CHAPTER 2
LITERATURE REVIEWS

2.1 Kombucha

Kombucha is a type of fermented beverage product that is quite popular in the world community or international market. It originally came from Manchuria (northeast China) during the Tsin (Ling Chi) dynasty around 220 BCE and is believed to have arrived in Japan in 414 CE (Chakravorty et al. 2019). The name kombucha comes from the name of a Japanese physician and is now used to refer to slightly fermented teas (Chakravorty et al. 2019). Kombucha is usually made from tea-containing drinks such as black tea or green tea with the addition of sucrose and then fermented using a starter known as the SCOBY. In its development, kombucha can be made using various other ingredients, such as spice teas and other herbal teas.

2.1.1 Tea in Thailand

Tea is a popular and well-known beverage among the general population. Apart from water, tea is one of the most extensively consumed drinks in the world (Suteerapataranon et al. 2009). In general, the term "tea" refers to products derived from the leaves of plants belonging to the camellia family. The tea cultivars discovered and commercially produced in Thailand include *Camellia sinensis* var. *Assamica* and *Camellia sinensis* var. *Sinensis*, generally known as Chinese cultivars (Theppakorn et al. 2014).

The parts taken from the tea plant are the leaves, especially the top two leaves, and the shoots. The leaves are then processed into a variety of dried tea leaves, including black tea, green tea, oolong tea, and white tea. Drying, complete oxidation, and withering are the steps in the preparation of black tea. Green tea bypasses the oxidation process and results in a light green or golden tint. Oolong tea is a mix of colors and flavors between black tea and green tea. Meanwhile, white tea is only withered and dried by steaming (Commins and Sampanvejsobha 2008). Assam tea is often utilized for green and black tea manufacture, while Chinese tea is mostly used for green and oolong tea production (Theppakorn et al. 2014). Assam tea is also commonly used to make red tea (Pongpruttikul and Yamsa-ard 2022).

Thailand is the 15th of the world's largest tea producers in the world with the production of 58,803.00 metric ton in 2019 (NationMaster.com 2023). Thai tea products such as black tea and green tea have gained popularity in the last three years, particularly with buyers from Western and Asian nations (Pongpruttikul and Yamsa-ard 2022). There are several commercial tea products available on the Thai market with different types, packing sizes, and prices, such as green tea, oolong tea, white tea, red tea, black tea, and barley tea (Teepprasarn 2015).

Tea contains nutrients and active components such as polyphenols, amino acids, vitamins, proteins, carbs, trace elements, and alkaloids such as caffeine (1,3,7-trimethylxanthine), theobromine, and theophylline that are beneficial to health (Fatima and Rizvi 2011). Various types of tea are made differently and may contain different ingredients. Aside from black and green tea, red Thai tea is a popular form of tea in Thailand. Red Thai tea is made with black tea and other herbs and spices, including star anise, cardamom, and tamarin seed (Devje 2022). Thai tea is a chilled drink made from strongly brewed Assam tea that has been sweetened with sugar and condensed milk. Additional ingredients may include orange blossom water, star anise, crushed tamarind seed, red and yellow food coloring, and sometimes other spices (Teapedia.org 2015). The nutrition facts of black tea, green tea, and spices used as additives in red Thai tea are demonstrated in **Table 2.1.**

Table 2.1 Nutritional value of green tea, black tea, and some spices used for additive in red Thai tea

Nutrient	Nutritional value per 100g						
	Black tea	Green tea	Star anise	Cardamom	Cinnamon	Cloves	Vanilla Extract*
Net carbohydrates	0.3g	7.16g	35.42g	40.47g	27.49g	31.63g	12.65g
Protein	0g	0g	17.6g	10.76g	3.99g	5.97g	0.06g
Fats	0g	0.18g	15.9g	6.7g	1.24g	13g	0.06g
Carbs	0.3g	7.16g	50.02g	68.47g	80.59g	65.53g	12.65g
Calories	1kcal	30kcal	337kcal	311kcal	274kcal	274kcal	288kcal
Fiber	0	0	14.6g	28g	53.1g	33.9g	0
Fructose	0	3.59g	0	0	1.11	1.07g	0
Sugar	0	6.87g	0	0	2.17g	2.38g	12.65g
Calcium	0	3mg	646mg	383mg	1002mg	632mg	11mg
Iron	0.02mg	0.02mg	36.96mg	13.97mg	8.32mg	11.83mg	0.12mg
Magnesium	3mg	1mg	170mg	229mg	60mg	259mg	12mg
Phosphorus	1mg	0	440mg	178mg	64mg	104mg	6mg
Potassium	37mg	5mg	1441mg	1119mg	431mg	1020mg	148mg
Sodium	3mg	2mg	16mg	18mg	10mg	277mg	9mg

Table 2.1 Nutritional value of green tea, black tea, and some spices used for additive in red Thai tea (Continued)

Nutrient	Nutritional value per 100g						
	Black tea	Green tea	Star anise	Cardamom	Cinnamon	Cloves	Vanilla Extract*
Zinc	0.02mg	0.01mg	5.3mg	7.47mg	1.83mg	2.32mg	0.11mg
Copper	0.01mg	0.01mg	0.91mg	0.38mg	0.34mg	0.37mg	0.07mg
Vitamin A	0	0	311IU	0	295IU	160IU	0
Vitamin E	0	0	0	0	2.32mg	8.82mg	0
Vitamin C	0	7.7mg	21mg	21mg	3.8mg	0.2mg	0
Vitamin B1	0	0.04mg	0.34mg	0.2mg	0.02mg	0.16mg	0.01mg
Vitamin B2	0.01mg	0	0.29mg	0.18mg	0.04mg	0.22mg	0.1mg
Vitamin B3	0		3.06mg	1.1mg	1.33mg	1.56mg	0.43mg
Vitamin B5	0.01mg	0	0.8mg	0	0.36mg	0.51mg	0.04mg
Vitamin B6	0		0.65mg	0.23mg	0.16mg	0.39mg	0.03mg
Vitamin K	0	0	0	0	0	141.8µg	0
Folate	5µg	0	10µg	0	6µg	25µg	0
Tryptophan	0	0	0	0	0.05mg	0.03mg	0
Threonine	0	0	0	0	0.14mg	0.18mg	0

Table 2.1 Nutritional value of green tea, black tea, and some spices used for additive in red Thai tea (Continued)

Nutrient	Nutritional value per 100g						
	Black tea	Green tea	Star anise	Cardamom	Cinnamon	Cloves	Vanilla Extract*
Isoleucine	0	0	0	0	0.15mg	0.24mg	0
Leucine	0	0	0	0	0.25mg	0.4mg	0
Lysine	0	0	0	0	0.24mg	0.37mg	0
Methionine	0	0	0	0	0.08mg	0.08mg	0
Phenylalanine	0	0	0	0	0.15 mg	0.23mg	0
Valine	0	0	0	0	0.22mg	0.34mg	0
Histidine	0	0	0	0	0.12mg	0.13mg	0
Saturated Fat	0	0	0.59g	0.68g	0.35g	3.95g	0.01g
Monounsaturated Fat	0	0	9.78g	0.87g	0.25g	1.39g	0.01g
Polyunsaturated fat	0	0	3.15g	0.43g	0.07g	3.61g	0

Source: (Foodstruct.com, 2022), (Nutrition-and-you.com, 2022)

2.1.2 Kombucha Fermentation

Kombucha tea is a traditional beverage product made from the fermentation of a tea and sugar solution using a kombucha starter, which contains bacteria such as *A. xylinum* and several other types of bacteria and other yeasts (Wistiana and Zubaidah 2015). The result of fermented kombucha tea is a suspension that can produce organic acids such as glucuronic acid, acetic acid, lactic acid, and folic acid, along with amino acids, vitamins, antibiotics, enzymes, and other products (Napitupulu and Lubis 2015).

Kombucha fermentation occurs in two stages: alcoholic fermentation and acetic acid fermentation. Yeast such as *S. cerevisiae* will break down sugar into alcohol, and acetic acid bacteria such as *A. xylinum* will oxidize the alcohol to acetic acid (Ardheniati and Amanto 2009). This continues until the sugar contained in the kombucha solution turns into organic acids needed by the body, such as acetic acid and others (Kustyawati and Ramli 2008). The resulting kombucha fermentation contains two phases: a floating biofilm and a sour liquid phase. The floating biofilm is known as BC, and the primary components of the liquid are acetic acid, gluconic acid, and ethanol, which are also present in the biofilm due to its high water absorption ability (Czaja et al. 2006).

In the kombucha fermentation process, BC can be produced as a by-product. This process can be simply illustrated in **Figure 2.1**. Bacteria can utilize several types of sugars, such as glucose and fructose, to be converted into various compounds or products, such as cellulose, gluconic acid, acetic acid, ethanol, and CO_2 (May et al. 2019).

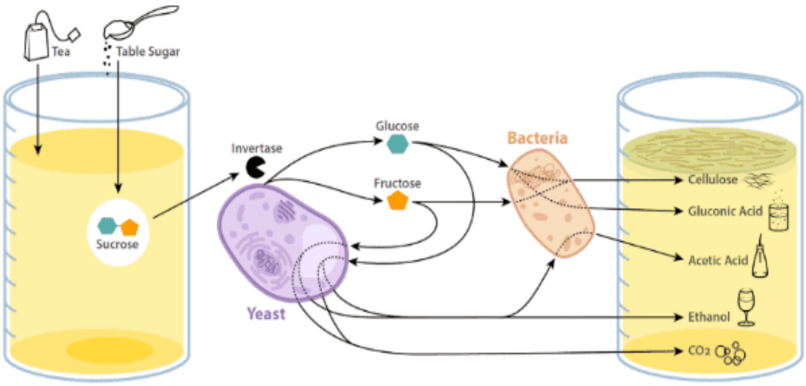

Figure 2.1 Formation of several types of compounds, including BC, in the fermentation of kombucha drinks (May et al. 2019)

2.2 Bacterial Cellulose

In general, cellulose is one of the main components of lignocellulosic materials and is mostly part of the plant cell wall along with other components such as hemicellulose, lignin, pectin, and wax (Mulyadi 2019). The composition of cellulose can reach one-third of the plant tissue and is the main component of several natural fibers such as cotton, flax, hemp, jute, and others (Moran et al. 2008). However, now cellulose has also been produced on a commercial scale using bacteria and is known as BC. The chemical structure of the cellulose polymer can be seen in **Figure 2.2.**

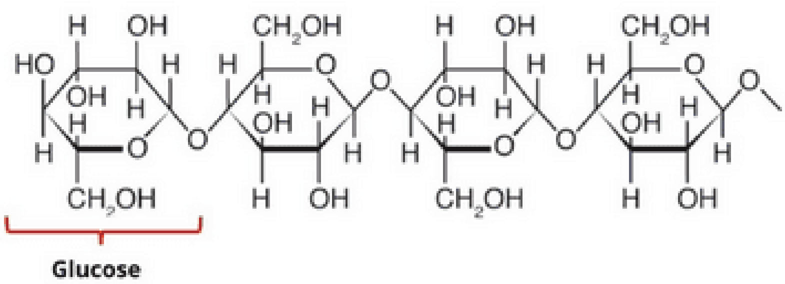

Figure 2.2 The structure of the cellulose chain composed of glucose monomers Source: (Amapex.net 2021)

BC, also known as bacterial nanocellulose (BNC), is cellulose synthesized by certain bacteria during the fermentation process. BC is produced as a metabolite from the activity of bacteria such as *A. xylinum* (Jasmania 2018). Bacteria use glucose or other carbohydrate foods to build cellulose through bacterial pathways (Dhali et al.

2021). Bacteria build cellulose (nanofiber) with nanoscale dimensions, with a nanometer diameter and length up to micrometers (Börjesson and Westman 2015). The diameter of BNCs usually ranges between 20 and 100 nm and is arranged in different types of nanofiber networks (Klemm et al. 2005). BC is called "bacteria nanocellulose" because the bacteria can only make cellulose on the nanoscale (Ho et al. 2022). Based on their length, BC can be classified as BCNFs (BC with longer whiskers) and BCNCs (BC with shorter whiskers) (Choi and Shin 2020).

Cellulose nanofibrils (CNFs) are the result of extraction from cellulose, which has a length ranging from 500–2000 nm and a width of about 20–50 nm with a flexible formation consisting of elementary nanofibrils (aggregates) composed of alternating crystalline and amorphous domains (Kargarzadeh et al. 2017). Meanwhile, crystalline nanocellulose (CNCs) is a type of nanocellulose that is also often referred to as nanocrystalline cellulose, nano whiskers, nanorods, and rod-like cellulose crystals (Kargarzadeh et al. 2017). CNCs have an elongated rod-like shape with less flexibility than CNFs due to their high crystallinity (Trache et al., 2020). CNCs are nanoparticles that range in size from 4 to 70 nm in width and 100 to 6,000 nm in length and have a crystallinity index of 54 – 88% (Naz et al. 2019).

BC is used in many applications due to its unique and good characteristics. Some of the unique properties of BC and its potential applications are demonstrated in **Table 2.2.**

2.2.1 Biosynthesis

Biosynthesis is a process in the cells of living organisms that is catalyzed by enzymes. The process transforms the substrate into a more complex product (bio.libretexts.org 2022). By using an envelope-spanning mechanism known as the BC complex synthase (BCS), bacteria may synthesize BC. The BCS gene cluster, which was initially discovered in *Gluconacetobacter* (Römling and Galperin 2015), encodes the BC complex synthase. In bacterial cultivation, gram-negative bacteria such as *Gluconacetobacter, Acetobacter, Agrobacterium, Achromobacter, Aerobacter,* *Sarcina, Azobacter, Rhizobium, Pseudomonas, Salmonella*, and *Alcaligenes* frequently create extracellular BC (Chen et al. 2022).

Table 2.2 The unique characteristic of BC and Its potential application

Characteristics	Potential application	Reference
• Biodegradability • High purity	• Food packaging	(Ludwicka et al. 2020)
• High Flexibility • High Water Holding Capacity • Hydrophilicity • High Crystallinity • Mouldability • Mechanical stability • High tensile strength	• Engineering of artificial skin, artificial blood vessels, wound dressing, nerve surgical covering, hemostatic material, electronic platforms, cartilage implants, and bone repair	(Gorgieva and Trček 2019)
• Thermostability • Biocompatibility • High degree of polymerization • Better biological adaptability	• A good prospect for a wide range of commercialization opportunities	(Hussain et al. 2019)
	• Synthetic skin, cartilage, vessels, wound dressing, and delivery systems	(Choi et al. 2022)
	• Food industry	(Lin et al. 2020)
• Highly porous structure • High permeability to liquids • Favorable for cell adhesion and proliferation	• Physics and chemistry, as well as medicine and mechanical engineering	(Volova et al. 2022)
• Considered as non-toxicity	• Food industry	(Dourado et al. 2017)

In conclusion, the BC production process can be summarized in two major stages: (1) the polymerization of β-1,4-glucan chains; and (2) the assembly and crystallization of these cellulose chains (Reiniati 2017). Additionally, Sutherland, (2001) outlines four key steps in the BC biosynthesis pathway: (1) activation of monosaccharides through the formation of sugar nucleotides; (2) polymerization into a repeating glucose chain; (3) elongation by the addition of glucose units; and (4) secretion of cellulose fibers through the bacterial cell membrane. The schematic representation of these biosynthetic pathways is illustrated in **Figure 2.3**.

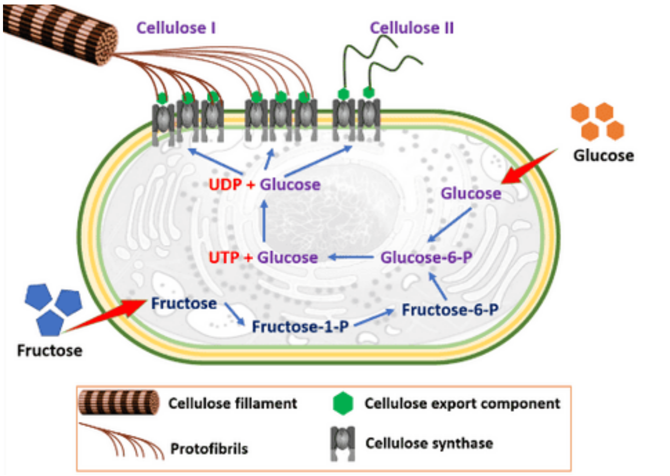

Figure 2.3 Schematic diagrams of BC biosynthesis by bacteria (Source: Modification of (Swingler et al. 2021))

2.2.2 Bacterial Cellulose Production

Bacterial nanocellulose (BNC) is cellulose produced during fermentation by certain bacteria. Utilizing glucose or other carbohydrates, bacteria employ bacterial processes to create cellulose (Dhali et al. 2021). The fermentation process to produce BC can be observed in the kombucha fermentation process, which produces a white layer on the surface of the broth. The general process of forming BC is illustrated in **Figure 2.4.**

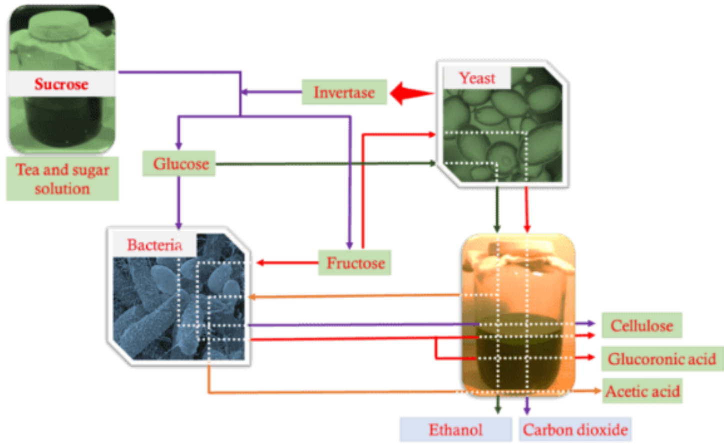

Figure 2.4 Schematic diagram of kombucha fermentation showing the production of BC and other compounds (source: modification of (May et al. 2019))

There are several cultivation methods that are commonly used in the process of producing BC, such as static cultivation, agitated cultivation (Azeredo et al. 2019a), and cultivation shaking methods (Ullah et al. 2019). Numerous factors, including the intended usage, morphology, and desirable BC properties, might affect the choice of the growing technique to be employed for the manufacture of BC (Zhong 2020). The cultivation method is discussed in more detail as follows:

1) Static Cultivation

The static cultivation method is a widely used and conventional approach for BC production (Ullah et al. 2019). In this method, a thick, white, jelly-like pellicle forms at the air–liquid interface of the fermentation vessel (Sharma et al. 2021). Despite its simplicity and broad application, static fermentation has several limitations, including long production times, high costs, uneven yields due to variable oxygen exposure among microbes, and depletion of carbon sources during fermentation (Swingler et al., 2021). Examples of BC production using this technique are presented in **Table 2.3.**

Table 2.3 Examples of some studies of BC production using static cultivation methods

Medium culture	Microorganisms / starter	Fermentation condition	Productivity	References
Hestrin-Schramm (HS) and its modification medium	*Gluconacetobacter hansenii* UCP1619	10 days, 30°C	51.8±0.6 g/L (ww)	(Costa et al. 2017)
Hestrin-Schramm (HS)	*G. xylinus* (ATCC No. 23768)	7–15 days, 28°C	-	(Badshah et al. 2018)
Hestrin-Schramm (HS)	*K. sucrofermentans* DSM 15973	7 days, 30°C	-	(Rovera et al. 2020)
Glycerol and Sunflower meal hydrolysate	*K. sucrofermentans* DSM 15973 strain	15 days, 30°C	Yield 0.6 g BC/g glycerol, 0.8 g/ (L.day)	(Efthymiou et al. 2022)

2) Agitated Cultivation

Ullah et al. (2019) mentioned that agitation cultivation can be used to produce BC in the form of granules and has a number of benefits over static and shaking cultivation, including a faster production rate, high cell density, and better cell contact with oxygen, thereby increasing productivity (Ullah et al. 2019). It has been suggested that agitated cultivation can boost production rates and the level of dissolved oxygen in the medium (Barja 2021a). BC produced in agitated cultivation has a different shape compared to that produced in static cultivation, which has shapes such as sphere-like, cocoon-like, or sometimes irregular clumps (Wang et al. 2019b).

Although agitation cultivation is believed to produce BC in a short time with high productivity, several studies report different results. The yield of BC produced by *G. xylinus* in static and agitated cultures was not significantly different (Ruka et al. 2015), as was the yield of BC produced by *Komagataeibacter* sp. CCUG73630 (Akintunde et al. 2022). Another study also reported the limitations of agitated cultivation methods. Agitated bacteria can cause the mutation of bacteria into non-cellulosic bacteria, thereby reducing the productivity of BC (Barja 2021a; Choi et al. 2022). This method cannot be applied to all types of bacteria (Barja 2021a).

3) Shaking Cultivation

The shaking cultivation method is used for BC production in the form of pellets (Ullah et al. 2019). The expressions "shaking" and "agitated", although usually used synonymously to describe a bacterial culture state, are sometimes used in reports to denote different culture conditions. For example, the development of bacteria or microorganisms in an incubator with a rotator is usually referred to as "shaking", but the growth of bacteria or microorganisms in a reactor may be referred to as "agitation" (Ruka et al. 2015).

Ullah et al. (2019) have provided a detailed description of the shaking process, including the rate of shaking, which is typically expressed in rotations per minute (RPM), the time period of fermentation, which is typically 24 to 36 hours, and the BC product, which is in the form of small pellets with a variety of pellet shapes depending on the type of microbial strain, the incubation period, and the rate of shaking (Ullah et al. 2019). Shaken culture fermentation on BC synthesis was performed with *A. xylinum* bacteria in media containing pineapple waste under optimal conditions (pH 5, 120 rpm, 28^{o}C) with the addition of microparticles, raising the BC yield to 15.19% (Pa et al. 2007).

2.2.3 Factor Affecting Bacterial Cellulose Production

Various factors can influence the fermentation process, including in the production of BC. Key parameters such as substrate type and concentration, fermentation duration, pH, temperature, and oxygen availability significantly affect both kombucha fermentation and BC yield (Villarreal-Soto et al. 2018a). Several nutrient sources, such as carbon, nitrogen, and caffeine, affect the fermentation substrate (Engström 2019). The surface area of the container and the depth of the culture medium are also important parameters (Engström 2019).

1) Microbial Starter

Microbial starters for BC production can be in the form of both monoculture and coculture (igem.org 2022). In the case of BC production using kombucha fermentation methods, the starter generally takes the form of a SCOBY. SCOBY is a cellulose biofilm generated by monosaccharide polymerization, and because of its similar form and look to the fruiting caps of macroscopic mushrooms, the SCOBY is also known as the tea mushroom (Kruk et al. 2021).

The SCOBY produced from kombucha production consists of many types of microorganisms from the genera of bacteria and yeast. A study of the composition of SCOBY starter cultures used by commercial kombucha brewers in North America showed that the most prevalent and abundant SCOBY taxa were the yeast genus *Brettanomyces* and the bacterial genus *Komagataeibacter* (Harrison and Curtin 2021). Some types of microorganisms found in kombucha starter, including bacteria such as *A. xylinum, A. aceti, A. pasteurianus, and Gluconobacter*, and yeasts, e.g. *Brettanomyces, B. bruxellensis, B. intermedius, Candida, C. fatama, Mycodicia, Saccharomyces, S. cerevisiae, S. cerevisiae* subsp*. Aceti, Schizo saccharomyces, Torula, Torulaspora delbrueckii, Torupsis, Zygosaccharomyces, Z. bailii, and Z. rouxii* (Greenwalt et al. 2000).

Different microbial species may produce BC with different yields and characteristics. Several selected bacteria grown in the same production media and conditions can produce BC with different yields (Angela et al. 2020). Furthermore, the inoculum concentration can affect the output of BC. According to research on different *Lactobacillus acidophilus* inoculum concentrations of 4%, 6%, 8%, and 10% (v/), a concentration of 6% (w/w) produces the best BC results of 1.843 g/L (dry weight) after 14 days fermentation (Jeff Sumardee et al. 2020).

2) Carbon Sources

Several studies have investigated the effect of different carbon sources on BC production during kombucha fermentation. While sucrose is the most commonly used carbon source, alternative substrates such as honey have been studied for partial or complete substitution. Reported concentrations of sucrose range from 70 to 190 g/L, while honey has been tested in the range of 1% to 20% (v/v). Al-Kalifawi (2018) reported that 100 g/L sucrose resulted in the highest wet BC yield of 66 g/L, while 10% (v/v) honey yielded 41.64 g/L. Goh et al. (2012) observed that 9% (w/v) sucrose resulted in the highest BC yield after 8 days of fermentation; however, 10% was not tested in that study. Optimal conditions for BC production using kombucha have been reported as 1% tea and 10% sucrose, with a fermentation time of 18 days (Al-Kalifawi and Hassan 2014). A larger surface area was also found to enhance BC formation.

The use of a 5% dextrose concentration in kombucha fermentation produced the highest yield of BC compared to glucose, fructose, and sucrose (Trevino-Garza et al., 2020). The use of glycerol produced the highest yield of BC compared to sucrose, fructose, glucose, mannitol, and lactose in a fermentation using *K. rhaeticu* (De Souza et al. 2021). The study of *A. xylinum* BC production at the same concentration from several carbon sources with 5% sucrose as the control medium showed that mannitol, fructose, and glycerol yielded 5, 3.5, and 3 times higher, respectively, than sucrose, while glucose medium and lactose produced less BC compared to the production on sucrose medium Yodsuwan et al., 2012). The combination of sucrose and fructose (1:1) at a total of 2% w/v in the BC production medium using *G. persimmonis* GH-2 had the highest yield, followed by fructose : lactose and galactose : sucrose (Hungund et al. 2013).

3) Nitrogen Sources

Another substrate component that impacts the productivity of BC synthesis is nitrogen. Nitrogen is essential for cell formation and microbial growth during the fermentation process with microorganisms (Kim et al. 2021). Nitrogen is required for cell metabolism and accounts for 8–14% of the dry cell mass of bacteria (Yodsuwan et al. 2012). The utilization of an appropriate nitrogen source will boost BC output (Engström 2019). The addition of a 0.1% (w/v) nitrogen source increased the productivity of BC by *Komagataeibacter* sp. bacteria, where beef extract produced the highest number of cellulose, followed by yeast extract, peptone, corn step liquor, and ammonium sulfate, respectively (Sutthiphatkul et al. 2020). The addition of some type of nitrogen source (at 0.5% concentration) to the HS medium in the fermentation to produce BC by *A. senegalensis* MA1 showed that yeast extract produced the highest yield of BC (Aswini et al. 2020).

4) Caffeine

Caffeine has been identified as a potential stimulator for BC production (Fontana et al. 1991). Black tea has a role as a source of caffeine in kombucha (Miranda et al. 2016). The presence of coffee ground (8 g/L) and sugarcane molasses increases the production of BC, but it can still be optimized (De Souza et al. 2021). The addition of coffee cherry husk (CCH) increased the yield of BC by more than three times (Rani and Appaiah 2013).

5) Trace Elements

The presence of trace elements in the medium has an impact on the yield of BC produced during fermentation. Almeida et al. reported that a number of trace elements were used during coconut water fermentation to produce BC (nata de coco). K (69%), Fe (84.3%), P (97.4%), SO_2^{-2} (64.9%), B (56.1%), NO_3^- (94.7%), and NH_4^+ (95.2%) are the most consumed ions in ripe coconut water fermentation. Na (94.5%) and Mg (67.7%) are the most consumed ions in green coconut water fermentation. Fermentation of cooked coconut water with the addition of KH2PO4, FeSO4, and NaH2PO4 was shown to produce the highest BC (6 g/L) (Almeida et al. 2013).

6) Environmental Conditions

Environmental elements including pH, temperature, the length of the fermentation process, and the presence of oxygen all have an impact on the formation of BC. When it comes to BC production, the surface area of the container and the depth of the broth are also important aspects to consider (Goh et al. 2012; Al-Kalifawi 2018). The temperature range for BC production in the kombucha fermentation process is 20–50°C; also, 18 days of fermentation and a larger container surface area are ideal circumstances (Al-Kalifawi 2018). Similar results were found in another study, which asserted that fermentation in containers with larger surfaces results in the production of more BC from the same quantity of substrate (Goh et al. 2012). The pH of the production medium is another environmental factor that affects the amount of BC produced. According to some studies, the ideal pH for the production of BC is 4.5 for *A. senegalensis* MA1 (Aswini et al. 2020), 5 for *Bacillus* sp. strain SEE-12 (El-Naggar et al. 2022), and 5.45 for *G. sucrofermentans* B-11267 (Revin et al. 2018).

2.2.4 Production of Bacterial Cellulose nanofibrils (BCNFs)

BCNFs are products derived from BC. BCNF is a fiber with a diameter of 10–50 nm and a micrometer length that is flexible, contains crystalline and amorphous regions, and can be made by mechanical techniques (Zhang et al. 2022d). Several methods that can be used for the production of BCNF include high pressure homogenizer (HPH), hydrochloric acid hydrolysis, TEMPO ((2,2,6,6-tetramethylpiperidin-1-yl)oxidanyl) oxidation, or a combination of HPH and TEMPO oxidation (Li et al. 2018, 2021; Wu et al. 2021).

High-pressure homogenizer (HPH) is one of the general methods that is frequently used for BCNF production (Zhang et al. 2022d). A high-pressure microfluidizer (HPM) is a mechanical method that can be used for the manufacture of nanomaterials (Yang et al. 2019). A high-pressure microfluidizer works at a high pressure of more than 100 MPa (Zhou 2022). One use of these microfluidizer technologies is in the development of a drug nano delivery system (Ganesan et al. 2018). The schematic for the preparation of nanomaterials with microfluidizer technology is illustrated in **Figure 2.5**.

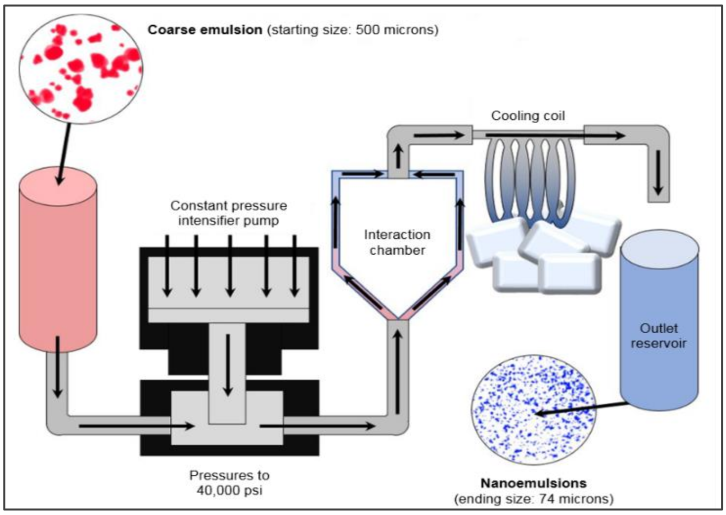

Figure 2.5 Schematic representation of the microfluidization process used to prepare the nano delivery system (Ganesan et al. 2018)

2.2.5 Application of BC in Nutraceutical

BC has been extensively researched and employed in the nutraceutical industry. Indeed, the phrases nutraceutical and functional food are still widely used interchangeably. Nonetheless, some literature defines the word nutraceutical. According to De Felice, nutraceuticals are "any substance that is a food or part of a food and provides medical or health benefits, including the prevention and treatment of disease" (DeFelice 1995). A nutraceutical is a substance derived by the isolation and purification of foodstuffs that is made in pharmaceutical form, is not related to food, and may obviously give physiological advantages or protection against chronic illness (Aronson 2017). Nutraceuticals are chemical or bioactive molecules with beneficial biological properties (Hoti et al. 2022).

Cellulosic nanoparticles can be used in nutraceuticals as emulsifiers, to immobilize bacterial and mammalian cells, to immobilize enzymes, and to immobilize bioactive compounds (Khan et al. 2018). Additionally, BC's inherent properties make it an intriguing candidate for use in nutraceuticals as a source of dietary fiber and meal replacement (Zhang et al. 2022c, b), immobilization agents (Jayani et al. 2020), and emulsifiers and Pickering emulsions (Z. Li et al., 2023). Following are the examples of the application of BC for nutraceutical.

1) BC for Dietary Fiber

A critical nutrient, dietary fiber, has been associated with reduced risks of obesity, diabetes, hypertension, coronary heart disease, cardiovascular disease, and stroke (Kushwaha and Maurya 2020), as well as enhanced digestive health (Guan et al. 2021). According to Shi et al. (2014), BC is a dietary fiber that has a number of benefits over other sources of dietary fiber, including high purity, the capacity to keep natural taste and color, and the capacity to be made in a variety of forms (Shi et al. 2014). According to studies, BC is used in foods like Nata de Coco, which is combined with other ingredients and processed into a fine powder for quick beverages. The instant drink's dietary fiber content ranged from 5.60 to 12.48% (Tangkanakul 2022). An ice cream product with a dietary fiber content of 2.39% was produced with the inclusion of 30% (w/w) wet BC and 1.4% (w/w) dry inulin in the creation of ice cream that was supplemented with dietary fiber (Xavier and Ramana 2022). In a different study, a meal replacement powder with a dietary fiber content of 15.09% was created by mixing buckwheat powder, fried cooked soybean powder, BC powder, konjac purified powder, and xylitol at a mass ratio of 80:60:20:3:1 (Zhang et al. 2022b).

2) BC for Immobilization Agents

BC and its derivative products have the potential to be used as cell immobilization agents, enzymes, and bioactive compounds (Khan et al. 2018). The purpose of immobilizing these samples is to prolong probiotic cell viability, enhance biocatalytic and enzyme processes, and protect enzymes from harmful environmental factors (Mitropoulou et al. 2013; Guzik et al. 2014; Maghraby et al. 2023).

The following research has looked into BC's potential as an immobilizing agent: The most efficient method for shielding bacteria from bile salts and digestive acids has been to employ BC to immobilize bacteria, such as *Lactobacillus* sp. (Fijałkowski et al. 2016). *L. acidophilus* 016 was a probiotic bacterium that was immobilized on BCNF and could last for up to 24 days, with 71% of the population surviving at 35°C (Jayani et al. 2020). Additionally, BC has been designed to immobilize "ready-to-use" freeze-dried cultures of lactic acid bacteria, which are subsequently utilized in the fermentation of milk (Lappa et al. 2022). Lysozyme, an enzyme with antibacterial activity, has been immobilized using BC without significantly affecting its function. Additionally, the pH and temperature ranges for appropriate activity were widened, and the storage stability of enzymes was improved (Bayazidi et al. 2018).

3) BC for Emulsifier and Pickering Emulsions

Emulsions are dispersion systems composed of two immiscible liquids, usually water and oil, with the oil phase typically consisting of organic liquids (Chen et al. 2020). Pickering emulsions (PEs) are a specific kind of emulsion that is solely sustained by solid particles at the oil-water interface (Yang et al. 2017). The food sciences have recently been interested in pickling emulsions, a revolutionary technology (Chen et al. 2020). The use of BC in the creation of emulsifiers and PEs has been documented in a number of investigations. Particle stabilizers for high internal phase emulsions (HIPEs) have been made using BCNs and soy protein isolate (SPI) with an optimum BCNs/SPI ratio of 7:25, the findings demonstrated that BCNs considerably boosted the emulsifying ability (Liu et al. 2021). An increase in curcumin bioaccessibility to 30.54% was observed following encapsulation in curcumin-loaded HIPEs stabilized by BCNs and SPI colloidal particles, demonstrating high encapsulation efficiency and antioxidant activity (Shen et al. 2021).

4) BC for Personalized Nutrition

A fresh method for BC applications is personalized nutrition, which is founded on the idea that every individual is different and has distinct needs. In order to help an individual achieve personalized nutrition and healthy eating habits, personalized nutrition entails gathering genetic, phenotypic, medical, nutritional, and other significant facts about the individual that are pertinent (Chaudhary et al. 2021). Only a few publications are currently accessible that discuss the use of BC in the creation of individualized nutrition. Future applications of BC in the development of customized nutrition can be guided by case studies in the production of low-fat 3D-printed cheese analogs and low-fat printable casein-based inks (Shahbazi et al. 2021b, a). Customized nutrition depending on a person's medical needs may be possible with the use of low-fat Pickering emulsions in 3D food printing (Shahbazi et al. 2021a). The use of 3D printing technology in the food industry has made edible components easily adjustable and capable of taking on a range of visually attractive designs (Shahbazi and Jäger 2021).

2.3 Response Surface Methodology (RSM)

Response surface methodology (RSM) is a group of mathematical and statistical methods used to plan experiments, adapt hypothesized models to data, and identify the best conditions to produce the most desired response (Khuri 2017). RSM is a technique for conducting design of experiments (DoE). According to Hadiyat (2012), RSM was originally introduced by Box and Wilson in 1951 as a version of DoE that not only examines the effect of experimental components but can also be used to determine the best points from multifactor experiments. DoE is a technique used to plan and analyze experiments, allowing a minimum number of experiments and varying several experimental parameters systematically and simultaneously (Whitford et al. 2018). Design of Experiment (DoE) is used to collect data and identify the principle of variables that influence process response, and RSM is used to determine the best parameter values to optimize process and equipment design (Hadiyat et al. 2022).

Central Composite Design (CCD) and Box-Behnken Design (BBD) are the two main design types used in RSM. Response surface design experiments using CCDs are the most popular. CCD is a factorial or fractional factorial design with a center point and a set of axial points (also known as star points) that allow curvature estimation, whereas BBD is a type of response surface design that excludes embedded factorial or fractional designs (support.minitab.com 2023). On CCD, the response data obtained is modeled with appropriate mathematical models such as average, linear, quadratic, 2-factor interaction (2FI), and cubic (Hidayat et al. 2020).

In practice, RSM is carried out using statistical software or programs such as SAS, MINITAB, STATISTICA, or Design Expert (Nassiri Mahallati 2020). Design-Expert is one such statistical program. It offers integrated design, robust parameter design, mix design, screening, characterization, and comparison testing (Tanco et al. 2008). It provides a test matrix to screen up to 50 variables and an analysis of variance (ANOVA) to ascertain its statistical significance. Tools for data visualization help identify abnormalities in the data and show how each factor affects the desired results (Comley 2009).

RSM is one of a common method used for optimizing production processes in fermentation techniques, including the production of BC. Studies have reported on the use of RSM in the production of BC, which primarily aims to increase the yield or productivity of BC. The process of cellulose production from *G. xylinus* C18 was optimized using RSM based on the CCD. The result showed that the maximum yield of BC (4.34 g/L) was reached at the best conditions, i.e., a sugarcane molasses concentration of 10.77% (w/v) supplemented with 12.47% (v/v) corn steep liquor, a temperature of 31°C, pH 6.5, and an incubation time of 172 h (Singh et al. 2017). A similar approach was applied to maximize BC production using *A. senegalensis* MA1. The ideal fermentation conditions were 50 ml/L of glycerol, 7.50 g/L of yeast extract at pH 6.0, and 7.76 g/L of polyethylene glycol 6000, which produced the maximum yield of 469.83 g/L (Aswini et al. 2020). Another study optimized the manufacture of nitrocellulose (NC) from BC to create a product with a high nitrogen content using the CCD of the RSM technique. The highest percentage nitrogen content of NC was 12.64% under the predicated ideal circumstances of mole ratio H_2SO_4/HNO_3 = 3:1 mol/mol, temperature = 35°C, and duration of 22 min (Roslan et al. 2019)

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