A RECENT UPDATE: MOLECULAR MECHANISM OF KOMBUCHA AS A PROBIOTIC FOR OBESITY MANAGEMENT

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ABSTRACT
The prevalence of obesity has continued to increase in the past decade which has an impact on several metabolic disorders in the body. Various efforts are made to reduce and overcome the effects of obesity such as pharmacological therapy. In addition, using natural ingredients such as probiotics is optimized to minimize the effects caused. The balance of gut microbiota has an important role in helping to improve dysbiosis, inflammation, and fatty liver in obesity. Method: This review used the scoping review necessary to collect and summarize scientific data as well as guide future investigations with the provision that articles are up to the last 10 years (2014) for kombucha as a drink rich in probiotics that could have potential as a natural therapy for obesity management. Results: A total of 244 articles were collected and 11 articles met the inclusion criteria. Conclusion: kombucha has beneficial effects and has the potential to improve obesity conditions from a variety of mechanisms.

Keywords: kombucha; obesity; probiotics

INTRODUCTION
Over the past half-century, the global incidence of obesity has surged to epidemic levels and increasing health problems worldwide (Mayoral et al., 2020). The incidence of obesity has increased significantly in all genders and all age groups, with elderly people and women having a disproportionately greater rate of obesity (Lin & Li, 2021). The prevalence of obesity (BMI ≥30 kg/m²) is estimated to increase to 892 million people in 2025 (World Obesity Federation, 2022). Obesity can negatively affect almost all physiological functions of the body and is at risk for the development of various non-communicable diseases (Chooi et al., 2019), such as type 2 diabetes mellitus (T2DM), cardiovascular disease (CVD), metabolic syndrome (MetS), chronic kidney disease (CKD), hyperlipidemia, hypertension, nonalcoholic fatty liver disease (NAFLD), some types of cancer, obstructive sleep apnea, osteoarthritis, and depression (Lin & Li, 2021). Moreover, the clinical complications of obesity affect almost every organ system, and the impact of obesity on morbidity, mortality, and healthcare costs is substantial (Hecker et al., 2022). A Meta-analysis of 2.88 million obese individuals, showed that obesity increased the risk of mortality by 1.18 higher than non-obesity (Abdelaal et al., 2017).

Obesity is a complex disorder that involves multiple molecular mechanisms such as energy imbalance, hormonal regulation, chronic inflammation, signaling pathways, autophagy, bile salt hydrolase, genetics, and neurologic (Wen et al., 2022) (Alruwaili et al., 2021). Furthermore, the incidence of obesity impacts changes in the composition of microbiota in the gut. Obese individuals experience an imbalance in the number of bacteria called dysbiosis (Breton et al., 2022). Dysbiosis causes a decrease in good bacteria such as Bifidobacterium, Bacteroides, Lactobacillus, and

Akkermansia and an increase in Firmicutes, Prevotella, and Methanobrevibacter which can affect the non-optimal production of SCFA (short chain fatty acids) (Anand & Mande, 2018). Dysbiotic conditions can also affect the increased risk of obesity in normal individuals because when SCFA production decreases, there is a disruption of the regulation of hunger and satiety systems in the digestive tract such as ghrelin and leptin hormones (12). In addition, SCFA plays a role in gastrointestinal physiology, decreases inflammation, promotes the healing of damaged tissues, and contributes to lipid metabolism and normal cell differentiation (13). Currently, the Federal Drug Administration (FDA) has approved six anti-obesity drugs for the long-term treatment of obesity such as Liraglutide, Orlistat, Semaglutide, Phentermine, and Bupropion-naltrexone (Tchang Beverly et al., 2021). Drugs for weight loss can be used, but have the potential to cause effects like nausea, vomiting, abdominal pain, and even diarrhea. Medications such as orlistat can reduce the absorption of fat-soluble vitamins A, D, E, and K (Tchang Beverly et al., 2021)(Othman et al., 2021). Therefore, this encour ages various parties to be able to develop natural obesity treatments for lower side effects.

Kombucha is a probiotic beverage that ferments tea with sugar and stater Symbiotic Culture of Bacteria and Yeast (SCOBY) (Kapp & Sumner, 2019). Kombucha contains various types of microbiota including acetic acid bacteria (Acetobacter, Gluconobacter, Gluconacetobacter, Komagataeibacter), lactic acid bacteria (Lactobacillus, Lactiplantibacillus, Lacticaseibacillus) and yeasts (Brettanomyces, Candida, Saccharomyces, Zygosaccharomyces), depending on raw materials, starter cultures, and fermentation temperature (Kruk et al., 2021). The taste of Kombucha tea evolved from sweet to sour, mildly bubbly, to a mild apple cider vinegar-like taste, increasing consumer acceptance of the taste and other sensory characteristics of the beverage (Marsh et al., 2014). Kombucha can be fermented for 7-14 days, The longer the fermentation time, the more acidic the taste of kombucha drinks and the more variety of lactic acid bacteria formed (Watawana et al., 2015).

Previous research proved that after four weeks of kombucha intervention, the number of bacteria that produce SCFA increased and the number of pathogenic and gram-negative bacteria decreased. Reduction of intestinal barrier damage caused by the improved gut microbiota decreased lipopolysaccharide (LPS) displacement and prevented in vivo inflammation and insulin resistance (Xu et al., 2022). Other studies prove that mice considering kombucha supplements after nine days showed improved glucose tolerance, decreased hyperinsulinemia, phosphofructokinase-1, and citrate synthase activity, regulated G-protein-coupled bile acid receptors (TGR5), farnesol X receptor gene expression, and steatosis repair (Moreira et al., 2022). On the other hand, Kombucha can act as an anti-inflammatory by reducing the production of nitric oxide, TNF-α, and IL-6, and increasing CD4+ T cells through IL-4 and TGF-β (Vázquez-Cabral et al., 2017)(Haghmorad et al., 2021). Interestingly, kombucha tea can reduce serum cholesterol levels, triglycerides, and LDL-C and increase HDL-C (Bellassoued et al., 2015). The comprehensive review focusing on the molecular mechanism of Kombucha in controlling obesity is still limited. This review aims to give a new insight into the molecular mechanism of bioactive compounds from kombucha in modulating obesity.

METHOD

An extensive literature search was conducted in Google Scholar, PubMed, Scopus, and Science Direct with the provision that articles are up to the last 10 years. Article searches using particular terms and keywords, such as (kombucha OR Obesity OR Profile lipids OR Inflammation OR Gut Health), kombucha AND obesity, kombucha AND gut health, kombucha AND inflammation, kombucha AND profil lipid, kombucha AND gut microbiota. Most articles have been published in the last decade and are limited to the English language only. From both the abovementioned databases, we identified articles related to obesity. Furthermore, the articles were classified based on obesity given a probiotic intervention in kombucha.

RESULTS AND DISCUSSION

The review used Arksey and O'Malley's framework, prepared following the guidelines "Preferred Reporting Items for Systematic Reviews and Meta-Analyses for Scoping Reviews (PRISMA ScR) and five-step scoping review approach (Page *et al*., 2021 and Westphaln *et al*., 2021). This method aims to ensure that the articles included in the review are fully reviewed carefully, clearly, and comprehensively. This review details the title, abstract, introduction, methods, results, and discussion using a four-phase flowchart detailing the inclusions and exceptions to the article presented in Figure 1.

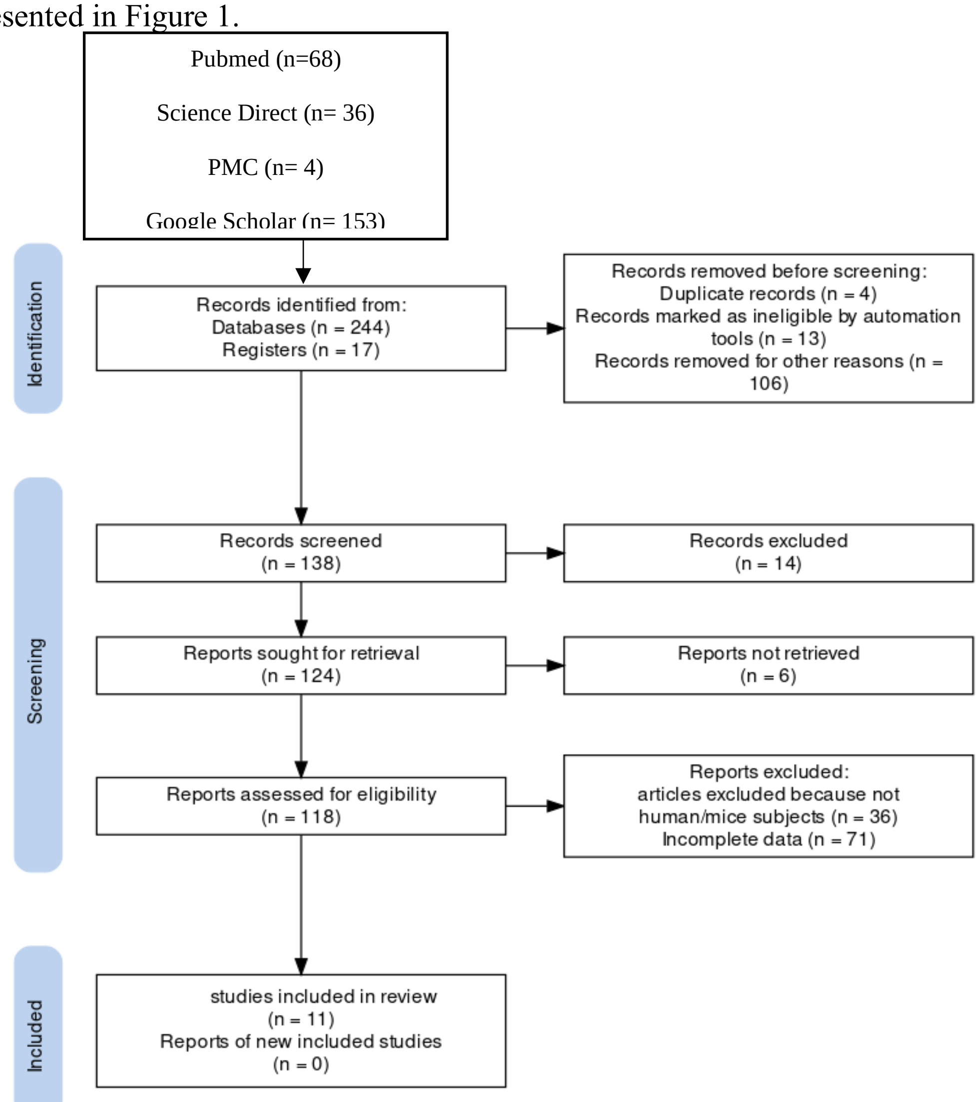

Figure 1. PRISMA flow chart

A total of 244 journals have been screened, and 11 journals that meet the requirements in this article were obtained. This study investigated the effects of administering various types of kombucha as a probiotic drink to improve obesity management. The results of the evidence findings are presented in Table 1:

Table 1.
Evidence Finding of Kombucha as Probiotic for Obesity Management

No	Titles	Models	Clinical parameters	Important findings	References
1.	Protective effect of kombucha on rats fed a hypercholesterolemic diet is mediated by its antioxidant activity	Adult male Wistar rats	Cholesterol, Triglycerides, LDL, HDL, AST, ALT, GGT, TBARS, SOD, CAT, Kreatinine, urea, Histopathology of Liver and kidney.	1) Kombucha tea induced lowered serum levels of Cholesterol, Triglycerides, LDL-C 2) Kombucha tea increases serum levels of HDL-C 3) Kombucha tea significantly decreases of liver dysfunction like AST, ALT, and GGT levels and improves liver and kidney function	(Bellassoued *et al*., 2015)
2.	The distinctive hepatoprotective activity of turmeric kombucha (Curcuma longa) induced by diethylnitrosamine in Balb/C mice Elok	Thirty male Balb/c	Alanine transaminase (ALT), Aspartate transaminase (AST), and Malondialdehyde (MDA) were measured, and the liver histology was established.	1) Turmeric Kombucha acts as an anti-inflammatory such as improving ALT and AST levels 2) Improvement of hepatic histopathological conditions	(Zubaidah *et al*., 2023)
3.	Comparison of in vivo antidiabetes activity of snake fruit Kombucha, black tea Kombucha, and metformin	Twenty -five male Wistar rats	Fasting plasma glucose (FPG) levels, superoxide dismutase (SOD) activities, malondialdehyde (MDA) levels and lipid profiles (total triglyceride, total cholesterol, LDL and HDL)	1) The products enhanced the oxidative stress indicators and lipid profiles and considerably decreased the fasting plasma glucose levels (67–76%). 2) The goods also enhanced the	(Zubaidah *et al*., 2019)

				pancreatic β-cells in diabetic rats based on the results of immunohistochemistry staining of pancreatic tissues. 3) Snake fruit kombucha is more effective than black tea kombucha for decreasing cholesterol, triglyceride, and LDL	
4.	Kombucha drink enriched with sea grapes *(Caulerpa racemosa)* as potential functional beverage to contrast obesity: An in vivo and in vitro approach	Forty male albino Swiss mice (M. musculus)	In vivo: total cholesterol, TG, HDL, and LDL In vitro: lipase inhibitory activity	1) Sea grapes kombucha as a treatment for weight loss 2) Good potential as a probiotic beverage for anti-obese and improving lipid activity	(Permatasari, Firani, *et al*., 2022)
5.	Kombucha tea improves glucose tolerance and reduces hepatic steatosis in obese mice	Six C57BL male mice	Glucose tolerance test, an inflammatory cytokine, lipogenesis enzyme, bile acid pathway gene expression, and histopathology hepar.	1) Kombucha improved glucose tolerance and inflammatory cytokine (TNF-α and SREBP-1 gene expression) 2) Kombucha attenuated hepatic steatosis 3) Beneficial effects in decreasing the changes in metabolism correlated to diet-induced obesity	(Moreira *et al*., 2022b)
6.	Modulation of gut microbiota and markers of metabolic syndrome in mice on cholesterol and fat-enriched diet by butterfly pea flower kombucha	Forty male albino mice (Mus musculus)	In vivo: total cholesterol, TG, HDL, LDL, blood glucose, PGC-1α, TNF-α, IL-10, SOD Liver and Gut microbiome In vitro: Lipase inhibition activity, α-Amylase inhibition activity, ABTS radical scavenging activity	1) Butterfly pea flower kombucha can improve lipid profiles levels, oxidative stress (SOD) and decrease inflammatory markers (PGC-1α, TNF- α, and IL-10)	(Permatasari, Nurkolis, *et al*., 2022)

7	Kombucha tea prevents obese mice from developing hepatic steatosis and liver damage	Fifteen db/db mice	Liver histology and immunohistochemistry, triglyceride, ALT and AST	1) Kombucha tea can reduce triglyceride synthesis, decrease ALT and AST 2) Kombucha tea reduces the accumulation of lipids and the risk of worsening liver conditions	(Hyun *et al*., 2016)
8	Anti-obesity effects of SCOBY Jackfruit beverages and their influence on gut microbiota	Thirty mice	Body weight, SCFA, AST, ALT, alkaline phosphatase, total protein, lipid profiles, pro-inflammatory cytokines, histopathology liver, kidney spleen, and stomach	1) Intervention for two months of SCOBY jackfruit beverages increases the ratio of *Bacteroides* and reduces the ratio of *Firmicutes* 2) SCOBY jackfruit potentially used as therapeutic for weight management in obesity 3) Significantly reduce the increase in pro-inflammatory cytokines	(Koh *et al*., 2022)
9	Effect of kombucha on gut-microbiota in mouse having non-alcoholic fatty liver disease	Twelve db/db mice	Liver histology, metagenomic DNA extraction	1) Kombucha tea protects against fat accumulation in obese mice 2) Kombucha tea improves dysbiosis in the gut microbiota of mice	(Jung *et al*., 2019)
10	Hepatoprotective effect of kombucha tea in rodent model of nonalcoholic fatty liver disease/nonalcoholic steatohepatitis	Fifteen db/db mice	Profiles lipid and liver function	1) Kombucha tea significantly decreases the level of hepatic triglyceride in the liver and reduces the risk of liver damage 2) Kombucha tea protects hepatocytes from apoptosis and reduces peroxisome	(Lee *et al*., 2019)

				proliferator-activated receptor gamma *(Ppary)* 3) Kombucha tea had an anti-inflammatory effect on the NASH mouse model 4) In an analysis of gene expression, treatment from kombucha can decrease free fatty acids in the liver and increase triglyceride synthesis	
11	Kombuchas from green and black tea modulate the gut microbiota and improve the intestinal health of wistar rats fed a high-fat high-fructose diet	Forty wistar rats	Intestinal permeability, fecal pH and short chain fatty acids, DNA extraction and microbiota profile	1) Green tea kombucha or black tea kombucha were able to modulate the gut microbiota in Wistar rats with HFHFr diet 2) Green tea kombucha has been shown to stimulate the growth of beneficial bacteria like Adlercreutzia and increase the synthesis of propionate	(Costa *et al*., 2022)

The molecular mechanism of kombucha in obesity relates to the modulation of gut microbiota

The intestinal microbiota has been recognized to have an important role in regulating the health of human digestive organs. In the digestive tract of healthy individuals, there are more than 1000 species of microbiota that play a role in the balance of gastrointestinal tract homeostasis (Ruan *et al*., 2020). The composition of intestinal microbiota in the adult digestive tract is dominated by two phyla, namely *Bacteroides* and *Firmicutes*, followed by *Actinobacteria* and *Proteobacteria* with smaller numbers. In obesity, there is an increase in the number of pathogenic bacteria such as *firmicutes* and a decrease of about 50% in the number of good bacteria, which can cause a decrease in the balance and diversity of intestinal microflora or called dysbiosis in the digestive tract (Cheng *et al*., 2022).

Dysbiosis is also defined as changes in the structure and/or function of microbiota communities, capable of causing/encouraging adverse distortions in homeostasis between microbe-hosts. Dysbiosis that occurs in the digestive tract can increase the risk of intestinal inflammation, colon cancer, cardiovascular disease, and IBD (Inflammatory Bowel Disease) and decreased immune system function (Buttó & Haller, 2016). Dysbiosis can also affect the non-optimization of lipid pathways in the liver involving bile acid metabolism as well as increased inflammation that can develop into fibrosis which is at risk of increasing the risk of developing cirrhosis and even hepatocellular carcinoma (HCC) (Byrne & Targher, 2015). Dysbiosis can be identified by three characteristics that are as follows: 1) fewer beneficial microorganisms in the gastrointestinal tract 2) An increase in dangerous germs 3) a decrease in the variety of microorganisms overall (Degruttola *et al*., 2016). Schema of the difference in bacterial composition in the gastrointestinal tract between normal individuals and dysbiosis presented in Figure 2:

A. Normal Intestine Individuals B. Dysbiosis Individuals

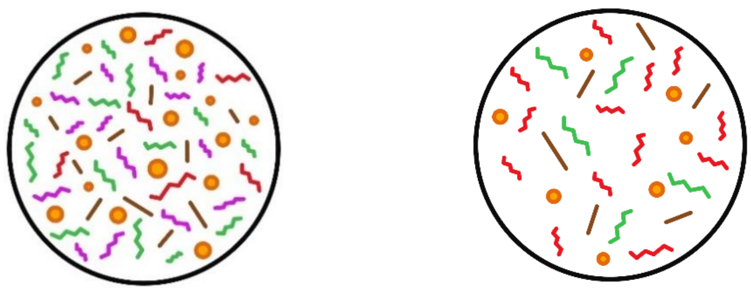

Figure 2. Differences in the composition of good bacteria and pathogens between normal healthy intestines in individuals and those undergoing dysbiosis.

*Green, purple, brown, and oranges are good bacteria and red is pathogen bacteria.

Obesity conditions can increase the composition of pathogenic bacteria such as Firmicutes and reduce the number of good bacteria such as Bacteroides (R. *et al*., 2018). On the other hand, Microbes that promote the gut barrier, such as *Lactobacillus, Bifidobacterium, Bacteriodetes species, Clostridiales*, and *Akkermansia muciniphilia* are temporarily reduced by a high-fat diet (HFD). In contrast, microbes that contribute to the breakdown of the barrier, such as *Oscillibacter* and *Desulfovibrio* are increased. HFD causes an increase in *Desulfovibrio*, particularly *Bilophila wadsworthia*, which causes the production of genotoxic hydrogen sulfide (H2S) gas and IEC hyperpermeability and hypoplasia (Lam *et al*., 2015). Kombucha is one of the probiotic drinks that contains several good bacteria such as *Acetobacter, Bacillus, Lactobacillus, Pediococcus*, and others as well as yeast fungi such as *Saccharomyces* contained in kombucha products. Apart from being a probiotic, kombucha also has a role as an antioxidant which contains amino acid compounds, vitamin C, and B complex. Probiotics also function as antimicrobial agents through the production of hydrogen peroxide, organic acids, and short-chain fatty acids (SCFA) (Xu *et al*., 2022). The following role of kombucha in improving the function of the digestive tract can be seen in Figure 3:

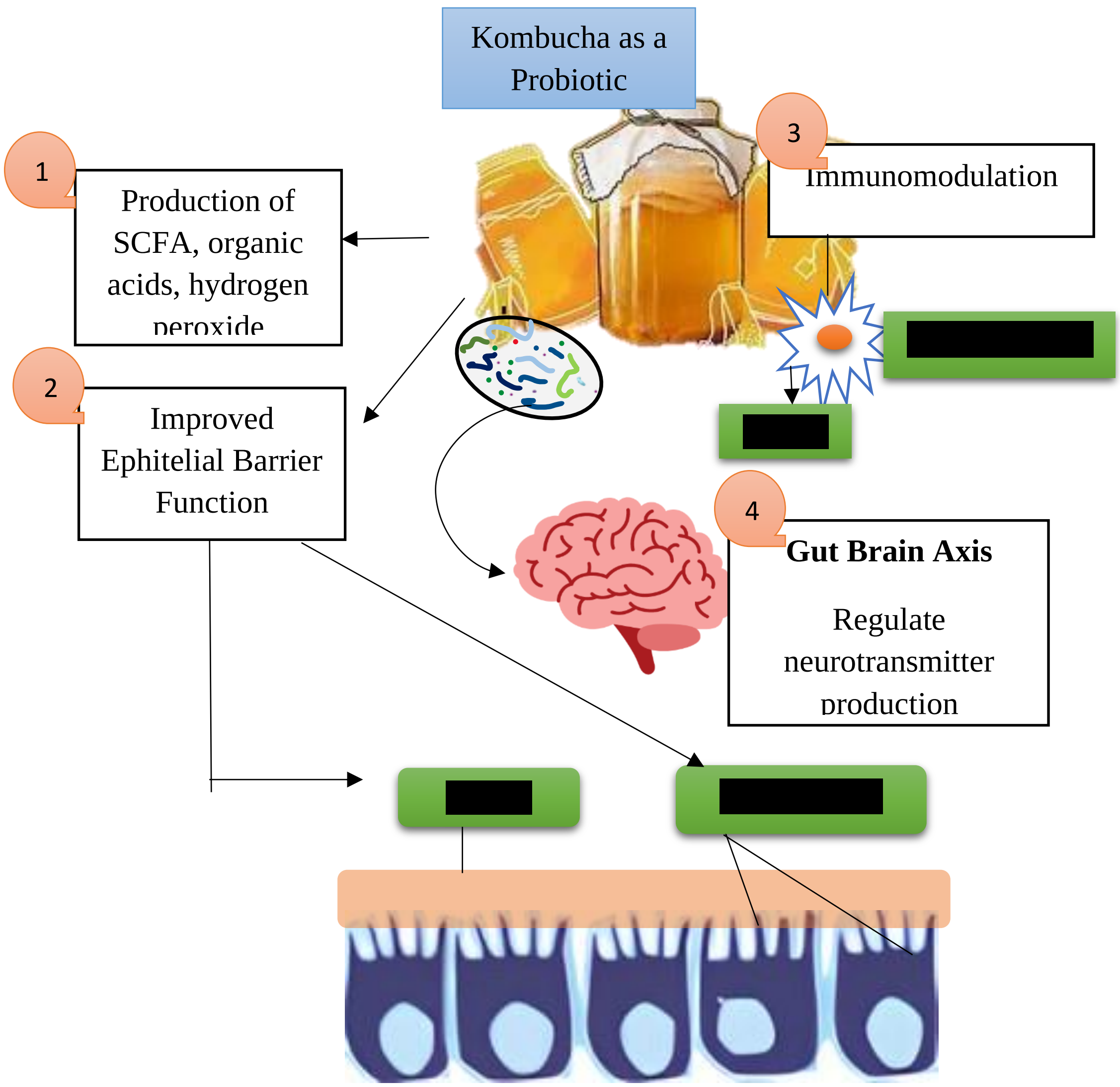

Figure 3.

Mechanism of action of probiotics in the gastrointestinal tract. 1) Probiotics generate antimicrobial compounds that stop the growth of pathogens. 2) Probiotics improve mucus formation and tight junction protein expression, which stop pathogens from moving from the intestine into the bloodstream and support the operation of the epithelial barrier. 3) Probiotics control the host's immunity by altering the maturation and function of dendritic cells, which in turn boosts the activity of T cells, which are crucial for maintaining immunological homeostasis. 4) Probiotics also control the synthesis of dopamine, gamma-aminobutyric acid (GABA), and serotonin, among other neurotransmitters through the Gut Brain Axis Mechanism (Latif *et al*., 2023).

The molecular mechanism of kombucha related to lipid metabolism

Lipid metabolism refers to the metabolic reactions within the body to control the synthesis, degradation, and utilization of lipids, or fats, as sources of energy, components of cell membranes, and messengers of cellular signals. The body's tissues and organs go through a multitude of intricate responses during this process (Chandel, 2021). Food-derived fats are transported to peripheral tissues by the small intestine, where they are effectively absorbed. Lipids will be stored in adipose tissue if they are given in excess, which will increase the mass of body fat. Non-alcoholic fatty liver disease is caused by an imbalance between the liver's absorption of free fatty acids (Wit *et al*., 2022). Two key mechanisms by which probiotics control lipid metabolism are through SCFA and secondary bile acids. Probiotics like kombucha contain bacteria that aid in the production of the enzyme bile salt hydrolase (BSH) (Allain *et al*., 2018), it is involved in the transformation of primary conjugated bile salts into secondary bile acids, which the body absorbs more easily. Cholesterol can bind to secondary bile acids and be excreted through the feces (Hernández-Gómez *et al*., 2021). In a study by Tonucci *et al*. (2017), probiotic supplementation in the form of dairy products up to 120 grams for six weeks was administered to 50 subjects with type 2 Diabetes Mellitus. The results demonstrated the potential of probiotics to improve lipid metabolism, as evidenced by a significant reduction in LDL and cholesterol levels (Tonucci *et al*., 2017).

The molecular mechanism of kombucha related to inflammation pathway in obesity

Obesity is also referred to as a condition that describes the presence of low-grade chronic inflammation that can cause metabolic disorders, including insulin resistance, type 2 diabetes mellitus, hypertension, dyslipidemia, and even cancer (Hotamisligil, 2017). Excess fat intake in obese individuals is stored in adipocyte cells. Adipose tissue is involved in the release of inflammatory cytokines, peptide hormones, miRNA, exosomes, and endocrine hormones. Anti-inflammatory adipokines, including transforming growth factor-beta (TGFβ), apelin, adiponectin, IL-1 receptor antagonists (IL-1Ra), IL-4, IL-10, and IL-13, are secreted by adipose tissue in healthy persons. On the other hand, pro-inflammatory cytokines including IL-6, TNF-α, leptin, angiotensin II, and plasminogen activator inhibitor 1 are mostly secreted by fat tissue in obese people (Khanna *et al*., 2022). Adiponectin reduces inflammation by regulating cytokines including TNF-α, MCP-1, and IL-6 (Luo & Liu, 2016). Obesity is associated with higher levels of leptin and lower levels of adiponectin. Reduced levels of adiponectin can raise the risk of inflammation and possibly cognitive decline (Tasnim *et al*., 2023).

The key function of controlling the metabolism of proteins, fats, and carbohydrates is handled by the liver, the primary metabolic organ in humans. It has been shown that NAFLD is up to 80% more common in obese patients than in those with a normal BMI and no metabolic risk factors. These findings demonstrate the substantial association between NAFLD and obesity (Milić *et al*., 2014). It plays a significant part in controlling the metabolism of fat, protein, and carbohydrates in the human body(Parry & Hodson, 2017). In LPS-induced mice, kombucha can successfully lower TNF-α, IL-6, and IL-1β levels while also raising macrophage and T cell counts. Additionally, this study demonstrated the immunomodulatory effects of kombucha and its ability to regulate defective cellular immunological activity in mice at an early stage of sepsis. Kombucha has anti-inflammatory properties by changing the variety of gut microbiota and encouraging the growth of butyrate-producing bacteria. Our findings demonstrate the potential of kombucha as a novel anti-inflammatory drug that prevents the onset of sepsis-related systemic inflammatory reactions (Sales *et al*., 2023).

CONCLUSION

In conclusion, the increased prevalence of obesity can lead to complications of other diseases and lower overall health. Kombucha as a probiotic has the potential to improve health issues related to obesity, including dysbiosis, lipid metabolism, and inflammation through the mechanism of various paths.

ACKNOWLEDGMENTS

This paper behind it would not have been possible without the exceptional support of my lecturer. Knowledge, attention and support provided so that this article can be completed properly.

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