REVIEW ARTICLE

The Effect and Mechanism of Sucrose Consumption to Liver Disease – A Systematic Literature Review

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ABSTRACT

Introduction: One liver disease caused by excessive fat in the liver, called non-alcoholic liver disease (NAFLD), commonly occurs with obesity, diabetes, and other disorders. NAFLD is also associated with hepatic insulin resistance, steatosis, non-alcoholic steatohepatitis (NASH), and cirrhosis. Sucrose consumption has increased recently, and known can promotes NAFLD and will accelerate NAFLD development. This study aimed to discuss the effect and mechanism of sucrose intake on liver disease using a systematic literature review.
Methods: The author identified the articles from 6 online search engines, including PubMed, Science Direct, Sinta, Garuda, Google Scholar, and EBSCOHost. A total of 2271 retrieved articles were obtained from combined search strings in Indonesian and English from the search through online search engines. Excluded articles include title not relevant, duplicate articles, not open access, secondary study or review articles, research objective not appropriate, abstract not suitable, and the results/findings not relevant to the aims of this paper.
Results: A final of twenty-three articles were retrieved using the Mendeley reference manager. Studies included were published studies, types of experimental and observational studies, and their specific findings of sucrose effects on liver disease. Results reveal that most research was primarily conducted experimentally and in case-control study types on male rats.
Conclusion: The most common disease related to sucrose is NAFLD, fibrosis/cirrhosis with the indication of NASH, obesity, insulin resistance (IR), triglycerides (TG), hepatic steatosis, hepatocyte ballooning, and weight gain, which we will discuss further in this review.

Introduction

Excessive fat in the liver will cause liver diseases such as NAFLD. Non-alcoholic fatty liver disease (NAFLD) is the most frequent chronic liver injury worldwide caused by excessive large fat droplets aggregation in hepatocytes (liver cells) and causes hepatic steatosis. NAFLD correlates with other diseases, including the occurrence of diabetes, cardiovascular disease, and metabolic disorders.[1] The global prevalence of NAFLD is estimated at 24%, reported in South America (31%), the Middle East (32%), Asia (27%), the USA (24%), Europe (23%), and Africa (14%). This prevalence is persistently increasing annually.[2]

Hepatic steatoses occur when excessive intrahepatic triglycerides (IHTG) accumulate in non-alcoholic steatohepatitis (NASH) patients. NASH constitutes the subset of NAFLD and causes some significant risk of developing cirrhosis. Its complications include hepatocellular carcinoma (HCC).[3] In NASH, some hepatic inflammation and cellular injury will occur in fibrosis, the critical driver of cirrhosis.1 In previous studies, many articles investigated the effect of fructose intake on liver disease, but no reviews on the impact of sucrose intake on liver disease, but we more often consume sucrose than fructose.[4,5]

Our dietary habits can contribute to NAFLD progression, including sugar in beverage consumption. Beverages like carbonated and fruit drinks are sugar-sweetened beverages, and their consumption can lead to weight gain. Recent studies indicated that chronic consumption of sugars could lead to NAFLD. Sugar consumption can increase triglyceride, abdominal fat, blood pressure, and insulin resistance and contribute to NAFLD and obesity progression.[1] Consumption of high added sugar beverages in our daily diet can lead to obesity and chronic liver disease before realizing that it is hazardous for liver health.

Sucrose is a disaccharide sugar consisting of glucose and fructose and occurs naturally in sugarcane.[6] Sucrose consumption has increased by 76 kcal/day per

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person from 400 kcal to 476 kcal. Sucrose consumption is higher than high fructose corn syrup and leads to obesity and diabetes. Sucrose has been used in foods and beverages, especially in soft drinks, containing high added sugar, which will lead to higher energy intake with less optimum nutrition. Pure fructose and glucose as sucrose constituents have been studied recently for their effect on liver disease and increased triglyceride content. But when we consume it, we primarily consume sugar in sucrose form, which has a different impact from pure fructose/sucrose,[6] and the author will discuss it further in this article.

Based on the background and some of the factors causing liver disease explained before, the author conducted a study to identify the relationship between sucrose consumption and its mechanism for liver disease using a systematic literature review as a study literature technique regarding previous research. This review will discuss more sucrose effects and how it promotes liver disease.

Methods

The author conducted a systematic review to identify the relationship between sucrose intake with liver disease. The systematic reviews follow the Preferred Reporting Items for Systematic Reviews (PRISMA 2020) guidelines.

Search Strategy

The author conducted literature research using PubMed, Science Direct, Sinta, Garuda, Google Scholar, and EBSCOHost up to April 2022. Search languages are limited to English and Indonesian language for potential inclusion. The author chose these databases because of their evidence synthesis. The articles included were also limited to published studies (no unpublished studies included). The author searched All keywords using keyword combinations (as string) as provided in Table 1 (for English Keywords) and Table 2 (for Indonesian keywords). English keywords and strings were searched in PubMed, Science Direct, EBSCOHost, and Google Scholar databases, while the author also searched Indonesian keywords on Sinta, Garuda, and Google Scholar databases. Search strings were outlined in Tables 1 and 2 and focused on the sucrose effect on liver-related disease. All search results as potential sources were retrieved using the Mendeley reference manager.

Table 1. English Keywords Search String

"Sucrose intake" OR "Sucrose consumption" OR "Sugar consumption" OR "Sugar intake" OR "Sucrose consumption effect" OR "Sucrose consumption negative effect" OR "Sucrose intake side effect" OR "Sucrose intake pro and cons"
AND
"Liver Disease" OR "NAFLD" OR "Cirrhosis" OR "Hepatic Disease" OR "Steatosis" OR "NASH"
NOT
"Fructose" OR "Cardiovascular"

Table 2. Indonesian Keywords Search String

"Konsumsi Sukrosa" OR "Asupan Sukrosa" OR "Efek sukrosa" OR "Suplementasi Sukrosa" OR "Efek konsumsi sukrosa" OR "Efek negative sukrosa" OR "Kerugian sukrosa" OR "Kerusakan akibat sukrosa"
AND
"NAFLD" OR "Perlemakan Hati" OR "Penyakit hati" OR "Statosis" OR "Steatohepatitis" OR "NASH"
NOT
"Fruktosa" OR "Kardiovaskular"

Eligibility Criteria

This review included all studies using experimental and observational analysis. Trials included are using in vivo trials and have effects on liver disease. Studies also need to evaluate sucrose intake's role in liver-related disease. The author will use published experiment trials and observational studies type in this review—and exclude studies investigating the effects of fructose intake with liver disease or sucrose intake with cardiovascular disease. Also, the author will exclude documents categorized as reviews and no subjects (no experiments or no observations). The research articles identified and obtained from databases that evaluated the effects of sucrose intake on liver diseases were screened and finalized as described in Figure 1. No further studies that met the inclusion were identified through hand searching and checking references.

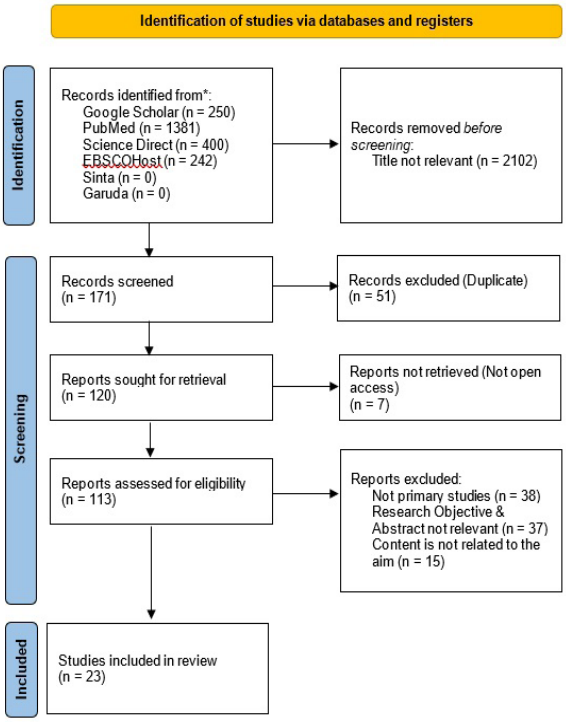

Figure 1. Systematic Review PRISMA Diagram

Results

Literature and Data Source

The combined string was searched in all databases, resulting in 2271 articles in 10 years of publishing limitation. Articles were screened manually from their title, resulting in 169 studies with a relevant title. All retrieved and screened articles using Mendeley

reference manager for duplication and removing the duplicates remained in 118 studies. Then papers were sought for retrieval manually and excluded seven studies that references could not access. After removing secondary articles, book chapters, comments, editorials, and letters, 74 articles remained. Studies with research objectives and abstracts not relevant to the article's research aim were excluded and stayed in 38 studies. After reading the complete reports, including 23 studies in this review study met the inclusion criteria.

Data extracted included (1) bibliographic information (author's name, publication year, publication status), (2) study aim, (3) region of the study, (4) sample number and criteria), (5) study type and study design, (6) results. Each primary research taken does not assess the effect of sucrose intake in different mechanisms that may provide biased results compared to each other. The author described the outcome from the list of quantitative studies evaluating sucrose intake's effect on liver disease in Table 3. The author produced a pie chart to visualize the gender effects on assessing liver disease, as shown in Figure 2.

The author also produced a pie chart to visualize the gender effects on assessing liver disease, as shown in Figure 2. From the chart, most gender used to evaluate in vivo effect of sucrose intake on liver disease was done in males (74%), followed by mixed-gender (17%) and females (9%). The large number of samples using the male gender shows that males have more noticeable effects than females.[27]

Table 3. List of Included Studies in the Review

Authors & Year	Subject	Total (N)	HSD Effects	Ref.
Zhou et al.; 2014	Rats	64	Heavier liver, fibrosis, cirrhosis, increased fatty and ballooning degeneration, inflammatory cell infiltration, hepatocyte apoptosis, lipid degeneration, fatty liver hepatitis, and insulin resistance.	7
Quintana-Castro, et al.; 2020	Wistar rats	20	Increase abdominal and epididymal fat, insulin levels, fat cells percentage, small adipocytes percentage, weight gain, body fat, IR, CD36 gene expression, dyslipidemia, serum FFA levels, triglycerides, and total cholesterol, LDL, VLDL, but a decrease in HDL level. HSD causes hepatic steatosis and lobular inflammation.	8
Lima, et al.; 2016	Wistar rats	60	Induced obesity, hepatic steatosis, hepatocyte ballooning, hyperleptinemia, hyperglycemia, hyperinsulinemia, hypertriglyceridemia, IR, NAFLD, serum VLDL-C levels, glucose serum levels, TG, hepatic lipogenesis, and MDA marker	9
Nojima et al.; 2013	(NSY) and C3H mice	15	Increased glucose intolerance, liver steatosis, hepatic gene expression. liver steatosis, body weight, liver weight, IR, intrinsic fat accumulation, liver fat accumulation, obesity, and hepatosteatosis	10
Sekkarie et al.; 2021	24 years adult	3095	Better fructose metabolizes and has up-regulated de novo lipogenesis.	11
Zagorova et al.; 2015	Wistar rats	14	Reproduce transition between simple steatosis and NASH, increase hepatocyte lipid accumulation, and TG concentration	12
Torres-Willalobos et al.; 2015	Wistar rats	>4	Develop steatosis, increased serum cholesterol level, hyperglycemia, hyperleptinemia, obesity, NAFLD, lipogenic genes expression, IR,	13
Sadowska et al.; 2017	Wistar rats	30	Increase body weight, liver rats, LDL-C, TAG levels, but lowering HDL-C, GI, and muscle fat.	14
Maj et al.; 2021	Iberian pigs	20	Increase blood urea nitrogen and serum creatinine, cause overt obesity, hyperleptinemia, and hepatic fat infiltration	15
Andayani et al.; 2016	Wistar rats	12	Causes fatty liver, increases IR, NAFLD, and SGPT and SGOT levels as a liver damage indicator, but SGPT and SGOT will not grow in large enough liver damage.	16
Castro et al.; 2018	Wistar rats	20	Increase CD36 mRNA gene expression, TG, VLDL, FFA, insulin content, total body fat, abdominal and epididymal fat, and IR associated with an inflammatory profile	17
Ragab et al.; 2015	Wistar rats	50	Increase LDL serum, TG, TC levels, hepatic lipids, lipase activity, lipid droplets number, hypertriglyceridemia, and liver lipids	18

Authors & Year	Subject	Total (N)	HSD Effects	Ref.
Plazas Guerrero et al.; 2021	Wistar rats	12	Increase body weight, glucose, insulin, IR, TG, VLDL-C, HDL-C levels, ballooned cells, inflammatory infiltrate, FFA levels, and NAFLD; also show hepatic parenchyma, macro-and microvesicular steatosis with hepatic steatosis, hyperinsulinemia, and hyperglycemia	19
Geidl-Flueck et al.; 2021	Male human	126	Increase hepatic FA synthesis and lowering LDL particle distribution	20
Baiges-Gaya et al.; 2021	Mice	24	Promotes NAFLD, NASH, oxidative stress, causes steatosis, increases serum cholesterol concentration, liver weight, and FA accumulation.	21
Da Silva et al.; 2021	Wistar rats	24	Increase catabolism in liver weight, liver cirrhosis, body weight, hepatic redox status, oxidative stress, inflammation, liver fibrosis, lactate levels, antioxidant enzymes, fibrosis reduction, and inflammatory infiltrate. HSD also can be an option for attenuating liver cirrhosis	22
Sun et al.; 2021	Wistar rats	40	Increase liver weight, TG serum, cholesterol levels, and hepatic lipids (including total lipids, TG, cholesterol, phospholipid) that indicate NAFLD	23
Corona-Perez et al.; 2017	Wistar rats	32	Ballooned hepatocytes, fat microvesicles, hepatic steatosis, fibrosis; increase collagen in the perisinusoidal zone but inhibit inflammation in the liver	24
Souza Cruz et al.; 2020	Wistar rats	12	Increase body weight, basal glucose level, serum TG, cholesterol, VLDL levels, hepatocyte size because of ballooning, collagen in hepatic parenchyma, IR, impaired glucose tolerance, glucose intolerance, IR, hyperinsulinemia, fat deposition, adiposity index, hepatocyte size, and show type 2 obesity early hallmark with obesity	25
Tallino et al.; 2015	Wistar rats	24	Induce transcript response in signaling, specific inflammation and fibrosis transcriptional responses in the liver, promote hepatology consistent with NAFLD and NASH, and influence particular gene expression with NAFLD spectrum.	26
Fernandes-Lima et al.; 2016	Swiss webster mice	20	Increase body mass, insulin levels, IR, glucose intolerance, hepatic lipid content (cholesterol and TAG), hepatic steatosis, hepatomegaly, hepatic gluconeogenesis, liver lipogenesis, and impairs insulin ability	27
Oliveira et al.;2014	Mice	40	Increase insulin serum level, macro-and microvesicular steatosis, liver cholesterol, SREBP-1c gene expression, inflammatory cytokines, fatty liver, hyperglycemia, hyperinsulinemia, blood glucose, IR, and resistin serum levels	28
Sun et al.; 2018	Wistar rats	20	Increase lipid accumulation in the liver, hepatic TG, phospholipids, cholesterol level, and IR.	29

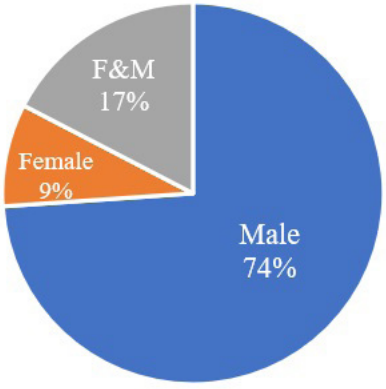

Figure 2. Sample Gender Distribution from Collected Articles

Discussion

The interventions reviewed in this study were various, either using induced sucrose drinks or fed high sucrose diets to evaluate the sucrose intake in samples. In addition, this study also included two studies conducted on humans to gain more accurate data on the sucrose effect on liver disease, whether in rats or human models. All data from retrieved articles will be extracted, including: (1) sucrose effect on liver disease as shown in Table 3, and (2) sucrose mechanism to liver disease as discussed below. From the result section, sucrose is one of the obesity inducers, as aldose reductase expression in the liver converts glucose into sorbitol by the polyol path and contributes to fatty liver development.[8] Sugars' metabolic effects can differ from starch due to the fructose component of sucrose, which causes many liver-related diseases.[30]

Based on Table 3 findings, we find that HSD has many effects experimented on in animals, especially rats. Some research also evaluated HSD effects in humans, but only using observation study type because of ethical reasons. Commonly used rats in this study are Wistar rats, known as more valuable than other species because of their smaller body size and high survival rates. From Figure 2. we understand that the most common gender in research findings is males. The large number of samples using the male gender shows that males have more noticeable effects than females.[27] Commonly, the researcher will use Wistar rats in diabetes determination because male rats can have more severe diabetic complications than females, and females also show a protective effect with their hormones, especially during the reproductive cycle on some diseases. There will be little or no hormonal interference in male rats during the study so that males will have a more stable hormonal status. Rats and humans are susceptible to many same diseases and have similar organs, whereas rats are biologically identical to humans for the same genetic reasons.

Some significant effects of HSD consumption are the occurrence of obesity, fibrosis, cirrhosis, ballooning degeneration, inflammatory cell infiltration, hepatocyte apoptosis, hepatitis, insulin resistance, NASH, NAFLD, steatosis, liver lipogenesis, and many more. These diseases are correlated with each other in specific mechanisms, such as via CD36 gene expression, increasing body weight, blood glucose levels, serum cholesterol effects, and even SGOT and SGPT levels. This review will further discuss how to complete HSD mechanisms that affect liver disease.

Obesity commonly occurs when there is no balance between energy intake and demand in our diets[8] and is also known as NAFLD risk promoter in children.[15] Obesity will increase body weight and fat,[8] associated with increased glucose serum levels in blood and liver.[3] It will raise some metabolic syndromes (such as insulin resistance (IR),[31] impaired glucose tolerance, and dyslipidemia),[25,29] increase VLDL-c (cholesterol) and triglycerides (TG) levels[9,19] which are related to hepatic disorders, including NAFLD.[25] But some studies reported no weight gain due to decreased food, protein, and lipids intake, which lowered total caloric intake and micronutrient deficiency and caused weight loss.[19] Excessive TG synthesis will be greater than liver capacity. Due to hepatic IR, insulin's ability to suppress glucose and VLDL-c production is impaired, so TG will be released to the bloodstream through VLDL-c lipoproteins[32] and lead to dyslipidemia.[19] Hepatic steatosis and hepatocyte ballooning (denoting cell injury[9]) due to structural changes in sugar ingestion[25] characterized obesity. Obesity is also observed clinically by increased BMI levels associated with hyperleptinemia, hyperinsulinemia,19 hypertriglyceridemia, increased VLDL-c (cholesterol) serum levels, depletion of antioxidants liver enzymes, and high MDA levels as oxidative stress[15] or lipid peroxidation marker that usually occurs in High-Sucrose Diet (HSD).[9]

Hyperglycemia and hyperinsulinemia happen because of sucrose's ability to stimulate higher insulin secretion by pancreatic β-cells,[19] promoting blood glucose and IR in samples.[28] Both will boost lipolysis in adipose tissue, causing raised free fatty acid (FFA) in the bloodstream and promoting tissue uptake. Higher FFA will stimulate hepatic lipid synthesis and impair beta-oxidation. FFA will influence insulin signaling by activating serine kinases and decreasing glucose transporters translocation in insulin-dependent tissues, leading to hepatic and peripheral IR development, associated with a greater risk of type II diabetes due to lipotoxicity and pancreatic β-cells failure.[19,27] Hyperinsulinemia can lead to increased fatty acids hepatic synthesis and TG accumulation in hepatocytes with subsequent steatosis,[9] while hypertriglyceridemia with central obesity will elevate hepatic lipase activity.[18] Hyperinsulinemia will stimulate hepatic de novo lipogenesis,[11] where sucrose will contribute to lipid metabolism by acting as SREBP-1c inducers. SREBP-1c is a mediator of hepatic lipogenesis and over induced in obese animals (as SREBP-1c accumulates, hepatic steatosis will result in higher).[27]

Increased sucrose levels will serve as acetyl-Co A sources to convert fatty acids (FA) for storage in hepatic and adipose tissue, contributing to obesity and liver disease.[25] Excessive FA will lead to mitochondrial dysfunction, increase lipid peroxidation, and reactive oxygen species (ROS) production (lead to hepatic stellate cells fibrogenesis and direct liver damage9 and promotes steatosis to NASH. A high level of FA will increase their absorption and cause chronic hepatic inflammatory state and progress to cell death and fibrosis.[19] Inflammatory markers—serum resistin levels also increased and secreted from adipose tissue.[28]

As liver weight increases, the fat liver will accumulate,[10,29] cause adipose tissue dynamic changes[21] and induce hepatic steatosis due to sucrose intake that will perform a rapid absorption at the intestinal level and the liver will use liver.[8] The most common type of NAFLD is steatosis, which shows in the early stage of NAFLD as a state of liver injury.[33] Evidence of hepatic steatosis with inflammatory cell infiltration increases hepatic TG concentration and transaminase enzymes and will indicate NAFLD development[8] positioning in grade 7 of NASH.[19] Hepatic steatosis will lead to hepatic IR, accelerated metabolic syndrome, and impaired insulin secretion.[10,28] Excessive TG synthesis will be greater than liver capacity, and insulin's ability to suppress glucose and VLDL-c production are damaged,

so TG28 will be released to the bloodstream through VLDL-c lipoproteins and lead to dyslipidemia.[19] Higher steatosis occurs in HSD samples[27] and will promote NAFLD evidenced by recent studies.[19] Hepatic steatosis also stimulates de novo lipogenesis, which increases FA availability to the liver and potentially drives hepatic TG over production[28] and has the same effect with hyperinsulinemia.

NAFLD is a hepatic disease not caused by alcohol consumption, evolving from non-alcoholic simple fatty liver (NAFL) to non-alcoholic steatohepatitis (NASH), hepatic fibrosis, and cirrhosis. Triglycerides (TG) is NAFLD characterized by triglycerides (TG) accumulation in hepatocytes,[17] known as steatosis, and associated with insulin resistance (IR),[7] obesity, type 2 diabetes mellitus, and dyslipidemia. Sucrose as a glucose container will be converted to fatty acids in enterocytes and hepatocytes as hepatic triglycerides synthesis, favoring steatosis development.[17]

One study also evaluated CD36 gene expression in the liver, which correlated with NAFLD development.8 CD36 is an FFA transporter and increases metabolic disorders risk such as IR, type II diabetes mellitus, obesity, and NASH. Hypertrophy and storage capacity of adipose tissue will allow it to maintain its basal levels of CD36 expression. Since the liver cannot increase its size, it will promote CD36 gene expression, which leads to receptor protein synthesis, ending in NAFLD development.[17] Another study evaluated SGPT and SGOT levels as liver damage indicators by indicating periportal liver tissue inflammation and enzymes release caused by necrosis or acute liver cell damage. SGOT and SGPT levels will increase due to hepatocellular injury and aminotransferase enzymes in liver cells that enter blood circulation due to changes in cell membranes permeability and increased enzyme levels in the blood. However, this indicator cannot detect acute liver damage. SGOT and SGPT levels will not increase or decrease due to the expansion of damaged hepatocyte cells, so the liver will not resynthesize the liver.[16] On the other hand, there is a report discussing the sucrose diet as an efficient diet in attenuating liver cirrhosis, reducing oxidative stress, inflammation, liver fibrosis, improving malnutrition and catabolism induced by thioacetamide, and suggested as an option for cirrhotic patients in catabolism situation[22]—but need further quantitative research to obtain more scientific data.

This systematic review has several limitations. First, all the papers included in this review mostly were in vivo experimental studies in animal models due to ethical reasons for human models,[7] so there is just a little data conducted on humans. Second, the author was only able to analyze the studies qualitatively since the outcome criteria of the studies were not homogeneous. Last, the author could not evaluate sucrose limit intake to influence liver disease development due to heterogeneous data of studies.

Conclusion

As discussed before, the most common disease-related to sucrose is NAFLD, fibrosis/cirrhosis with the indication of NASH, obesity, insulin resistance (IR), triglycerides (TG), and hepatic steatosis, hepatocyte ballooning, and weight gain with connected mechanisms. The author recommends conducting a meta-analysis quantitative review to establish conclusions about sucrose intake limitations to prevent liver disease and sucrose benefit to liver disease.

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Conflict of Interest

The author stated there is no conflict of interest to declare.

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