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# FORMULATION METHOD, COMPOSITION AND MEDICAL APPLICATIONS OF THE MIRACULOUSLY DRINK - KOMBUCHA: A SYSTEMICALLY REVIEW

**Ioan Sarac[1], Emilian Onisan[1], Corina Beiușanu[2], Andrei George Teodorescu[2]*, Oana Cristina Daciana Teodorescu[3], Alina Hanga-Farcas[4], Csaba Nagy[5], Tunde Horvath[6]**

1. ***Department of Genetic Engineering, University of Life Sciences "King Mihai I" Timișoara, Timișoara, Romania.***
2. ***Department of Morphological Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania.***
3. ***Saint John Emergency Hospital Department of Anaesthesia and Intensive Care Bucharest, Romania.***
4. ***Department of Preclinical Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, 410087, Oradea, Romania.***
5. ***Department of Pharmacy, University of Medicine and Pharmacy, Science and Technology of Targu Mures, Targu Mures, 540142, Romania.***
6. ***Department of Pharmacy, Faculty of Medicine and Pharmacy, University of Oradea, 410087, Oradea, Romania.***

***† All authors contributed equally to this work.***

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**ABSTRACT**

Maintaining the health of the human body and increasing the quality of life have become central elements of interest in current research. Modern medicine emphasizes the fact that the health of the body and the increase in longevity are closely related to nutrition during the individual's life. Thus, the kombucha drink represents one of the functional foods extremely rich in active bio-compounds and microorganisms that have proven to be beneficial for health. In this review, the method of obtaining the drink, its composition, and the present compounds are described in an easy-to-understand approach. The emphasis is on highlighting the multiple biological activities of this drink in distinct medical spheres, such as oxidative stress, cancer, cardiovascular diseases, dermatological diseases, antimicrobial anti-inflammatory capacity. Also described are the elements that make up this miraculous drink (substrate type, SCOBY, and added carbon source), respectively innovative elements from recent literature with reference to the replacement of the classic substrate. Finally, there are some aspects related to the contraindications of kombucha consumption; the paper ends with the conclusions.



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## Introduction

Currently, the paths in the world of alternative medicine and nutrition are directed towards the prevention of diseases in different spheres, such as cardiovascular pathologies, oxidative stress, liver pathologies, neurological, cancer, inflammatory diseases, etc. [1-4].

The quality of life is currently at the center of all development ideas, and it has been proven that it can be increased primarily through a healthy diet [5-8]. For this reason, the development of technologies that propose new functional foods is of great interest [9]. Functional foods, in addition to offering the main classes of macronutrients, are much improved by also offering

**Corresponding Author:** Andrei George Teodorescu; Department of Morphological Disciplines, Faculty of Medicine and Pharmacy, University of Oradea, Oradea, Romania. E-mail: teodorescu_andrei_george@yahoo.com.

compounds with bioactive properties that will thus prevent the development of some pathologies during the individual's life [10].

Thus, studying the inclusion in the diet of some functional foods based on microbial proteins, fungi, yeasts, or bacteria is currently in the foreground [11]. Probiotics and prebiotics, antioxidant compounds, vitamins, and complex food supplements are also in the foreground at this moment, proving that they have a positive effect in terms of mental, immunological, and anti-stress health, thus increasing the quality of life [12]. Regarding the inclusion of probiotics in the daily diet, they are known to be part of foods based on fermented milk [13].

In recent years, however, attention has been focused on a new product fermented in other types of liquids (green tea, black tea, juices, or vegetable extracts), namely Kombucha [14-16]. This product is a functional food with multiple benefits for health, but its regulation must be implemented because, until now, it does not exist [17-20]. In this review, the main purpose is to highlight the methods of obtaining the functional food called Kombucha, to highlight the advantages and disadvantages of its use for human health and in various ailments, the identification of the chemical composition, and the future perspectives regarding the regulated consumption of this drink.

To carry out this literature study, platforms containing valid databases such as Pubmed, Scopus, Research Gate, Web of Science were used, where the following keywords were included: "kombucha," "cardiovascular disease," "cancer," "antioxidant," "*in vitro*," "*in vivo*," "tea," "fermentation," “raw materials,” “polyphenols” etc. and studies from the last five years were selected **(Figure 1)** [21].

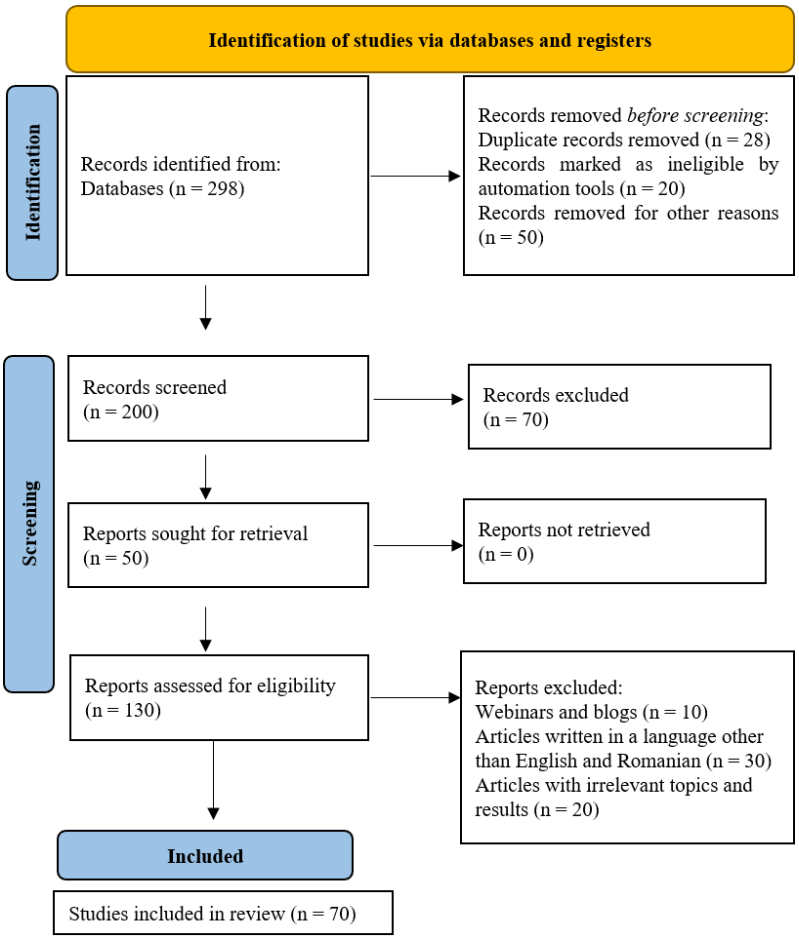


**Figure 1.** PRISMA 2020 flow diagram for the present review. The criteria taken into account for the selection of the articles studied for the writing of this review-type study.

*Brief History of the Functional Drink Known Today as Kombucha*

The Kombucha drink is a functional food obtained through the fermentation process in teas or plant extracts of a symbiotic mixture of bacteria and yeasts (symbiotic culture of bacteria and yeasts (SCOBY)) [15, 19, 22, 23]. It is considered that this drink has been part of the Chinese tradition since 220 BC, then became popular in Japan as a universal medicine, and with the migration of the population and the appearance of wars, it became known in the U.S. and later in Europe [13]. During the Second World War, the popularity of this drink decreased greatly due to the lack of sugar, a key element in the preparation of the Kombucea drink [13, 24-26]. Since 2016, according to the authors Julie *et al*. (2018), this drink has regained ground; the interest has increased, especially in the U.S., with sales increasing by up to 49% compared to the previous year [16]. Depending on the area, the drink can be found under the names "Mushroom tea kvass," "Teakwass," "Manchu Fungus," "Indian Tea

Fungus," "Tea Beer," etc [9, 13, 27]. Regardless of the name of this drink obtained through the fermentation process at home or in small factories, it is the most popular functional drink in the world both for its pro-health benefits and due to its low alcohol content [9, 19, 28-33].

*Obtaining the Kombucha Drink*

Three elements are used to obtain the Kombucha drink through fermentation: the substrate (which is classically represented by green tea, black tea, or oolong), the symbiotic mixture of bacteria and yeast (SCOBY), and sugar [12, 15, 16, 34].

Green tea, black tea, and oolong tea come from the *Camellia sinensis* plant, whose leaves are harvested [16]. In green form, the leaves represent green tea; in dry and fermented form, the leaves produce black tea, and oolong tea actually represents green leaves subjected to a rapid drying process at very high temperatures in front of the sun and a chemical oxidation process [10, 13, 15, 16, 22, 23, 35, 36].

Green tea is the richest in bioactive compounds, containing high amounts of polyphenols, including catechins and tannins. By degrading catechins, black tea becomes rich in theaflavins and thearubigins with strong antioxidant properties [12, 31, 37-42].

The SCOBY symbiotic mixture is characterized by the presence of bacteria such as *Acetobacter aceti, A. pasteurianus, A. estunensis, Gluconobacter oxydans, K. rhaeticus, K. xylinus and Komagataeibacter kombuchae and yeasts such as Brettanomyces/Dekkera, Candida, Saccharomyces, Schizosaccharomyces, Starmerella sp., Torulopsis, Pichia sp.,* and *Zygosaccharomyces* and in some studies the use of lactic acid bacteria, *Lactobacillus sp* [13, 14, 36].

Sugar is used as a substrate for the existing microorganisms and is finally hydrolyzed into glucose and fructose, glucose being finally transformed into carbon dioxide and ethanol, and the resulting ethanol is transformed into acetic acid, thus changing the acidity of the final drink [9, 22, 23, 27, 43-46]. The nitrogen source in the fermentation process is represented by the tea used, and the carbon source by the added sugar [29].

The mixture is kept for 10-14 days in the dark when the existing microorganisms form a cellulosic biofilm in the area of contact with the tea used; this biofilm is called a SCOBY-mushroom cap [14, 16].

An alternative substrate can be used, replacing green, black, or oolong tea with various plant infusions (eucalypt, oak leaves, bay leaves, oregano, lavender), milk, fruit juice, soy, etc [47, 48].

The stages of formulating functional kombucha drinks are presented in **Figure 2**.

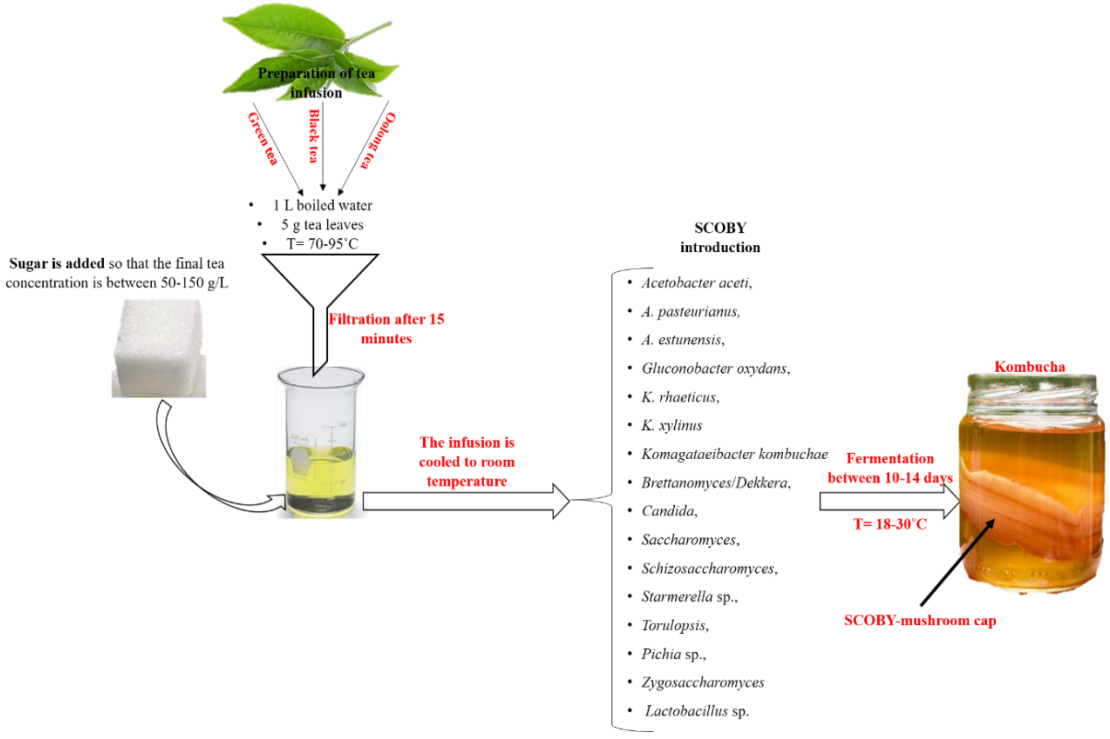


**Figure 2.** The stages of formulating the kombucha drink in a classic way using the *Camellia sinensis* plant.

Thus, according to **Figure 2**, in the first stage of the formulation of the kombucha drink, the substrate used is taken into account, generally using teas; in the second stage, the carbon source is added, namely sugar, and after the cooling process at room temperature in order not to destroy the symbiotic mixture, add the SCOBY.

According to specialized literature, parameters such as temperature and fermentation time are key elements in the final chemical composition of the kombucha drink [2, 13-15, 30, 35, 49].

Thus, for a better extraction, it is considered that for phenolic bioactive compounds such as catechins, gallic acid, caffeic acid, the use of extraction temperatures above 80˚C even up to 95˚C is recommended. At temperatures of 100 ˚C, a waiting time of

3 minutes is recommended for a high content of polyphenols [13, 22, 50, 51].

Also, the water used to obtain the tea and its pH was demonstrated by Antolak *et al*. that it has an overwhelming role in the extraction of active principles. Water with a neutral-alkaline pH destroys the existing catechins and reduces the antioxidant effect of the tea [13]. Extracts formulated in purified water prove to be the richest in active antioxidant principles [13, 27, 43].

The authors Ferreira de Miranda *et al*. (2021) recommend that the fermentation period should not exceed 14 days because, in these conditions, over a longer period of time, the concentration of acetic acid increases, and the taste of the drink becomes sour [15].

Finally, in order to be able to consume the fermented drink, it must be filtered to remove the formed SCOBY cap, after which a second fermentation follows for the production of $CO_2$, which lasts 2-3 days [31, 32, 46, 52]. Afterward, the drink can be supplemented according to the consumer's desire with different flavors obtained from teas or fruits. The drink is stored at 4˚C to stop the fermentation process [9, 12, 27, 28, 52].

The biochemical reactions produced in the existing fermentation process in the formation of the kombucha drink are multiple and complex; these reactions are briefly presented in **Figure 3**.

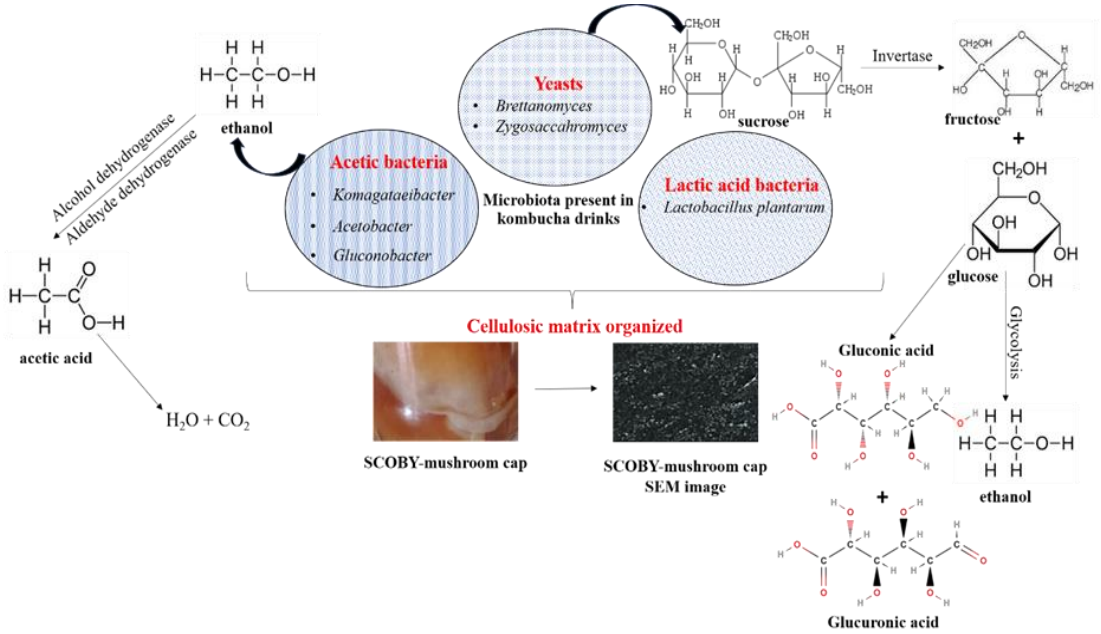


**Figure 3.** The main chemical reactions that take place in the fermentation process and the main chemical compounds that result from this process.

**Figure 3** systematizes the main chemical reactions that take place in the fermentation process, but it is known that the type of bacteria or yeast used also dictates the transformation of the substrate. For example, the genus *Saccharomyces* spp. has the ability to transform the carbohydrate substrate into final reaction products, and the genus *Zygosaccharomyces* spp. can use fructose as a substrate [16, 23, 25, 30, 44]. There are also studies that highlight that malic acid can be a substrate for *Schizosaccharomyces* pombe yeast, reaching the final decomposition product of acetic acid in aerobic environments [17, 39, 53].

*Alternative Substrates in the Production of Kombucha Drink*

The classic way to obtain the kombucha drink is the use of green tea that is semi-fermented or fermented with sucrose, but recent studies emphasize the importance of using other substrates in order to produce other reaction products that are beneficial to the human body, so the aim is to increase the variation of the compounds resulting from the fermentation process and implicitly the modification of the final composition of the kombucha drink and the organoleptic properties [2, 12, 15, 48].

Thus, studies were carried out to obtain the kombucha drink using non-conventional substrates such as leaves of some plants, juices, fruits, cereals, herbaceous plants, etc. **(Figure 4)**.

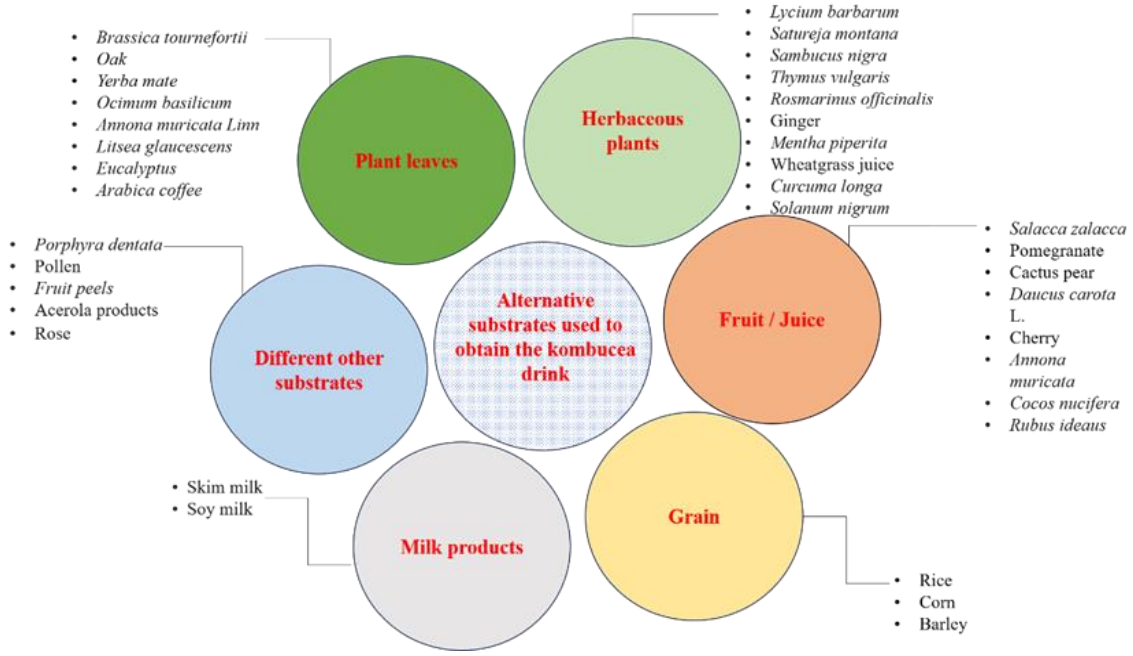


**Figure 4.** Alternative substrate examples were found in the literature and used to formulate the kombucha drink.

Following recent studies, it has been demonstrated that the raw materials used as a substrate influence the amount and type of final products found in Kombucha after fermentation [22, 29].

Thus, Kaewkod *et al*. (2019) demonstrated that using the green tea substrate after fermentation resulted in a greater amount of total polyphenols, acetic acid, and alcohol and also reported the presence of theaflavins, glucuronic and gluconic acid, and vitamin C compared to the T0 time of the fermentation process [54].

Ziemlewska *et al*. (2021) studied the formulation of the kombucha drink using Yerba mate as a substrate and observed that following the fermentation process, the products found were Caffeic acid, 3-caffeoylquinic acid, 4-caffeoylquinic acid, 5-caffeoylquinic acid, 3,4-dicaffeoylquinic acid, 3,5-dicaffeoylquinic acid, 4,5-dicaffeoylquinic acid, phenolic acids, theobromine, caffeine, rutin, but the alkaloids and vitamins such as vitamin C, B1, B2 that were present before fermentation were not preserved [25]. Abuduaibifu *et al*. (2019) highlighted using the goji substrate that after fermentation for up to 14 days in the kombucha drink, the amount of total polyphenols and acidity increased considerably compared to day 1 of the fermentation process [55]. Vitas *et al*. (2018) highlighted the increase in the level of oxalic acid, formic acid, acetic acid, succinic acid, malic acid, citric acid, the level of vitamins but also the decrease of total flavonoids when it was used as the raw material of the Yarrow flower substrate [26, 56].

Ginger, cinnamon, cardamom, thyme, and garlic used as alternative substrates improve the properties of the drink in the fermentation interval of 1-21 days, considerably increasing its antioxidant, anti-inflammatory, antimicrobial properties due to the high level of polyphenols, total flavonoids, organic acids, vitamins, minerals, and amino acids [14, 57].

Also, the use of different leaves from plants such as African mustard, basil, oak, oolong tea, red tea, white tea leads to an increase in bioactive content in total polyphenols, total flavonoids, glucuronic and gluconic acids, amino acids, vitamins, minerals, acetic acid, and ethyl alcohol as regards the fermented kombucha drink [58].

In other words, the elements that lead to the fermentation process and the kombucha drink in its final form (substrate, SCOBY, and sucrose) have singular bioactive properties inferior to the drink obtained after fermentation, this having the bioactive properties and the level of Kombucha of interest for the health of the human body much improved [25, 30, 51, 52, 54, 55].

*Bioactive Compounds Identified in Kombucha Drink*

The chemical composition of the kombucha drink comes from the two sources of bioactive compounds, namely the raw material used and the mixture of bacterial strains and yeasts (SCOBY) [15, 16].

Thus, the final chemical composition of Kombucha can vary a lot, but **Table 1** shows some of the most common compounds.

**Table 1.** Compounds are frequently identified in the kombucha drink, depending on their origin.

| **Compounds** | | | |
|---|---|---|---|
| **Compounds resulting from the raw material** | gallocatechin | **Acid acetic bacteria** | Vitamin C |
| | catechin gallate | | Glucuronic acid |
| | gallocatechin gallate | | Gluconic Acid |
| | epicatechin | | Acid acetic |
| | Epigallocatechin | | D-saccharic acid-1,4-lactone |

| | | | |
|---|---|---|---|
| | epicatechin gallate | | |
| | epigallocatechin gallate | | |
| | glycoside | | Ethanol |
| | kaempferol | | |
| | quercetin | | |
| | gallic acids | | |
| | p-coumaric | | Vitamin B complex |
| | | | Acid folic |
| | ferulic acid | | Aminoacids |
| | caffeic acid | **Yeast** | |
| | chlorogenic acid | | |
| | luteolin-6-C-glucoside | | Hydroxystyrenes |
| | isovitexin | | |
| | ellagic acid | | |
| | rutin | | Vitamin B complex |
| | Kempherol | | Lactic acid |
| | Quercetin | **Acid lactic bacteria** | Bioactive peptides |
| | Myricetin | | Vanillic acid |
| | Catechins | | |

*Biological Activity of Kombucha Drink*

The biological activity of Kombucha is a rich one; among the main properties include antioxidant capacity, antimicrobial, anti-inflammatory, anti-aging, antihypertensive, scar healing, neuroprotective, hepatoprotective, anti-cancer, antihypercholesterolemic, antiobesity, intense probiotic and immunostimulating activity. It should be mentioned, however, that the studies carried out are limited to in vitro or in vivo tests on animals, and very little has been studied about the effect on human individuals [10, 12, 28, 29, 31, 33, 34, 36, 37, 42, 49, 52, 59, 60].

In recent literature, it has been demonstrated through numerous studies that the antioxidant capacity of the material used as a substrate in the production of Kombucha is much improved and significantly higher after the fermentation process [61]. The mechanism of action that determines a stronger antioxidant activity is simple: the antioxidant capacity of the kombucha drink is given by the total number of polyphenols present, and they increase quantitatively following the fermentation of the substrate in the presence of SCOBY [36]. The significant increase in the total value of polyphenols is highlighted by laboratory methods such as Folin-Ciocalteu, DPPH, TEAC, and CUPRAC in most of the studies taken into account to make this review [15, 16, 23, 62, 63].

The strong antioxidant properties are also present due to the fact that the microorganisms present in SCOBY, especially those of the *Acetobacter* and *Saccharomyces* type, produce enzymes that break down polyphenols into smaller-sized compounds with a more intense antioxidant effect due to increased bioavailability [64].

Cardoso *et al*. (2020) identified over 120 compounds with antioxidant properties, among which most were part of the class of flavonoids, followed by phenolic acids and other polyphenols [65]. Also, authors such as Ayed *et al*. (2017) demonstrated an increase in total polyphenols and theaflavin-type compounds when non-conventional raw materials such as grape juice were used compared to the level of bioactive compounds with antioxidant properties existing in conventional Kombucha (formulated with green, black or oolong tea) [66].

Due to the strong antioxidant properties given by the existing phenolic compounds and their metabolites from fermentation, Kombucha also possesses anti-aging properties, being demonstrated in in vitro studies to increase the level of hyaluronic acid and collagen, stimulate cell regeneration and protect the skin [25, 61].

In the studies carried out up to this moment, it is considered that diabetes, like many other pathologies, is due to the existence of an increased number of free radicals in the body or oxidative stress. This oxidative stress finally disrupts the metabolism of glucose and the enzymes involved in its metabolism or influences the secretion of the pancreatic hormone, and thus, this pathology begins [30, 57, 67]. Due to its strong antioxidant properties, Kombucha also intervenes with enzymatic elements such as glucose-6 phosphatase, fructose 1,6-phosphatase, and hexokinase, causing a decrease in the level of glucose in the blood, thus lowering glycemia. These enzymes are involved in the anabolic and catabolic processes of the molecule. There are also recent studies that highlight the fact that the kombucha drink has hypoglycemic properties, lowering the level of glycosylated hemoglobin in the blood, thus positively influencing the pathways of glucose metabolism and also increasing the level of insulin [18, 28, 42, 52, 68].

The antimicrobial activity is one of the most tested activities for the kombucha drink in recent specialized literature. The test methods used are generally the agar-agar diffusion method, the paper disk method, the method using impregnated disks, the dilution method, etc. [14, 26, 33, 34].

The bacterial strains that are tested and found in the multiple scientific works included in this review are the following: *Staphylococcus epidermidis*, *S. aureus*, *Escherichia coli*, *Micrococcus luteus*, *Salmonella typhimurium*, *Pseudomonas*

*aeruginosa, Listeria monocytogenes, Candida albicans, C. tropicalis, Aspergillus flavus, Bacillus cereus, Malassezia sp.* [15].
Following the studies carried out, the bacteriostatic or even bactericidal effect was demonstrated, and this effect was attributed especially to the reactive products obtained from the fermentation of polyphenols such as organic acids and acetic acid. Just as the antioxidant and antimicrobial activity was shown in every study to be more intense after the fermentation process [6, 27, 67].
Due to its strong antioxidant, anti-proliferative, and anti-inflammatory properties, Kombucha also possesses anti-cancer activity, being thus highly recommended in the diet of cancer patients. In vitro studies demonstrate that Kombucha has a beneficial effect in treating and improving the symptoms of skin & breast cancer and colorectal cancer symptoms, acting as an anti-proliferative and stimulator of cancer cell apoptosis [12, 69].
Due to the presence of probiotics in the composition of this drink, it is considered to be an excellent drink to increase the quality of life and longevity, determining through consumption the growth of the beneficial intestinal bacterial population, thus regulating the intestines-brain axis [9, 29, 68]. According to the *in vitro* studies, the hypocholesterolemic properties of this drink and the ability to reduce blood pressure in hypertensive patients were also highlighted. The hepatoprotective activity was also reported in *in vitro* studies. Pauline *et al*. have indicated through in vitro studies that the kombucha drink has a detoxifying role in the liver, improving hepatocyte activity [38, 40].
Ziemlawska *et al*. beneficial effects of Kombucha have been demonstrated *in vitro* studies on keratinocytes and dermal fibroblasts. The results of the studies showed that the drink inhibits lipoxygenase, cholestasis, and elastase, resulting in a cellular protective effect against stress factors such as exposure to the sun [25].
Regarding fields other than the medical one, Kombucha has been considered a miraculous "preservative" in recent years, being able to be used in the food field without having harmful effects on the human body like other chemical preservatives and even improving the respective product [14, 16].

*Limitations of Kombucha Drink Consumption*
It is important to mention that although this drink has multiple medicinal properties and a vast composition of bioactive compounds beneficial to the human body, it is not recommended to be consumed by immunocompromised people, pregnant women, children, or alcoholics (the effect of alcohol and compounds active with frequently consumed alcohol) and thus reaching liver necrosis [14-16].
Among the adverse effects encountered in excessive consumption, the following can be highlighted: allergies, dizziness, headaches, gastric disorders due to the content of acetic acid or acidosis, gastric toxin infection when it was not properly handled in the manufacturing, storage, and handling process. Due to the fact that this drink contains live bacterial strains, it is very important that it be produced, stored, and consumed according to the protective norms in force [17, 29, 47].

## Conclusion

In conclusion, this review-type work brings to the fore elements of the novelty of the last 5 years in the field of kombucha drink manufacturing and the research of its effects in the medical sphere.
This paper presents the stages of the formulation of the kombucha drink, mentioning clearly and easily the working parameters, the elements used in the formulation, and the method of preservation and consumption. Also, the work brings to the fore the existing compounds in this drink, but also their origin, subsequently being attributed to a biological activity highlighted by *in vitro* or *in vivo* tests on animals.
In other words, the work is presented in a way that is easy for the reader to understand and concentrates the information on the topic chosen by bringing together the results of recent research.

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