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Applications of Cyclodextrin-gluconotransferase in the Biosynthesis of Cyclodextrins: Characteristics, Sources and Production

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Abstract Cyclodextrin-gluconotransferases are microbial enzymes belonging to the α-amylase family. They synthesize cyclic oligosaccharides called cyclodextrins from starch substrates. The production of cyclodextrin-glucosyltransferases is generally carried out by fermentation in a liquid or solid medium. The review article aims to provide a comprehensive and in-depth overview of cyclodextrin-glucosyltransferases, highlighting their characteristics, sources, production, and applications in producing cyclodextrins. Websites such as ScienceDirect, NCBI, researchgate.net, scholar.google, core. Ac. uk, serve as a search engine for documents related to our review article. This article provides the answers to the in-depth understanding of cyclodextrin-gluconotransferases, production methods, industrial applications, and the diversity of strains that produce them.

Keywords: *applications, sources, production, cyclodextrin, bacteria, Cyclodextrin-gluconotransferase*

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1. Introduction

Many bacteria use starch as a source of carbon and energy for their growth. To utilize this carbon and energy source, they produce a range of extracellular enzymes to convert large molecules into usable metabolites. A large number of starch-hydrolyzing enzymes have been identified and characterized, including α-amylase, glucoamylase, and cyclodextrin-glucosyltransferase (CGTase) [1]. CGTase is therefore a microbial enzyme capable of four major chemical reactions, including cyclization, coupling, dismutation, and hydrolysis [2]. CGTases are enigmatic enzymes that play a key role in the creation of remarkably important compounds in the starch utilization pathway of certain bacteria and catalyze various glucan transfer reactions with starch yielding a mixture of cyclodextrins (CDs) [3,4]. CDs are cyclic α-1,4-glucans produced from starch or starch derivatives using CGTase [5]. CDs have opened the way to an infinite range of applications, from pharmaceuticals to food, cosmetics, and textiles [6,7]. However, to understand this story of molecular transformation, it is essential to delve into the world of CGTases. In this scientific odyssey, we'll explore CGTases through their characteristics, the sources from which they emerge, the methods of their production, and, finally, their applications in the synthesis of cyclodextrins. Beyond their role as catalysts, we'll discover how these enzymes exert their influence in fields as varied as pharmacology, the design of innovative cosmetics, and the resolution of complex food challenges.

2. General Information on Cyclodextrinegluconotransferases

CGTases are biological catalysts classified in the family of glycoside hydrolases 13 or α-amylases with the enzymatic commission number EC 2.4.1.19 [8]. They are classified in the transferases, a subclass of the

transglycosylases, and the sub-subclass of the hexosyltransferase [8,9,10]. They degrade intra-and intermolecular trans-glycosylation reactions with an α-retentive double displacement mechanism carried out by a catalytic triad composed of three conserved carboxylates [11]. Initially, CGTases were detected in a strain of *Bacillus macerans* and subsequently, they were identified in other microbial species such as Bacillus, certain species of the genus Klebsiella, Thermoanaerobacteria and also in archaea such as Thermococci [11].

2.1. Characteristics of Cyclodextringluconotransferase

CGTases are monomers whose number of amino acids and molecular weight vary depending on their source. Molecular weights between 33 and 110 kDa have been reported for CGTases from various organisms. Therefore, the properties of CGTases depend on the microorganism from which they are extracted [9], their optimal pH, their temperature, the specificity of their substrate, and their catalytic efficiency [8].

Generally, the structure of CGTase consists of five protein domains (A to E), and its active site is located in domain A [8,12] Domain A is the catalytic domain (α/β)-8 and catalytic residues are located at the C-termini of the β-strands. The B domain contributes to substrate binding [8,9). The substrates bind to a groove formed by the A and B domains containing ten sugar-binding subsites labeled -7 to +3. Sugar binding subsites are labeled from -n to +n where the "n" is an integer. The sugar-binding subsite -n constitutes the non-reducing end while +n constitutes the reducing end. The C domain shows an antiparallel β-sandwich fold and its function is to bind the substrate while the E domain serves to bind starch and maltose. However, the function of the D domain is still unexplored [8,9,13]. CGTases open α-1,4-glycosidic bonds between the +1 subsites in α-glucans, which produce a stable covalent glycosyl intermediate linked to the donor subsites [13]. The glycosyl intermediate is then transferred to the 4-hydroxyl of its non-reducing end forming a new α-1,4-glycosidic bond to yield a cyclic product. CGTases can also transfer the glycosylated intermediate to a second α-glucan to give a linear product (disproportionation) or to water (hydrolysis). Additionally, CGTase can degrade CDs by opening the CD ring and transferring the linearized CD to a sugar acceptor to yield a linear oligosaccharide (coupling). The large amount of structural information together with site-directed mutagenesis data has been used to elucidate the mechanistic functions of residues at the catalytic center of CGTases [9,13]. For example, CGTase from *circulating Bacillus* strain 8 has 80 to 108 residues in domain A, 185 to 192 residues in domain B, 407 to 494 residues in domain C, 495 to 580 residues in domain D, and 581 to 684 residues in domain E [9).

2.2. Production of Cyclodextrineglucanotransferases

CGTases are generally produced extracellularly from the original host organisms or by recombination of one or more microbial genera [1,11]. Microbial species from bacterial genera such as Brevibacteria, Clostridium, Corynebacteria, Klebsiella, Micrococci, Pseudomonas, Thermoanaerobacteria and Thermoanaerobacteria produce CGTases [14]. The ability of CGTases for the transglycosylation of various molecules attracts the attention of scientists in the field of biotransformation [14]. All CGTases can synthesize cyclodextrin from starch in different proportions. CGTases with the capacity to synthesize a single type of cyclodextrin are increasingly preferred for industrial uses nowadays because the individual separation of cyclodextrin generates relatively high costs [15]. The formation of CGTases is similar to other enzyme manufacturing processes. This formation of CGTase depends on the presence of starch and is inhibited by glucose. The first method includes optimization of the culture conditions of the CGTase-producing bacterial strain.

The second method involves heterologous expression of CGTase in a suitable host and a third method to enhance CGTase production is metabolic regulation of CGTase-producing strains [1].

2.3. Different Source of Cyclodextringluconotransferases

CGTase is an extracellular enzyme derived exclusively from bacterial cells. They have certain functional similarities with amylases which are products of linear hydrolysis of starch or its derivatives [16]. CGTases are the enzymes generally used for the synthesis of CDs. CDs are synthesized by enzymatic conversion of starch or related substances, and each CGTase has its characteristic synthesis ratio of α, β, and γ [8]. CGTases derive their sources from microbial metabolites [2] They are also produced by chemical modification [17]. Microbial species capable of producing CGTases often grow in extreme pH conditions, high temperatures, and high salinity environments. Their natural habitats are lakes, soil, and freshwater. In recent years, several bacterial genera have been identified as having the capacity to produce CGTases, led by strains of the Bacillus genus. See III. general information on producing microorganisms of CGTase.

2.4. Applications of Cyclodextrineglucanotransferases

CGTases are effective in the production of cyclodextrins from starch by the cyclization reaction. Which is the basis of their industrial application [1]. Indeed, work in recent years focuses on the use of CGTase-catalyzed coupling and disproportionation reactions for the synthesis of modified oligosaccharides using alternative acceptor substrates [18]. Aside from the production of cyclodextrins by the cyclization reaction, CGTase could be used for its coupling and disproportionation reactions for the transfer of oligosaccharides from donor substrates such as cyclodextrins or starch to various acceptor molecules [12] Increasingly, the use of alternative acceptors is reported, resulting in novel glycosylated compounds [19].

3. General Presentation of Cyclodextrins

3.1. History

The genesis of cyclodextrins (CDs) dates back more than a century, and since then, the scientific community has contributed to the study of these molecules. It is thanks to them that we can understand the different aspects of CDs, namely their production, their structure, and their physicochemical properties [20,21]. Antoine Villiers- Moriamé has isolated 3g of a crystalline compound from the bacterial digestion of 1000g of starch.

He determined the chemical composition of this substance as (C6 H10 O5)2-3H2O, and it was named" cellulose" because of its properties similar to cellulose. He also observed the existence of two different crystal forms which probably correspond to α-CD and β-CD [20,22,23]. It was only after 20 years that Shardinger identified the *Bacillus macerans strain* as being responsible for the production of these crystalline dextrins. From then on, He distinguished two different crystalline products, “crystalline D-dextrin” and “crystalline E-dextrin”, because of their ability to form specific adducts with diiodine molecules of different colors. In 1936, Freudenberg demonstrated the ability of these dextrins to form complexes with various organic compounds. He concludes that cyclodextrins are oligosaccharides composed of a series of maltose units linked by D(1t4) glycosidic bonds and assumes that these products are cyclic. The structures and molecular weights of D-CD and E-CD were determined by French and Rundle in 1942, while J-CD was discovered, and its structure clarified. at the end of the 1940s [24,25]. The inclusion properties of cyclodextrins were widely studied in the early 1950s. It was not until 1953 that Freudenberg, Cramer, and Plieninger were able to file the first patent on the application of cyclodextrin to the formulation of compounds for biological use. Beginning in the 1970s, numerous studies demonstrated the lack of inherent toxicity of cyclodextrins that could preclude its use. The quantity of cyclodextrins was low and the price was high approximately 2000 US$/kg for β-cyclodextrin at that time. Nowadays, they are produced at around 10,000 tonnes/year and their prices have fallen considerably [26]. Many derivatives are now produced industrially, while others are commercially available in small quantities [22].

3.2. Structure OF Cyclodextrins

Cyclodextrins are cyclic oligosaccharides produced by the degradation of amylose by cyclodextringlucosyltransferase of bacterial origin [26]. The three most common cyclodextrins are α-, β- and γ-cyclodextrins, composed respectively of 6, 7, and 8 glucopyranoside units [21,22]. These glucopyranose units in chair conformation are linked together by α-1,4 glycosidic bonds. This arrangement is the origin of the cyclodextrin form, that is to say, the shape of a truncated cone or lampshade with a central cavity (Figure 1), the opening of which is lined with hydroxyl group [20,24]

There are CDs of larger sizes respectively made up of 9, 10… units and of smaller size cyclo-D(1t4)-glucopentaoside which have been isolated or completely synthesized [27]. Different nomenclatures are used in literature for the naming of CDs. The CDs have a three-dimensional structure in the shape of a conical cylinder or the shape of donuts for those with a sweet tooth, the wall of which is made up of glucose units, in a chair conformation [23]. On the narrowest part of the cone are all the primary hydroxyls (primary side) and on the other, wider part, the secondary hydroxyls (secondary side). In addition, the formation of two crowns of hydrogen bonds, on these two faces, gives a relatively rigid structure. According to the numbering commonly used in sugar chemistry, the H 3 and H 5 protons are oriented towards the interior of the cavity, while the H1, H2, and H4 protons and the two H 6 protons are directed towards the cavity exterior [27].

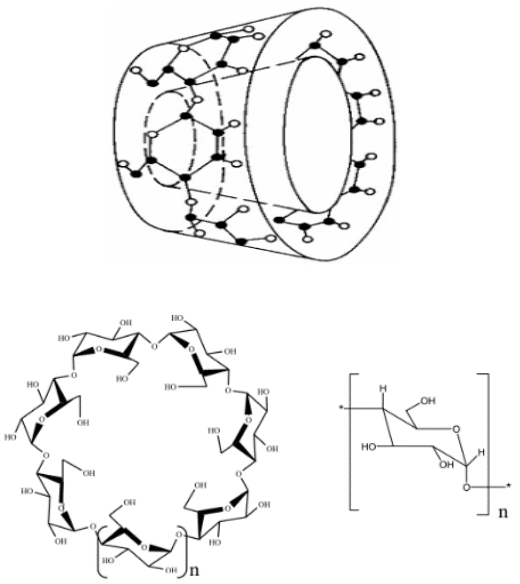

Figure 1. Schematic representation of cyclodextrins (26)

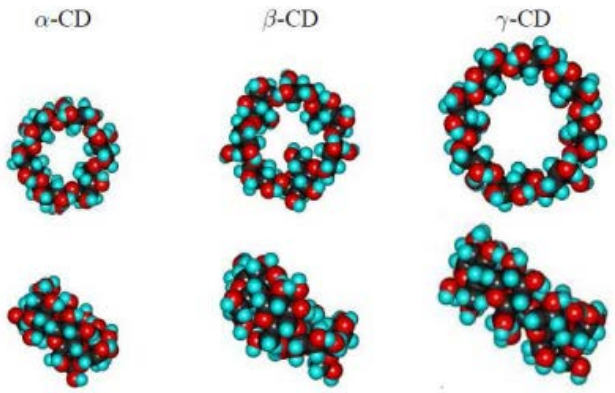

Figure 2. Three-dimensional structure of the different natural cyclodextrins (from left to right α-CD, β-CD, and γ-CD) with a view of the secondary face at the top [27]

The secondary hydroxyl groups of the glucopyranose units, having carbons at C2 and C3, are located near the widest entrance to the cavity and are often referred to as the "secondary face". The production of hydrogen bonds within the hydroxyl groups located at the C2 and C3 carbons between two adjacent units increases the rigidity of the cyclodextrin structure. The primary hydroxyl groups, which carry the C6 carbons, are found around the

other opening which is called the “primary face”. They are narrower thanks to their free rotation [10]. The presence of these numerous hydroxyl groups allows the exterior of the CDs to acquire hydrophilic properties. The wall of the central cavity is composed of carbon, hydrogen, and ether oxide bonds. The free doublets of oxygen atoms which form glycosidic bonds are directed towards the interior of the cavity rich in electron density. The interior of the CDs is therefore a relatively non-polar and hydrophobic cavity. In summary, CDs have a macrocyclic structure characterized by a hydrophilic exterior and a hydrophobic interior. These structural characteristics justify the particular properties of CDs.

It should also be noted that CDs are subject to several names which vary depending on the era and the authors. Thus, β-CD is also referred to as Schardinger's β-dextrin, cyclomaltoheptaose, cycloheptaamylose, BCD, etc. [28].

3.3. Physicochemical Characteristics

The best-known property of cyclodextrins is their ability to improve the solubilization in water of organic molecules, which are poorly or not water-soluble, by forming inclusion complexes thanks to their hydrophobic cavity [27]. To improve their physicochemical properties, namely solubility and complexing properties, it is possible to modify native cyclodextrins by functionalizing the hydroxyl groups of the cyclodextrin. The best-known commercial cyclodextrins are methylated and hydroxypropylated cyclodextrins [29].

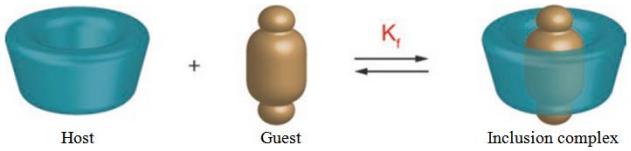

Figure 3. Formation of an inclusion complex between a cyclodextrin molecule (the host) and an organic molecule (Guest); Kf represents formation constant [29,30].

The three main CDs most used are crystalline, homogeneous, and non-hygroscopic compounds. Their main physicochemical characteristics are gathered in Table 1.

Table 1. Physicochemical characteristics of the main CDs [26,36]

	α - cyclodextrin	β - cyclodextrin	γ - cyclodextrin
Number of glucose units	6	7	8
Brute formula	C 36 H 60 W 30	C 42 H 70 W 35	C 48 H 80 W 40
Molar mass (g.mol-1)	97	1135	1297
Solubility in water (gL-1)	145	18.5	232
Ø cavity (Å) (small face-large face)	4.3-5.3	6.0-6.5	7.5-8.3
Cone height (Å)	7.9 ± 0.1	7.9 ± 0.1	7.9 ± 0.1
Approximate volume of the cavity (Å3)	174	262	427
Average number of water molecules	6 – 8	12	13

It is interesting to note that by increasing the number of glucose units, only the diameter increases while the height of the torus remains constant. The CDs are surrounded on the outside by a layer of water molecules which can be removed quite easily by freeze-drying. On the other hand, in the absence of any other non-polar molecule, the cavity contains numerous water molecules which can only be replaced, and not eliminated [24,27].

3.3.1. Inclusion Complex

It was only in 1938 that Freudenberg first advocated the hydrophobic nature of the internal surface of dextrin and noted the ability of dextrins to form complexes because of their cyclic structure [30]. To provide explanations for these complexes, Freudenberg was the first to show the involvement of hydrophobic forces in the formation of complexes. He was also convinced that the dextrins and the amylose helix were covered with a hydrocarbon interior. Which allows us to qualify the cavity of dextrins as a hydrocarbon in nature [6,32]. In his thesis written in 1949, Cramer mentioned that the three native cyclodextrins were capable of accommodating molecules of different sizes: this was the first statement about the ability of cyclodextrins to form inclusion complexes. It was not until 5 years later that Cramer subsequently demonstrated the capacity of cyclodextrins to accept various molecules within their cavity. He was therefore the first scientist to provide scientific evidence about the hypothesis put forward by Schardinger at the beginning of the 19th century [30]. An inclusion complex consists of an arrangement of at least two molecules, one of which, the receptor (host), fully or partially encapsulates the substrate (or “guest”) under the effect of weak interactions. Note that in this association, no covalent bond is established, which facilitates the dissociation of the complex formed [22]. The important factor for inclusion complex formation is that the guest molecule must be able to enter the internal cavity of the cyclodextrin. However, geometric shape is not the only factor in the formation of stable inclusion complexes, as previous studies have shown that some guest molecules that are well compatible with cyclodextrins cannot insert satisfactorily within the internal cavity of the host molecule [30]. The formation of an inclusion complex between cyclodextrins and guest molecules is attributed to this complex physicochemical and biological properties different from those of cyclodextrins and inclusion molecules taken alone [22].

3.3.2. Main cyclodextrins

3.3.2.1. Alpha-cyclodextrin (Alpha-CD)

The three natural cyclodextrins have approximately the same structures, apart from the structural requirements of accommodating different glucose units [33].

CDs are rigid by a hydrogen bond between the 3-OH and 2-OH groups around the wider edge. The flexible 6-OH hydroxyl groups around the narrower edge are also capable of forming hydrogen bonds, but they are easily dissociated in aqueous solution. Alpha-CD has the lowest hydrogen bond strength [33]. The structure of alpha-cyclodextrin forms a torus-shaped cavity, which can accommodate guest molecules inside. This ability to include molecules makes alpha-CD a useful agent in the food and pharmaceutical industries. In the food industry, alpha-CD is used as a solubilizing agent to improve the solubility of certain active ingredients, such as vitamins,

flavors, and colors [34]. It is also used to improve the stability of certain foods, such as oils and fats, by protecting them from oxidation [35]. Alpha-CD is also used as an encapsulating agent to protect sensitive active ingredients, such as vitamins and antioxidants, from degradation during storage and transportation. In the pharmaceutical industry, alpha-CD is used as an excipient to improve the bioavailability of drugs [36]. It can form inclusion complexes with drugs to improve their solubility and absorption. It can also be used as a release control agent to release medications in a controlled manner into the body. In addition to its industrial applications, alpha-CD has also been studied for its beneficial health effects. It has been shown to reduce the absorption of dietary fat and cholesterol, which may help reduce the risk of cardiovascular disease [35]. However, a preclinical study carried out by [37]revealed no significant effect of alpha-CD on cholesterol and blood sugar control in prediabetic and overweight or obese people. It has also been studied for its effect on blood sugar and insulin sensitivity, which may be helpful for people with diabetes. In summary, alpha-CD is a versatile molecule with many applications in the food and pharmaceutical industries. It also has potential beneficial effects on health, making it an interesting molecule to study for future applications.

3.3.2.2. Beta-cyclodextrin (beta-CD)

Also called cycloheptaamylose, beta-CD, is the cyclodextrin that has been the subject of several scientific studies due to the formation of inclusion complexes with various ions, molecules, and polymers [38]. beta-CD is a cyclic oligosaccharide composed of seven glucose units linked together by alpha-1,4-glycosidic bonds. It is a type of cyclodextrin, which is a family of compounds formed by the enzymatic degradation of starch [20,39]. It is a molecule used in many fields, notably as an excipient in pharmacology, in the food and cosmetic industries, or even for industrial applications. In pharmacology, beta-CD is used as an inclusion agent to improve the solubility of drug molecules that are poorly soluble in water [40]. This is because this molecule has a hydrophobic cavity that can encapsulate the hydrophobic drug molecule and protect it from water, which improves its stability and bioavailability.

Beta-CD thus makes it possible to increase the therapeutic effectiveness of poorly soluble drugs and to reduce side effects [41]. In the food industry, beta-CD is used as a food additive to improve the organoleptic properties of foods. It can encapsulate aromatic molecules and mask unpleasant odors and tastes while increasing their stability and shelf life [42,43]. In cosmetics, beta-CD is used to encapsulate active molecules, protect them from water, and increase their stability and effectiveness. It can also be used to improve the texture and appearance of cosmetic products [44]. To sum up, beta-CD makes it possible to improve the solubility, stability, bioavailability, shelf life, and effectiveness of the molecules it encapsulates, which makes it an interesting compound.

3.3.2.3. Gamma-cyclodextrine (Gamma-CD)

Gamma-CD is a cyclic glucose polymer consisting of eight glucose units. Each glucose unit is connected to the next by an α(1-4) glycosidic bond [5], which gives the molecule a toroidal structure with a hydrophobic central cavity. Gamma-CD is a member of the CD family, which also includes alpha-CD and beta-CD [45]. The size of the central cavity is approximately 7.8 Å in diameter and 5.5 Å in height, which allows it to form inclusion complexes with small hydrophobic molecules. Gamma-CD is used in a variety of applications, including pharmaceuticals, foods, and cosmetics [46]. In the pharmaceutical industry, it is used to improve the solubility and bioavailability of poorly soluble drugs such as anticancer drugs, anti-inflammatories, and antifungals, as well as to protect drugs from degradation. In the food industry, it is used as a flavor and aroma enhancer, as well as to stabilize food ingredients [47]. In cosmetics, it is used as a solubilizer and stabilizer for active ingredients [5]. Gamma-CD is generally considered safe for these applications because it is not metabolized by the body and is excreted unchanged [31]. However, like other CDs, it can cause gastrointestinal side effects such as bloating and flatulence when consumed in large quantities. Compared with α- and β-CD, γ-CD has unique properties. First, Gamma-CD has the advantage of having a larger internal cavity, which allows the formation of inclusion complexes with large molecules having several applications, unlike α-and β-cyclodextrins which cannot be trapped by these [5). Meanwhile, Gamma-CD has higher solubility (232 g/L) in water than α-CD (145 g/L) and that of β-CD (18.5 g/L), which facilitates the preparation of solutions more concentrated in active molecules [10]**.** Based on the dimensions of their cavities, α-cyclodextrin can only form inclusion complexes with low molecular weight molecules or compounds with aliphatic side chains, and β-cyclodextrin can complex aromatics or heterocycles, while Gamma-CD can accommodate a wider variety of compounds [5].

Then, Gamma-CD can be rapidly and essentially completely digested by human salivary amylase and pancreatic amylase, which are incapable of digesting α-cyclodextrin and β-cyclodextrin. Thus, Gamma-CD is rapidly degraded and absorbed in the human small intestine, unlike α-cyclodextrin and *beta-CD*, which are generally recognized as non-digestible. The high bioavailability of Gamma-CD makes it ideal for some specific applications in the food and pharmaceutical fields [5].

3.3.3. Cyclodextrin derivatives

Several studies have described cyclodextrin derivatives. They are generally produced chemically to increase the aqueous solubility of CDs; increase their complexing capacity; increase their affinity for a given molecule; introduce specific groups facilitating complexation; synthesize polymers; and ultimately reduce the damage caused to cell membranes [31,48]. They are obtained by the method of grafting groups onto the hydroxyl functions of native CDs. The derivatives of cyclodextrins often encountered on the market are methyl, hydroxypropyl, and sulfobutyl ether cyclodextrins [49,50].

3.3.3.1. Methylated derivatives

The addition of a methyl group generously improves the solubility of CDs in water. The two commercial forms of interest are RAMEB (β-CD methylated, randomly, on all primary hydroxyls as well as on 7 to 9 secondary

hydroxyls) and CRYSMEB (methylated at position 2 of β-CD). These derivatives have better solubility than natural CD and good inclusion capacity for products that are poorly soluble in water. However, RAMEB remains more attractive for the pharmaceutical field due to its significant complexation capacity [5,48].

3.3.3.2. Hydroxypropyl derivatives

Hydroxypropyl derivatives are produced in an alkaline medium by the reaction of *beta-CD* with propylene oxide. HP-β-CDs are defined by high solubility in water because of their strong hydrophilic character. This is what justifies their broad interest in the pharmaceutical field [5].

3.3.3.3. Sulfobutylated derivatives

Sulfobutyl derivatives are compounds synthesized to improve the solubility and stability of medicinal substances. Sulfobutyl ether-β-CDs have high aqueous solubility and significant solubilization power (Stella and Rajewski, 2020). Sulfobutyl derivatives are manufactured industrially under the name Captisol [51].

The latter has a degree of substitution between 6 and 7 and carries a negative charge under physiological conditions. This is attributable to the sulfonic acid groups which give it a fairly low pKa. Butyl chains and the repulsion of negative charges make it possible to elongate the cavity. Therefore, this CD has a better affinity for welcoming guests. The negative charge also allows it to complicate guests with a positive charge. Like hydroxypropyl-β-CD, captisol has a rather fascinating pharmaceutical use given its low toxicity and high solubility [5].

3.4. Production of Cyclodextrin

Mass production of CDs is a necessary step to develop these compounds. The first step in the CD synthesis process involves liquefying the starch by increasing the temperature [52]. CDs are produced in thousands of tonnes each year from starch by several manufacturers, and demand continues to increase (Figure 4a). Natural CDs are obtained by enzymatic degradation followed by intramolecular transglycosylation of starch under the action of CGTase. Primarily, the cyclization reaction of the linear chains of starch glucopyranose is carried out by CGTases, originating from the microbial species *Bacillus firmus* for example. This step ends with a mixture of alpha, beta, and gamma CD, designated by Figure 4b, composed of six, seven, and eight units of D (+)glucopyranose, respectively, linked by α 1.4 bonds [53]. Then, the separation and purification of the three cyclodextrins are carried out. Selective precipitation, forming inclusion complexes with an appropriate guest molecule is one of several methods used to isolate α, β, and γCDs, e.g. α, β and γCDs crystallize with 1decanol, toluene, and cyclohexadec8en1one, respectively. However, separation has a relatively high cost, making the entire production process somewhat expensive [53]. Over the years, research into the production of CGTases has taken off, which has allowed the isolation of α, β, and γCGTase, thus increasing the yield and consequently reducing the production costs of cyclodextrins [53]. In this way, CDs, Figure 2, are composed of glucose units that together generate conical frustum cyclic structures, capable of solubilizing in an aqueous environment and encapsulating hydrophobic molecules inside [53].

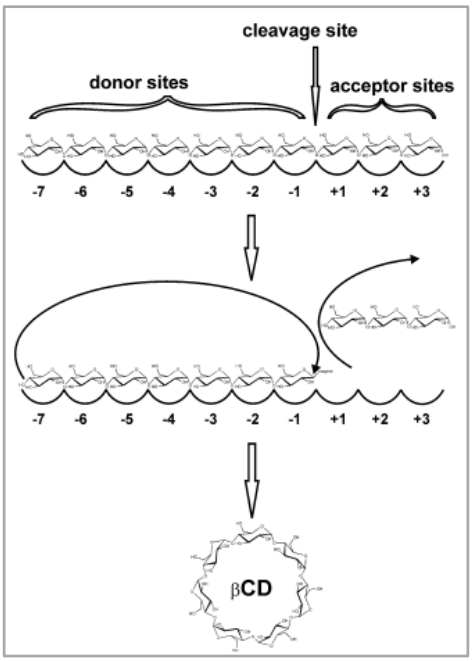

Figure 4a. Schematic view of CD formation by CGTase [13]

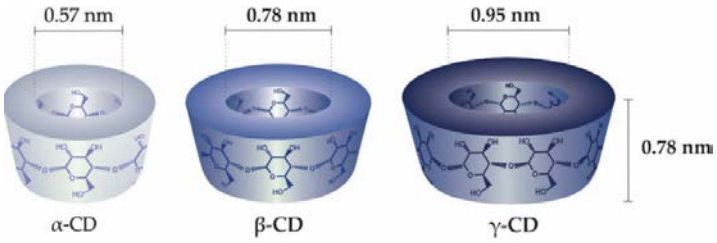

Figure 4b. Cyclodextrins and their respective D(+)glucopyranose units [53]

3.5. Applications of Cyclodextrins

CGTases are enzymes with multiple functions and catalyze four different reactions: cyclization, disproportionation, coupling, and hydrolysis reaction [54]. The inclusion property of cyclodextrins, developed in the 1930s and widely used from the 1950s, is the basis of the majority of industrial applications of CDs [22]. They have been synthesized on an industrial scale for 40 years. Many industry sectors regularly use CDs in the formulation of their products. Apart from their daily uses, CDs are the subject of research in both the public and private domains [27]. The formation of inclusion complexes leads to changes in the chemical and physical properties of the guest molecules. These altered characteristics of encapsulated compounds have led to various applications of cyclodextrins in analytical chemistry, agriculture, biotechnology, pharmacy, food processing, chemicals, textiles, and cosmetics [10].

3.5.1. Industrial applications

Due to their remarkable ability to complex a wide range of molecules, CDs open up a vast field of industrial applications. If the first applications were essentially for therapeutic purposes, CDs are now used in many sectors

such as the pharmaceutical, food, and cosmetics industries but also for chiral separation in both analytics and preparation [27].

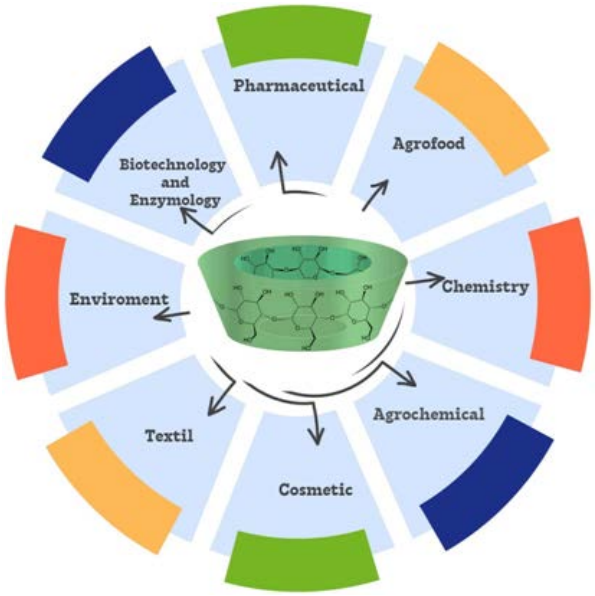

Figure 5. Areas of application of CDs

3.5.1.1. Pharmaceutical Applications

Pharmaceutical industries such as Servier, Novartis, Pierre Fabre, Pfizer, CTP, NCI, Takeda, and Ono have been using CDs for many years because of their multiple applications [23,27]. CDs are often used as an excipient in the composition of drugs. They are often used to improve the solubility of drugs [18,22]. They act as a transport system for bioactive molecules via biological membranes. They are also used for masking side effects, storage, and absorption of the drug. Because cyclodextrins are degradable by the enzyme α-amylase which comes from microorganisms in the intestinal microbiota, most drugs made from cyclodextrins are administered orally (tablets, syrups, etc.). They can display bad smell or taste [22,23). Through their ability to form inclusion complexes, CDs allow the transformation into solids such as powders, capsules, or tablets. This inclusion process significantly enhances the bioavailability and stability of hydrophobic active substances by protecting them from degradation during storage and reducing premature metabolism in the body [27].

3.5.1.2. Agri-food applications

There are several advantages to using CGTase. They exhibit high substrate specificity, high stability, and the ability to produce cyclodextrins with unique properties. In the food industry, CDs are used to stabilize flavors and colorings, they are also used to reduce bitterness in drinks and reduce viscosity in foods, etc. [1]. CGTases can be used to produce oligosaccharides from starch. Oligosaccharides have physicochemical properties with enhanced prebiotic effects and can be used as natural sweeteners [55,56]. The food industry has been using β-CDs as a flavor enhancer for over 20 years. β-CDs make it very easy to add taste compounds or to fix volatile molecules such as aromas and perfumes and to extend their release period as in the case of chewing gum [22,27]. β-CDs are also used to remove certain undesirable molecules, such as cholesterol in butter, and certain bitter or oxidizable compounds present in cooked dishes or fruit juices. Finally, β-CDs are used to stabilize emulsions such as mayonnaise or kinds of margarine as well as many dehydrated dishes [27]. In summary, CGTases are versatile enzymes that can be used in many food applications. Their high substrate specificity, their great stability, and their ability to produce cyclodextrins with unique properties make them valuable tools for the food industry.

3.5.1.3. Cosmetic applications

Cyclodextrins are compounds used in various industries, including the cosmetic industry. They are located, in terms of requirements halfway between the pharmaceutical and agri-food industries, the cosmetics industry uses CDs in the formulation of their products [9,27]. The main CDs advantages include the stabilization and control of odors, the reduction of the volatility of perfumes, and the processes to increase the conversion of a liquid substance to its solid form by precipitation of the inclusion complex. Thus, CDs are used to stabilize or release active substances [9]. They could be found in toothpaste, body creams, and softeners [22,27]. Cyclodextrins are used in cosmetics to encapsulate active ingredients, improve the stability of formulas, and control the release of active ingredients. This increased stability reduces and /or minimizes the risk of allergic reactions [57]. The use of CGTase in the cosmetic industry allows the development of products that are more efficient, more stable, and more comfortable to use. This meets the needs of consumers looking for high-quality cosmetic products and opens up opportunities for innovation in this area.

3.5.1.4. Applications in Analytical Chemistry

Cyclodextrins are widely used in the field of analytical chemistry, particularly in HPLC and capillary electrophoresis, grafted to the stationary phase or diluted in the mobile phase [26].

Cyclodextrins are capable of forming complexes with chiral molecules, which makes it possible to separate the enantiomers of these molecules [20,57]. CDs participate in the retention modification time of the analyzed molecules, including differentiating enantiomers. CDs can also complex certain photosensitive molecules [27]. They are used in the analysis of organic compounds and drug detection by improving the solubility of certain organic compounds and producing enzymatic sensors that are capable of detecting drugs in body fluids [20]. In summary, CGTases have important applications in analytical chemistry, particularly in chromatography and, the detection of organic compounds, heavy metals, pesticides, and drugs.

3.5.1.5. Applications textiles

Cyclodextrins are used for many applications, including the textile industry. The applications of cyclodextrins in the textile industry are constantly evolving, and new developments are underway to exploit their potential in this area [53]. Cyclodextrins have encapsulation properties that allow hydrophobic molecules to be incorporated into

their cavity. This property can be used to encapsulate active compounds such as fragrances, antioxidants, antibacterial agents, or dyeing agents [58]. Cyclodextrins can also be used as finishing agents for textiles. For example, cyclodextrins can be applied to fabrics to create a protective layer that improves resistance to water and dirt. Additionally, cyclodextrins can be used to improve the dyeing properties of textiles. Dyes can be encapsulated in cyclodextrins before being applied to fabrics [59]. This can improve dyeing efficiency by allowing better penetration of dyes into fabric fibers [53,60]. Additionally, the use of cyclodextrins can reduce the amount of dye needed to dye fabrics, which can reduce the costs and environmental impacts of textile production [61]. Finally, cyclodextrins can also be used for medical applications in the textile industry, such as the manufacture of dressings or protective clothing that release drugs or antibacterial agents to treat wounds or prevent infections [39]. In conclusion, it should be remembered that CGTases have important applications in the textile industry, notably in dyeing, finishing, reducing pollution, improving fiber quality, and reducing production costs.

4. General Information on Producing Microorganisms of Cgtase

Transglycosylation is the *in vivo* or *in vitro process of transferring* glycosyl groups from a donor to an acceptor. One of the enzymes commonly used in the transglycosylation reaction is CGTase [62]. Transglycosylated products, catalyzed by CGTase, are widely used in food additives, supplements, and personal care and cosmetic products.

Since the discovery of CGTase secreted by *Bacillus macerans* [63], CGTase has been successively isolated from several microbial strains, such as *Bacillus stearothermophilius* [64], *Bacillus megaterium* [65], *Bacillus licheniformis* [66], *Bacillus circulams*, *Bacillus subtilis* [67], *Bacillus firmus lentus* [68], *Klebsiella pneumoniae* [69], *Micrococcus spp.* [70], *Pseudomonas spp.* And *Alcalibacterium spp* [71].In industrial production, many bacteria can be used for the production of CGTase. There are mesophilic aerobic strains such as *Bacillus circulars* and *Bacillus megaterium*, thermophilic aerobic strains such as *Bacillus stearothermophilus* [72], and thermophilic anaerobes such as *Thermoanaerobacterium . thermosul-furigenes* [73]. There are also alkaliphilic aerobic bacteria such as *Bacillus circulars*, *Bacillus fat*, and halophilic aerobic bacteria such as *halophilic bacilli*, etc. The CGTase secreted by most of these microbial species are extracellular enzymes, and the yield of CD, the main product of these enzymes, are different mainly α-CD, β-CD, and γ-CD.

4.1. Description of Some Cgtase-Producing Microbial Genera

4.1.1. Bacillus

Species of the genus Bacillus are Gram-positive bacteria that are widely distributed in various ecological niches [74]. Several species of this microbial genus are known for their ability to produce a wide variety of enzymes, including CGTases [75]. The stability and selectivity activity of CGTases produced by species of the genus Bacillus was studied. These are used in several applications, including the production of cyclodextrins, water purification, and the synthesis of chemical compounds. Here are some examples of studies that have isolated and characterized strains of Bacillus producing CGTases: Menocci et *al*., (2008) demonstrated through a study carried out in Brazil the isolation and identification of new strains of Bacillus [75]. A CGTase from the alkalinophilic LS-3C strain *of B. agaradhaerens* was isolated from an Ethiopian soda lake with a yield of 50%. Another study isolated a CGTase-producing Bacillus strain from wastewater lake soil of cassava industries in Cruz das Almas County, Bahia, Brazil. The authors optimized the culture conditions to maximize the production of CGTases [76]. In this same perspective, Szerman *al.*, (2007) then characterized a strain of *Bacillus circulans* DF 9R producing CGTases from rotten potatoes [77]. A study also optimized the production of CGTases from *Bacillus licheniformis*. The authors noted that CGTases are produced by various genera of bacteria, including Bacillus, Klebsiella, Pseudomonas, Brevibacterium, Micrococus, and others [66]. In summary, the production of CGTase by species of the genus Bacillus is a promising area of research, because these bacteria are known to be producers of industrial enzymes. Several species of the Bacillus genus are known to produce CGTases, and studies have been carried out to isolate, characterize, and optimize the production of these enzymes.

4.1.2. Paenibacillus

Paenibacillus are anaerobic or strictly aerobic, Gram-positive, motile, facultative bacteria that primarily exhibit optimal growth at neutral pH *in* the temperature range of 28-0°C [78]. the genus *Paenibacillus* was initially included under Bacillus; however, the latest developments in 16S rRNA sequencing technology have provided a tool to place morphologically similar entities into different groups and thus *Paenibacillus*was separated as a new genus [78,79]. Several *Paenibacillus* species isolated from various environments are also reported to possess xenobiotic bioremediation potential under adverse environmental conditions [80). Some species of the genus Paenibacillus are known to produce CGTases. Several studies report the synthesis of CGTases from strains of the genus *Paenibacillus.* Zheng and his collaborator demonstrated the capacity of *Paenibacillus campinasensis strains* to produce thermophilic β-CGTase [73]. An effective anti-aging agent and a good candidate for the production of cyclodextrins has been characterized through the CGTase produced by *Paenibacillus pabuli* US132 [81]. The current work provided valuable insights into the ability of *B. pseudofirmus* and *P. macerans* to produce CGTase and, therefore, to design a process for the bioproduction of cyclodextrins [82]. Another study performed heterologous expression of CGTase from *Paenibacillus macerans* in *Escherichia coli* and demonstrated its application in the production of 2-O-α-D-glucopyranosyl-L-ascorbic acid [83]. The production of

CGTase by species of the genus Paenibacillus follows a process similar to that of Bacillus. Paenibacillus are also producers of industrial enzymes. It is essential to note that the production of CGTases from Paenibacillus strains is a research and development process that requires a thorough understanding of microbiology, biotechnology, and biochemistry.

4.1.3. Klebsiella sp

Microbial species of the genus Klebsiella are opportunistic pathogens associated with serious nosocomial infections such as sepsis, pneumonia, and urinary tract infections [84]. Ecological habitats of Klebsiella include surface waters, sewage, soils and plants, and the mucous surfaces of mammals. In humans, *K. pneumoniae* can be present in the nasopharynx and intestinal tract. In humans, the carrier rate varies from 5% (respiratory tract) to 38% (stool) [84,85]. Some species of the genus Klebsiella are known to produce CGTases. A study carried out by Gawande et *al* ., (2003) isolated a strain of Klebsiella *pneumoniae* AS-22 capable of producing a CGTase which converts starch into alpha-cyclodextrin with high efficiency [69]. The authors optimized the culture conditions using batch, fed-batch, and continuous cultures and obtained a more than 6-fold increase in CGTase activity.

Another study optimized CGTase production from *Klebsiella pneumoniae* AS-22 using a statistical experimental design approach [86]. The authors optimized the composition of the culture medium and obtained a 9-fold increase in CGTase activity compared to the basal medium.

4.1.4. Thermoanaerobacter

Thermoanaerobacter is a thermophilic anaerobic bacterial genus belonging to the family Thermoanaerobacteraceae. Bacteria from this genus can metabolize various substrates by producing energy from chemical reactions that do not require oxygen [87]. Species of the genus Thermoanaerobacter are ubiquitous. They have been isolated from various environments such as soils, sewage, hot springs, volcanic soils, and animal intestines [88]. Some species are also known for their ability to produce ethanol from biomass [89,90]. Certain species of the Thermoanaerobacter genus are capable of producing CGTases [90]. Another study carried out in Japan characterized a thermostable CGTase from a hyperthermophilic archaeon, *Thermococcus sp*. The authors compared this CGTase with those of the thermophilic anaerobic bacteria *Thermoanaerobacter sp.* and *T. thermosulfurigenes* and demonstrated their thermostable production [91]. Another study concluded that a novel CGTase isolated from a strain of Thermoanaerobacter is stable at an optimal temperature of 90 to 95°C at pH 6.0. In the presence of starch, the enzyme is stable at temperatures above 100°C. In addition to producing cyclodextrins from starch, *Thermoanaerobacter sp*. CGTase has excellent starch liquefying properties [92]. Finally, it should be remembered that certain species of the Thermoanaerobacter genus are known to produce thermostable CGTases, and studies have been carried out to isolate, characterize, and optimize the production of these enzymes. Thermoanaerobacter CGTases have demonstrated their potential in various applications, including starch liquefaction and saccharification.

4.1.5. Anaerobranch

Anaerobrancais a genus of thermophilic anaerobic bacteria belonging to the family Synergistaceae. These are bacteria with obligate anaerobic, heterotrophic, and proteolytic growth [93]. *Anaerobranca*species have been isolated from various environments, such as hot springs, sewage sludge, and stream sediments [94]. Bacteria of the genus *Anaerobranca* are important for their ability to break down complex organic compounds using fermentation, a process that does not require oxygen. They can metabolize many substrates, including carbohydrates, proteins, and lipids, producing organic acids, gas, and other metabolic products [95].

Additionally, some species of *Anaerobranca* have been implicated in important environmental processes, such as the degradation of organic matter in sediments and the production of methane in anaerobic ecosystems. The CGTase enzyme produced by *Anaerobranca* bacteria can produce cyclodextrins from various substrates, such as starch, and maltodextrin [96].

4.1.6. Amphibacillus

Amphibacillusis a genus of Gram-positive, thermophilic, facultatively anaerobic bacteria belonging to the Bacillaceae family [97]. Species of the genus Amphibacillus have been isolated from warm, acidic environments such as hot springs, volcanic soils, oil wells, and geothermal ecosystems [98]. Bacteria of the genus Amphibacillus are important for their ability to survive and grow in extreme conditions, including high temperatures and acidic conditions. The genus Amphibacillus includes both aerobic and facultative anaerobic bacteria. Species of this genus have been isolated from a variety of habitats, including extreme habitats, including soda environments with their high alkalinity [99]and as model organisms to study the bioenergetics of alkaliphiles (Krulwich and Guffanti, 1989) and osmoregulation in haloalkaliphiles [100]. An article published on ResearchGate reports the production of CGTase by *Amphibacillus sp.* NPST-10. The study revealed that this Amphibacillus strain produced CGTase extracellularly with enzymatic activity under a wide range of pH and temperature conditions [101]. A comprehensive study on CGTase transglycosylation from various sources published on PMC and ScienceDirect mentions that Amphibacillus is one of the bacteria that produces CGTase [9]. Ibrahim et *al*., (2013] reported the isolation of a novel CGTase from alkalinophilic bacteria collected from Egyptian soda lakes, identified as Amphibacillus sp. NRC-WN [101]. In summary, Amphibacillus is a genus of bacteria that produces CGTases, and certain strains derived from the bacterial genus have been studied for their CGTase production and properties. CGTases produced by Amphibacillus are extracellular enzymes and are active under a wide range of pH and temperature conditions.

4.1.7. Brevibacterium

The Brevibacillus genus was created in 1996, derived from a genetic reclassification of strains previously

assigned to the *Bacillus brevis group*. *Bacillus brevis* was first described in [102] and reclassified as a species belonging to the new genus Brevibacillus, along with nine other species [54].

The results of a genetic sequence study by Shida et *al.*, (1996) demonstrated that the *Bacillus group brevis* includes ten species, namely *Bacillus brevis, Bacillusagri, Bacilluscentrosporus, Bacilluschoshinensis, Bacillusscrewbar, Bacillus reuszeri, Bacillus formosus, Bacillus borstelensis, Bacillus laterosporus and Bacillus thermoruber*. Currently, the genus Brevibacillus includes 20 species [103]. The genus is best known for its important role in the ripening of certain cheeses and for its supposed overproduction of L-amino acids. Other interesting industrial applications, including the production of ectoine, have recently been proposed [103]. Cyclodextrin glucanotransferase from *Brevibacterium sp*. showed broad acceptor specificity for various monosaccharides similar to Bacillus *stearothermophilus*. It has specially produced a large quantity of transfer products from D-mannose and L-rhamnose. CGtase *Brevibacterium* also formed a much larger amount of transfer products than *Bacillus macerans* and*Bacillus stearothermophilus* CGTases from 1,3-dihydroxybenzene,1,3,5-trihydroxybenzene, 3-hydroxybenzyl alcohol and (+)-catechin used as acceptors [104].

4.1.8. Mycobacterium

Mycobacterium terrae was first isolated by Richmond and Cummings in 1950 from radish washings and was described as an acid-fast saprophyte [105]. This organism is sometimes called “radish bacillus”; the Latin name of this organism implies that it is a *mycobacterium* of the earth". Despite the common opinion that isolates of the *M. terrae complex* are nonpathogenic [106]. these organisms are sometimes identified in the clinical laboratory as part of the clinical disease of the joints, tendons, lungs, gastrointestinal tract, and genitourinary tract [107]. Cyclodextrin glucanotransferase produced using of the new microbacteria alkaliphilic *Microbacteria terrae* KNR 9 was purified to homogeneity in a single step by the starch adsorption method. The specific activity of purified CGTase was 45 U/mg compared to 0.9 U/mg crude. This resulted in a 50-fold purification of the enzyme with a yield of 33% (54,107].

4.1.9. Thermoactinomyces

Thermoactinomyces is a genus of thermophilic bacteria, which can grow at high temperatures ranging from 45 to 75°C. Species of this genus are mainly found in soils, thermal waters, and composts, as well as in clinical samples such as abscesses and skin infections. Thermoactinomyces are known to produce enzymes at high temperatures such as amylases, proteases, cellulases, and xylanases which can be used in various industrial applications [108].

Due to their ability to produce enzymes at high temperatures, Thermoactinomyces have also been studied for their potential as a source of enzymes for the production of biofuels from lignocellulosic biomass [109].

4.1.10. Thermococci

Thermococcusis a genus of hyperthermophilic bacteria, which is part of the phylum Archaea. These bacteria can grow at very high temperatures, up to 100 °C, making them suitable for extreme environments such as hydrothermal vents on the ocean floor and terrestrial hot springs [110]. Thermococcus are strict anaerobic organisms and produce energy using sources such as sulfur, iron, or hydrogen, using chemical reactions to produce ATP. Some species are also capable of methanogenesis, thus producing methane [111,112]. These bacteria have been studied for their potential as sources of industrial enzymes. Additionally, Thermococcus have been used as models to study molecular biology Research on these organisms has also contributed to a better understanding of the evolution of Archaea and their functional diversity [91]. The expression and characterization of cyclodextrinase derived from *Thermococcus sp* B1001 in *Bacillus subtilis*. The enzyme exhibited high substrate specificity for cyclodextrins and reached a specific activity of 637.9 U/mg under optimal conditions of 90 °C and pH 5.5 [113].

4.1.11. Archaea

Archaea are a group of microorganisms that were initially classified as bacteria but were later discovered as a distinct domain of life. They are prokaryotic organisms. Archaea are found in a wide variety of environments, including extreme environments such as hot springs, seafloor black smokers, and salt marshes. They are also present in more moderate environments such as soil and the digestive tracts of animals. Archaea are important in many ecological processes, such as nitrogen fixation and methane production. They are also of interest to scientists because they can survive in extreme environments and may have applications in biotechnology and other fields [114]. The B1001 enzyme of *Thermococcus sp* is α-CGTase, which has been reported in *B. macerans*, *B. stearothermophilus*, and *K. pneumoniae* [115]. In general, the α-CD formed mainly at the beginning of the reaction is decomposed, and α-, β-, and γ-CD are produced from the decomposition products. Interestingly, B1001 CGTase produced mainly α-CD in the later reaction as well as in the initial reaction. B1001-derived CGTase, which mainly produced α-CD with a small amount of β-CD and γ-CD from starch, may provide advantages in manufacturing α-CD [91].

4.1.12. Aspergillus

Aspergillus is a genus of filamentous fungi that is commonly found in soil, air, and decaying organic matter [116]. *Aspergillus niger* is a filamentous ascomycete fungus that is ubiquitous in the environment and has been implicated in opportunistic infections in humans. In addition to its role as an opportunistic human pathogen, *Aspergillus niger* is economically important as a fermentation organism used for citric acid production. It consists of a large number of species, some of which are used for industrial and biotechnological purposes, while others can cause diseases in humans and animals [117,118]. Species of the genus Aspergillus are capable of producing a wide variety of secondary metabolites, including toxins and enzymes. Some species of Aspergillus are used in the production of alcoholic beverages, cheeses, and other food products, while others

are used to produce enzymes used in the food and textile industries [65] [119,120,121]. Aspergillus is a genus of fungi that also produces CGTases. A comprehensive study by Lim and collaborators on CGTase transglycosylation from various sources mentions that Aspergillus is a fungus used to produce CGTase. Table II lists the different microbial species known to produce CGTase. The most studied species are those of the genus Bacillus, but CGTases have also been identified in species of the genus Klebsiella, Streptococcus, Lactococcus, Streptomyces, and Rhizopus. This table is important because it allows us to understand the diversity of CGTase sources [62]. This diversity is an asset for the development of new methods of producing CGTase and new applications for this enzyme. In this context, this table can serve as a reference for future research aimed at improving the production of cyclodextrins through the exploitation of these microorganisms.

Table 2. Microbial species producing CGTase (122)

Gender	Species	Yield (%)	Molecular Mass (kDa)	References
Bacteria				
Bacillus	*Bacillus megaterium strain 5*	-	-	[123]
	Bacillus sp . ATCC 21783	35	88	[124]
	Bacillus sp . HA 3-2-2	7	68	[125]
	Bacillus stearothermophilus TC-91	15.3	75.5	[126]
	Coagulant bacillus	37.8	65	[127]
	Bacillus autolyticus 11149	31.1	70	[128]
	Bacillus strain A2-5a	51	80	[129]
	Bacillus sp. PS304	58	76	[130]
	Bacillus stearothermophilus ET1	31.6	66.8	[72]
	Bacillus firmus NCIM 5119	64	78	[131]
	Bacillus macerans strain 15	66.3	54	[132]
	Bacillus agaradherens LS-3C	50	110	[133]
	Bacillus sp . G1	4.18	75	[134]
	Bacillus sp . 7-12	18.9	69	[135]
	Bacillus circulans ATCC 21783	75.5	97.4	[136]
	Bacillus firmus strain 7B	91.6	56.23	[137]
	Bacillus sp . BL-31	21.7	92	[138]
	Bacillus cereus N1	3. 63	75	[139]
	Bacillus sphaericus strain 41	31	59	[140]
	Bacillus pseudacaliphilus 20RF	63	70	[141]
	Bacillus agaradherens strain WN-I	26.4	85	[100]
	Bacillus pseudacaliphilus 8SB	62	71	[142]
	Bacillus halodurans	49.44	33	[143]
	B. halophilus BIO-12H *B. halophilus BIO-13H*	-	70 70	[132]
Paenibacillus (anaerobe thermophile)	*Paenibacillus campinasensis strain 324*	26.6	75	[144]
	Paenibacillus sp . KJ-12	5	82	[145]
	Paenibacillus illinoisensis ST-12 K	27	70	[146]
	Paenibacillus campinasensis H69-3	13.3	70	[147]
	Paenibacillus pabuli US132	20	70	[81]
	Paenibacillus sp . RB01	38	-	[148]
	Paenibacillus illinoisensis ZY-08	26.6	70	[80]
Klebsiella (anaerobe thermophile)	*Klebsiella pneumoniae AS-22*	68	75	[131]
Thermoanaerobacter (thermophilic anaerobes)	*Thermoanaerobacterium thermosulfurigenes EM1*	79	68	[149]
	Thermoanaerobacter sp . P4	17.8	68.7	[150]
Anaerobranch (anaerobic thermoalkaliphile)	*Anaerobrancha gottschalkii*	13.5	78	[96]
Amphibacillus (anaerobie thermoalkaliphile)	*Amphibacillus sp NPST-10*	44.7	92	[151]
Brevibacterium (aerobic mesophile)	*Brevibacterium sp . No. 9605*	16	75	[104]
Brevibacillus (aerobic mesophile)	*Brevibacillus brevis CD162*	-	75	[152]
Microbacterium (alkaliphile)	*Microbacterium terrae KNR 9*	33	27.72	[54]
Thermoactinomyces (aerobic thermophile)	*Thermoactinomyces vulgaris Tac-5354*	-	66	[63]
Archaea				
Thermococcus (thermophilic anaerobes)	*Thermococcus sp . strain B1001*	16	83	[91]
Pyrococcus	*Pyrococcus of Kodakara*	-	79	[153]

	Pyrococcus crazy DSM3638	-	65	[154]
Haloferax (archaeon halophile)	*Haloferax Mediterranean*	3	77	[155]
Mushrooms				
Aspergillus	*Aspergillus niger CCRC 31494*	-	-	[156]
Trichoderma	*Trichoderma viride*	-	-	[157]

5. Assessment of the Synthesis and Future Research Perspectives on Cgtases

Research on CGTases has progressed significantly in recent decades. Knowledge about the structure, function, and properties of CGTases has been significantly improved [158]. These advances have led to the development of new methods for producing CGTases and new applications for these enzymes [62]. CGTases are multifunctional enzymes that catalyze four different types of reactions: cyclization, coupling, disproportionation, and hydrolysis [2]. CDs are produced from starch by CGTase which are used in many industrial applications due to their ability to form inclusion complexes with hydrophobic compounds [32]. CGTases are generally produced by eubacteria, particularly by strains of Bacillus. Nevertheless, a few archaea and fungi have been cited as producers of CGTase, such as Thermococcus, Haloferax, Pyrococcus, and Trichoderma [62,159]. Several studies have demonstrated that thermostable CGTases function optimally at high temperatures, 60°C and above. The CGTase of *Thermoanaerobacter thermosulfurigenes* has an optimal temperature of 80-85°C, while that of *Bacillus stearothermophilus* has optimal enzymatic activity at 70°C. Additionally, recombinant CGTase from *Pyrococcus furiosus* expressed in *Escherichia coli* has an optimal temperature of 95°C [159]. This therefore opens up prospects for application in industrial processes requiring high-temperature conditions. Future research perspectives on CGTases should focus on the few points listed below: Development of more efficient, more cost-effective, and more sustainable CGTase production methods; Exploration of new microbial sources of these enzymes; Improvement of the properties of CGTases in particular activity, stability and selectivity; The elucidation of their mechanism of action and the identification of new industrial applications for the CDs they produce such as therapeutic, environmental and industrial applications; Research on CGTases is a growing field. Advances made over the past decades have opened new perspectives for the development of new methods of producing CGTases and new applications for these enzymes.

6. Conclusion

In conclusion, CGTase is an enzyme produced by various microorganisms, including bacteria. *Bacillus* strains are most commonly used for the industrial production of CGTase. CGTases are versatile enzymes that catalyze the conversion of starch into CDs, which are compounds of interest in many fields such as the pharmaceutical, food, chemical, and cosmetic industries. CGTases offer vast possibilities in the biosynthesis of CDs, thanks to their unique characteristics, a wide range of sources, and efficient production. Their use continues to gain importance in various industrial sectors, and further studies and applications are awaited to fully exploit their potential.

Declarations

Author contribution statement

All cited authors contributed significantly to the development and writing of this article.

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