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Article

Health benefits of Kombucha: drink and its biocellulose production

Luis Otávio Aguiar Cavicchia[1], Martha Elisa Ferreira de Almeida[1*]

[1]*Federal University of Viçosa (UFV), Campus Rio Paranaíba, Rio Paranaíba, MG, Brazil*

Kombucha (tea and biocelluose) has been used worldwide due to its high nutritional, functional, and economic potential. This fermented tea has been used in folk medicine to treat several pathological conditions and its biocellulose in the industrial sector. In this context, this paper presents a scientific literature review on the main phytochemicals of Kombucha and respective biological activities to assess their potential uses. The tea has presented a wide range of bioactive compounds such as amino acids, anions, flavonoids, minerals, polyphenols, vitamins, and microorganisms. Moreover, its biocellulose is rich in fibers. These compounds contribute to various biological responses such as antioxidant, hepatoprotective, antitumoral, antidiabetic, and antihypercholesterolemic effects. In this sense, both the tea and its biocellulose are promising for human use. Besides, Kombucha presents itself as a drink option for vegetarians and/or those seeking healthier diets, as its biocellulose can bring metabolic benefits. Our review demonstrates that both can be used as functional foods and/or sources of bioactive compounds for food and industrial applications.

Keywords: Kombucha. Fermentation. Tea. Biocellulose. Polyphenols.

INTRODUCTION

Human consumption of fermented milk dates from about 10.000 years ago. Fermentation has been used for alcohol production from grains, fruits, and beetroots. In the excavation of the tomb of an Egyptian pharaoh in 1995, papyri were found describing a liquor to treat diseases, which consisted of a combination of wine and herbs. Wine was the first fermented beverage according to Arnaldus de Villa Nova, in books of the XVI century, besides being described as a medicinal drink to treat dementia and sinusitis (Ozen, Dinleyici, 2015).

Every food has its own importance to human metabolism whether as a source of energy, nutrients, or bioactive compounds (Leal *et al*., 2018). Functional foods promote beneficial effects on one or more human organism functions and ensure bodily health and well-being. Kombucha is a functional beverage produced from a symbiosis of bacteria and yeasts, whose metabolisms are interdependent and with mutual benefits (Kapp, Sumner, 2019). The microorganisms in this beverage can become part of the intestinal flora of those who drink it (Shi *et al*., 2016; Amarasinghe, Weerakkody, Waisundara, 2018). Kombucha or fungus tea (Chen, Liu, 2000) is the name of a carbonated beverage consumed worldwide, which has a slightly sweet and citrusy taste, with low alcohol content and vinegar-like taste. The term “Kombucha” derives from the Japanese words kombu (seaweed) and cha (tea) (Ernst, 2003). It is also popularly known as Chainii grib, Chainii kvass, Champignon de longue vie, Kocha kinoko, Ling zhi, and Red tea fungus (Amarasinghe, Weerakkody, Waisundara, 2018).

The term probiotic refers to living microorganisms that promote nutritional benefits. Some bacteria and yeasts are used in beverage production (acetic and alcoholic) and foods such as sauerkraut, yogurts, and dairy drinks (Kapp, Sumner, 2019). Fermented foods have beneficial effects on human cognition, intestinal flora composition, and the immune system. They also have anti-allergic,

***Correspondence:** M.E.F. Almeida. Universidade Federal de Viçosa (UFV). Campus Rio Paranaíba. Rio Paranaíba, MG, Brasil. Phone: 34-991049004. E-mail: martha.almeida@ufv.br. Luis Otávio Aguiar Cavicchia (http://orcid.org/0000-0002-9835-8566). Martha Elisa Ferreira de Almeida (http://orcid.org/0000-0002-5906-2244).

anti-atherosclerosis, and anti-inflammatory effects, besides being used in the treatment of cancer, *diabetes mellitus*, and hypertension (Bellassoued *et al.*, 2015; Marco *et al.*, 2017; Şanlier *et al.*, 2019; Xia *et al.*, 2019). In turn, prebiotics are chemical compounds metabolized by the gut microbiota (e.g., fructooligosaccharides, and galactooligosaccharides) (Davani-Davari *et al.*, 2019), which bring benefits to human health. Symbiotic foods contain probiotic microorganisms and prebiotic nutrients. Their intake increases microbial survival after passing through the gastrointestinal tract and then be incorporated into the human microbiome (Pandey, Naik, Vakil, 2015; Markowiak, Śliżewska, 2017)..

Kombucha is believed to originate from Manchuria, northeastern China (Greenwalt *et al.*, 2000; Goh *et al.*, 2012; Salafzoon, Hosseini, Halabian, 2017), during the Jin Dynasty (220 BC) (Greenwalt *et al.*, 2000; Jayabalan *et al.*, 2014; Kapp, Sumner, 2019). After spreading to countries near China, its use became common and disseminated due to trade routes and globalization. It became popular after World War II and gained the interest of consumers and beverage companies. In 2016, PepsiCo bought the company Kevita, a Kombucha producer; then, in 2017, its consumption and of other fermented drinks increased by 37.4%. In 2018, its sales grew by 49 million dollars due to its commercial rise (Kapp, Sumner, 2019). This beverage is mainly consumed in Asian countries, but it has gained popularity in other parts of the world (Pakravan *et al.*, 2018).

In Russia, Kombucha is used to treat metabolic diseases, hemorrhoids, and rheumatisms, whereas in Europe for digestive system improvement and blood detoxification (Greenwalt *et al.*, 2000). Studies have shown that such a drink can mitigate *diabetes mellitus*, dyslipidemia, and non-alcoholic liver sclerosis, as well as decrease the action of free radicals and act against enteric parasites and scalp fungi (Greenwalt *et al.*, 2000; Aloulou *et al.*, 2012; Bellassoued *et al.*, 2015; Mahmoudi *et al.*, 2016; Leal *et al.*, 2018; Dimidi *et al.*, 2019; Jung *et al.*, 2019; Xia *et al.*, 2019).

Given the great diversity of eating habits and advances in food and health technologies, several dietary patterns have emerged, among them vegetarianism with emphasis on veganism. This aims to reduce animal suffering, meat consumption, and some environmental problems related to animal protein production (Key, Appleby, Rosell, 2006; Le, Sabaté, 2014; Appleby, Key, 2016). Thus, tea and biocellulose from Kombucha can be suitable not only for vegetarians but also for those who seek a quality of life by preventing and treating diseases.

This review proposes to describe the benefits of Kombucha regarding the effects of symbiotic fermentation on body metabolism and its biocellulose.

FROM KOMBUCHA PREPARATION TO DISEASE TREATMENT

Kombucha can be made at home using sterilized utensils and good quality water to avoid contamination by pathogenic microorganisms (Greenwalt *et al.*, 2000). It is prepared from an infusion of herbs (5 g of a chosen herb per liter of water) and addition of sugar for fermentation (from 50 to 200 g/L) (Greenwalt *et al.*, 2000; Leal *et al.*, 2018). Black tea (*Camelia sinensis*) is the most used infusion since it has high concentrations of antioxidant compounds after fermentation (Cardoso *et al.*, 2020). Green tea, meanwhile, stands out for its antibiotic functions (Primiani *et al.*, 2018; Cardoso *et al.*, 2020). Other substrates used are mint, jasmine, lemongrass teas (Leal *et al.*, 2018), oolong (May *et al.*, 2019), rooibos (Gaggìa *et al.*, 2019), and coconut water (Watawana *et al.*, 2016). Herbal teas of mint, lime flower, and barley have been tested but have not obtained good fermentation results nor the same compounds as in Kombucha using *Camelia sinensis* (Greenwalt *et al.*, 2000). After 10 minutes boiling in water with sugar, tea leaves can be removed, letting the drink cool down to introduce the microbial colony (Greenwalt *et al.*, 2000), whose microorganisms are called SCOBY (*Symbiotic Culture of Bacteria and Yeast*), which vary with the season and geographical region (Leal *et al.*, 2018).

The most common SCOBY bacteria are *Acetobacter aceti*, *Acetobacter pasteurianus*, *Acetobacter xylinoides*, *Acetobacter xylinum*, *Bacterium gluconicum*, *Enterococcus sp*, *Gluconobacter oxydans*, *Lactobacillus sp.*, *Lactococcus sp.*, *Leuconostoc sp.*, *Propionilbacterium sp.*, and *Spacobum*. Yet the main yeasts are *Brettanomyces bruxellensis*, *Brettanomyces lambicus*, *Saccharomyces cerevisiae*, *Saccharomyces ludwigii*, *Schizosaccharomyces pombe*, *Zygosaccharomyces bailii*, *Zygosaccharomyces rouxii*, *and Torulaspora delbrueckii* (Greenwalt *et al*., 2000; Goh *et al*., 2012; Jayabalan *et al*., 2014; Leal *et al*., 2018).

During fermentation, Kombucha drink pH must be 2.5 (Greenwalt *et al*., 2000). Yet the final pH should be 4.2 to avoid a high concentration of acetic acid (Kovacevic *et al*., 2014), as it acidifies the beverage and produces a vinegar odor (Leal *et al*., 2018). Sucrose fermentation was reported to produce 11 g/L acetic acid on the 30th day, which decreases to 8 g/L on the 60th day (Chen, Liu, 2000). However, this amount is smaller when molasses is fermented (Jayabalan *et al*., 2014).

Kombucha beverage is commercially prepared by adding preservatives such as sodium benzoate (0.1%) and potassium sorbate (0.1%), and then maintained under refrigeration (Watawana *et al*., 2015).

Villarreal-Soto *et al.* (2019) fermented Kombucha for 21 days in two 1.15-cm-high containers (9- and 23-cm diameter, respectively) and identified 47 different compounds (e.g., alcohols, sugars, and phenols). They also noted that the larger container had higher concentrations of anti-inflammatory molecules. Therefore, the larger the fermentation containers, the greater the quantity and the final effect of chemical compounds produced.

Fermented Kombucha is usually stored for 3 to 10 days (Greenwalt *et al*., 2000; Jayabalan *et al*., 2014; Leal *et al*., 2018). This period can last up to 60 days, depending on the culture of bacteria or yeasts (Watawana *et al*., 2015). At longer fermentation times, storage temperature should be close to 30 °C, as lower temperatures may decrease counts of yeasts and of acetic and lactic bacteria (Fu *et al*., 2014; Leal *et al*., 2018). Moreover, fermentation containers must be covered with a cloth or other porous media to allow gas exchange, as microbial colonies perform anaerobic respiration and thus produce gases (Greenwalt *et al*., 2000; May *et al*., 2019). After fermentation, the fermented tea or just a biocellulose film can be added to another infusion to form a new drink and new biocellulose films (Greenwalt *et al*., 2000). Amarasinghe, Weerakkody, Waisundara (2018) reported that a 2-month fermentation decreases beverage antioxidant activity and increases its acidity and turbidity, thus changing its sensory properties. Thus, the tea must be consumed before such period so that its bioactive compounds could bring benefits to consumers.

SCOBY metabolism

Biochemically, fermentation is a metabolic process of obtaining energy from the SCOBY microorganisms in Kombucha. This process is influenced by storage-room temperature, fermentation time, and sucrose content (Goh *et al*., 2012; Fu *et al*., 2014; Leal *et al*., 2018). Yeasts (*Brettanomyces*, *Candida*, *Pichia*, *Saccharomyces*, *Saccharomycodes*, and *Zygosaccharomyces*) (Cottet *et al*., 2020) produce the enzyme invertase, which catalyzes the hydrolysis of sucrose into glucose and fructose (May *et al*., 2019). These, in turn, are substrates used by Kombucha bacteria and yeasts to produce ethanol and carbon dioxide (Leal *et al*., 2018; May *et al*., 2019; Cottet *et al*., 2020). The main bacterial genera in the SCOBY are *Acetobacter* and *Gluconobacter*. From the actions of alcohol dehydrogenase and aldehyde dehydrogenase, *Acetobacter* transform ethanol into acetic acid, which reduces the pH of the beverage (May *et al*., 2019), and enters the Krebs Cycle, producing CO_2, H_2O, NADH, $FADH_2$, ATP, and other compounds (Bellassoued *et al*., 2015).

The acetic acid produced during Kombucha fermentation has antibacterial activity and prevents beverage contamination with pathogenic bacteria (Watawana *et al*., 2015). High ethanol levels in tea can alter cell membranes of bacteria and yeasts, decreasing their concentrations (May *et al*., 2019). Some phenolic compounds in tea infusions are degraded by enzymes and increase contents of antioxidant molecules in drinks (Bellassoued *et al*., 2015). Bacteria in tea drinks transform fructose and glucose into gluconic acid and cellulose, which will compose biocellulose or biofilm (May *et al*., 2019).

Importance of bacterial biocellulose

Polymers are divided into three groups: biopolymers, synthetic polymers, and bioengineering polymers. Cellulose produced by microorganisms is known as biocellulose and is 100% biodegradable. It stands out for its fiber size and purity of 99%, while plant-produced cellulose has only 80% (Cottet *et al*., 2020). This is because bacterial cellulose does not have impurities such as hemicellulose, lignin, and pectin (Reiniati, Hrymak, Margaritis, 2017; Cottet *et al*., 2020).

When using sucrose, *Acetobacter xylinum* bacteria ferment part of the sugar and produce a floating cellulose membrane as a secondary metabolite (Leal *et al*., 2018), which is known as biofilm or bacterial biocellulose (Cottet *et al*., 2020). The bacterial genera *Acetobacter*, *Agrobacterium*, *Erwinia*, *Gluconacetobacter*, *Komagataeibacter*, *and Pseudomonas* synthesize cellulose. *Acetobacter* produce higher amounts of extracellular cellulose in form of pure microfibers from carbon sources such as fructose, glucose, sucrose, and ethanol. Whereas the genera *Gluconacetobacter* and *Komagataeibacter* do not produce satisfactory amounts of cellulose (Cottet *et al*., 2020).

Macroscopically, biocellulose is a light brown gelatinous multilayered membrane. It is gelatinous when kept at rest, but when stirred, it forms irregular masses accumulated in dispersed suspension such as granule, stellate, and fibrous strand (El-Saied, Basta, Gobran, 2004). Microscopically, filaments with diameters below 100 nm until 30 µm emerging from bacterial pores can be observed (Cottet *et al*., 2020). The 1,4 β-glucans chains of cellulose are strongly assembled by hydrogen bonds have a high degree of crystallinity, and good mechanical strength (Reiniati, Hrymak, Margaritis, 2017).

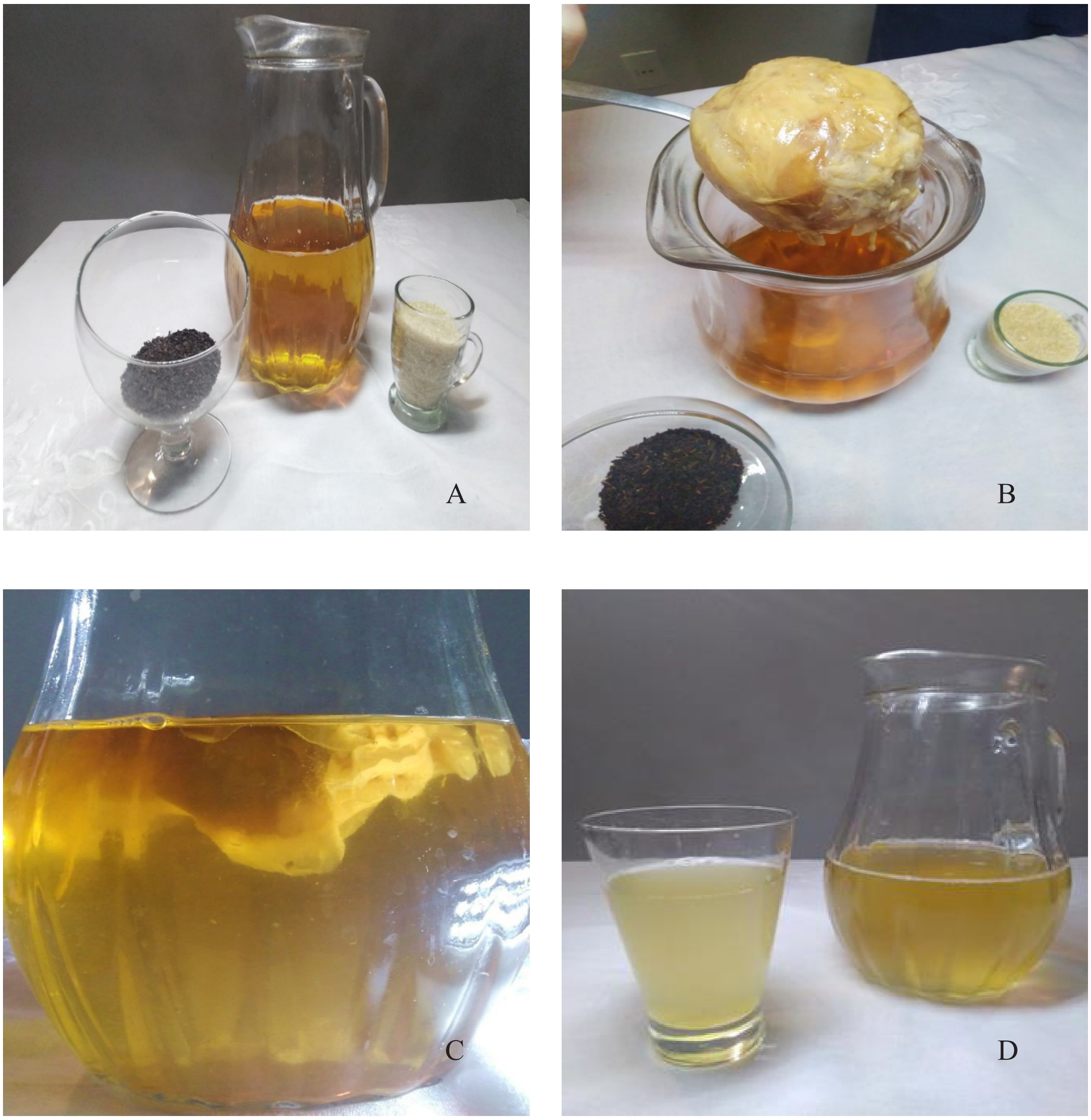
Although the main carbon source for biocellulose formation by *Acetobacter xylinum* or *Gluconacetobacter xylinus* is glucose, other molecules can also be used such as monosaccharides (e.g., D-fructose, D-galactose, D-glucose, D-mannose, D-xylose, L-arabinosis, and L-sorbose), disaccharides (e.g., cellobiose, lactose, maltose, and sucrose), oligosaccharides (e.g., starch), alcohol (e.g., diethylene glycol, ethanol, ethylene glycol, glycerol, myo-inositol, propylene glycol, D-arabitol, and D-mannitol), and acids (e.g., citrate, L-malate, and succinate). Among the monosaccharides, galactose and xylose provide less biocellulose growth (El-Saied, Basta, Gobran, 2004).

Microorganisms must have carbon and nitrogen sources to produce biocellulose. This is because its formation is complex and involves several enzymes and regulatory proteins (Azeredo *et al*., 2019). The first step is the intracellular formation of 1,4 β-glucans chains through phosphorylation of glucose by glucokinase, isomerization of glucose-6P to glucose-1P by phosphoglycutase, synthesis of uridine diphosphate (UDP-glucose) by UDP-glucose phosphorylase, and cellulose synthesis by cellulose synthase (Reiniati, Hrymak, Margaritis, 2017). In the second step, cellulose chains will be released from cells to assemble fibers, which undergo crystallization (Reiniati, Hrymak, Margaritis, 2017; Azeredo *et al*., 2019). In *Acetobacter xylinum*, cellulose synthase is a membrane-anchored protein (molecular mass of 400-500 kDa), which releases cellulose fibers in form of 1,4 β-glucans (El-Saied, Basta, Gobran, 2004).

Biocellulose starts its macroscopic formation from a thin layer of cellulose filaments, 2 days after bacterial incubation (Reiniati, Hrymak, Margaritis, 2017). Such structure works as protection mechanisms for microorganisms (Cottet *et al*., 2020) against UV light effects, as well as keeps bacteria and yeasts closer to the medium surface, wherein oxygen supply is adequate (Reiniati, Hrymak, Margaritis, 2017; May *et al*., 2019). The thin layers overlap to form a structure like pastry dough (May *et al*., 2019).

Gases from yeast alcoholic fermentation allow biocellulose sheets to float to the drink surface (Greenwalt *et al*., 2000). In several bacteria and yeasts, remaining cellulose microfibrils make up biocellulose (Greenwalt *et al*., 2000; Villarreal-Soto *et al*., 2019). The association among antimicrobial metabolites, low pH, and biocellulose inhibits the growth of competing microorganisms in Kombucha (May *et al*., 2019). *In vitro* and *in vivo* studies have suggested that probiotics (*Lactobacillus* and *Saccharomyces*) have an anti-*Helicobacter pylori* effect, which helps in curing gastritis and ulcers (Nair *et al*., 2016). However, Kombucha has a low pH, so it should be used moderately.

Biocellulose production may vary from 1.76 to 15.3 g/L, which depends on the microbial genera and sources of carbon and nitrogen used (Reiniati, Hrymak, Margaritis, 2017). Kombucha has a great potential for biocellulose production, wherein 10.8 ± 0.5 g/L cellulose can be obtained using a black tea with 100 g/L sucrose (Cottet *et al*., 2020). Figure 1 shows images from preparation to the consumption of Kombucha tea.



Photos: the author.

FIGURE 1 - Kombucha from preparation to consumption. A - black tea preparation (water, sugar, and dehydrated leaves of *Camellia sinensis*); B - SCOBY colony addition; C - biocellulose floating in kombucha; D - ready-to-drink kombucha (acid and citrus-flavored beverage in the glass cup, and slightly acid and sweet-flavored beverage in the jug).

Kombucha composition

Kombucha consumption benefits come from its amounts of organic and inorganic compounds, which may vary with the herb chosen for infusion (Salafzoon, Hosseini, Halabian, 2017; Shahbazi *et al*., 2018).

Kombucha beverage is a cocktail of chemical components (Kapp, Sumner, 2019), including probiotics (Fu *et al*., 2014; Bogdan *et al*., 2018), acids (e.g., acetic, citric, gluconic, lactic, malic, malonic, oxalic, pyruvic, saccharic, succinic, and tartaric) (Greenwalt *et al*., 2000; Jayabalan *et al*., 2014; Leal *et al*., 2018; Ivanišová *et al*., 2020), essential amino acids (e.g., isoleucine, lysine, methionine, phenylalanine, threonine, tryptophan, and valine), non-essential amino acids (e.g., alanine, aspartic acid, cysteine, glycine, glutamic acid, proline, and tyrosine), caffeine (Greenwalt *et al*., 2000; Goh *et al*., 2012), vitamins (e.g., B1, B2, B6, B12, and C), purines, hydrolytic enzymes, biogenic amines, fibers, ethanol (Greenwalt *et al*., 2000; Jayabalan *et al*., 2014; Leal *et al*., 2018), minerals (e.g., cadmium, chromium, cobalt, iron, manganese, nickel, potassium, and zinc), anions (e.g., bromide, chloride, floret, iodide, nitrate, phosphate, and sulfate) (Greenwalt *et al*., 2000; Jayabalan *et al*., 2014; Leal *et al*., 2018; Xia *et al*., 2019), polyphenols (e.g., epicatechin, epicatechin gallates, and epigallocatechin) (Shahbazi *et al*., 2018), and flavonoids (Pakravan *et al*., 2018; Jakubczyk *et al*., 2020).

The ethanol content in Kombucha ranges from 3.6 to 10 g/L (Greenwalt *et al*., 2000; Jayabalan *et al*., 2014). The alcohol content produced by bacteria and yeasts is proportional to fermentation time and reach 5.5 g/L on the 20th day (Chen, Liu, 2000). However, this content must not exceed 10 g ethanol/liter of drink to prevent invasion by competing microorganisms (May *et al*., 2019).

Toxicity

Despite promoting metabolic changes, dizziness, and nausea (Leal *et al*., 2018), Kombucha tea is not toxic (May *et al*., 2019). However, it should be used sparingly since it has been linked to liver toxicity, hyponatremia, and lactic acidosis (Kapp, Sumner, 2019). Accordingly, individuals with immune system disorders (Greenwalt *et al*., 2000), as well as kidney, liver, and lung diseases, must avoid drinking it (Kapp, Sumner, 2019). Its consumption is also contraindicated for pregnant women because it interferes with clotting processes and hence being harmful to fetal development (Leal *et al*., 2018). Daily consumption of 118 mL Kombucha poses no risk to consumers (Anonym, 1995).

Still, there is no consensus on a daily Kombucha intake. Currently, it is suggested to be between 100 and 300 mL (Greenwalt *et al*., 2000). Above 355 mL, it was reported to promote metabolic acidosis in 2 patients (Nummer, 2013). A continuous 12-week intake by rats has shown to promote internal perforations of organs, kidney injuries, and necrosis in duodenum, pancreas, and intestine (Greenwalt *et al*., 2000; Jayabalan *et al*., 2014). Hyperthermia, lactic acidosis, and kidney failure have also been reported in one HIV carrier 15 hours after drinking the tea. Another study showed that its consumption by 4 HIV patients promoted an allergic reaction, jaundice, nausea, vomiting, and neck and head pains (Jayabalan *et al*., 2014). One individual was told to die of intestinal tract perforations and severe acidosis (Perry, 1995). Liver toxicity has been observed after 2-year Kombucha consumption (Kovacevic *et al*., 2014). Besides, hospitalization cases due to tea intake have been reported in patients with past health problems (Anonym, 1996).

Bactericidal and fungicidal effect

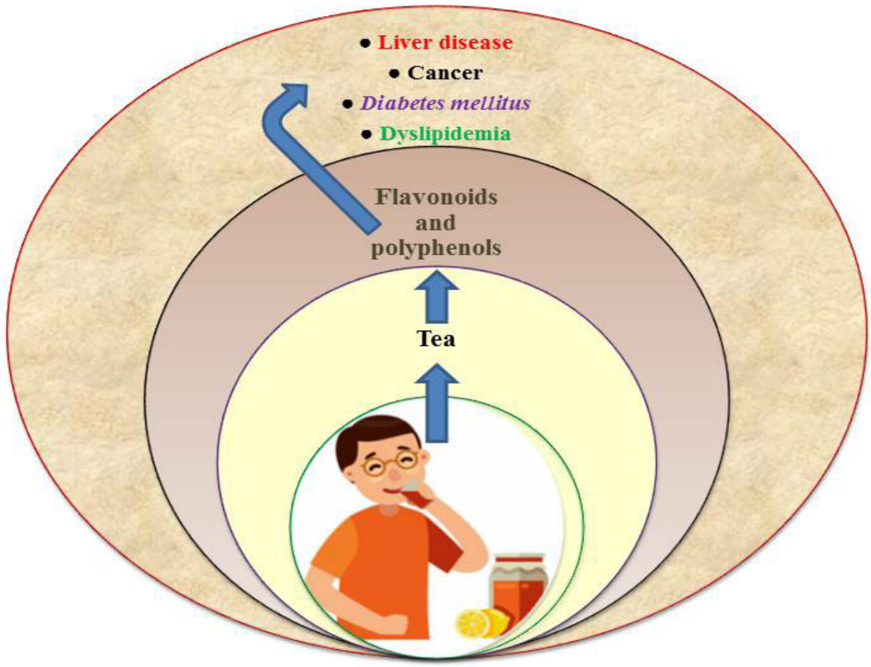
On the 14th day of Kombucha fermentation, it is rich in acetic acid, catechins, and isorhamnetin, with a bactericidal effect on enteric bacterial pathogens (e.g., *Escherichia coli*, *Salmonella typhimurium*, *Shigella flexneri*, and *Vibrio cholera*) (Bhattacharya *et al*., 2016). It also has an antibacterial activity against *Agrobacterium tumefaciens*, *Escherichia coli*, *Helicobacter pylori*, and *Staphylococcus aureus* (Steinkraus *et al*., 1996). Kombucha tea with 0.7% acetic acid is reported to have *in vitro* antimicrobial activity against *Agrobacterium tumefaciens*, *Bacillus cereus*, *Escherichia coli*, and *Staphylococcus aureus* (Greenwalt *et al*., 1998). Kombucha has antimicrobial properties that can remain neutralized up to pH 7 when heated at 80 ^{o}C for 30 minutes (Sreeramulu, Zhu, Knol, 2000).

Ethyl acetate in Kombucha tea has an *in vitro* antifungal effect on *Malassezia* species (Mahmoudi *et al*., 2016).

Effect on some diseases

Several studies have been carried out on animal models (e.g., cats, chickens, cows, dogs, ducks, mice, pigs, rabbits, and rats) and human lymphocytes (Kapp, Sumner, 2019) to evaluate Kombucha effects on blood pressure and serum cholesterol levels, cancer scattering, as well as on the functioning of the liver and the gastric and immune systems (Leal *et al*., 2018).

Flavonoids and other polyphenols produced during Kombucha fermentation (Figure 2) are suggested to confer beneficial effects in prevention and treatment of diseases (Leal *et al*., 2018; Kapp, Sumner, 2019), as they inhibit hydrolytic and oxidative activities of some enzymes, besides their anti-inflammatory effects (Pakravan *et al*., 2018).



Source: the authors.

FIGURE 2 - Effect of kombucha consumption on the treatment of diseases.

Tea type and SCOBY microorganisms have a direct influence on levels of polyphenols (May *et al*., 2019), which have antioxidant actions. These concentrations progressively increase during Kombucha fermentation until reaching their highest contents on the 12th day (Bhattacharya, Ahmed, Chakraborty, 2011). However, Kombucha beneficial effects have already been attributed to bacteria (*Acetobacter* and *Gluconobacter*) and yeasts (*Saccharomyces*) that produce glucuronic acid (Leal *et al*., 2018). Below are the findings of studies on Kombucha use for the treatment of diseases.

Liver disease

Non-alcoholic fatty liver disease results from an accumulation of lipids in the liver and can occur due to the consumption of high-fat or low choline and methionine diets by sedentary and obese individuals (Jung *et al*., 2019). Kombucha was reported to act on rat intestinal flora, decreasing bacterial population (*Allobaculum* and *Turicibacter*) involved in non-alcoholic liver sclerosis, and increasing *Mucispirillum* population. The latter has a positive effect on the secretion of leptin, which is a hormone that regulates hunger and stimulates lipolysis, thus improving oxidation of fat stored in the liver. Such microbiota change is suggested to improve non-alcoholic liver sclerosis (Jung *et al*., 2019). For 3 weeks and together with a healthy diet, Kombucha is said to increase lipolysis in obese mice and attenuate fat accumulation in the liver, thus preventing progression of non-alcoholic fatty liver disease (Hyun *et al*., 2016).

Kombucha proved to reverse liver problems caused by carbon tetrachloride poisoning (Leal *et al*., 2018). The drink has glucuronic acid, which acts in the hepatic detoxification of drugs and metabolism of bilirubin (Nguyen *et al*., 2015).

Cancer

In rats with breast cancer, ginger Kombucha (*Zingiber officinale*) promoted tumor homogeneity and reduced activity of enzymes (e.g., catalase, glutathione peroxidase, and superoxide dismutase) that control reactive oxygen and nitrogen species, besides reducing molecular marker of oxidative stress (malondialdehyde). Also, free radicals widely produced in anaerobic cancer metabolism decrease (Salafzoon, Hosseini, Halabian, 2017).

Kombucha tea reduces survival of prostate cancer cells and their metastasis by altering expression of angiogenic stimulators such as HIF-1α (hypoxia-inducible factor-1α), IL-8 (interleukin-8), VEGF (vascular endothelial growth factor), COX-2 (cyclooxygenase 2), MMP-2 (metalloproteinase 2), and MMP-9 (metalloproteinase 9). These findings suggest that a daily and limited consumption of Kombucha drink could prevent and treat neoplastic cell proliferation (Srihari *et al*., 2013).

Jayabalan *et al.* (2014) noted that a Kombucha ethyl acetate fraction shows cytotoxic activities against human renal carcinoma cells (786-0) and human osteosarcoma (U2OS) by decreasing metastasis.

Green tea (*Camellia sinensis*) reduces carcinoma cell growth by decreasing enzymatic actions (e.g., acetylase, kinase, and methylase). The polyphenols in the drink act against cancer by decreasing free radicals (Leal *et al*., 2018).

Pollen, which is rich in polyphenolic compounds and short-chain fatty acids, stimulates fermentation by Kombucha microorganisms and increases phytonutrient bioavailability in beverages, which promote a moderate antitumor effect on Caco-2 cells (Uțoiu *et al*., 2018).

Diabetes mellitus and dyslipidemia

Kombucha increased the number of beta cells in the pancreas of rats and decreased fasting glucose and oxidative stress (Aloulou *et al*., 2012; Zubaidah *et al*., 2019).

Aloulou *et al.* (2012) observed that a daily administration of 5 mL/kg Kombucha in diabetic rats for 30 days inhibits α-amylase and lipase and results in lower postprandial glycemia. It also improves renal function and decreases levels of creatinine, urea, and activity of serum enzymes (e.g., alanine transaminase, aspartate transaminase, and gamma-glutamyl transpeptidase).

Likewise, Bellassoued *et al.* (2015) administered daily 5 mL Kombucha/kg rat body weight for 16 weeks and noted improvements in renal function and hypercholesterolemia by decreasing levels of triglycerides, total cholesterol, VLDL-C (very-low-density lipoprotein cholesterol), LDL-C (low-density lipoprotein cholesterol), and lipid peroxidation, while increasing HDL-C (high-density lipoprotein cholesterol) and levels of antioxidant molecules.

El-Saied, Basta, Gobran (2004) highlighted that when *Gluconacetobacter xylinus* is added to coconut milk, its biocellulose decreased plasma cholesterol.

VARIETY OF KOMBUCHA USE

Beverage

Kombucha tea can be used in the cosmetics industry and food nutritional enrichment (Xia *et al*., 2019). Pakravan *et al.* (2018) showed that intradermal injection of Kombucha ethyl acetate fraction, with high flavonoid contents, promoted neither skin sensitivity nor irritation. It actually increased collagen production in elderly mice with dyschromia and wrinkles, which result from reductions in collagen fibers and dysfunctions in melanocytic cells and keratinocytes.

After Kombucha injection, skin appearance improved, which has been attributed to flavonoids (Moulishankar, Lakshmanan, 2020), anti-inflammatory compounds (Fernández-Rojas, Gutiérrez-Venegas, 2018), amino acids, antioxidants, minerals, polyphenols, vitamins, and enzymes. Such compounds reduce skin inflammation, free radicals, and UV ray penetration, allowing cellular DNA protection (Bhattacharya, Ahmed, Chakraborty, 2011; Pakravan *et al*., 2018). Thus, Kombucha use has been suggested for the preparation of cosmetics, so that it could promote skin improvement or regeneration in the elderly (Pakravan *et al*., 2018).

Kombucha SCOBY is used in the industry for the production of fermented foods (Soares, Lima, Schmidt, 2021). When fermented with Kombucha, soy milk has its total contents of phenolic compounds and vitamins increased, which improves its nutritional quality (Xia *et al*., 2019).

Biocellulose

Microbial-produced biocellulose is a substitute for plant-synthesized cellulose and can be used to reduce environmental impacts.

In Kombucha production, biocellulose is disposed of during filtration (Soares, Lima, Schmidt, 2021). But it has economic value and can be used as a raw material in the textile industry. This is because after its dehydration it looks like leather. For this reason, it has been useful in the manufacturing of clothing and bags (Tünay *et al*., 1995; Ghalachyan, 2017; Domskiene, Sederavičiūtė, Simonaityte, 2019; Kamiński *et al*., 2020), in addition to cigarette papers (Shaun, Cutter, 2019).

Biocellulose can be produced from microorganisms of the genera *Achromobacter*, *Aerobacter*, *Agrobacterium*, *Alcaligenes*, *Azotobacter*, *Dickeya*, *Gluconacetobacter*, *Pseudomonas*, *Rhizobium*, *Rhodobacter*, and *Sarcina*. The *Gluconacetobacter* is the main producer when using carbon and nitrogen sources (Azeredo *et al*., 2019).

Bacterial cellulose can be produced in juices (e.g., muskmelon, orange, pear, pineapple, pomegranate, sugarcane juice, tomato, and watermelon), molasses, starch hydrolysate, coconut milk, coconut water (Azeredo *et al*., 2019), and sisal juice (Lima *et al*., 2017).

Due to its characteristics such as biodegradability, crystallization index, fiber composition, hydrophilicity, mechanical properties, purity, transparency, and water-holding capacity, microbial biocellulose is a biopolymer with applications in the following areas: food (e.g., dietary fiber, enzyme immobilization, and functional packaging), biomedical (e.g., artificial bone, artificial skin, cartilage, cell therapy, dental implant components, medical pads, regenerative tissues, scaffold tissues, vascular grafts, and wound care), pharmaceutical (e.g., delivery of drugs, film coating, hormones, and proteins), engineering (e.g., flat panel display, nanocomposites, and soil conditioning), environmental (e.g., biosensors, degradation pollutants, dye decolorization, and heavy metal removal) (Reiniati, Hrymak, Margaritis, 2017; Azeredo *et al*., 2019; Cottet *et al*., 2020; Soares, Lima, Schmidt, 2021).

Kombucha biocellulose can be used as a dietary matrix and source of fiber (Keshk, 2014) to produce dietary foods, as its fibers do not undergo enzymatic digestion in the human digestive tract (Azeredo *et al*., 2019). Some bacteria and yeasts adhere to gelatinous layers, which can be dehydrated and improve the quality of ingested diet (Leal *et al*., 2018). Nata-de-coco is one of the Filipino favorite desserts and has gained prominence in other parts of the world (El-Saied, Basta, Gobran, 2004; Keshk, 2014). This sweet can be produced in several manners such as custard cream (with pineapple juice) (Azeredo *et al*., 2019).

Other cellulose biomembranes have been widely used. In medicine, gelatinous biocellulose membranes have been used since the 1990s as an artificial substitute for burns, grafts, skin, ulcers, and as an adjuvant in dermal abrasions (Fontana *et al*., 1991). *Acetobacter xylinum*-derived biocellulose can be used as artificial skin in areas of low mobility due to its permeability for liquids and gases and low irritability. The bacterial cellulose product Biofill® is used as a skin substitute for burns (2nd and 3rd degree) and ulcers, with the following advantages: close wound bed adhesion, diminished post-surgery discomfort, faster healing, immediate pain relief, improved exudates retention, reduced infection rate, spontaneous detachment following reepithelization, wound inspection easiness (transparency), as well as reduced treatment time and costs (Keshk, 2014). Moreover, other products such as Gengiflex® and Cellumed are used in dentistry and veterinary medicine. The latter is applied in the treatment of dogs and horses, replacing the duramater in the brain (El-Saied, Basta, Gobran, 2004).

In Brazil, a purified gelatinous membrane from bacterial cellulose has been commercialized as artificial skin for being superior to conventional gauze to temporarily cover the skin (Fontana *et al*., 1991). Moreover, biocellulose has also been used as an artificial blood vessel (1 mm diameter, 5 mm length, and 0.7 mm wall thickness). It has lower risks than those synthetic ones used in bypass operations (Keshk, 2014). Human plasma proteins (e.g., albumin, c-globulin, and fibrinogen) are reported to adhere to biocellulose blood vessels with a tripeptide (Arg-Gly-Asp) in large quantities, without changing their structure. This suggests that biocellulose compatibility with blood could bring benefits to human health (Andrade *et al*., 2011).

Biocellulose can be used to manufacture paper (El-Saied, Basta, Gobran, 2004) since its cellulose microfibers contribute to durability (El-Saied, Basta, Gobran, 2004; Keshk, 2014). Padrão *et al.* (2016) modified a bacterial cellulose film for bovine lactoferrin adsorption on fresh sausage, and it showed 94% inhibition of *Escherichia coli* and *Staphylococcus aureus*. Moreover, biocellulose has also been used as a fat substitute (Azeredo *et al*., 2019) for the production of meatballs (Lin, Lin, 2004) and ice cream (Guo *et al*., 2018).

Bacterial cellulose has shown satisfactory results in biometric applications due to its binding to the metals (Au^{3+}, Cu^{1+}, and Pt^{1+}) (Cottet *et al*., 2020), as well as in environmental applications due to its capacity to bind heavy metals (Cd^{2+}, Ni^{2+}, and Pb^{2+}) (Cerrutti *et al*., 2016). As biocellulose microorganisms remove heavy metals (As^{3+}, Cd^{2+}, Cr^{6+}, Hg^{2+}, and Pb^{2+}), they can be used in environmental decontamination (Najafpour *et al*., 2020). In the field of electronics, biocellulose was used to develop the first headphone (El-Saied, Basta, Gobran, 2004).

CONCLUSIONS

Kombucha fermented drink is a symbiotic food product that is easy to prepare and can be used as a functional beverage. When used sparingly, it improves human health in prevention and treatment of pathologies, as it contains several chemical compounds and species of bacteria and yeasts. Its biocellulose layer can be used as raw material for medicine and in the textile, food, and environmental industries, resulting in a reduction in the emission of pollutants from industrial production. Both can be used as functional foods and/or sources of bioactive compounds for food and industrial applications.

Some doubts remain about dosage, frequency, and duration of consumption for populations in different regions of the planet. Thus, studies with groups of animals and human beings are needed, as symbiotic yeasts are known and used worldwide.

COMPLIANCE WITH ETHICAL STANDARD

Authors declare no conflict of interest for this paper.

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