

ANTICHOLESTEROL ACTIVITY AND MECHANISMS OF KONJAC GLUCOMANNAN: A SYSTEMATIC REVIEW

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Abstract

The traditional Chinese medicinal herb konjac glucomannan has been used for centuries, and its active component, glucomannan, is well-known. Glucomannan is a naturally occurring polysaccharide found in some plant species. Glucomannan's special capacity as a dietary supplement has led to its widespread usage in clinical settings for the treatment of obesity, high cholesterol, constipation, diabetes, and atherosclerosis. The therapeutic impact and underlying processes in treating arterial sclerosis illnesses have been the subject of growing study in recent years, adding to its regulatory function in gastroenterology and metabolic syndrome. This review aims to provide insight on the several mechanisms by which konjac glucomannan achieves its cholesterol-lowering effect.

Keywords: konjac glucomannan; metabolic syndrome; anti-cholesterol; traditional Chinese medicinal herb; arterial sclerosis.

INTRODUCTION

The corm of the plant *Amorphophallus konjac* is the source of the main polysaccharide known as konjac glucomannan (KGM) (Devaraj et al., 2019; Zhu, 2018). A. konjac dormant corms contain 49–60% (w/w) glucomannan, 10–30% (w/w) starch, 2.6–7% (w/w) inorganic elements (aluminium, calcium, chromium, cobalt, iron, magnesium, manganese, phosphorus, potassium, selenium, sodium, tin and zinc), 5–14% (w/w) crude protein, 3–5% serotonin and its derivatives cis-N-(p-coumaroyl) serotonin and trans-N-(p-coumaroyl) serotonin have also been found in fresh corm tissue (Chua et al., 2010). The health benefits include a reduction in body fat and an increase in satiety, improved dental health, increased development and viability of beneficial organisms in the colon, and cholesterol (sugeng mashudi et al., 2022; Tester & Al-Ghazzewi, 2016; Zhu, 2018).

Cholesterol is a kind of steroid that is found in cell membranes and serves as a precursor of other steroids, as well as vitamins and bile ((Zárate et al., 2016). It is also a necessary part of the myelin that covers the nerves and lets the electrical impulses pass through to make sure that some of the effector tissues respond in the right way (Rodriguez-Concepcion et al., 2018). A part of cholesterol is received through diet, but the vast majority is generated in the liver and then enters the general circulation via lipoproteins of varying

molecular weight (Shumskaya & Wurtzel, 2013). Researchers who have earned the Nobel Prize for their contributions to the research of cholesterol: 1) Heinrich Otto Wieland won the Nobel Prize in Chemistry for his work on biliary acids in 1927; 2) Adolf Otto Windaus described atheromas made of cholesterol crystals in his investigations, which earned him the Nobel Prize in Chemistry in 1928; 3) Cholesterol production research by Konrad Bloch and Feodor Lynen won the Nobel Prize in Physiology and Medicine in 1964; cholesterol metabolism research by Michael S. Brown and Joseph L. Goldstein won the same honor in 1985 (Zárate et al., 2016). In the same way that Fleming obtained penicillin, the notion of acquiring a pharmaceutical product that might be utilized in the clinic for the treatment of hypercholesterolemia emerged. This medicine was originally called as compactin, and the research of similar compounds became known as statins, implying a major development in treatments; for these results, Endo was awarded the Lasker Prize in 2008 (Endo, 2010). Konjac glucomannan as Anticholesterol medication derived from konjac glucomannan for schizophrenia (Sugeng Mashudi, et.,al, 2022; sugeng mashudi et al., 2022) and restore health damaged by metabolic syndrome (Tran et al., 2022).

RESEARCH METHODS

This research makes use of a narrative approach to examine previous research on konjac glucomannan that has been conducted elsewhere in the globe and published in databases, such as ScienceDirect, Pubmed, Cochrane, and Proquest, as well as other international journals. There is no restriction placed on the articles based on the location of the study, and the selection of papers is done based on the inclusion and exclusion criteria. The study excluded any publications that were deemed to be irrelevant to the topic. The terms anticholesterol and konjac glucomannan have been used as the search terms. Each article that is used is assessed according to a number of criteria, including keywords, limits, the precision of the techniques used, the quality of the findings produced, the interpretation of the results, the impact, and the conclusions.

RESULT AND DISCUSSION

Regulation of cholesterol metabolism

Both dietary cholesterol and cholesterol synthesized in the body (mostly by the liver) contribute to total blood cholesterol levels (Endo, 2010). The former is supplied by the latter if the needed levels are not obtained, but if the former sort of "exogenous" cholesterol achieves the required level, the liver's synthesis function is regulated to avoid excessive cholesterol formation. Changes in the activity of HMG-CoA reductase, the enzyme responsible for catalyzing the conversion of HMG-CoA to mevalonate, are the mechanism by which dietary cholesterol inhibits cholesterol production in the liver (Endo, 2010). Modifications to reductase activity are closely linked to changes in cholesterol synthesis. The quantity of cholesterol produced by the liver much outweighs the amount absorbed from food, even when a lot of cholesterol is eaten. These findings suggest that blocking HMG-CoA reductase might be an effective strategy for lowering plasma cholesterol in humans (Endo, 2010). Intense PPAR agonist treatment causes browning of white adipose tissue (WAT) and improvement in WAT insulin sensitivity. Consequently, glucose metabolism throughout the body improves. However, PPAR agonist-induced improvement in lipid metabolism may occur without FGF21 being present (Figure 1).

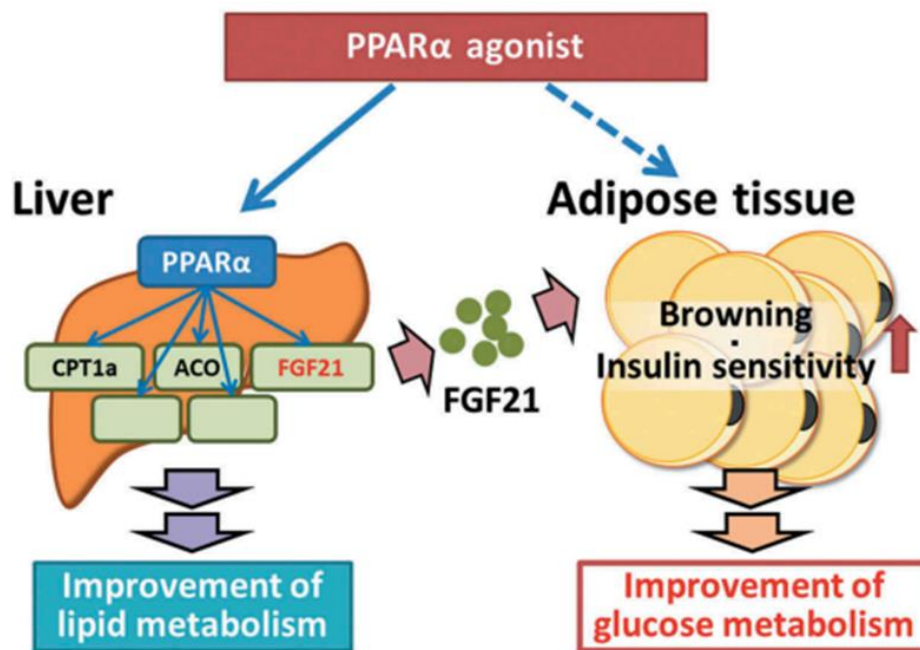


Figure 1. The Role of FGF21, a Hepatokine, in Obesity-Induced Anticholesterol Effects Treated by PPAR Agonists Sources : (Goto, 2019)

PPAR and the Metabolism of the Liver

During fasting as well as after meals, the liver is responsible for managing the balance of glucose and lipids in the body, in addition to the body's energy metabolism. Enzymes that are upregulated by PPAR activity are denoted in green. ACADM stands for medium-chain acyl-coenzyme A (CoA) dehydrogenase; ACADVL stands for very-long chain acyl-CoA dehydrogenase; ACOX1 stands for acyl-CoA oxidase 1; ACSL1 stands for acyl-CoA synthetase long chain family member 1; ATP stands for adenosine triphosphate; CPT1A stands for (figure 2).

Organs express the three PPARs differently, reflecting their diverse physiological functions (Wang et al., 2020). Hepatocytes, cardiomyocytes, proximal renal tubular cells, and brown adipocytes express PPAR. PPAR α is more widespread but mostly present in skeletal muscle, skin, fat, heart, liver, and inflammatory cells. PPAR has three splicing variant isoforms (1, 2, and 3) with different tissue localizations despite the identical DNA binding specificity: 1 (ubiquitous), 2 (adipose tissue), and 3. (localized in macrophages, colon, and adipose tissue). PPAR 2 has 5-10 times more transcriptional activity than PPAR 1 (Temelkova-Kurktschiev et al., 2004). FA activates PPAR, which increases FA-oxidation, ATP generation, and ketogenesis in nutrient-deprived states. PPAR activates multiple proteins, including FA-binding protein 4 (FABP4, also known as aP2), which stores FAs in adipocytes as triacylglycerol (TAG). Nutrient excess and obesity activate PPAR in the liver, which stores FA as lipid droplets (Madsen et al., 2022; Matsusue et al., 2008; Temelkova-Kurktschiev et al., 2004). Thus, differences in cell-specific expression, ligands, and target genes imply that the three PPARs play different roles in liver energy/nutrient metabolism.

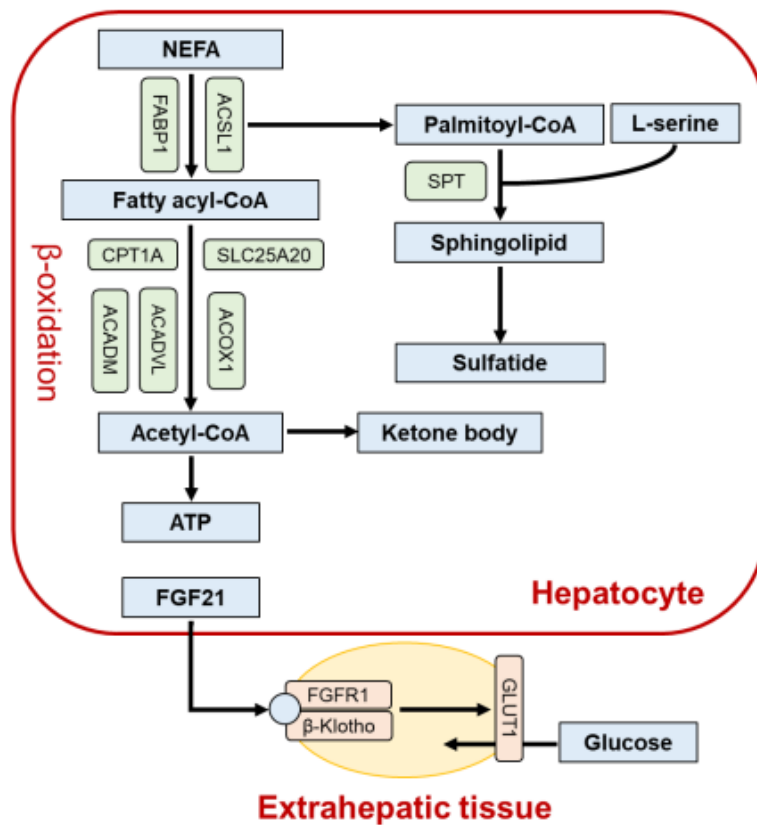


Figure 2.

The role of peroxisome proliferator-activated receptors (PPARs) in hepatic lipid metabolism and associated alterations in NASH development: a brief summary (red arrows)

Sources:(Wang et al., 2020)

NASH and Peroxisome Protein Activator Receptor

Hepatocytes, which are found in the liver, have more and bigger peroxisomes than other cell types. An estimated 2% of the liver's parenchymal volume is occupied by these structures. Hepatic peroxisomes perform α - and ω -oxidation and ether lipid synthesis as metabolic functions. Phytanic acid, a branched chain fatty acid, and 2-hydroxylated fatty acids each had one of their carbon atoms removed during the α -oxidation process. The process of ω -oxidation results in the destruction of very long chain fatty acids (VLCFA), dicarboxylic fatty acids (DCA), and pristanic acids (produced from phytanic acids). The anabolic function includes the synthesis of docosahexaenoic acid, a polyunsaturated fatty acid, and the production of mature bile acids from cholesterol (Shao et al., 2022). Many steps of peroxisomal fatty acid metabolism are transcriptionally regulated by PPAR. One factor in the development of NASH is an increase in fatty acid synthesis, which may be caused by altered PPAR expression by drastically disrupting fatty acid oxidation and triggering lipogenesis. To reduce liver fat accumulation while maintaining elevated ex novo lipogenesis, PPAR agonists like fenofibrate boost gene expression. As an added bonus, fenofibrate therapy completely corrected high-fructose-induced glucose intolerance, hepatic steatosis, and changed hepatic insulin signaling (pAkt and pGSK3). Additionally, peroxisomes include detoxifying enzymes like catalase and superoxide

dismutase, which neutralize reactive oxygen species (ROS) produced by other oxidation processes. Peroxisomal-oxidation is limited by the activity of multiple Acyl-CoA oxidases, which in turn generate H₂O₂. Deficiencies in peroxisomal -oxidation and hepatic steatosis are seen in acyl-CoA oxidase null mice. D-amino acid oxidases, 2-hydroxy acid oxidases (HAO), L-pipecolate oxidase, and alanine glyoxylate aminotransferase all play roles in oxidative reactions that generate H₂O₂ (Dutta et al., 2022). Therefore, peroxisomes have two challenges: first, they must neutralize reactive oxygen species (ROS), which are produced mostly during fatty acid oxidation (Figure 3); and second, they must create ROS. Accelerated levels of circulating fatty acids and increased rates of fatty acid oxidation result in a high volume of reactive oxygen species (ROS) that need to be neutralized, suggesting that the liver in NASH depends significantly on peroxisomes for safe ROS disposal. Scavenging reactive oxygen species is essential for protecting against oxidative stress. Fatty diet-induced steatosis of the liver in catalase knock-out mice leads to increased oxidative stress and inflammation at an earlier stage than in wild-type animals.

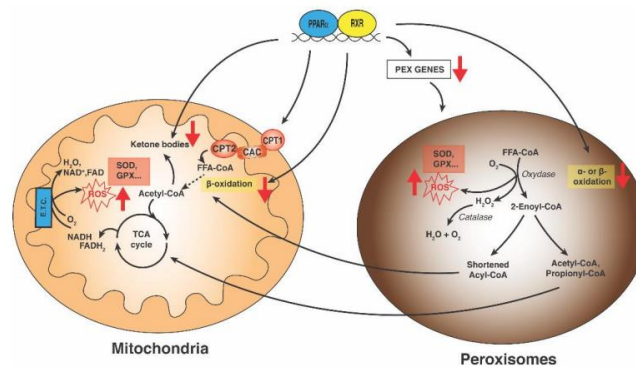


Figure 3. Role of peroxisome and mitochondrial PPAR in lipid metabolism
Sources: (Todisco et al., 2022)

PPAR is involved in the regulation of gene expression in hepatocytes along lipid metabolic pathways such as FABP1, which regulates the trafficking, transport, and storage of FFA, and LCAD and MCAD, which are involved in mitochondrial -oxidation. Lipotoxicity in NASH is produced by the accumulation of free fatty acids in the liver, which is also induced by the mobilization of triglycerides from adipose tissue and a decrease in PPAR activity (red arrows). Atherosclerosis and foam cell production are both aided by dysregulation of lipoprotein metabolism, which causes HDL levels to decline and LDL and oxidized LDL to grow.

As was previously mentioned, dietary fatty acids may stimulate PPAR in the liver. Particularly potent PPAR activators are polyunsaturated fatty acids, which are superior than saturated and monounsaturated fatty acids. Therefore, fish oil, which is rich in n-3 polyunsaturated fatty acids, encourages the expression of PPAR target genes more effectively than other common dietary oils (Todisco et al., 2022). Increased fatty acid oxidation through a PPAR-stimulated mechanism is only one of the many health advantages associated with the omega-3 fatty acids eicosapentaenoic acid and docosahexaenoic acid, both of which are found in fish oils (Jump et al., 2005). We observed that certain, food-based fatty acids, such as oxo fatty acids and branched fatty acids, had considerable PPAR ligand activity, and that some of these fatty acids also demonstrated PPAR ligand activity (An et al., 2018). Twelve fatty acids generated from linoleic acid were analyzed for their PPARs ligand activity

(Hirata et al., 2015). These modified unique fatty acids, when included in the diet, helped alleviate obesity-related metabolic abnormalities in mouse models of obesity. Researchers have discovered that lactic acid bacteria in the stomach may convert polyunsaturated fats like linoleic acid into a variety of other fatty acids via a process called "saturated metabolism" (Kishino et al., 2013). This research suggests that metabolites of dietary fatty acids generated by lactic acid bacteria in the gut may function as PPARs ligands in the host and play a role in the regulation of host energy metabolism. In addition, it was shown that 10-oxo-11(E)- octadecenoic acid significantly suppresses inflammation in obese adipose tissue, which is one of the key causes of obesity-related metabolic issues due to the interaction between hypertrophied adipocytes and activated macrophages (Yang et al., 2017).

We observed that the isoprenoid farnesol, which is present in many different types of fruits and berries (including apricots, peaches, plums, blueberries, cranberries, raspberries, and strawberries), is an effective PPAR activator using a luciferase reporter assay. Hyperglycemia, glucose intolerance, insulin resistance, and hepatic triglyceride levels were significantly reduced in obese KK-Ay mice fed a diet containing 0.5% farnesol. Increased mRNA expression of PPAR target genes involved in fatty acid oxidation in the liver was seen after a high-farnesol diet. Experiments with PPAR-deficient animals showed that PPAR activity was required for the effects of a farnesol-containing diet on blood glucose and the activation of genes involved in fatty acid oxidation. On the other hand, a meal high in farnesol inhibited PPAR-dependent hepatic lipid biosynthesis (Li et al., 2007).

Conversely, farnesol did not affect the mRNA expression of PPAR target genes in WAT. This research suggests that farnesol may ameliorate metabolic issues in mice through PPAR-dependent and -independent pathways (Figure 4). The PPARs LBD has a large pocket where the ligand molecule is bound. Consequently, their ligands have been narrowed down to a few of naturally occurring and food-based compounds. Recognizing PPAR dietary ligands and incorporating them into one's diet may be helpful in the fight against obesity due to the PPARs' central function in coordinating whole-body glucose and lipid metabolism.

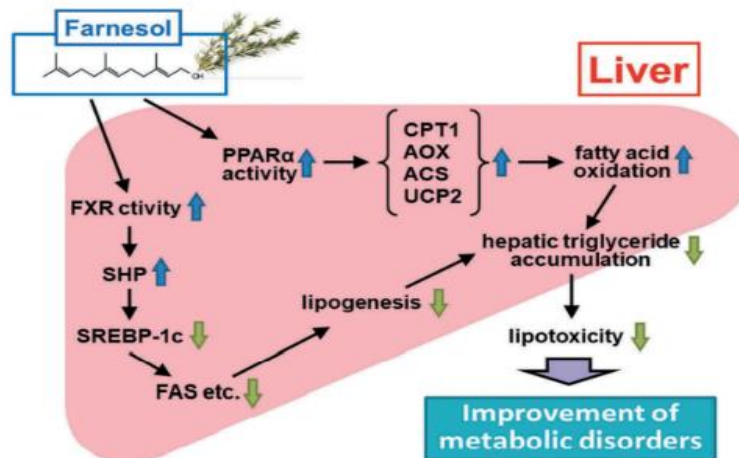


Figure 4. Consumption of farnesol controls glucose and lipid metabolism

Sources: (Goto et al., 2011).

Fatty acid oxidation was boosted by farnesol in the diet because of PPAR activation, whereas hepatic TG synthesis was lowered because of FXR-SHP-SREBP-

1c activation. The combined action of farnesol in the liver on hepatic steatosis and hyperglycemia suggests that it may help ameliorate these obesity-related metabolic disorders (Rizzo, 2014). The abbreviations for these proteins are as follows: CPT1 = carnitine palmitoyl transferase 1, AOX = acyl-CoA oxidase, ACS = acyl-CoA synthase, UCP2 = uncoupling protein 2, FXR = farnesoid X receptor, SHP = small heterodimer partner, and SREBP-1c = sterol regulatory element-binding protein-1c.

CONCLUSION

Amorphophallus konjac's corm produces konjac glucomannan (KGM), the primary polysaccharide. Health advantages include a decrease in body fat and satiety, better dental health, enhanced colonic beneficial organism formation and viability, and cholesterol. Anticholesterol medicine developed from konjac glucomannan for schizophrenia.

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