more obvious response to resveratrol, and the effect of continuous intervention with moderate doses (about 500 mg per day) for more than 12 weeks was better than high doses, indicating that there was a cumulative effect and a nonlinear dose-reaction relationship. In the field of obesity research, a randomized, double-blind, cross-trial trial found that a single dose of grape polyphenols (about 1.5 grams) did not significantly improve the postprandial blood sugar or triglyceride levels of obese participants [5] Two randomized, placebo-controlled trials further found that during the 31-day period of high-calorie overfeeding Supplementing grape polyphenols (2 grams per day) did not significantly improve insulin resistance; however, for female participants, the expression of angiogenesis-related genes in adipose tissue was significantly downregulated, indicating that there is a gender-specific metabolic effect [6] Compared with polyphenols, the clinical research on glucose polysaccharide is extremely scarce. Lack. At present, only a small number of exploratory studies have investigated the effect of pectin dietary fiber on postprandial blood sugar and insulin sensitivity. The lack of large-scale randomized controlled trial data using glucose polysaccharide as a single intervention, and there has been no human trial of polysaccharide and polyphenol combined intervention, which constitutes the most critical evidence gap in this field. In addition, differences in grape varieties and extraction processes lead to inconsistency in polyphenols and polysaccharides, while standardized dietary supplements face the challenge of regulatory inconsistency and lack of quality control, both in the European Union and the United States [7] .

According to the present study, most of the previous works have investigated grape polyphenols and polysaccharides individually, ignoring the significant point that they are in complex form within natural food substances. Recent studies indicate that there are synergistic relationships among polyphenols and polysaccharides in three aspects: improved bioavailability, shared target tissues and synergistic metabolic pathways; however, a comprehensive assessment of this cooperative approach in enhancing glucose and lipid metabolism has not been carried out yet. This paper mainly

focuses on three main points: First, to systematically investigate the differences in signal pathways and targets of different grape polyphenol monomers such as resveratrol, proanthocyanidins, anthocyanins and quercetin, in order to clarify the molecular basis of their multiple-target metabolic regulatory networks; secondly, to carry out a detailed investigation of the whole processes by which grape polysaccharides (HG-type and RG-I-type pectins) influence metabolic changes through gut microbiota fermentation, short chain fatty acid signaling and intestinal barrier restoration; Third, a mechanistic model for the cooperative improvement of polyphenols and polysaccharides has been established from three aspects—polysaccharide carrier effect, simultaneous action on host and microbiota, and metabolic network cooperation—and a method for the quantitative assessment of cooperative effects has been suggested. Finally, this paper evaluates the possibilities of converting the aforementioned synergistic mechanisms into three application fields: functional wines, grape pomace dietary supplements and functional ingredients including polysaccharide-polyphenol complexes, and also outlines the current research limitations and future perspectives

2. Signalling Pathways through Which Grape Polyphenols Regulate Glucose and Lipid Metabolism: Monomeric Differences and Network Synergy

2.1. Resveratrol: The AMPK/SIRT1 Energy-Sensing Axis

Resveratrol is the most researched monomer component in grape polyphenols; its metabolic regulation mainly depends on the activation of the AMPK/SIRT1 energy perception pathway. Resveratrol can increase the phosphorylation level of AMPK at Thr172 by directly interacting with SIRT1 or indirectly activating the LKB1-AMPK pathway, thus reducing PEPCK and G6Pase, which are key enzymes in the process of liver glucose etetology - Expression, and reduce the production of glucose in the liver. At the same time, through phosphorylation of ACC, it can overcome the inhibitory effect on CPT1α, thereby promoting the beta-oxidation process of fatty acids in skeletal muscle and liver [3] There is a positive feedback loop between SIRT1 and AMPK: SIRT1 is activated by deacetylation LKB1, which leads to the phosphorylation of AMPK; in addition, the activation of AMPK will increase the concentration of NAD+ in cells, which in turn enhances the activity of SIRT1. Resveratrol can induce mitochondrial organisms through the SIRT1/PGC-1α pathway, thus converting temporary metabolic advantages into lasting adaptive changes. As for the lipid metabolism regulated by PPAR, resveratrol can not only activate the PPARα-FGFR21 pathway (which can enhance the oxidation capacity of fatty acids in the liver), but also activate the PPARγ-adiponectin pathway (which can improve the islets in adipose tissue. Prime resistance); the simultaneous activation of these two pathways has a significant impact on the removal of liver lipids in the NAFLD model [2]. The main disadvantage is the low bioavailability of resveratrol, which is mainly attributed to the rapid process of sulfate and glucoside acidification reactions, which leads to its systemic absorption lower than the body. The level shown by the external test. This problem hinders its application as a single functional food additive, and is also the main reason for the adoption of collaborative methods including polysaccharides.

2.2. Proanthocyanidins: Selective PPARγ Regulation and the Intestinal Barrier

Proanthocyanidins are the major polyphenolic polymers found in grape seeds and skins, and their metabolic regulations are different from those of resveratrol. The action of proanthocyanidins on PPARγ is opposite to that of thiazolidinedione (TZD) drugsProanthocyanidins are the main polyphenolic macromolecules in grape seeds and skins, and their metabolic pathways are different from those of resveratrol. The influence of proanthocyanidins on PPARγ is contrary to that of thiazolidinedione (TZD) drugs: TZD drugs act as complete PPARγ agonists leading to both insulin-sensitivity and lipid synthesis consequently resulting in an increase of body weight; Furthermore, proanthocyanidins inhibit the phosphorylation at the PPARγ S273 site without activating the lipogenic pathway, which prevents the weight gain induced by TZD drugs. This kind of regulation of PPARγ is beneficial for the development of new insulin sensitizers. Furthermore, due to their high polymerization degree (from dimers to decamers and so on), proanthocyanidins have a very low intestinal absorption rate (less than 5 percent); most of them are excreted in their original form and are further transformed into low molecular weight phenolic acids by the gut microflora. This characteristic enables them to exhibit outstanding local antioxidant and anti-inflammatory effects in the intestine: proanthocyanidins can increase the expression of tight junction proteins in the intestine, reduce intestinal permeability and alleviate metabolic endotoxemia by blocking the intestinal NF-κB signal transduction, which shows their unique advantages in protecting the intestinal barrier compared with resveratrol.

2.3. Anthocyanins and Quercetin: Nrf2/NF-κB Regulation of Oxidative Stress and the NLRP3 Inflammasome

Anthocyanin and qercetin belong to the grape polyphenol family and play a role in regulating oxidative stress and inflammation. Anthocyanin enhances the antioxidant enzyme system through the Nrf2/ARE pathway, such as SOD, CAT, GPx and HO-1, inhibits the phosphorylation of IκBα, prevents NF-κB from entering the nucleus, and reduces the production of inflammatory factors such as TNF-α and IL-6. Curcetin has an inhibitory effect on NLRP3 inflammatory body, which can prevent ASC oligomerization, inhibit Caspase-1 activation and IL-1β maturation, which is crucial for regulating fat tissue inflammation associated with obesity. By activating the AMPK and PPARγ signaling pathways, these two components can convert macrophages in adipose tissue from the pro-inflammatory M1 state to the anti-inflammatory M2 state, thus reducing adipose tissue inflammation. However, the bioavailability of anthocyanins and quercetin is constrained by rapid metabolism and intestinal excretion, and their metabolic improvement in the body mainly depends on the secondary effects of metabolites produced by intestinal microbiota.

A comprehensive study shows that the four main grape polyphenol components have a synergistic effect on metabolic regulation. Among them, resveratrol mainly regulates energy perception and mitochondrial biosynthesis through the AMPK/SIRT1 pathway; the main pigment mainly acts on specific PPARγ and maintains intestinal barrier

function; while anthocyanin and quercetin through Nrf2/NF-κB/NLRP3 The pathway acts on the oxidative stress-inflammatory pathway. This functional compatibility shows that the comprehensive effect of high-concentration polyphenol mixture is significantly better than that of any single component, which provides a molecular explanation for the preparation of polyphenol components in functional food.

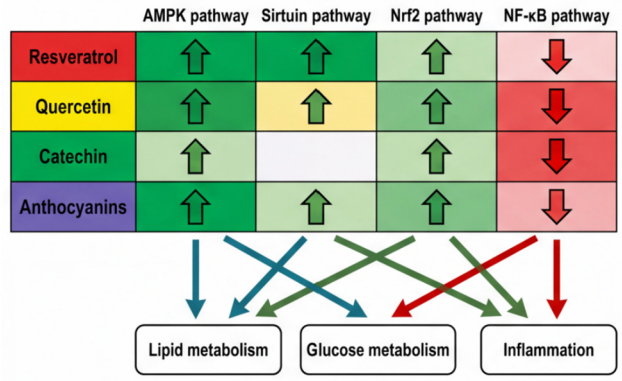


Figure 1. Grape Polyphenol Monomer Signaling Pathway Preference Comparison

3. Grape Polysaccharides Improve Metabolism Via the Gut Microbiota: Structure–Function Relationships and Dual Pathways

3.1. SCFAs–GLP-1/PYY gut–pancreas axis

Grape polysaccharides (particularly pectin-type polysaccharides) are fermented by specific bacterial populations in the colon, producing short-chain fatty acids (SCFAs), predominantly acetic, propionic and butyric acids. Although the fermentation characteristics vary depending on the source of pectin, all significantly increase the production of SCFAs in the colon, particularly the proportion of butyric acid [4] .The metabolic effects of SCFAs are primarily mediated via the G protein-coupled receptors GPR41 and GPR43: upon activation, GPR41/43 on the surface of L cells in the distal colon promote the secretion of GLP-1 and PYY.GLP-1 promotes glucose-dependent insulin secretion and inhibits glucagon release, whilst PYY suppresses appetite and delays gastric emptying via Y2 receptors in the arcuate nucleus of the hypothalamus; together, these two hormones form the gut-pancreas-brain axis through which the metabolic benefits of polysaccharide metabolism are realised.It is worth noting that a review article has elucidated the complementary relationship between this pathway and polyphenol-mediated host signalling regulation from the perspective of the polyphenol–microbiota–gut–brain axis, pointing out that the gut microbiota acts as a translator and amplifier of their interaction [9] .

3.2. The Adiponectin–AMPK Axis and Intestinal Barrier Repair

In addition to the SCFAs-GLP-1 axis, there exists another way in which polysaccharides bring about metabolic benefits. Low-molecular-weight pectin oligosaccharides (degree of polymerization 3-8) can activate AMPK phosphorylation in the liver by enhancing the synthesis and secretion of adiponectin in adipocytes, thus promoting fatty acid oxidation [11], thus connecting the microbial metabolic effects of polysaccharides with the improvement of host hepatic lipid metabolism. The SCFAs-GLP-1 axis and the adiponectin-AMPK axis form two pathways for the metabolic benefits of polysaccharides: the former influences the metabolic changes immediately after meals, while the latter causes chronic metabolic adjustment.

Byric acid plays an important role in protecting the intestinal barrier. Metabolic endotoxemia has a situation where the intestinal barrier is destroyed. This destruction causes lipopolysaccharides, that is, LPS, to be released into the circulatory system, thus activating the TLR4-NF-κB pathway, which is the main cause of obesity and non-alcoholic fatty liver disease, that is, NAFLD. Need the reason. By inhibiting the activity of histone deacetylase, that is, HDAC, butylic acid can enhance gene expression and increase the protein content of closely connected proteins such as Occludin, ZO-1 and Claudin-1, so as to reduce LPS in the blood. Concentration, and prevent endotoxemia induced by inflammation.

3.3. Structure–Function Relationships of Pectin and Targeted Modification Strategies

Research about the relation between the structure and function of pectin shows that various structural parts have different influences on metabolic effects. The degree of methoxylation (DM) is an important factor affecting the fermentability of pectin: low-methoxyl HG-type pectin is rapidly fermented in the proximal colon, generating a variety of SCFAs mainly including butyrate, and is more effective than highly methoxylated pectin in enhancing the expression of tight junction proteins[12,13]. RG-I-type pectin, containing a lot of arabinogalactan side chains, is more efficient in altering the gut microbiota and decreasing body fat. RG-I enriched pectin has been found to markedly increase the amount of Akkermansia muciniphila and prevent high-fat-diet induced obesity in mice, while commercial pectin with less RG-I content could not achieve the same anti-obesity result, indicating that enrichment of RG-I domain is essential for the metabolic effects of pectin [14].

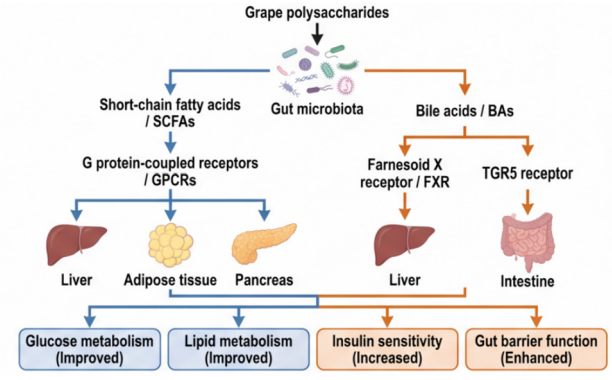


Figure 2. Grape Polysaccharide-Gut Microbiota Metabolic Improvement Dual Pathway

Carrot-derived RG-I (cRG-I) has been found to specifically promote the growth of health-related bacteria such as Bifidobacterium longum, Bacteroides dorei and Faecalibacterium prausnitzii, and enhance the barrier function in a Caco-2/PBMC co-culture system[15]. According to these structure-function relations, the specific optimization of the SCFA yield pattern and the butyrate/acetate ratio in pectin by using methods like enzymatic de-esterification, controlled

acid hydrolysis and modification of side chains is a significant engineering method to improve the effectiveness of polysaccharide-induced metabolic benefits [16].

4. Synergistic Effects of Polyphenols and Polysaccharides: Mechanisms, Evaluation and Perspectives

4.1. Polysaccharide Carrier Effect: Mutual Enhancement of Colonic-Targeted Delivery and Bioavailability

There are many synergistic effects between polyphenols and polysaccharides, which are mainly reflected in physics and chemistry. For example, intermolecular hydrogen bonds can be formed between the phenol hydroxyl group in polyphenol and the carboxyl group and hydroxyl group in polysaccharides. These hydrogen bonds are relatively stable in a low acidic environment of gastric acid. At this time, the pH is about 1.2 to 2.0, which can protect polyphenols from pepsin degradation. When the mixture passes through the small intestine, the pectin gel network will slow down the release of polyphenols to avoid its rapid absorption and metabolism in the upper digestive tract. When the mixture reaches the colon, pectin will be fermented and degraded by a specific microbial community, thus releasing the polyphenols wrapped in it, so as to achieve targeted colon delivery. The polysaccharide-polyphenol complex (PPC) extracted from grape residue showed a better blood sugar-lowering effect in the diabetic mouse model than a single component, and its fasting blood glucose level was reduced by about 30% higher than that of the single polyphenol group [8]. In the mulberry leaf polyphenol-polysaccharide complex, the release of polyphenols in the simulated colon environment is 2.3 times that of free polyphenols, and the polyphenols released by colon targets exist in the form of glycoside ligands, which is more biologically active[17].

4.2. Dual Host-microbiota Targeting: Spatial Complementarity of Molecular Targets

The second synergistic effect is reflected in the complementary spatial distribution of molecular targets. Polyphenols primarily target host metabolic signalling pathways, including the AMPK/SIRT1/PGC-1α energy-sensing axis, PPARα/PPARγ lipid metabolism reprogramming, and Nrf2/NF-κB oxidative stress–inflammation regulation;polysaccharides primarily target the gut microbiota, achieving metabolic improvements via the SCFAs–GPR41/43–GLP-1/PYY axis and gut barrier repair.The two also complement each other in terms of tissue distribution: the target tissues for polyphenols tend to be metabolically active organs such as the liver, adipose tissue and skeletal muscle, whilst those for polysaccharides tend to be the intestinal mucosa and the systemic circulation.Whilst polyphenols upregulate the AMPK/SIRT1 pathway to reduce hepatic gluconeogenesis, polysaccharides promote GLP-1 secretion via the butyrate-GPR41 axis, further enhancing insulin sensitivity and peripheral glucose utilisation, thereby forming a dual regulatory model of ‘upstream signalling pathway activation + downstream effector hormone amplification’.

4.3. Considerations on the Synergy and Quantitative Evaluation of Metabolite Networks

The third synergy is particularly obvious at the metabolite level. Polyphenols that are not absorbed by the upper digestive tract (about 90% to 95%) will enter the colon, where they are metabolized into small molecule metabolites by the intestinal microbiota, such as urethia and phenolic acid; these metabolites play a synergistic regulation in the liver and adipose tissue together with SCFAs produced by polysaccharide fermentation. Use. Studies on mulberry leaf complexes show that after collaborative intervention, the mRNA levels of SREBP-1c and FASN in the liver are significantly lower than those in the single polysaccharide group, while the mRNA levels of CPT1α and PPARα are significantly higher than those in the single polyphenol group; in addition, this The effect is positively related to the concentration of phenolic acid metabolites and butyrates in the liver [12] Another study found that the wine grape polysaccharide extracted from the wine residue showed significant antioxidant and immunomodulatory activity in vitro, and the intensity of this activity is closely related to the residual polyphenol content, which shows that before extraction, these two There may be synergistic effects in the natural polysaccharide-polyphenol complex [18] .

One of the main shortcomings of the current collaborative research is the lack of quantitative evaluation methods. Generally speaking, the evaluation of the synergistic effect is only based on the difference in the degree of effect between "single group" and "compound group", so there is no way to exclude the impact of additional effects. This document shows that the use of mature collaborative evaluation techniques, such as Chou-Talalay combination index (CI) and Isobologram analysis, is necessary to promote research in this field from the qualitative statement stage to the quantitative evaluation stage. If the CI value is less than 1, it means that there is synergy. If the value is 1, it means that there is an addition. If it is greater than 1, it means that there is antagonism.

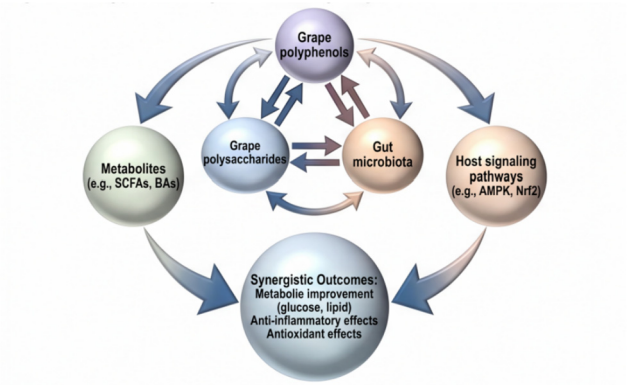


Figure 3. Polyphenol-Polysaccharide Synergistic Mechanism Overview

5. Pathways for Application and Commercialisation: From Laboratory to Industry

Based on the aforementioned framework of synergistic mechanisms, the three complementary pathways for application and commercialisation each possess technical feasibility and market potential. Table1 provides a systematic

comparison of the three pathways across four dimensions: technical maturity, regulatory barriers, market prospects and industrialisation feasibility.

Table 1. Comparison of the Feasibility of the Three Application-Translation Pathways

Evaluation Dimensions	Functional Wine	High-value utilisation of grape pomace	Functional Ingredients Composed of Polysaccharide–Polyphenol Complexes
Core Strategies	Natural compound carriers, optimisation of fermentation processes	Waste-to-resource conversion, green extraction	Standardised ingredients, multi-category applications
Technical Maturity	Moderate; maceration and fermentation processes are well-established, but the balance between sensory and functional properties requires further optimisation	High; green extraction and microencapsulation technologies are now well-established	High; the stability of complexes and masking techniques has been validated
Active ingredient content	Polyphenols 1–3 g/L, polysaccharides 0.5–1 g/L	Varies significantly between batches depending on the raw material variety and extraction process	Can be standardised in terms of composition, offering the greatest potential for quality control
Regulatory barriers	Most severe; carcinogenic risk associated with alcohol; neither the EFSA nor the FDA has approved any health claims	Moderate; dietary supplement regulations are relatively lenient, but quality control standards are lacking	Moderate; the approval pathway for functional ingredients is relatively clear, but clinical validation is required
Market positioning	Harm reduction (low sugar, low alcohol), non-therapeutic claims	Dietary supplements, functional food ingredients	Meal replacements, functional beverages, dairy additives
Feasibility of commercialisation	Low to moderate; regulatory breakthroughs required	High; technically and economically feasible	Highest; greatest flexibility and market demand
Immediate Priority	Third	Second	First

Functional wine is the main way for grape polyphenols and natural polysaccharides to coexist. Red wine contains 1–3 g/l of polyphenols (measured by galic acid equivalent) and about 0.5–1 g/l of polysaccharides; during fermentation and storage, these ingredients form stable non-covalent complexes. From a technical point of view, the amount of functional ingredients can be increased by prolonging the impregnation time, selecting grape varieties rich in polyphenols and low in sugar content (such as Tanat and Sagrantino), and adjusting the lactic acid fermentation conditions; however, the amount of sensory quality (tannin, bitterness, color stability) and functional ingredients needs to be Reach a balance.

Regulatory barriers are the main bottleneck facing the industrialization of functional wine. According to the European Union's Regulation No. 1924/2006 on nutrition and health claims, the European Food Safety Agency has expressed negative opinions on health claims related to red wine polyphenols, pointing out that the description of food is insufficient and there is a lack of proven causal relationship [19,20]. The International Agency for Research on Cancer has listed alcohol as a Class 1 carcinogen, which makes any health claim subject to a double review - both ethical and regulatory review. In the United States, health claims are subject to prior approval under the framework of the Nutrition Labeling and Education Act (NLEA) and the Dietary Supplements Health and Education Act (DSHEA). So far, no health claims related to the metabolic benefits of drinking have been approved [21] Therefore, the way to commercialization is more likely to be achieved through a "harm reduction" positioning - that is, the production of functional wine, which has low sugar content and low alcohol content (<10% volume percentage), and the content of polyphenols is high - instead of gaining market access by putting forward "therapeuc" claims.

Grape residue (peel, seeds and stems) accounts for about 20% to 25% of the total weight of winemaking raw materials, with a global annual output of about 14 million metric tons; it is the most economical and sustainable source of polyphenols and polysaccharides. The polysaccharide-polyphenol complex extracted from grape residue showed a better hypoglycemic effect than a single component in the diabetic mouse model [8], which provides direct scientific evidence for the transformation of grape residue from waste to functional food raw materials. Green extraction technology (ultrasonic-assisted, microwave-assisted and enzyme-assisted) is gradually replacing the traditional organic solvent extraction method, while microencapsulation technology (spray drying and co-precipitation method) can further improve the stable storage performance of polyphenols and the efficiency of targeted delivery to the intestine. However, ensuring the consistency of polyphenol-polysaccharide components between batches and the establishment of a standardized quality control system are the key prerequisites for these high-value residue products to move from the laboratory to the market.

Integrating polysaccharide-polyphenol complexes into various food products as a new functional ingredient represents the third way of application and the way of commercialization, and it is also the most flexible way. These complexes show higher stability than free polyphenols in heat processing (pasteurization, ultra-high temperature treatment), because the polysaccharide gel network provides thermal protection for polyphenols. Microcapsulation technology can effectively cover the astringency and bitter taste of polyphenols; in product forms such as meal replacement powder, functional drinks and yogurt, the addition of polyphenol-polysaccharide complexes has natural advantages in terms of taste and texture.

Taking a comprehensive comparison, the common bottlenecks across all three pathways lie in the standardisation of efficacy (batch consistency in active ingredient content and synergistic effects), clinical validation of bioavailability (translating in vitro simulation data into actual in vivo absorption), and adaptability to the regulatory framework (approval pathways for functional food claims). Functional ingredients based on polysaccharide–polyphenol complexes offer the greatest near-term feasibility at both technical and market levels and are recommended as a priority for

industrialisation; the high-value utilisation of grape pomace offers distinct advantages in terms of sustainability and economic viability and can be considered for medium-term development; whilst functional wines are the most conceptually appealing, their advancement requires substantial progress in regulatory breakthroughs and their positioning as “harm-reduction” products.

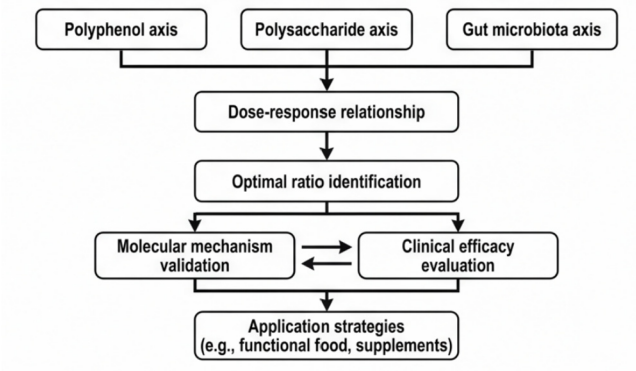


Figure 4. ‘Three-Axis Synergistic Evaluation Framework’ Operational Logic

6. Conclusion

This paper systematically integrates the independent and synergistic mechanisms by which grape polyphenols and polysaccharides improve glucose and lipid metabolism, proposing a “three-axis synergistic evaluation framework for polyphenols, polysaccharides and the gut microbiota”. At the level of independent action, the four major polyphenolic compounds exhibit complementary target preferences: resveratrol dominates AMPK/SIRT1 energy sensing and mitochondrial biosynthesis; proanthocyanidins focus on selective PPARγ regulation and maintenance of the intestinal barrier; whilst anthocyanins and quercetin emphasise the Nrf2/NF-κB/NLRP3 oxidative stress–inflammation axis; polysaccharides achieve microbiota-mediated metabolic improvement via dual pathways—the SCFAs–GPR41/43–GLP-1/PYY gut–pancreas axis and the adiponectin–AMPK axis—as well as through the repair of the intestinal barrier. In terms of synergistic effects, the two components work together through the protection of colon-targeted release of polyphenols by the polysaccharide carrier (mutually enhancing bioavailability), complementary targeting of host signalling pathways and gut microbiota metabolic remodelling, and the synergistic interaction of metabolite networks involving urolithin/phenolic acids and SCFAs in the liver and adipose tissue, resulting in the combined intervention being significantly more effective than either component alone. In terms of translational application, functional ingredients comprising polysaccharide–polyphenol complexes offer the greatest immediate feasibility from both a technical and market perspective; the high-value utilisation of grape pomace presents distinct advantages in terms of sustainability; whilst the development of functional wines requires progress in regulatory breakthroughs and the establishment of a “harm reduction” positioning before it can be advanced.

This manuscript concentrates on polyphenols and polysaccharides extracted from grapes; however, other plant materials containing polyphenol-polysaccharide complexes like blueberries, pomegranates and mulberry leaves are not compared, which may restrict the generalization of our results to other species. The available clinical evidences mainly come from single-component treatments; there are very few human trial data on the synergistic effects of polyphenol-polysaccharide combinations. Moreover, no quantitative evaluation methods for the synergistic effects (such as the Chou-Talalay combination index and isobologram analysis) have been established yet, thus it is hard to make a direct comparison of the synergistic efficacy in different studies. Future research should be guided by the following prioritised agenda:

1. Most urgent: Establish a standardized quantitative evaluation system to evaluate the effect of synergy, including the use of Chou-Talalay combination index and Isobologram analysis methods, and use the responsive surface method to optimize the ratio of polyphenols/polysaccharides.

2. High priority: For the multicenter, long-term randomized controlled trial of grape polyphenol-polysaccharide complex in human subjects, stratified according to the baseline intestinal microbiota composition (intestinal type) to verify the clinical efficacy and safety of collaborative intervention measures.

3. Medium priority: Compare polyphenol-polysaccharide complexes in different plant sources (blueberries, pomegranate, mulberry leaves) to explore whether this synergy is applicable to various plant materials.

4. Long-term: A study on adjusting the regulatory framework to evaluate the feasibility of the health efficacy of functional wine and grape residue derivative supplements. The study was conducted in accordance with the current European Food Safety Authority (EFSA) Regulation 1924/2006 and the NLEA/DSHEA guidelines of the U.S. Food and Drug Administration (FDA), and involves the long-term safety assessment of grape residue derivative extracts.

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