Heliyon 7 (2021) e06305

Contents lists available at ScienceDirect

Heliyon

journal homepage: www.cell.com/heliyon

Review article

Comprehensive study on transglycosylation of CGTase from various sources

Chin Hui Lim [a], Babak Rasti [a,*], Joko Sulistyo [b], Mansoor Abdul Hamid [a]

[a] Faculty of Food Science and Nutrition, Universiti Malaysia Sabah, Jalan UMS, 88400, Kota Kinabalu, Sabah, Malaysia
[b] Faculty of Biotechnology, University of Surabaya, Jalan Ngagel Jaya Selatan, Surabaya, 60294, Indonesia

ARTICLE INFO

Keywords:
Transglycosylation reaction
Cyclodextrin glucanotransferase
CGTase

ABSTRACT

Transglycosylation is the *in-vivo* or *in-vitro* process of transferring glycosyl groups from a donor to an acceptor, which is usually performed by enzymatic reactions because of their simplicity, low steric hindrance, high region-specificity, low production cost, and mild processing conditions. One of the enzymes commonly used in the transglycosylation reaction is cyclodextrin glucanotransferase (CGTase). The transglycosylated products, catalyzed by CGTase, are widely used in food additives, supplements, and personal care and cosmetic products. This is due to improvements in the solubility, stability, bioactivity and length of the synthesized products. This paper's focus is on the importance of enzymes used in the transglycosylation reaction, their characteristics and mechanism of action, sources and production yield, and donor and acceptor specificities. Moreover, the influence of intrinsic and extrinsic factors on the enzymatic reaction, catalysis of glycosidic linkages, and advantages of CGTase transglycosylation reactions are discussed in detail.

1. Introduction

Cyclodextrin glucanotransferase also known as cyclodextrin glucosyltransferase (CGTase) is a biological catalyst that is categorized under glycoside hydrolase family 13 or α-amylase family with enzyme commission number (EC numbers) of EC 2.4.1.19 [51,63], classified under transferase (EC 2), a subclass of transglycosylase (EC 2.4) and sub-subclass of hexosyltransferase (EC 2.4.1).

In previous studies, researchers usually focused on the cyclization reaction of CGTase and its product, cyclodextrin, and its function. However, coupling and disproportionation reactions catalyzed by CGTase also play a vital role in enzymatic synthesis of compounds that are widely used in food additives, dietary supplement, detergents, and medical and cosmetic products. The coupling reaction of CGTase opens the cyclodextrin ring and transfers glycosyl groups to acceptors, while the disproportionation reaction by CGTase shifts the linear oligosaccharides to another oligosaccharides. This transition of the glycosyl group improves water solubility [85], bioavailability [94], absorption [169], and bioactivity [116] of acceptors. This paper summarizes the information on the compounds that have been transglycosylated by CGTase in the past 30 years and highlights the advantages of enzymatic transglycosylation using coupling and disproportionation reactions catalyzed by this enzyme.

2. Importance of enzymatic transglycosylation

Transglycosylation reaction is a process of transferring glycosyl group from a donor, carbohydrates, to an acceptor that contains hydroxyl or other functional groups and form glycoconjugates. *In vivo* glycoconjugates such as glycoproteins, glycopeptides, glycolipids and glycosides are involved in cellular recognition, cellular adhesion, and detoxification process. On the other hand, *in vitro* transglycosylation is an important method of improving functional properties, including their hydrophilicity, chemical stability, and bioavailability, of natural compounds and products [172].

The advantages of using enzymatic transglycosylation include simple reaction steps, low steric hindrance, high regiospecificity, low production cost, mild reaction conditions and being eco-friendly, while chemical transglycosylation comprises complicated reaction steps, such as protection and deprotection processes, to achieve regioselectivity and stereoselectivity. The transglycosylation provides defined anomeric configuration in a single step, without any necessity for protecting groups [171]. Chemical transglycosylation using acid catalysts requires higher reaction temperature compared with enzymatic transglycosylation and thus requires higher energy demand. Besides, harsh chemical transglycosylation decomposes an aglycone, produce lower yields and unwanted anomers, containing a mixture of α- and β-anomers, which causes purification process to be difficult and complicated. Furthermore, the

* Corresponding author.
E-mail address: rasti_babak@ums.edu.my (B. Rasti).

https://doi.org/10.1016/j.heliyon.2021.e06305
Received 25 March 2019; Received in revised form 19 January 2021; Accepted 12 February 2021

catalysts used in chemical transglycosylation are heavy metals, which have negative effects such as toxicity and higher production cost [76]. The purification complication is mainly due to the interruptions by other water-soluble compounds that are extremely difficult to separate from the desired glycoside compounds. Therefore, the enzymatic transglycosylation is the most preferred method to synthesis glycoside [18].

2.1. Type of enzymes used in enzymatic transglycosylation

Enzymatic transglycosylation can be catalyzed by glycosyltransferases (EC 2.4) and glycoside hydrolases also known as glycosidases (EC 3.2.1). Glycosyltransferases catalyze the transglycosylation reaction, which transfers sugar moieties or glycosyl groups from donor to acceptor, and form glycosidic bonds between sugar moieties and acceptor [78]. There are two types of glycosyltransferase, namely Leloir glycosyltransferase and non-Leloir glycosyltransferase [178].

The Leloir glycosyltransferases use sugar nucleotides as activated donors when catalyze the transglycosylation reaction. For example, UDP-glycosyltransferase is a Leloir glycosyltransferase that catalyzes transglycosylation reaction by transferring glycosyl groups from activated donors, such as uridine diphospho-D-glucose, to acceptors [25]. On the other hand, non-Leloir glycosyltransferases use either sugar phosphates or non-activated sugars as donors when catalyze transglycosylation reaction. Glycoside phosphorylase is an example of non-Leloir glycosyltransferase that uses sugar phosphates as donor, while CGTase is a non-Leloir glycosyltransferase that uses non-activated sugars, such as starch, as donors [119, 129]. Enzymatic characteristic of glycoside hydrolases (glycosidases) is their ability to hydrolyze glycosidic bonds but some glycoside hydrolases can also synthesis glycoside under certain reaction conditions. Example of glycoside hydrolases are α-amylase, β-galactosidase and α-rhamnosidase [29, 132, 179].

2.2. Importance of CGTase for enzymatic transglycosylation

CGTase is a non-Leloir glycosyltransferase. CGTase uses non-activated sugar, which has free cleavage energy of maltooligosaccharides, as donors [123]. Normally, Leloir glycosyltransferases are rare enzymes that are more costly, more vulnerable to environmental conditions, require exclusive donors, and often require special buffers or detergents for solubilization. In contrast, non-Leloir glycosyltransferase, such as CGTase, are commonly available enzymes, which are less expensive, require commercially available donors, and can be used with a wider range of acceptors. Moreover, CGTase extracted from microorganisms with rapid growth rate, is preferred as it is readily available [146].

Although glycosidases have similar properties as CGTase but they tend to partially hydrolyze glycoside compounds and produce undistinguishable or low yields of glycosylated products [178]. Others disadvantages of glycosidases are poor regioselectivity and production of undesired compounds in various proportions, when there are more available –OH groups [76]. On the other hand, CGTase has low hydrolytic activity, good conversion yield to convert compounds into glycosylated product, effective transglycosylation of certain acceptors, and excellent regioselectivity, which particularly catalyze α (1→4)-glycosyl transfer reactions [99, 149]. For instance, synthesizing the stevioside, a sweetener, was best achieved by using CGTase from *Bacillus macerans* when compared with other enzymes such as pullanase, dextrin dextranase, β-galactosidase, and isomaltase [3].

Another example would be conversion of benzo[h]quinazolines to transglycosylated benzo[h]quinazolines that could be catalyzed efficiently by CGTase while other enzymes such as β-fructofuranosidase, β-amylase, pullulanase and β-galactosidase could not yield any transglycosylated benzo[h]quinazolines [95]. Furthermore, the CGTase extracted from *Bacillus circulans* 251 could couple the artificial rhamnoside acceptors with maltodextrin donors to synthesize α-D-glucosylated products [161]. In addition, CGTase can tolerate high percentage of organic solvent in a reaction mixture [173]. Therefore, CGTase is considered as a useful biocatalyst for enzymatic transglycosylation for its board acceptor specificity, availability of low cost donors, and effectiveness in transglycosylation.

2.3. Characteristics of CGTase

CGTase is a monomer with different number of amino acids and molecular weight depending on its source (Table 1). Molecular weights in the range of 33–110 kDa have been reported for CGTase from various organisms, such as *Pyrococcus furiosus* DSM3638 (65kDa) [80], *Thermoactinomyces vulgaris* Tac-5354 (66 kDa) [4], *Thermoanaerobacterium thermosulfurigenes* EM1 (68 kDa) [175], *Paenibacillus pabuli* US132 (70kDa) [57], *Haloferax mediterranei* (77 kDa) [13], *Bacillus agaradhaerens* WN-I (85 kDa) [52], *Amphibacillus sp.* NPST-10 (92 kDa) [53], and *Bacillus agaradhaerens* LC-3C (110 kDa) [98]. However, there are contrasting views on the molecular weight of CGTase extracted from alkaliphilic strains [2, 4, 126]. Moreover, the number of amino acids in the CGTase produced by various microorganisms, including *Haloferax mediterranei* (713 amino acids) [13], *Anaerobranca gottschalkii* and *Bacillus agaradhaerens* (679 amino acids) [98, 156], *Thermoanaerobacterium thermosulfurigenes* EM1 (567 amino acids) [176], *Bacillus stearothermophilus* ET1 (711 amino acids) [24], *Bacillus sp*. Strain 251 (686 amino acids) [122] and *Bacillus sp*. Strain 1011 (713 amino acids) [67], has been identified. Therefore, the properties of CGTase depend on the microorganism that they are extracted from [15].

The structure of CGTase extracted from *Bacillus circulans* strains 8, *Bacillus circulans* strains 251, alkalophilic *Bacillus sp*. 1011, and *Thermoanaerobacterium thermosulfurigenes* strain EM1 has been determined by X-ray structure analysis [49, 72, 73, 79]. Generally, the structure of CGTase consists of five protein domains (A to E) and its active site is situated in the A domain [79, 83]. Domain A is the catalytic (α/β)-8 domain and catalytic residues are situated at the C-terminal ends of the β-strands. Domain B contributes to substrate binding. Substrates bind with a groove formed by domains A and B containing ten sugar-binding sub sites labeled −7 to +3 [148]. Sugar binding sub sites are labeled from -n to + n whereby the 'n' is an integer. The -n sugar binding sub site constitutes the non-reducing end while + n constitutes the reducing end [27]. According to Leemhuis et al. [83], sugar-binding sub sites labeled from -7 to -1 are donor, and from 1 to 3 are acceptor sub sites. The domain C shows an antiparallel β-sandwich fold and its function is to bind substrate [122] while domain E used to bind starch and maltose [20]. However, the function of domain D is still unexplored [83]. CGTase from different microorganisms has different numbers of residues in 5 domains (A-E). CGTase from *Bacillus circulans* strains 8 has 80–108 residues in domain A, 185–192 residues in domain B, 407–494 residues in domain C, 495–580 residues in domain D and 581–684 residues in domain E [72]. CGTase from alkalophilic *Bacillus sp*. 1011.14 has 1–406 residues in domain A, 139–203 residues in domain B, 407–496 residues in domain C, 497–584 residues in domain D and 585–686 residues in domain E [49]. CGTase from *Bacillus circulans* strains 251 has 261–268 residues in domain A, 183–186 residues in domain B and 599–602 residues in domain E. However, the number of residues in domain C and D of CGTase from *Bacillus circulans* strain 251 have not been identified [79]. CGTase from *Thermoanaerobacterium thermosulfurigenes* strain EM1 -88-95 residues at domain A, 335–339 residues in domain B, 495–499 residues in domain C, 534–540 residues in domain D and 654–657 residues in domain E [73].

3. Catalytic mechanism of CGTase

Catalytic reactions of the CGTase are based on the α-retaining, double displacement, and random ternary complex mechanisms [165, 174]. The α-retaining mechanism maintains the substrate's α-anomeric

Table 1. CGTase producing microorganisms.

Genus	Organisms	Yield (%)	Molecular mass (kDa)	Ref
Bacteria				
Bacillus	*Bacillus megaterium strain 5*	-	-	[69]
	Bacillus sp. ATCC 21783	35	88	[112]
	Bacillus sp. HA 3-2-2	7	68	[117]
	Bacillus stearothermophilus TC-91	15.3	75.5	[77]
	Bacillus coagulans	37.8	65	[7]
	Bacillus autolyticus 11149	31.1	70	[157]
	Bacillus strain A2-5a	51	80	[74]
	Bacillus sp. PS304	58	76	[124]
	Bacillus stearothermophilus ET1	31.6	66.8	[24]
	Bacillus firmus NCIM 5119	64	78	[37]
	Bacillus macerans strain 15	66.3	54	[2]
	Bacillus agaradhaerens LS-3C	50	110	[98]
	Bacillus sp. G1	4.18	75	[144]
	Bacillus sp. 7-12	18.9	69	[19]
	Bacillus circulans ATCC 21783	75.5	97.4	[167]
	Bacillus firmus strain 7B	91.6	56.23	[106]
	Bacillus sp. BL-31	21.7	92	[38]
	Bacillus cereus N1	3. 63	75	[34]
	Bacillus sphaericus strain 41	31	59	[107]
	Bacillus pseudalcaliphilus 20RF	63	70	[11]
	Bacillus agaradhaerens strain WN-I	26.4	85	[52]
	Bacillus pseudalcaliphilus 8SB	62	71	[70]
	Bacillus halodurans	49.44	33	[104]
	B. halophilus BIO-12H *B. halophilus BIO-13H*	-	70 70	[4]
Paenibacillus (anaerobic thermophilic)	*Paenibacillus campinasensis strain 324*	26.6	75	[180]
	Paenibacillus sp. KJ-12	5	82	[60]
	Paenibacillus illinoisensis ST-12 K	27	70	[31]
	Paenibacillus campinasensis H69-3	13.3	70	[9]
	Paenibacillus pabuli US132	20	70	[57]
	Paenibacillus sp. RB01	38	-	[22]
	Paenibacillus illinoisensis ZY-08	26.6	70	[82]
Klebsiella (anaerobic thermophilic)	*Klebsiella pneumoniae AS-22*	68	75	[37]
Thermoanaerobacter (anaerobic thermophilic)	*Thermoanaerobacterium thermosulfurigenes EM1*	79	68	[175]
	Thermoanaerobacter sp. P4	17.8	68.7	[12]
Anaerobranca (anaerobic thermo alkaliphilic)	*Anaerobranca gottschalkii*	13.5	78	[156]
Amphibacillus (anaerobic alkaliphilic)	*Amphibacillus sp NPST-10*	44.7	92	[53]
Brevibacterium (aerobic mesophilic)	*Brevibacterium sp. No. 9605*	16	75	[105]
Brevibacillus (aerobic mesophilic)	*Brevibacillus brevis CD162*	-	75	[64]
Microbacterium (alkaliphilic)	*Microbacterium terrae KNR 9*	33	27.72	[126]
Thermoactinomyces (thermophilic aerobic)	*Thermoactinomyces vulgaris Tac-5354*	-	66	[4]
Archaea				
Thermococcus (thermophilic anaerobic)	*Thermococcus sp. strain B1001*	16	83	[153]
Pyrococcus	*Pyrococcus kodakaraensis*	-	79	[128]
	Pyrococcus furiosus DSM3638	-	65	[80]
Haloferax (halophilic archeon)	*Haloferax mediterranei*	3	77	[13]
Fungi				
Aspergillus	*Aspergillus niger CCRC 31494*	-	-	[81]
Trichoderma	*Trichoderma viride*	-	-	[115]

configuration during transglycosylation [164]; however, the α-retaining mechanism of glycosyltransferase enzymes is not clearly understood [178]. Generally, catalytic carboxylate residues of the CGTase are Asp 229, Asp 328 and Glu 257, the same as other members of α-amylase family [72]. The function of three carboxylic amino acids were explained when an inhibitor, such as Acarbose, bound at active site of the CGTase. Glu257 catalyzes proton donor, Asp229 acts as the nucleophile, stabilizing the intermediate, while Asp328 acts as substrate binding [71, 110, 111].

Double displacement, also known as Ping-Pong mechanism, initiates by S_N2 nucleophilic reactions. The carboxylate residues of the CGTase (Glu or Asp) interact with donors and form β-covalently linked enzyme-glycosyl intermediates. Then, another carboxylate residue activates the glycosyl acceptors to attack the enzyme-glycosyl intermediates, which results in reversing the β-covalent bonds and forming α-linkage products with retained α-anomeric configuration [135, 155, 174]. In contrast, the random ternary complex mechanism involves simultaneous and random binding of glycosyl donors and acceptors to active sites of the CGTase.

The glycosyl donor covalently bonds with acceptor to form a product and subsequently the product is released.

The CGTase has four enzymatic reactions, namely cyclization, coupling, disproportionation and hydrolysis [164]. Figure 1 shows the four enzymatic reactions of the CGTase. The cyclization activity of CGTase is an intramolecular transglycosylation reaction, where linear and long maltooligosaccharides chains, such as starch, are broken down and form oligosaccharide cyclic ring structures, called cyclodextrin. Cyclodextrins can be divided into α, β and ϒ types. The coupling and disproportionation activities of CGTase are intermolecular transglycosylation. The coupling activity is a reverse reaction to cyclization, which is opening the cyclic oligosaccharides (cyclodextrin) and converting them to linear oligosaccharides before transferring linearized oligosaccharides to an acceptor through random ternary complex mechanism [165]. Moreover, disproportionation activity, the main transferase reaction of CGTase, is the process of cleaving linear maltooligosaccharides and then transferring glycosyl groups to an acceptor molecule via double displacement mechanism [165]. Furthermore, CGTase also has a weak hydrolysis reaction.

Generally, CGTase cleaves α (1–4) glycosidic bond of donor between sub sites -1 and +1 and yields a stable covalent glycosyl-intermediate complex covalently linked to catalytic residues, Asp 229, at sub site -1. The covalent glycosyl-intermediate complex which binds at the sub sites (sugar-binding sub sites labeled from -7 to -1) is called donor. The leaving group is expelled from acceptor sites (sugar-binding sub sites labeled 1 to 3) before being replaced by acceptor molecule. Finally, a new α (1–4) glycosidic bond is formed between the donor and acceptor to form a product and subsequently the product is being released [99, 160]. The following sections of this paper focus on the coupling and disproportionation activities of CGTase, which transfer glucosyl groups to the acceptors.

3.1. Synthesis of glycosidic linkage catalyzed by CGTase

Generally, CGTase has been used to catalyze α (1→4) glycosyl transfer reactions. However, production of other glycosidic linkages such as α (1→3) and α (1→6) glycosidic linkage are also reported. For example, α (1→3) glycosidic linkage is produced by transglycosylation of

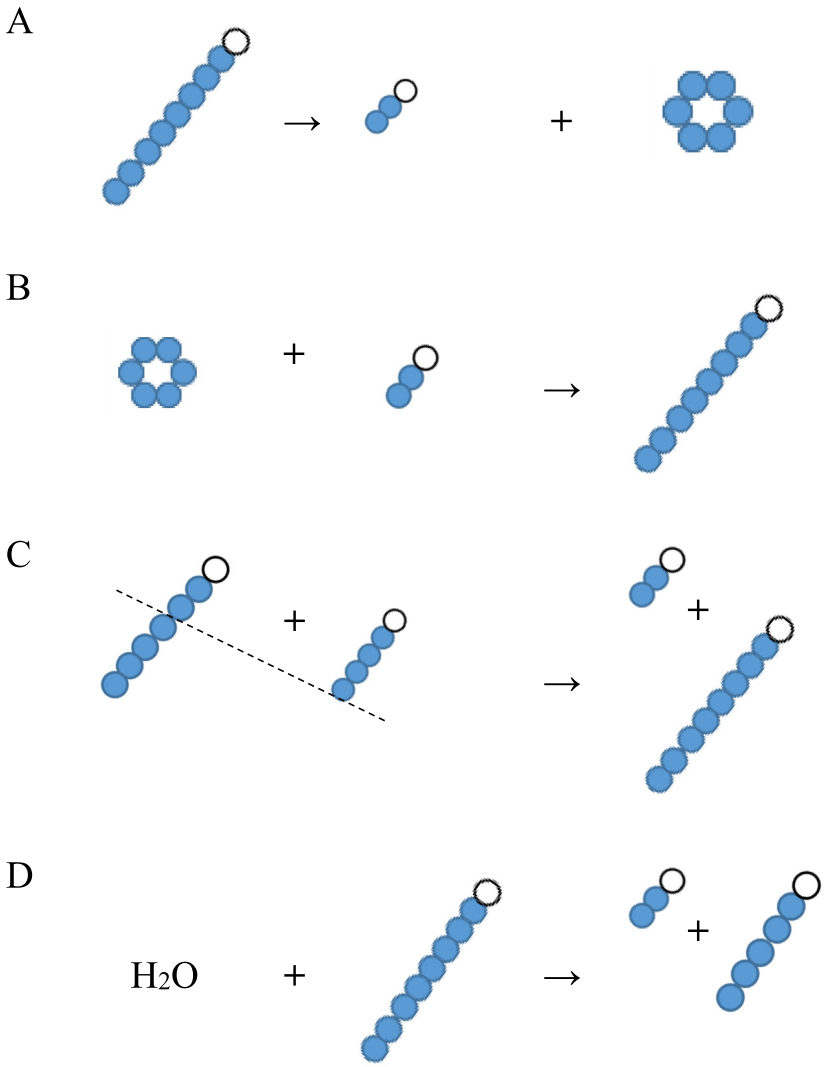

Figure 1. Schematic representation of four enzymatic reactions by CGTase. A) Cyclization B) Coupling C) Disproportionation D) Hydrolysis. ● glucose residue ○ reducing end glucose.

rhamnopyranoside using CGTase [161]. This is because the formation of a glycosidic linkage can be influenced by time and anomeric configuration of the acceptor [149]. The glycosidic linkages produced by the CGTase have been investigated using α and β anomers of p-nitrophenyl-D-glucopyranoside as acceptors. The α anomers of p-nitrophenyl-D-glucopyranoside only form α (1→4)-glycosyl linkages with their donors, while α (1→4), α (1→3) and α (1→6) glycosylation products are produced when β anomers of p-nitrophenyl-D-glucopyranoside used as acceptors. Moreover, during longer reaction times, α (1→4)-glycosylation products slowly change to α (1→3) and α (1→6) glycosylation product, by using β anomers of p-nitrophenyl-D-glucopyranoside as acceptors.

3.2. Sources and production yield of CGTase

Most CGTase enzymes are produced extracellularly by various genera of bacteria. *Bacillus* [11, 69], *Paenibacillus* [9], *Klebsiella* [38], *Brevibacterium* [105], *Brevibacillus* [64], *Thermoanaerobacter* [175], *Thermococcus* [153], *Thermoactinomyces* [4], *Haloferax* [13], *Pyrococcus* [80], *Anaerobranca* [156], *Microbacterium* [126] and *Amphibacillus* [55] are some of the bacteria that produce CGTase. The archaea and fungi can also produce CGTase. The genera of archaea that are commonly studied for production of CGTase are *Thermococcus* [128, 153], *Haloferax* [13] and *Pyrococcus* [80]. *Aspergillus* [81] and *Trihoderma viride* [115] are the fungi that are used to produce CGTase. However, the CGTase is mostly produced by strains of *Bacillus,* such as *B. circulans* [163], *B. macerans* [2], *B. firmus* [36], *B. cereus* [54], and *B. pseudalcaliphilus* [11].

Other known CGTase producing bacteria include *Paenibacillus illinoisensis* [81], *Klebsiella pneumoniae* [37], *Thermoanaerobacter sp. P4* [12], *Amphibacillus sp NPST-10* [53], *Brevibacterium sp.* 9605 [105], *Brevibacillus brevis* [64], *Microbacterium terrae KNR 9* [127] and *Thermoactinomyces vulgaris* Tac-5354 [4]. The CGTase producing microbes are mainly found in soil, lake water, hot springs, wastewater from flour industry and rotten potatoes [22, 28, 53]. Table 1 shows a summary of the CGTase producing microorganism.

3.3. Donor specificity

Generally, since CGTase is a common starch-degrading enzyme, donors of CGTase are carbohydrate sources. Common carbohydrates used by CGTase are dextrin, maltodextrin, maltose, maltoheptaose, maltotriose, starch and cyclodextrin, as summarized in Table 2. The usage of cyclodexrins as donors has the advantage of enhancing the solubility of acceptor through complex inclusion [179]. However, the substrate may become inert to enzymatic catalysis and cyclodexrins are more costly compared with other donors.

Several cheaper carbohydrate sources have been studied for their application as donors, such as maltodextrin, maltose, maltotriose, sucrose and glucose. Although the effectiveness of donor substrates used for glycoside synthesis are in decreasing order of α-cyclodextrin > maltodextrin > maltotriose > maltose, but conversion yield of transglycosylated products can be improved by increasing the donor concentrations [100]. Thus, it has been found that, if used in high concentrations, maltodextrin can be used as an efficient alternative to α-cyclodextrin [100].

According to Go et al. [38], starch and maltodextrin can act as a better donor than low molecular weight carbohydrates, such as cyclodextrin, maltotriose, maltose, and dextrin. Moreover, donor substrates for CGTase should have at least two glucose units. Therefore, glucose cannot be used as a donor for the CGTase [100]. Furthermore, donor's chain length and concentration will also influence the glycosides' chain length. For instance, short chain donors such as maltose would form shorter glycoside, while long chain donors, such as starch, or high concentrations of donor would result in glycosides with longer chain length [99, 100].

3.4. Acceptor specificity

Generally, good acceptors for CGTase contain available hydroxyl group(s) (-OH group) located at carbon position(s) 2, 3 and 4. There are two groups of acceptors which are sugar and non-sugar compounds. The sugar compounds acting as an acceptor for CGTase include lactose, sucrose, 1, 5-anhydro-D-fructose and methyl α-D-glucopyranoside. Meanwhile, non-sugar compounds used as acceptors for CGTase are sugar alcohols, sugar fatty acid esters, polyols, phenolic compounds, capsaicinoids, saponins, vitamins, diterpenoid, triterpene glycoside, alkyl glucoside and artificial rhamnoside. Table 2 provides a list of acceptors previously used in transglycosylation.

3.5. Effects of pH and temperature on transglycosylation reaction

The pH range of buffer is vital for enzymatic activity since extreme acidity or alkalinity will denature the enzyme. The optimum pH for CGTase isolated from alkaliphilic, mesophilic, halophilic and thermophilic bacilli is in the range of 6.0–7.5 [3]. For example, optimum pH for transglycosylation of the piceid by the CGTase from *Bacillus macerans* is in the rage of 5.5–7.0. The conversion yield of piceid was reduced when enzymatic reactions carried out at lower pH such as pH 4.5 and pH 5.0 [94].

The reaction temperature plays an important role in the enzymatic activity. The CGTase extracted from different microorganisms have different optimum reaction temperatures. For instance, the optimum temperature for the CGTase isolated from halophilic and mesophilic strains is in the range of 45–50 °C, while for the CGTase isolated from alkalophilic and thermophilic strains is 50–55 °C [3]. The temperature used in most studies on CGTase has been in the range of 40–60 °C [23, 129]. Table 2 provides a summary of temperatures used in transglycosylation of different compounds.

Achieving the optimum temperature can be assisted by using the microwave and ultrasound techniques. Microwave and ultrasound produce heat and can be used to maintain the optimum temperature for enzymatic reaction, using different frequencies and heat transfer mechanism [13, 92, 108, 131, 133, 166]. The ultrasound produces sound with frequencies between 2 to 15 MHz, while microwave produces electromagnetic radiation with frequencies between 1 to 1000 GHz. The ultrasound is a transmitter to produce sound, which vibrating molecules transfer energy from one location to another with back and forth motion. The energy produced by ultrasound can be absorbed by the reaction mixture and converted into heat. On the other hand, a microwave transmits thermal radiation that induces polar molecules in the reaction mixture to rotate and produce thermal energy, providing optimum temperature for enzymatic reaction [5, 118].

According to Jaitak et al. [56], transglycosylation by using microwave-assisted techniques was faster than traditional and ultrasound-assisted techniques. The reaction by microwave-assisted techniques yielded 66% 4′-O-alpha-D-glycosyl stevioside and 24% 4′-O-alpha-D-maltosyl stevioside in 1 min, while the ultrasound assisted techniques were able to yield 50% and 25% for 4′-O-alpha-D-glycosyl stevioside and 25% 4′-O-alpha-D-maltosyl stevioside, respectively, but the process required 10 min to achieve those results. In comparison, the production yield for traditional technique (without any assistance) was 46% for 4′-O-alpha-D-glycosyl stevioside and 24% for 4′-O-alpha-D-maltosyl stevioside but only after 12h.

3.6. Effects of organic reagents and metal ions on transglycosylation reaction

In order to achieve good solubility for a hydrophobic acceptor, like polyphenols, in an aqueous system, it is first dissolved in water-miscible organic solvents or co-solvents, such as dimethyl sulfoxide (DMSO), before being added into the buffer solution. The examples of suitable co-solvents include DMSO, ethanol, dioxane, sulfolane, dimethylformamide, isopropanol, *n*-propanol, glycerol and ethyl-lactate. The ratio of buffer to

Table 2. Factors influencing the CGTase enzymatic reaction and its conversion yield.

Acceptor	Donor	Strain/Type of CGTase	Product	pH	Temp (C)	Yield (%)	Ref.
Sugar							
lactose (4-O-β-D-galactosyl-D-glucose)	Soluble Starch	*Bacillus stearothermophilus* (CGTase)	α-D-glucosyl O-β-D-galactosyl-(1–4)-β-D-glucoside	5.6	50 °C	64	[68]
1,5-anhydro-D-fructose	β-CD	*Bacillus stearothermophilus* (CGTase)	Glucosyl 1,5-anhydro-D-fructose (1,5-anhydro-3-O-α-glucopyranosyl-D-fructose)	5.0	35 °C	-	[183]
Acarbose	α-CD	*Bacillus macerans* (CGTase)	D-glucopyranosyl-acarbose	6.0	37 °C	-	[181]
Sucrose	β-CD	*Thermoanaerobacter sp.* (CGTase)	Polyglucosyl-fructosides	5.5–6.5	60 °C	-	[102]
Sucrose	Soluble Starch	*Thermoanaerobacter sp.* (CGTase)	Maltooligosyl fructofuranosides	5.5	60 °C	≥80	[96]
Sugar glycosides							
i-menthyl α-D-glucopyranoside	Starch	*Bacillus macerans* (CGTase)	i-Menthyl α-D-glucopyranosyl-(1→4)-α-D-glucopyranoside	6.0	70 °C	74.2	[30]
Sugar alcohols							
Myo-inositol	β-CD	*Bacillus ohbensis* (CGTase)	Oligoglucosyl-inositols	6.0	50 °C	58.8	[134]
Inositol	β-CD	*Thermoanaerobacter sp.* (CGTase)	Monoglucated product of L-chiro-, D-chiro-, muco-, and allo-inositol.	6.0	50 °C	-	[101]
Sugar Fatty Acid Esters							
Sucrose monolauroyl esters	Dextrin	CGTase	Additional 1–3 glucose residues on the pyranose ring of sucrose moiety in the ester	6.5	50 °C	58.8	[120]
Polyols							
Pentaerythritol	Starch	*Bacillus stearothermophilus* (CGTase)	Glucosyi pentaerythritol	5.5	40 °C	-	[114]
Trimethylolethane			Glucosyl trimethylolethane			-	
Trimethylolpropane			Glucosyl trimethylolpropane			-	
Glycerol	Soluble Starch	*Thermoanaerobacter sp.* (CGTase)	Glycosyl Glycerol -O-α-D-glucosyl-(1-1)-glycerol -O-α-D-glucosyl-(1–2)-glycerol -O-α-D-Glucosyl-(1–4)-O-α-D-glucosyl-(1-1)-glycerol	6.0	80 °C	-	[113]
		G.stearothermophilus (CGTase)			60 °C		
Phenolic compound							
(+)catechin (flavan-3-ol)	Soluble Starch	*Bacillus macerans* (CGTase)	(+)catechin3′-O-α-D-glucopyranoside	6.5	40 °C	18.3	[34]
Hesperidin (Flavan-on glycoside)	Soluble Starch	Alkalophilic *Bacillus sp.* (CGTase)	Hesperidin monoglucoside	9.0	40 °C	75	[75]
Hesperetin 3′- O-α-glucosides Hesperetin 5- O-α-glucosides Hesperetin 7-O-α-glucosides	Starch	CGTase	Hesperetin 3′-O-α-maltoside Hesperetin 5-O-α-maltoside Hesperetin 7-O-α-maltoside	7.0	40 °C	49 62 50	[139]
Hesperidin	Soluble Starch	*Thermoanaerobacter sp.* (CGTase)	Hesperetin 7-O-α-D-glucopyranoside	5.0	60 °C	4.1	[40]
4-hydroxyphenyl α-glucopyranoside (α-arbutin)	Soluble Starch	*Bacillus macerans* (CGTase)	Arbutin-α-glycosides -4-hydroxyphenyl β-maltoside (β-Ab-α-G1)	7.0	40 °C	70	[149]

(*continued on next page*)

Table 2 (*continued*)

Acceptor	Donor	Strain/Type of CGTase	Product	pH	Temp (C)	Yield (%)	Ref.
			-4-hydroxyphenyl *β*-maltotrioside (*β*-Ab-α-G2)				
Genistin	Soluble Starch	alkalophilic *Bacillus sp.* I-5 (CGTase)	Glucosyl-α(1–4)-genistin Maltosyl-α(1–4)-genistin	6.0	60 °C	-	[87]
Genistin	α-CD	*Paenibacillus macerans* (CGTase)	Genistin diglucoside	6.5	30 °C		[42]
Quercetin 7-O-*β*-D-glucoside	Starch	CGTase	Quercetin 7-O-*β*-maltoside	7.0	40 °C	36	[141]
			Quercetin 7-O-*β*-maltotrioside			10	
Quercetin 3-O-*β*-D-glucoside			Quercetin 3-O-*β*-maltoside			40	
			Quercetin 3-O-*β*-maltotrioside			14	
Genistein 4-O-*β*-D-glucoside			Genistein 4-O-*β*-maltoside			32	
			Genistein 4-O-*β*-maltotrioside			12	
Genistein 7-O-*β*-D-glucoside			Genistein 7-O-*β*-maltoside			30	
			Genistein 7-O-*β*-maltotrioside			7	
Naringin	Malto dextrin	alkalophilic *Bacillus sp.* BL-31 (CGTase)	Monoglycosyl naringin	8.5	40 °C	92.1	[39]
α-tocopheryl *β*-glucoside	Starch	CGTase	α-tocopheryl *β*-maltoside	7.0	40 °C	51	[137]
			α-tocopheryl *β*-maltotrioside			35	
δ-tocopheryl *β*-glucoside			δ-tocopheryl *β*-maltoside			45	
			δ-tocopheryl *β*-maltotrioside			29	
Hesperetin α-glucoside (Vitamin P)	Starch	*Bacillus macerans* (CGTase)	Hesperetin 3′-O-α-maltoside	7.0	40 °C	49	[92]
			Hesperetin 5-O-α-maltoside			62	
			Hesperetin 7-O-α-maltoside			50	
Curcumin 4′-O-*β*-D-glucopyranoside	Starch	*Bacillus macerans* (CGTase)	Curcumin 4′-O-*β*-glucooligosaccharides Curcumin 4′-O-*β*-maltoside Curcumin 4′-O-*β*-maltotrioside	7.0	40 °C	51 21	[139]
Glycitein	Soluble Starch	*Bacillus macerans* (CGTase)	Glycitein 4′-O-*β*-D-maltoside	7.0	40 °C	45	[140]
			Glycitein 4′-O-*β*-maltotrioside			39	
			Glycitein 7-O-*β*-maltotrioside			33	
Daidzein	Soluble Starch		Daidzein 4′-O-*β*-maltoside			46	
			Daidzein 4′-O-*β*-maltotrioside			35	
			Daidzein 7-O-*β*-maltoside			39	
			Daidzein 7-O-*β*-maltotrioside			30	
Resveratrol	Starch	*Thermoanaerobacter sp.*(CGTase)	α-glucosyl derivatives of resveratrol (3,5,4′-trihydroxy stilbene)	5.6	60 °C	50	[159]
Epicatechin	Soluble Starch	*Paenibacillus sp.* RB01 (CGTase)	Epicatechin glucosides	6.0	40 °C	22.6	[10]
	β-CD					22.4	
	Malto heptaose					21.4	
Piceid (stilbenoid glucoside)	Maltose	*Bacillus macerans* (CGTase)	Piceid glycosides	6.0	40 °C	17.8	[99]
	Malto triose					56.4	
	Malto dextrin					72.1	
	α-CD					78.9	

(*continued on next page*)

Table 2 (*continued*)

Acceptor	Donor	Strain/Type of CGTase	Product	pH	Temp (C)	Yield (%)	Ref.
Pterostilbene (trans-3,5-dimethoxy-4′-hydroxystilbene)	Partial hydrolysed starch	*Thermoanaerobacter sp.*(CGTase)	Pterostilbene α-Glucoside	-	60 °C	-	[39]
Hydroquinone	α-CD	*Thermoanaerobacter sp.*(CGTase)	Hydroquinone-1-O-α-D-glucopyranoside (α-arbutin)	5.5	40 °C	31.8	[100]
	Malto dextrin					29.2	
Kaempferol (flavonol)	Y-CD	CGTase (Toruzyme)	Kaempferol-3-O-*β*-D-glucopyranosyl-(1→4)-O-α-D-glucopyranoside	6.0	60 °C	8.6	[23]
Capsaicinoids							
Capsaicin	Starch	CGTase	Capsaicin *β*-maltoside	7.0	40 °C	41	[143]
			Capsaicin *β*-maltotrioside			35	
Saponins							
α-glucosyl ginsenoside, R_{b1}	Dextrin	*Bacillus macerans* (CGTase)	α-maltosyl ginsenoside	6.0	50 °C	10.3	[66]
α-glucosyl ginsenoside, R_c			α-maltosyl ginsenoside			10.5	
α-glucosyl ginsenoside, R_e			α-maltosyl ginsenoside			16.9	
α-glucosyl ginsenoside, R_{g1}			α-maltosyl ginsenoside			18.6	
Ginsenoside F1	Dextrin	CGTase	α-Glucosyl Ginsenoside F1	7.0	50 °C	-	[105]
Vitamins							
L-ascorbic acid (Vitamin C)	α-CD	*Bacillus stearothermophilus* (CGTase)	2-O-α-D-Glucopyranosyl-L-ascorbic acid	5.5	60 °C	97	[5]
D-Erythorbic acid	Y-CD	*Thermoanaerobacter sp.* (CGTase)	2-O-α-D-glucopyranosyl-d-erythorbic acid	4.0	40 °C	49.1	[154]
L-ascorbic acid (Vitamin C)	α-CD	*Thermoanaerobacter sp.* (CGTase)	2-O-α-D-Glucopyrano syl-L-ascorbic acid	4.5	50 °C	30	[41]
L-ascorbic acid (Vitamin C)	α-maltosyl fluoride (aG2F)	*engineered cyclodextrin glucanotransferase*	3-O-α-maltosyl-L-ascorbate	7.5	25 °C	29	[6]
Diterpenoid							
Rubusoside	Soluble starch	*Bacillus circulans* (CGTase)	Tri and tetra-glucosylated rubusoside	5.4	40 °C	-	[119]
Stevioside	Malto dextrin	Alkalophilic *Bacillus sp.* BL-12 (CGTase)	mono-, di-, and oligo-glycosyl stevioside	9.0	40 °C	76	[62]
Taxol (paclitaxel)	Soluble starch	*Bacillus macerans* (CGTase)	7-Glycolylpaclitaxel 2″-O-α–glucobioside	7.0	40 °C	17	[139]
			7-glycolylpaclitaxel 2′-O-α-glucotrioside			14	
			7-glycolylpaclitaxel 2′-O-α-glucotetraoside			11	
			7-glycolylpaclitaxel 2′-O-α-glucopentaoside			7	
Stevioside	Corn starch	*Paneibacillus macerans* JFB05-01 (CGTase)	Monoglucosylated stevioside	7.0	60 °C	77.11	[89]
			Diglucosylated stevioside			76	

(*continued on next page*)

Table 2 (*continued*)

Acceptor	Donor	Strain/Type of CGTase	Product	pH	Temp (C)	Yield (%)	Ref.
Stevioside	Starch	*Paenibacillus sp.*CGMCC 5316 (CGTase)	mono-glycosylated stevioside	7.0	37 °C	85.6	[184]
Benzo[h] quinazolines	ϒ-CD	*Bacillus stearothermophilus* ST-88 (CGTase)	3-Ethyl-2-carboxy methylsulfanyl-4-oxo-3,4,5,6 tetrahydrospyro (benzo[h]quinazoline-5,1′-cyclohexane)	5.5	60 °C	19.8	[95]
			4-Carboxy-6-oxo-3,4,5,6,7,8-hexahydrospyro (thiazolidine-[2.3-b]-benzo[h]quinazoline-7,1′-cyclohexane)			18.7	
Triterpene glycoside							
Mogroside V	Tapioca starch	*Bacillus macerans* (CGTase)	Monoglycoside mogroside V Diglycoside mogroside V Triglycoside mogroside V	6.5	50 °C	≥90	[182]
Mogroside II_E	Starch	*Bacillus macerans* (CGTase)	Diglycoside mogroside II_E	6.0	55 °C	≥80	[170]
Alkyl glucoside							
Dodecyl *β*-maltoside	α-CD	*Bacillus macerans* (CGTase)	Dodecyl *β*-D-maltooctaoside	5.2	60 °C	50	[152]
Dodecyl-*β*-D-maltoside	α-CD	*Bacillus macerans* (CGTase)	Dodecyl-*β*-D-maltooctaoside	5.2	60 °C	80	[151]
Dodecyl *β*-D-glucoside	α-CD	*Bacillus macerans* (CGTase)	Dodecyl glucooligosides	6.0	70 °C	78	[99]
Dodecyl *β*-D-maltoside						93	
Tert-butyl alcohol	Starch	*Thermoanaerobacter sp.* (CGTase)	tert-butyl-α-D-glucoside tert-butyl-α-D-maltoside	6.0	60 °C	44	[35]
Non-natural							
Methyl or allyl α-L-rhamno-pyranoside	Malto dextrin	*Bacillus circulans* 251 (CGTase)	Cis-Glucosylated L-Rhamnosides	6.0	50 °C	70	[161]

N*β*-CD = *β*-cyclodextrin, α-CD = α-cyclodextrin, ϒ-CD = ϒ-cyclodextrin.

organic solvent must be adjusted in such a way that ensures it does not pose denaturing or inhibiting effects on the enzyme while ensuring a good level of solubility for the hydrophobic acceptor. DMSO mixed with buffers exhibits the best performance in terms of solubility of the hydrophobic acceptors and product's yield as compared with other co-solvents [159]. According to Blackwood and Bucke [16], the addition of small quantities of organic solvents increases the production yield of transglycosylation reaction carried out by CGTase.

Addition of metal ions also shows similar effects on the production yield of transglycosylation reaction by CGTase. This is because some metal ions such as Ca^{2+} can enhance the enzyme stability. Most CGTase enzymes contain two Ca^{2+} binding sites which located at the N-terminal end and the active site region, which influence their activity and stability [87]. Calcium also acts as a protective agent for CGTase against heat [87]. It has been shown that the β-CGTase activity can be stimulated by presence of Ca^{2+} which resulted in an increase, up to 123%, of its transglycosylation yield [62]. Besides, Mn^{2+} metal ions also exhibit positive effect on transglycosylation by CGTase. Enzyme activity of CGTase from *Alkalophilic Bacillus sp. BL-31* was stimulated by presence of Mn^{2+} which resulted in increased yield of glycosylated naringin from 80.2% to 92.1% [38]. However, some other metal ions such as Zn^{2+}, Cu^{2+} and Fe^{2+} are inhibitors for most CGTase [158].

3.7. Effects of concentration and source of CGTase on transglycosylation reaction

The transglycosylation activity of CGTase is dependent on the amount of CGTase in reaction mixture and enzyme source. Although, high amount of CGTase added into a reaction mixture would increase the initial reaction rate of transglycosylation significantly, but excess amount of CGTase used in catalyzing reaction would produce unwanted side reactions such as excess formation of cyclodextrins [38, 89].

Furthermore, conversion yield can be affected by the source, microorganism, of CGTase isolation [3]. In their study, Abelyan et al. [3] used CGTase extracted from mesophilic (*B. macerans* and *B. circulans*), thermophilic (*B. stearothermophilus*), alkaloiphilic (*B. alcalophilus*), and halophilic (*B. halophilus*) bacilli to synthesize stevioside glycoside. The effectiveness of enzymes in stevioside glycoside formation was in the decreasing order with CGTase from *B. halophilus* and *B. alcalophilus* > *B. circulans* > *B. stearothermophilus* and *B. macerans*. The enzyme activity of CGTase from *B. halophilus* and *B. alcalophilus* was 15–16 U/g followed by *B. circulans,* and lastly *B. macerans* and *B. stearothermophilus*, producing 11–11.5 U/g and 8–9 U/g respectively. According to Jaitak et al. [56], the enzyme activity of CGTase extracted from *B. firmus* was 2 U/g; although they used the same acceptor and stevioside as the experiment conducted by Abelyan and his colleagues [3]. Other studies have shown that CGTase from *Thermoanaerobacter sp.* produces higher yield of resveratrol glucoside when compared with *B. macerans* [159]. This might be due to the higher thermo-stable properties of CGTase isolated from *Thermoanaerobacter sp.* (thermophilic anaerobic bacterium) which displays a high disproportionation activity [96]. Moreover, studies on the elongation of carbohydrate groups in alkyl glycosides found that CGTase from *Paenibacillus macerans* yield the highest β-dodecyl maltooctaoside concentration compared with the CGTase from *Paenibacillus Thermoanaerobacter sp.*, *Carboxydocella sp.* and *B. stearothermophilus* [129].

4. Strategies to improve the transglycosylation activity of CGTase

Several protein modification techniques have been used in order to improve the transglycosylation activity of CGTase, including chemical modification, immobilization and recombinant DNA techniques. For example, succinylation, a chemical modification, has been applied on CGTase from *Thermoanaerobacter* sp. 501 to improve its disproportionation [8]. Succinylation is the reaction of transferring a succinyl group to lysine (K) residue of protein molecule [50].

Immobilization is another method of improving the transglycosylation activity of CGTase. Advantages of enzyme immobilization include reusability of enzymes, shortening purification process as enzymes are not mixed with the final product, and simplicity of steps for enzyme immobilization on supports (insoluble matrix) [26]. In addition, immobilization can improve stability of the enzyme that useful for application in industrial scale. The covalent binding, adsorption and entrapment are different methods applied for the immobilization of CGTase. The CGTase has been covalently immobilized on different supports, including porous glass [147], polyvinyl chloride (PVC) [1], polyethylene film [21], Eupergit® C [97], alumina [125], and chitosan [128]. The synthetic adsorption resin (DIAION® HP-20) [61] and purified sand [55] are examples of supports used for immobilization of CGTase through absorption method. Meanwhile, alginate, polyacrylamide [80], curdlan and vegetable sponge natural supports [33] have been used in entrapment immobilization technique.

The immobilized CGTase has been used to synthesize xylitol [65], maltooligosyl fructofuranosides [96], 2-O-α-glucopyranosyl L-ascorbic acid [125, 185] and alkyl glycosides [150]. The α-CGTase immobilized on sodium alginate has shown higher optimal temperature (45 °C) and 2-fold 2-O-α-glucopyranosyl L-ascorbic acid production yield compared with free α-CGTase [185]. Furthermore, the immobilized CGTase from *Paenibacillus sp.* A11, used for transglycosylation of L-ascorbic acid, exhibits 20% higher thermal stability than free CGTase and can be stored for a longer period of up to two months [125]. In addition, the CGTase from *Thermoanaerobacter sp.* immobilized on Amberlite® IRA-900, which has been used for transglycosylation of xylitol, have longer half-life and higher optimal temperature (90 °C) compared with it free form (70 °C) [65].

Protein engineering is an alternative method of improving the transglycosylation activity of CGTase. Different approaches have been studied for protein engineering of CGTase, including site-directed mutagenesis, directed evolution [84], and combination of x-ray crystallography with site-directed mutagenesis [176]. The site-directed mutagenesis has been used for replacement of Tyr 188 in CGTase from *Bacillus ohbensis* [145]; Tyr 195 in CGTase from *Bacillus circulans* Strain 251 [121]; Lys-232, Phe-183, Phe-259 and Glu-264 in CGTase from *Bacillus circulans* strain 251 [162]; Ala 223 and Gly 255 in CGTase from *Bacillus clarkia* 7364 [109]; lysine 47 in CGTase from *Paenibacillus macerans* strain JFB05-01 [90]; and Asp372 and Tyr89 in CGTase [91]. The protein engineering of CGTase is mainly used to improve the specificity in the cyclodextrin production, such as enhanced production of α-cyclodextrin.

Moreover, protein engineering is used to synthesize other products such as ascorbic acid and genistein diglucoside [42]. The 2-O-D-glucopyranosyl-L-ascorbic acid can be synthesized by chimeric modification and/or site-saturation mutagenesis of the α-CGTase from *Paenibacillus macerans*. Previous studies have found that maltodextrin specificity is enhanced by site-saturation engineering of lysine 47 [46], tyrosine 195, tyrosine 260, and glutamine 265 [48], or the iterative saturation mutagenesis of -6 sub site residues [47] in α-CGTase extracted from *Paenibacillus macerans* when used to synthesize 2-O-D-glucopyranosyl-L-ascorbic acid. Moreover, starch specificity can be enhanced by chimeric modification, including fusion of the carbohydrate-binding module to the carboxyl terminus of CGTase, fusion of self-assembling amphipathic oligopeptides with α-CGTase [45], or replacing the E domain of α-CGTase [43], to synthesize 2-O-D-glucopyranosyl-L-ascorbic acid. The donor's specificity improvement makes the glycosyl donors more soluble and the synthesis of 2-O-D-glucopyranosyl-L-ascorbic acid cheaper [44]. In addition, fusion of carbohydrate-binding modules with CGTase enhances hydrolysis and disproportionation activities of CGTase, resulting in an increased 2-O-D-glucopyranosyl-L-ascorbic acid production yield. The CGTase hydrolysis and disproportionation activities play an important role in enzymatic synthesis of 2-O-D-glucopyranosyl-L-ascorbic acid. The hydrolysis activity leads to conversion of starch to oligosaccharides while disproportionation activity transfers the glycosyl group from the oligosaccharides to the acceptor. The changes in hydrolysis and disproportionation activities of fusion enzymes can lead to an increase in 2-O-D-glucopyranosyl-L-ascorbic acid production yield.

The mutation of Glu 284 in CGTase to alanine residue catalyzes regioselective transglycosylation at 3-OH group of L-ascorbic acid resulting in direct production of 3-O-α-maltosyl-L-ascorbate, without requiring any hydrolysis process by glucoamylase [6, 86]. 3-O-α-maltosyl-L-ascorbate has higher anti-antioxidant activity than ascorbic acid. Furthermore, protein engineering not only improves the transglycosylation of CGTase, but it also can increase the yield of enzymatic products by employing systematic codon optimization strategy. For instance, the systematic codon optimization strategy improves the heterologous expression of *Paenibacillus macerans* cgt gene in *Escherichia coli* [58], and it has been used to increase production of the genistein diglucoside by α-CGTase, which resulted in 1.5-fold increase in production compared with the native α-CGTase [42].

4.1. Improved conversion yield of transglycosylated products

The conversion yield of transglycosylated products is the most important factor in the industry. Li et al. [89] had used starch as glycosyl donor and the CGTase extracted from *B. macerans* to synthesize diglucosylated stevioside with 76% conversion yield. Similarly, Mathew et al. [100] reported that use of the CGTase from *B. macerans* to transfer the glycosyl group from a donor, α-cyclodextrin, to acceptor lead to a very good conversion yield of 93%. According to Svensson et al. [146], the conversion yield of dodecyl-*β*-D-maltoside to dodecyl-*β*-D-maltooctaoside using CGTase and α-cyclodextrin, as a donor, was 80%. Table 2 provides information on the conversion yield of different transglycosylated products.

4.2. Carbohydrate elongation of alkyl glycosides

Alkyl glucosides are non-ionic surface-active agents and widely used in food, personal care and detergent productions, and protein extractions [17]. Surface-active agents are amphipathic molecules with hydrophobic and hydrophilic moieties. The reasons for wide application of alkyl glucosides are their antimicrobial activity, biodegradability and low toxicity [99]. CGTase not only can synthesize alkyl glycosides, using sugars and fatty alcohols with simple reaction steps compare with chemical synthesis [129], it can also elongate the carbohydrate group of alkyl glycosides to a desired length, such as elongation of dodecyl-*β*-maltoside to dodecyl-*β*-maltooctaoside. In fact, commercial alkyl glycosides are only available with relatively short carbohydrate parts. Elongation of the sugar moieties of alkyl glycosides makes the surfactant milder on cells and tissues [32]. The dodecyl-*β*-maltooctaoside and tert-butyl α-D-glucopyranosides are examples of alkyl glycosides synthesized by CGTase.

4.3. Improved water-solubility of transglycosylated products

Transglycosylation reaction influences both physicochemical and biological properties of molecules. The most obvious advantage of this reaction is to render hydrophobic compounds to have a better solubility in aqueous systems. Improvement of the solubility of hydrophobic compounds can increase their bioavailability in our body and their biological and pharmacological functions. For instance, polyphenols are hydrophobic compounds, which exhibit deficient absorption, causing entry of a low concentration of polyphenols into circulatory streams [14]. Adding a sugar moiety to improve the water solubility of a hydrophobic compound may improve its intestinal absorption and subsequently its bioavailability [130, 136]. Phenolic compounds such as tocopherols exhibit useful biological, including anti-cancer, anti-aging, anti-carcinogenic and anti-allergic, effects [137]. However, low water solubility of tocopherols limits their biological and pharmacological applications. The transglycosylation of α- and δ-tocopherols catalyzed by CGTase has shown to improve their anti-allergic activities [137]. In addition, transglycosylation of genistein, quercetin, curcumin, hesperetin, glycitein, and daidzein can improve their anti-allergic activities, through inhibiting the release of histamine and increasing the production of IgE antibody [137, 140, 141, 142].

The water solubility of different phenolic compounds has been improved by transglycosylation reaction using CGTase, including hesperidin [75], genistin [88] naringin [38], resveratrol [159], epicatechin [10], hydroquinone [95] and kaempferol [23]. Besides, transglycosylation reaction catalyzed by CGTase also could improve water solubility of the sugar-glycoside-menthyl α-D-glucopyranoside [30], and diterpenoid compound benzo[h]quinazolines [95]. A summary of transglycosylated products and their water solubility is provided in Table 3.

4.4. Improved stability of transglycosylated products

Transglycosylation can improve the stability of compounds. For instance, it has been shown that the epicatechin-3′-O-α-D-

Table 3. Increase in water solubility of glycosylated products compared with their aglycon.

Acceptor	Product	Increase in Water Solubility, Fold	Ref.
Sugar glycosides			
i-menthyl α-D-glucopyranoside	i-Menthyl α-D-glucopyranosyl-(1→4)-α-D-glucopyranoside	1.57×10^3	[30]
Phenolic compound			
Hesperidin	Hesperidin Glycosides	3.0×10^2	[75]
Genistin	Glc(α1-4)-Glc(*β*1-7)-genistein	3.7×10^3	[88]
	Glc(α1-4)-Glc(α1-4)-Glc(*β*1-7)-genistein	4.4×10^4	
Naringin	Monoglycosyl naringin	1.0×10^3	[38]
Quercetin 7-O-*β*-D-glucoside	Quercetin 7-O-*β*-maltoside	2.7×10^2	[142]
	Quercetin 7-O-*β*-maltotrioside	6.9×10^2	
Quercetin 3-O-*β*-D-glucoside	Quercetin 3-O-*β*-maltoside	3.3×10^2	
	Quercetin 3-O-*β*-maltotrioside	8.5×10^2	
Genistein 4-O-*β*-D-glucoside	Genistein 4-O-*β*-maltoside	6.4×10^2	
	Genistein 4-O-*β*-maltotrioside	1.7×10^3	
Genistein 7-O-*β*-D-glucoside	Genistein 7-O-*β*-maltoside	4.5×10^2	
	Genistein 7-O-*β*-maltotrioside	1.0×10^3	
Resveratrol	α-glucosyl derivatives of resveratrol (3,5,4′-trihydroxy stilbene)	6.5×10^1	[159]
Epicatechin	Epicatechin glucosides	4.4×10^1	[10]
Hydroquinone	Hydroquinone-1-O-α-D-glucopyranoside	1.8	[100]
Kaempferol (flavonol)	Kaempferol-3-O-*β*-D-glucopyranosyl-(1→4)-O-α-D- glucopyranoside	1.21×10^2	[23]
Diterpenoid			
Taxol (paclitaxel)	7-Glycolylpaclitaxel 2″-O-α-glucooligosaccharide	6.8×10^3	[138]

glucopyranoside has browning resistance [10] due to presence of the glucosyl moiety that helps to protect the epicatechin catechol rings from polymerization, the cause of browning [159]. Kometani et al. [75] found that transglycosylation of hesperidin stabilizes the color of pigments by absorbing ultraviolet light. The L-ascorbic acid undergoes rapid degradation when exposed to heat, neutral pH, and heavy metals [151]. However, transglycosylation of L-ascorbic acid to 2-O-α-D-glucopyranosyl-L-ascorbic acid improves its stability, and transglycosylated L-ascorbic acid is widely used in food and cosmetic products [46, 124].

4.5. Application of transglycosylated products in foods and cosmetics

Tyrosinase (EC 1.14.18.1) is a copper-containing oxidase enzyme that catalyzes melanin synthesis [148]. Melanin is a natural pigment that protects, through melanogenesis, human skin cells when exposed to UV radiation. The melanin pigment in skin cell absorbs the UV light and dissipates absorbed UV radiation. Melanogenesis is a process that produces melanin in melanosomes [168]. Excessive melanin synthesis causes hyperpigmentation in the skin cell and darkens the skin [148]. One way to control the excessive melanin synthesis is by using inhibitors to inhibit tyrosinase, the enzyme that synthesizes melanin, and thus they are considered as skin whitening agents and a vital element of skin whitening products. According to Kazuhisa et al. [62], tyrosinase inhibition effect of α-arbutin was more effective than arbutin in human malignant melanoma cells. Newly synthesized α-arbutin, catalyzed by CGTase, had shown 39.7% inhibitory effect on tyrosinase [100]. Another study showed that (+) catechin-α-glucoside exhibits 50% tyrosinase inhibitory activity [34]. Furthermore, α-glycosyl ginsenoside F1 shows higher tyrosinase inhibitory activity than ginsenoside F1, its non-transglycosylated form [103].

Transglycosylation is also able to reduce the bitter taste or aftertaste of food additives such as mogroside V. The sweetness of stevioside and mogroside V are 300–400 times higher than sucrose but they have a bitter aftertaste [170, 177]. Previous studies [93] have shown that glucosyl, sucrosyl, sophorosyl and fructosyl groups can be attached to the C13 position of stevioside, which eliminates the bitter aftertaste of stevioside. Currently, transferring glycosyl groups to stevioside through transglycosylation catalyzed by CGTase is the most common method used to remove bitterness of stevioside [59, 89].

5. Conclusion

Transglycosylation reaction is a process of transferring glycosyl groups from a donor to an acceptor, which contains hydroxyl or other functional groups, to form a glycoconjugate. Transglycosylation can be catalyzed by enzymatic reactions using CGTase. Catalytic mechanisms of the CGTase are retaining, double displacement, and random ternary complex mechanisms. The CGTase is mainly used to catalyze glycosyl transfer reactions. Most CGTase are produced extracellularly by bacteria and predominantly by strains of *Bacillus*. The CGTase can be used with a wide range of acceptors, using non-activated sugars as the donor, and tolerate high concentrations of organic solvent in the reaction mixtures. In addition, the transglycosylation reaction using CGTase improves the water solubility and stability of transglycosylated products, inhibits tyrosinase, and reduces bitterness of transglycosylated products. Therefore, it is widely used in the production of ingredients used in dietary supplements, detergents, and food, medical and cosmetic products.

Declarations

Author contribution statement

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

Funding statement

This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Data availability statement

No data was used for the research described in the article.

Declaration of interests statement

The authors declare no conflict of interest.

Additional information

No additional information is available for this paper.

References

[1] M.A. Abdel-Naby, Immobilization of *Paenibacillus macerans* NRRL B-3186 cyclodextrin glucosyltransferase and properties of the immobilized enzyme, Process Biochem. 34 (4) (1999) 399–405.
[2] V.A. Abelyan, K.B. Afyan, L.S. Manukyan, New cyclomaltodextrin glucan transferases produced by *Bacillus macerans*, Appl. Biochem. Microbiol. 36 (4) (2000) 338–343.
[3] V.A. Abelyan, A.M. Balayan, V.T. Ghochikyan, A.A. Markosyan, Transglycosylation of stevioside by cyclodextrin glucanotransferases of various groups of microorganisms, Appl. Biochem. Microbiol. 40 (2) (2004) 129–134.
[4] V.A. Abelyan, A.M. Balayan, L.S. Manukyan, K.B. Afyan, V.S. Meliksetyan, N.A. Andreasyan, A.A. Markosyan, Characteristics of cyclodextrin production using cyclodextrin glucanotransferases from various groups of microorganisms, Appl. Biochem. Microbiol. 38 (6) (2002) 527–535.
[5] H. Aga, M. Yoneyama, S. Sakai, I. Yamamoto, Synthesis of 2-O-α-D-glucopyranosyl L-ascorbic acid by cyclomaltodextrin glucanotransferase from *Bacillus stearothermophilus*, Agric. Biol. Chem. 55 (7) (1991) 1751–1756.
[6] H.J. Ahn, C. Li, H.B. Cho, S. Park, P.S. Chang, Y.W. Kim, Enzymatic synthesis of 3-O-α-maltosyl-L-ascorbate using an engineered cyclodextrin glucanotransferase, Food Chem. 169 (2015) 366–371.
[7] K. Akimaru, T. Yagi, S. Yamamoto, Purification and properties of *Bacillus coagulans* cyclomaltodextrin glucanotransferase, J. Ferment. Bioeng. 71 (5) (1991) 322–328.
[8] M. Alcalde, F.J. Plou, M.T. Martin, I. Valdes, E. Mendez, A. Ballesteros, Succinylation of cyclodextrin glycosyltransferase from *Thermoanaerobacter sp.* 501 enhances its transferase activity using starch as donor, J. Biotechnol. 86 (1) (2001) 71–80.
[9] H.F. Alves-Prado, E. Gomes, R. da Silva, Purification and characterization of a cyclomaltodextrin glucanotransferase from *Paenibacillus campinasensis strain H69-3*, Appl. Biochem. Biotechnol. 137–140 (1–12) (2007) 41–55.
[10] P. Aramsangtienchai, W. Chavasiri, K. Ito, P. Pongsawasdi, Synthesis of epicatechin glucosides by a *β*-cyclodextrin glycosyltransferase, J. Mol. Catal. B Enzym. 73 (1–4) (2011) 27–34.
[11] N. Atanasova, T. Kitayska, I. Bojadjieva, D. Yankov, A. Tonkova, A novel cyclodextrin glucanotransferase from alkaliphilic *Bacillus pseudalcaliphilus* 20RF: purification and properties, Process Biochem. 46 (1) (2011) 116–122.
[12] A. Avci, S. Donmez, A novel thermophilic anaerobic bacteria producing cyclodextrin glycosyltransferase, Process Biochem. 44 (1) (2009) 36–42.
[13] V. Bautista, J. Esclapez, F. Pérez-Pomares, R.M. Martínez-Espinosa, M. Camacho, M.J. Bonete, Cyclodextrin glycosyltransferase: a key enzyme in the assimilation of starch by the halophilic archaeon Haloferax mediterranei, Extremophiles 16 (1) (2011) 147–159.
[14] L. Biasutto, E. Marotta, A. Bradaschia, M. Fallica, A. Mattarei, S. Garbisa, M. Zoratti, C. Paradisi, Soluble polyphenols: synthesis and bioavailability of 3,4',5-tri (α-D-glucose-O-succinyl) resveratrol, Bioorg. Med. Chem. Lett 19 (23) (2009) 6721–6724.
[15] A. Biwer, G. Antranikian, E. Heinzle, Enzymatic production of cyclodextrins, Appl. Microbiol. Biotechnol. 59 (2002) 609–617.
[16] A.D. Blackwood, C. Bucke, Addition of polar organic solvents can improve the product selectivity of cyclodextrin glycosyltransferase, Enzym. Microb. Technol. 27 (9) (2000) 704–708.
[17] T. Börner, K. Roger, P. Adlercreutz, Hydrophobic complexation promotes enzymatic surfactant synthesis from alkyl glucoside/cyclodextrin mixtures, ACS Catal. 4 (8) (2014) 2623–2634.
[18] J. Burns, T. Yokota, H. Ashihara, M.E.J. Lean, A. Crozier, Plant foods and herbal sources of resveratrol, J. Agric. Food Chem. 50 (11) (2002) 3337–3340.
[19] X. Cao, Z. Jin, X. Wang, F. Chen, A novel cyclodextrin glycosyltransferase from an alkalophilic *Bacillus* species: purification and characterization, Food Res. Int. 38 (3) (2005) 309–314.

[20] H.Y. Chang, P.M. Irwin, Z.L. Nikolov, Effects of mutations in the starch-binding domain of *Bacillus macerans* cyclodextrin glycosyltransferase, J. Biotechnol. 65 (2-3) (1998) 191–202.

[21] S.H. Choi, M.S. Kim, J.J. Ryoo, K.P. Lee, H.D. Shin, S.H. Kim, Y.H. Lee, Immobilization of a cyclodextrin glucanotransferase (CGTase) onto polyethylene film with a carboxylic acid group and production of cyclodextrins from corn starch using CGTase-immobilized PE film, J. Appl. Polym. Sci. 85 (11) (2002) 2451–2457.

[22] K. Chotipanang, W. Bhunthumnavin, M.H. Prousoontorn, Synthesis of alkyl glycosides from cyclodextrin using cyclodextrin glycosyltransferase from *Paenibacillus sp.* RB01, J. Inclusion Phenom. Macrocycl. Chem. 70 (3–4) (2011) 359–368.

[23] W.J. Choung, S.H. Hwang, D.S. Ko, S.B. Kim, S.H. Kim, S.H. Jeon, H.D. Choi, S.S. Lim, J.H. Shim, Enzymatic synthesis of a novel kaempferol-3-O-β-D-glucopyranosyl-(1→4)-O-α-D-glucopyranoside using cyclodextrin glucanotransferase and its inhibitory effects on aldose reductase, inflammation, and oxidative stress, J. Agric. Food Chem. 65 (13) (2017) 2760–2767.

[24] H.J. Chung, S.H. Yoon, M.J. Lee, M.J. Kim, K.S. Kweon, I.W. Lee, J.W. Kim, B.H. Oh, H.S. Lee, V.A. Spiridonova, K.H. Park, Characterization of a thermostable cyclodextrin glucanotransferase isolated from *Bacillus stearothermophilus ET1*, J. Agric. Food Chem. 46 (3) (1998) 952–959.

[25] Y. Dai, S. Zhang, D. Liu, H. Li, T. Ma, Q. Huo, C. Wu, Phytochemistry Letters Enzymatic biosynthesis of novel bavachin glucosides via Bacillus UDP-glycosyltransferase, Phytochem. Lett. 23 (2018) 9–14.

[26] S. Datta, L.R. Christena, Y.R.S. Rajaram, Enzyme immobilization: an overview on techniques and support, Materials. 3 Biotech. 3 (2013) 1–9.

[27] G.J. Davies, K.S. Wilson, B. Henrissat, Nomenclature for sugar-binding subsites in glycosyl hydrolases, Biochem. J. 321 (1997) 557–559.

[28] T.L. De Freitas, R. Monti, J. Contiero, Production of CGTase by a *bacillus Alkalophilic CGII* strain isolated from wastewater of a manioc flour industry, Braz. J. Microbiol. 35 (3) (2004) 255–260.

[29] D. Divakaran, A. Chandran, R. Pratap Chandran, Comparative study on production of a-Amylase from *Bacillus licheniformis* strains, Braz. J. Microbiol. 42 (4) (2011) 397–404.

[30] H. Do, T. Sato, K. Kirimura, K. Kino, S. Usami, Enzymatic synthesis of i-menthyl alpha-maltoside and i-menthyl alpha-maltooligosides from i-menthyl alpha-glucoside by cyclodextrin glucanotransferase, J. Biosci. Bioeng. 94 (2) (2002) 119–123.

[31] N. Doukyu, H. Kuwahara, R. Aono, Isolation of *Paenibacillus illinoisensis* that produces cyclodextrin glucanotransferase resistant to organic solvents, Biosci. Biotechnol. Biochem. 67 (2) (2003) 334–340.

[32] K. Ekelund, K. Osth, C. Pahlstorp, E. Bjork, S. Ulvenlund, F. Johansson, Correlation between epithelial toxicity and surfactant structure as derived from the effects of polyethyleneoxide surfactants on Caco-2 cell monolayers and pig nasal mucosa, J. Pharmacol. Sci. 94 (2005) 730–744.

[33] V.C. Fenelon, J.H. Miyoshi, C.S. Mangolim, A.S. Noce, L.N. Koga, G. Matioli, Different strategies for cyclodextrin production: ultrafiltration systems, CGTase immobilization and use of a complexing agent, Carbohydr. Polym. 192 (2018) 19–27.

[34] M. Funayama, T. Nishino, A. Hirota, S. Murao, S. Takenishi, H. Nakano, Enzymatic-synthesis of (+) catechin-alpha-glucoside and its effect on tyrosinase activity, Biosc. Biotech. Biochem. 57 (10) (1993) 1666–1669.

[35] H. Garcia-Arellano, J.L. Gonzalez-Alfonso, C. Ubilla, F. Comelles, M. Alcalde, M. Bernabé, J.L. Parra, A.O. Ballesteros, F.J. Plou, Production and surfactant properties of tert-butyl α-d-Glucopyranosides catalyzed by cyclodextrin glucanotransferase, Catalysts 9 (7) (2019) 575.

[36] B.N. Gawande, A. Goel, A.Y. Patkar, S.N. Nene, Purification and properties of a novel raw starch degrading cyclomaltodextrin glucanotransferase from *Bacillus firmus*, Appl. Microbiol. Biotechnol. 51 (4) (1999) 504–509.

[37] B.N. Gawande, A.Y. Patkar, Purification and properties of a novel raw starch degrading-cyclodextrin glycosyltransferase from *Klebsiella pneumoniae AS- 22*, Enzym. Microb. Technol. 28 (2001) 735–743.

[38] Y.H. Go, T.K. Kim, K.W. Lee, Y.H. Lee, Functional characteristics of cyclodextrin glucanotransferase from alkalophilic *Bacillus sp. BL-31* highly specific for intermolecular transglycosylation of bioflavonoids, J. Microbiol. Biotechnol. 17 (9) (2007) 1550–1553.

[39] J. González-Alfonso, D. Rodrigo-Frutos, E. Belmonte-Reche, P. Peñalver, A. Poveda, J. Jiménez-Barbero, A.O. Ballesteros, Y. Hirose, J. Polaina, J.C. Morales, M. Fernández-Lobato, F.J. Plou, Enzymatic synthesis of a novel pterostilbene α-glucoside by the combination of cyclodextrin glucanotransferase and amyloglucosidase, Molecules 23 (6) (2018) 1271.

[40] J. González-Alfonso, N. Míguez, J. Padilla, L. Leemans, A. Poveda, J. Jiménez-Barbero, J. Jimenez-Barbero, A.O. Ballesteros, G. Sandoval, F. Plou, Optimization of regioselective α-glucosylation of hesperetin catalyzed by cyclodextrin glucanotransferase, Molecules 23 (11) (2018) 2885.

[41] R.K. Gudiminchi, A. Towns, S. Varalwa, B. Nidetzky, Enhanced synthesis of 2-O-α-D-Glucopyranosyl-L-ascorbic acid from α-cyclodextrin by a highly disproportionating CGTase, ACS Catal. 6 (3) (2016) 1606–1615.

[42] R. Han, B.B. Ge, M.Y. Jiang, G.C. Xu, J.J. Dong, Y. Ni, High production of genistein diglucoside derivative using cyclodextrin glycosyltransferase from *Paenibacillus macerans*, J. Ind. Microbiol. Biotechnol. 44 (9) (2017) 1343–1354.

[43] R. Han, J.H. Li, H.D. Shin, R.R. Chen, G.C. Du, L. Liu, J. Chen, Carbohydrate-binding module–cyclodextrin glycosyltransferase fusion enables efficient synthesis of 2-O-D-Glucopyranosyl-L-Ascorbic acid with soluble starch as the glycosyl donor, Appl. Environ. Microbiol. 79 (10) (2013a) 3234–3240.

[44] R. Han, J.H. Li, H.D. Shin, R.R. Chen, G.C. Du, L. Liu, J. Chen, Site-saturation engineering of lysine 47 in cyclodextrin glycosyltransferase from *Paenibacillus macerans* to enhance substrate specificity towards maltodextrin for enzymatic synthesis of 2-O-D-glucopyranosyl-L-ascorbic acid (AA-2G), Appl. Microbiol. Biotechnol. 97 (13) (2013b) 5851–5860.

[45] R. Han, J.H. Li, H.D. Shin, R.R. Chen, L. Liu, G.D. Du, J. Chen, Fusion of self-assembling amphipathic oligopeptides with cyclodextrin glycosyltransferase improves 2-O-D-Glucopyranosyl-L-Ascorbic acid synthesis with soluble starch as the glycosyl donor, Appl. Environ. Microbiol. 80 (15) (2014) 4717–4724.

[46] R. Han, L. Liu, J. Li, G. Du, J. Chen, Functions, applications and production of 2-O-D-glucopyranosyl-L-ascorbic acid, Appl. Microbiol. Biotechnol. 95 (2) (2012) 313–320.

[47] R. Han, L. Liu, H.D. Shin, R.R. Chen, J.H. Li, G.C. Du, J. Chen, Iterative saturation mutagenesis of -6 subsite residues in cyclodextrin glycosyltransferase from *Paenibacillus macerans* to improve maltodextrin specificity for 2-O-D-Glucopyranosyl-L-Ascorbic acid synthesis, Appl. Environ. Microbiol. 79 (24) (2013c) 7562–7568.

[48] R. Han, L. Liu, H.D. Shin, R.R. Chen, J.H. Li, G.C. Du, J. Chen, Site-saturation mutagenesis of tyrosine 195, tyrosine 260 and glutamine 265 in cyclodextrin glycosyltransferase from *Paenibacillus macerans* to enhance substrate specificity towards maltodextrin for enzymatic synthesis of 2-O-D-glucopyranosyl-L-ascorbic acid (AA-2G), Appl. Environ. Microbiol. 79 (2) (2013d) 672–677.

[49] K. Harata, K. Haga, A. Nakamura, M. Aoyagi, K. Yamane, X-ray structure of cyclodextrin glucanotransferase from alkalophilic Bacillus sp. 1011: comparision of two independent molecules at 1.8 Å resolution, Acta Crystallogr. 52 (1996) 1136–1145.

[50] A. Hashiguchi, S. Komatsu, Impact of post-translational modifications of crop proteins under abiotic stress, Proteomes 4 (42) (2016) 1–14.

[51] B. Henrissat, A classification of glycosyl hydrolases based on amino acid sequence similarities, Biochem. J. 1 (1991) 309–316.

[52] A.S.S. Ibrahim, A.A. Al-Salamah, H. Bahl, An alkaliphilic cyclodextrin glycosyltransferase from a new *Bacillus agaradhaerens WN-I strain* isolated from an Egyptian soda lake: purification and properties, Afr. J. Biotechnol. 10 (32) (2011) 6107–6119.

[53] A.S.S. Ibrahim, A.A. Al-Salamah, M.A. El-Tayeb, Y.B. El-Badawi, G. Antranikian, A novel cyclodextrin glycosyltransferase from *alkaliphilic amphibacillus sp. NPST-10*: purification and properties, Int. J. Mol. Sci. 13 (8) (2012) 10505–10522.

[54] S.A. Ismail, Y.M. Ahmend, N.R. Mohammad, Production, purification and biochemical characteriztion of cyclodextrin glucanotransferase from *Bacillus cereus N1*. Egypt, J. Microbiol. 6 (2009) 370–377.

[55] J.L. Iyer, P. Shetty, J.S. Pai, Immobilisation of cyclodextrin glucanotransferase from *Bacillus circulans* ATCC 21783 on purified seasand, J. Ind. Microbiol. Biotechnol. 30 (1) (2003) 47–51.

[56] V. Jaitak, V.K. Kaul, Bandna, N. Kumar, B. Singh, L.S. Savergave, V.V. Jogdand, S. Nene, Simple and efficient enzymatic transglycosylation of stevioside by β-cyclodextrin glucanotransferase from *Bacillus firmus*, Biotechnol. Lett. 31 (9) (2009) 1415–1420.

[57] S. Jemli, Messaoud EBen, D. Ayadi-Zouari, B. Naili, B. Khemakhem, S. Bejar, A β-cyclodextrin glycosyltransferase from a newly isolated *Paenibacillus pabuli US132 strain*: purification, properties and potential use in bread-making, Biochem. Eng. J. 34 (1) (2007) 44–50.

[58] Y. Jiang, J. Zhou, R. Wu, F. Xin, W. Zhang, Y. Fang, J.F. Ma, W. Dong, M. Jiang, Heterologous expression of cyclodextrin glycosyltransferase from Paenibacillus macerans in *Escherichia coli* and its application in 2-O-α-D-glucopyranosyl-L-ascorbic acid production, BMC Biotechnol. 18 (1) (2018) 53–63.

[59] S.W. Jung, T.K. Kim, K.W. Lee, Y.H. Lee, Catalytic properties of β-cyclodextrin glucanotransferase from *Alkalophilic Bacillus sp. BL-12* and intermolecular transglycosylation of stevioside, Biotechnol. Bioproc. Eng. 12 (2007) 207–212.

[60] Y. Kang, S.K. Kim, H.K. Jun, Purification and characteristic of cyclodextrin glucanotransferase from *Paenibacillus sp. JK-12*, Nutraceuticals Food 7 (2002) 310–316.

[61] T. Kato, K. Horikoshi, Immobilized cyclomaltodextrin glucanotransferase of an alkalophilic *Bacillus sp.* No. 38-2, Biotechnol. Bioeng. 26 (6) (1984) 595–598.

[62] S. Kazuhisa, N. Takahisa, K. Takashi, Development of α -arbutin: production at industrial scale and application for a skin-lightning cosmetic ingredient, Trends Glycosci. Glycotechnol. 19 (110) (2007) 235–246.

[63] R.M. Kelly, L. Dijkhuizen, H. Leemhuis, The evolution of cyclodextrin glucanotransferase product specificity, Appl. Microbiol. Biotechnol. 84 (1) (2009) 119–133.

[64] M.H. Kim, C.B. Sohn, T.K. Oh, Cloning and sequencing of a cyclodextrin glycosyltransferase gene from *Brevibacillus brevis CD162* and its expression in *Escherichia coli*, FEMS Microbiol. Lett. 164 (2) (1998) 411–418.

[65] P.S. Kim, H.D. Shin, J.K. Park, Y.H. Lee, Immobilization of cyclodextrin glucanotransferase on amberlite IRA-900 for biosynthesis of transglycosylated xylitol, Biotechnol. Bioproc. Eng. 5 (2000) 174–180.

[66] Y.H. Kim, G.L. Lee, K.J. Choi, K. Uchida, Y. Suzuki, Transglucosylation to ginseng saponins by cyclomaltodextrin glucanotransferases, Biosci. Biotechnol. Biochem. 56 (4) (2001) 875–883.

[67] K. Kimura, S. Kataoka, Y. Ishii, T. Takano, K. Yamane, Nucleotide sequence of the beta-cyclodextrin glucanotransferase gene of alkalophilic Bacillus sp. strain 1011 and similarity of its amino acid sequence to those of alpha-amylases, J. Bacteriol. 169 (9) (1987) 4399–4402.

[68] S. Kitahata, K. Hara, K. Fujita, H. Nakano, N. Kuwahara, K. Koizumi, Acceptor specificity of cyclodextrin glycosyltransferase from Bacillus stearothermophilus

and synthesis of α-D-glucosyl O-β-D-galactosyl-(1→4)-β-D-glucoside, Biosci. Biotechnol. Biochem. 56 (9) (1992) 1386–1391.
[69] S. Kitahata, S. Okada, Action of cyclodextrin glycosyltransferase from *Bacillus megaterium strain No. 5* on starch, Agric. Biol. Chem. 38 (12) (1974) 2413–2417.
[70] T. Kitayska, P. Petrova, V. Ivanova, A.I. Tonkova, Purification and properties of a new thermostable cyclodextrin glucanotransferase from *Bacillus pseudalcaliphilus 8SB*, Appl. Biochem. Biotechnol. 165 (5–6) (2011) 1285–1295.
[71] C. Klein, J. Hollender, H. Bender, G.E. Schulz, Catalytic center of cyclodextrin glycosyltransferase derived from X-ray structure analysis combined with site-directed mutagenesis, Biochem. 31 (37) (1992) 8740–8746.
[72] C. Klein, G.E. Schulz, Structure of cyclodextrin glycosyltransferase refined at 2.0 Å resolutions, J. Mol. Biol. 217 (4) (1991) 737–750.
[73] R.M. Knegtel, R.D. Wind, H.J. Rozeboom, K.H. Kalk, R.M. Buitelaar, L. Dijkhuizen, B.W. Dijkstra, Crystal structure at 2.3 Å resolution and revised nucleotide sequence of the thermostable cyclodextrin glycosyltransferase from Thermoanaerobacterium thermosulfurigenes EM1, J. Mol. Biol. 256 (1996) 611–622.
[74] T. Kometani, Y. Terada, T. Nishimura, H. Takii, S. Okada, Purification and characterization of cyclodextrin glucanotransferase from an alkalophilic *bacillus* species and transglycosylation at alkaline pHs, Biosci. Biotechnol. Biochem. 58 (3) (1994a) 517–520.
[75] T. Kometani, Y. Terada, T. Nishimura, H. Takii, S. Okada, Transglycosylation to hesperidin by cyclodextrin glucanotransferase from an alkalophilic *bacillus* species in alkaline pH and properties of hesperidin glycosides, Biosci. Biotechnol. Biochem. 58 (11) (1994b) 1990–1994.
[76] V. Kren, J. Thiem, Glycosylation employing bio-systems: from enzymes to whole cells, Chem. Soc. Rev. 26 (1997) 463.
[77] M. Kubota, B. Mikami, Y. Tsujisaka, Y. Morita, Crystallization of and preliminary crystallographic data for *Bacillus stearothermophilus* cyclodextrin glucanotransferase, J. Biochem. 104 (1) (1988) 12–13.
[78] L.L. Lairson, B. Henrissat, G.J. Davies, S.G. Withers, Glycosyltransferases: structures, functions, and mechanisms, Annu. Rev. Biochem. 77 (1) (2008) 521–555.
[79] C.L. Lawson, R. van Montfort, B. Strokopytov, H.J. Rozeboom, K.H. Kalk, G.E. de Vries, D. Penninga, L. Dijkhuizen, B.W. Dijkstra, Nucleotide sequence and X-ray structure of cyclodextrin glycosyltransferase from *Bacillus circulans strain 251* in a maltose-dependent crystal form, J. Mol. Biol. 236 (1994) 590–600.
[80] M.H. Lee, S.J. Yang, J.W. Kim, H.S. Lee, J.W. Kim, K.H. Park, Characterization of a thermostable cyclodextrin glucanotransferase from *Pyrococcus furiosus DSM3638*, Extremophiles 11 (3) (2007) 537–541.
[81] S.L. Lee, W.C. Chen, Optimization of medium composition for the production of glucosyltransferase by *Aspergillus niger* with response surface methodology, Enzym. Microb. Technol. 21 (6) (1997) 436–440.
[82] Y.S. Lee, Y. Zhou, D.J. Park, J. Chang, Y.L. Choi, β-cyclodextrin production by the cyclodextrin glucanotransferase from *Paenibacillus illinoisensis* ZY-08: cloning, purification, and properties, World J. Microbiol. Biotechnol. 29 (5) (2013) 865–873.
[83] H. Leemhuis, R.M. Kelly, L. Dijkhuizen, Engineering of cyclodextrin glucanotransferases and the impact for biotechnological applications, Appl. Microbiol. Biotechnol. 85 (4) (2010) 823–835.
[84] H. Leemhuis, H.J. Rozeboom, M. Wilbrink, G.J.W. Euverink, B.W. Dijkstra, L. Dijkhuizen, Conversion of cyclodextrin glycosyltransferase into a starch hydrolase by directed evolution: the role of alanine 230 in acceptor subsite +1, Biochemistry 42 (24) (2003) 7518–7526.
[85] A. Lepak, A. Gutmann, S.T. Kulmer, B. Nidetzky, Creating a water-soluble resveratrol-based antioxidant by site-selective enzymatic glucosylation, Chembiochem 16 (13) (2015) 1870–1874.
[86] C. Li, H.J. Ahn, J.H. Kim, Y.W. Kim, Transglycosylation of engineered cyclodextrin glucanotransferases as O-glycoligases, Carbohydr. Polym. 99 (2014) 39–46.
[87] C. Li, X. Ban, Z. Gu, Z. Li, Calcium ion contribution to thermostability of cyclodextrin glycosyltransferase is closely related to calcium-binding site CaIII, J. Agric. Food Chem. 61 (37) (2013a) 8836–8841.
[88] D. Li, S.A. Roh, J.H. Shim, B. Mikam, M.Y. Baik, C.S. Park, K.H. Park, Glycosylation of genistin into soluble inclusion complex form of cyclic glucans by enzymatic modification, J. Agric. Food Chem. 53 (16) (2005) 6516–6524.
[89] S. Li, W. Li, Q.Y. Xiao, Y. Xia, Transglycosylation of stevioside to improve the edulcorant quality by lower substitution using cornstarch hydrolyzate and CGTase, Food Chem. 138 (2–3) (2013b) 2064–2069.
[90] Z.F. Li, J.Y. Zhang, Q. Sun, M. Wang, Z.B. Gu, G.C. Du, J. Wu, Jian Chen, Mutations of lysine 47 in cyclodextrin glycosyltransferase from *Paenibacillus macerans* enhance β-cyclodextrin specificity, J. Agric. Food Chem. 57 (18) (2009a) 8386–8391.
[91] Z.F. Li, J.Y. Zhang, M. Wang, Z.B. Gu, G.C. Du, J.K. Li, J. Wu, J. Che, Mutations at subsite −3 in cyclodextrin glycosyltransferase from *Paenibacillus macerans* enhancing α-cyclodextrin specificity, Appl. Microbiol. Biotechnol. 83 (3) (2009b) 483–490.
[92] M. Lindsay Rojas, J. Hellmeister Trevilin, P.E.D. Augusto, The ultrasound technology for modifying enzyme activity, Sci. Agropecu. 7 (2) (2016) 145–150.
[93] S.V. Lobov, R. Kasai, K. Ohtani, O. Tanaka, K. Yamasaki, Enzymic production of sweet stevioside derivatives: transglucosylation by glucosidases, Agric. Biol. Chem. 55 (12) (1991) 2959–2965.
[94] T. Makino, R. Shimizu, M. Kanemaru, Y. Suzuki, M. Moriwaki, H. Mizukami, Enzymatically modified isoquercitrin, α-oligoglucosyl quercetin 3-O-glucoside, is absorbed more easily than other quercetin glycosides or aglycone after oral administration in rats, Biol. Pharm. Bull. 32 (12) (2009) 2034–2040.
[95] A.A. Markosyan, L.A. Abelyan, A.I. Markosyan, V.A. Abelyan, Transglycosylation of benzo[h]quinazolines, Appl. Biochem. Microbiol. 45 (2) (2009) 130–136.
[96] M.T. Martin, M.A. Cruces, M. Alcalde, F.J. Plou, M. Bernabé, A. Ballesteros, Synthesis of maltooligosyl fructofuranosides catalyzed by immobilized cyclodextrin glucosyltransferase using starch as donor, Tetrahedron 60 (3) (2004) 529–534.
[97] M.T. Martin, F.J. Plou, M. Alcalde, A. Ballesteros, Immobilization on Eupergit C of cyclodextrin glucosyltransferase (CGTase) and properties of the immobilized biocatalyst, J. Mol. Catal. B Enzym. 21 (4-6) (2003) 299–308.
[98] R.F. Martins, R. Hatti-Kaul, A new cyclodextrin glycosyltransferase from an alkaliphilic *Bacillus agaradhaerens* isolate: purification and characterisation, Enzym. Microb. Technol. 30 (1) (2002) 116–124.
[99] S. Mathew, P. Adlercreutz, Cyclodextrin glucanotransferase (CGTase) catalyzed synthesis of dodecyl glucooligosides by transglycosylation using β-cyclodextrin or starch, Carbohydr. Polym. 87 (1) (2012) 574–580.
[100] S. Mathew, P. Adlercreutz, Regioselective glycosylation of hydroquinone to α-arbutin by cyclodextrin glucanotransferase from *Thermoanaerobacter sp*, Biochem. Eng. J. 79 (2013) 187–193.
[101] A. Miranda-Molina, S. Marquina-Bahena, A. López-Munguía, L. Álvarez, E. Castillo, Regioselective glucosylation of inositols catalyzed by *Thermoanaerobacter sp*, CGTase. Carbohydr. Res. 360 (2012) 93–101.
[102] C. Monthieu, A. Guibert, F.R. Taravel, R. Nardin, D. Combes, Purification and characterisation of polyglucosyl-fructosides produced by means of cyclodextrin glucosyl transferase, Biocatal. Biotransform. 21 (1) (2003) 7–15.
[103] S.S. Moon, H.J. Lee, R. Mathiyalagan, Y.J. Kim, D. Yang, D.Y. Lee, J.W. Min, Z. Jimenez, D.C. Yang, Synthesis of a novel α-glucosyl ginsenoside F1 by cyclodextrin glucanotransferase and its in vitro cosmetic applications, Biomolecules 8 (4) (2018) 142.
[104] S.S. More, R. Niraja, C. Evelyn, A.M. Byadgi, V. Shwetha, Mangaraj SDas, Isolation, purification and biochemical characterization of CGTase from *Bacillus halodurans*, Croat. J. Food Technol. Biotechnol. Nutr. 7 (1–2) (2012) 90–97.
[105] S. Mori, S. Hirose, T. Oya, S. Kitahata, Purification and properties of cyclodextrin glucanotransferase from *brevibacterium sp. no. 9605*, Biosci. Biotechnol. Biochem. 58 (11) (1994) 1968–1972.
[106] C. Moriwaki, G.L. Costa, R. Pazzetto, G.M. Zanin, F.F. Moraes, M. Portilho, G. Matioli, Production and characterization of a new cyclodextrin glycosyltransferase from *Bacillus firmus* isolated from Brazilian soil, Process Biochem. 42 (2007) 1384–1390.
[107] C. Moriwaki, L.R. Ferreira, J.R.T. Rodella, G. Matioli, A novel cyclodextrin glycosyltransferase from *Bacillus sphaericus strain 41*: production, characterization and catalytic properties, Biochem. Eng. J. 48 (1) (2009) 124–131.
[108] M. Munir, M. Nadeem, T.M. Qureshi, T.S.H. Leong, C.J. Gamlath, G.J.O. Martin, M. Ashokkumar, Effects of high pressure, microwave and ultrasound processing on proteins and enzyme activity in dairy systems-A review, Innov. Food Sci. Emerg. 57 (102192) (2019) 1–14.
[109] Y. Nakagawa, M. Takada, K. Ogawa, Y. Hatada, K. Horikoshi, Site-directed mutations in alanine 223 and Glycine 255 in the acceptor site of γ-cyclodextrin glucanotransferase from alkalophilic *Bacillus clarkii* 7364 affect cyclodextrin production, J. Biochem. 140 (3) (2006) 329–336.
[110] A. Nakamura, K. Haga, K. Yamane, The transglycosylation reaction of cyclodextrin glucanotransferase is operated by a ping-pong mechanism, FEBS Lett. 337 (1) (1994) 66–70.
[111] A. Nakamura, K. Haga, K. Yamane, Three histidine residues in the active center of cyclodextrin glucanotransferase from alkalophilic *Bacillus sp.* 1011: effects of the replacement on pH dependence and transition-state stabilization, Biochem. 32 (26) (1993) 6624–6631.
[112] N. Nakamura, K. Horikoshi, Purification and properties of cyclodextrin glycosyltransferase of an *alkalophilic Bacillus sp*, Agric. Biol. Chem. 40 (5) (1976) 935–941.
[113] H. Nakano, T. Kiso, K. Okamoto, T. Tomita, M.B. Abdul Manan, S. Kitahata, Synthesis of glycosyl glycerol by cyclodextrin glucanotransferases, J. Biosci. Bioeng. 95 (6) (2003) 583–588.
[114] H. Nakano, S. Kitahata, Y. Tominaga, Y. Kiku, K. Ando, Y. Kawashima, S. Takenishi, Syntheses of glucosides with trimethylolpropane and two related polyol moieties by cyclodextrin glucanotransferase and their esterification by lipase, J. Ferment. Bioeng. 73 (3) (1992) 237–238.
[115] S. Nazir, J.S. Soetikno, A.L. Ho, Antioxidant properties of polyphenol glycoside catalyzed by transglycosylation reaction of cyclodextrin glucanotransferase derived from *Trichoderma viride*, J. Food Biochem. (2018) 1–8.
[116] M. Nieto-Domínguez, L.I. de Eugenio, P. Peñalver, E. Belmonte-Reche, J.C. Morales, A. Poveda, J. Jiménez-Barbero, A. Prieto, F.J. Plou, M.J. Martínez, Enzymatic Synthesis of a novel neuroprotective hydroxytyrosyl glycoside, J. Agric. Food Chem. 65 (2017) 10526–10533.
[117] M. Nomoto, C.C. Chen, D.C. Sheu, Purification and characterization of cyclodextrin glucanotransferase from an alkalophilic bacterium of Taiwan, Agric. Biol. Chem. 50 (11) (1986) 2701–2707.
[118] W. O`BrienJr, Ultrasound-biophysics mechanisms, Prog. Biophys. Mol. Biol. 93 (1-3) (2007) 212–255.
[119] K. Ohtani, Y. Aikawa, H. Ishikawa, R. Kasai, S. Kitahata, K. Mizutani, S. Doi, M. Nakaura, O. Tanaka, Further study on the 1,4-α-transglucosylation of rubusoside, A sweet steviol-bisglucoside from *rubus suavissimus*, Agric. Biol. Chem. 55 (2) (1991) 449–453.
[120] K. Okada, H. Zhao, M. Izumi, S. Nakajima, N. Baba, Glucosylation of sucrose laurate with cyclodextrin glucanotransferase, Biosci. Biotechnol. Biochem. 71 (3) (2007) 826–829.
[121] D. Penninga, B. Strokopytov, H.J. Rozeboom, C.L. Lawson, B.W. Dijkstra, J. Bergsma, L. Dijkhuizen, Site-directed mutations in tyrosine 195 of cyclodextrin

glycosyltransferase from *Bacillus circulans* strain 251 affect activity and product specificity, Biochem. 34 (10) (1995) 3368–3376.
[122] D. Penninga, B.A. van der Veen, R.M.A. Knegtel, S.A.F.T. van Hijum, H.J. Rozeboom, K.H. Kalk, W. Dijkstra, L. Dijkhuizen, The raw starch binding somain of cyclodextrin glycosyltransferase from *Bacillus circulans strain 251*, J. Biol. Chem. 271 (51) (1996) 32777–32784.
[123] F. Plou, M. Martín, A.G. de Segura, M. Alcalde, A. Ballesteros, Glucosyltransferases acting on starch or sucrose for the synthesis of oligosaccharides, Can. J. Chem. 80 (6) (2002) 743–752.
[124] S. Prasert, P. Jintana, D. Nisarat, H.T. Nongporn, Purification and properties of CGTase from an alkaline-tolerant *Bacillus sp. PS304*, J. Sci. Soc. Thail. 23 (1997) 381–388.
[125] M.H. Prousoontorn, S. Pantatan, Production of 2-O-α-glucopyranosyl L-ascorbic acid from ascorbic acid and *β*-cyclodextrin using immobilized cyclodextrin glycosyltransferase, J. Inclusion Phenom. Macrocycl. Chem. 57 (1–4) (2007) 39–46.
[126] K.N. Rajput, K.C. Patel, U.B. Trivedi, A novel cyclodextrin glucanotransferase from an alkaliphile *Microbacterium terrae KNR 9*: purification and properties, 3 Biotech 6 (180) (2016a) 1–11.
[127] K.N. Rajput, K.C. Patel, U.B. Trivedi, *β* -cyclodextrin production by cyclodextrin glucanotransferase from *alkaliphile Microbacterium terrae KNR 9* using different starch substrates, Biotechnol. Res. Int. (2016b) 1–7.
[128] N. Rashid, J. Cornista, S. Ezaki, T. Fukui, H. Atomi, T. Imanaka, Characterization of an archaeal cyclodextrin glucanotransferase with a novel C-terminal domain, J. Bacteriol. 184 (3) (2002) 777–784.
[129] M.Y. Rather, K.Z.G. Ara, E. Nordberg Karlsson, P. Adlercreutz, Characterization of cyclodextrin glycosyltransferases (CGTases) and their application for synthesis of alkyl glycosides with oligomeric head group, Process Biochem. 50 (5) (2015) 722–728.
[130] D.V. Ratnam, D.D. Ankola, V. Bhardwaj, D.K. Sahana, M.N.V.R. Kumar, Role of antioxidants in prophylaxis and therapy: a pharmaceutical perspective, J. Contr. Release 113 (3) (2006) 189–207.
[131] B. Rejasse, S. Lamare, M.D. Legoy, T. Besson, Influence of microwave irradiation on enzymatic properties: applications in enzyme chemistry, J. Enzym. Inhib. Med. Chem. 22 (5) (2007) 519–527.
[132] V. Sangwan, S.K. Tomar, B. Ali, R.R.B. Singh, A.K. Singh, Production of *β*-galactosidase from *streptococcus thermophilus* for galactooligosaccharides synthesis, J. Food Sci. Technol. 52 (7) (2014) 4206–4215.
[133] K. Sarma, N. Borthakur, A. Goswami, A rapid 1,2-dihydroxylation of alkenes using a lipase and hydrogen peroxide under microwave conditions, Tetrahedron Lett. 48 (38) (2007) 6776–6778.
[134] M. Sato, T. Matsuo, N. Orita, Y. Yagi, Synthesis of novel sugars, oligoglucosyl-inositols, and their growth stimulating effect for Bifidobacterium, Biotechnol. Lett. 13 (2) (1991) 69–74.
[135] J. Seibel, R. Beine, R. Moraru, C. Behringer, K. Buchholz, A new pathway for the synthesis of oligosaccharides by the use of non-Leloir glycosyltransferases, Biocatal. Biotransform. 24 (1-2) (2006) 157–165.
[136] K.D.R. Setchell, N.M. Brown, L. Zimmer-Nechemias, W.T. Brashear, B.E. Wolfe, A.S. Kirschner, J.E. Heubi, Evidence for lack of absorption of soy isoflavone glycosides in humans, supporting the crucial role of intestinal metabolism for bioavailability, Am. J. Clin. Nutr. 76 (2) (2002) 447–453.
[137] K. Shimoda, M. Akagi, H. Hamada, Production of *β*-maltooligosaccharides of α- and δ-tocopherols by *klebsiella pneumoniae* and cyclodextrin glucanotransferase as anti-allergic agents, Molecules 14 (8) (2009) 3106–3114.
[138] K. Shimoda, H. Hamada, H. Hamada, Chemo-enzymatic synthesis of ester-linked taxol-oligosaccharide conjugates as potential prodrugs, Tetrahedron Lett. 49 (4) (2008a) 601–604.
[139] K. Shimoda, H. Hamada, Production of hesperetin glycosides by Xanthomonas campestris and cyclodextrin glucanotransferase and their anti-allergic activities, Nutrients 2 (2) (2010a) 171–180.
[140] K. Shimoda, H. Hamada, Synthesis of *β*-maltooligosaccharides of glycitein and daidzein and their anti-oxidant and anti-allergic activities, Molecules 15 (2010b) 5153–5161.
[141] K. Shimoda, H. Hamada, Enzymatic synthesis and anti-allergic activities of curcumin oligosaccharides, Biochem. Insights 3 (2010c) 1–4.
[142] K. Shimoda, T. Kobayashi, M. Akagi, H. Hamada, H. Hamada, Synthesis of oligosaccharides of genistein and quercetin as potential anti-inflammatory agents, Chem. Lett. 37 (8) (2008b) 876–877.
[143] K. Shimoda, N. Kubota, M. Akagi, Synthesis of capsaicin oligosaccharides and their anti-allergic activity—synthesis of capsaicin oligosaccharides as anti-allergic food-additives, Adv. Chem. Eng. Sci. 2 (1) (2012) 45–49.
[144] H.K. Sian, M. Said, O. Hassan, K. Kamaruddin, A.F. Ismail, R.A. Rahman, N.A.N. Mahmood, R.M. Illias, Purification and characterization of cyclodextrin glucanotransferase from *alkalophilic Bacillus sp. G1*, Process Biochem. 40 (3–4) (2005) 1101–1111.
[145] K.A. Sin, A. Nakamura, H. Masaki, Y. Matsuura, T. Uozumi, Replacement of an amino acid residue of cyclodextrin glucanotransferase of *Bacillus ohbensis* doubles the production of y-cyclodextrin, J. Biotechnol. 32 (3) (1994) 283–288.
[146] R. Singh, M. Kumar, A. Mittal, P.K. Mehta, Microbial enzymes: industrial progress in 21st century, 3 Biotech. 6 (2) (2016) 1–15.
[147] J. Steighardt, R. Kleine, Production and immobilization of a proteinase-reduced cyclodextrin glycosyltransferase preparation, Appl. Microbiol. Biotechnol. 39 (1) (1993) 63–68.
[148] B. Strokopytov, R.M. Knegtel, D. Penninga, H.J. Rozeboom, K.H. Kalk, L. Dijkhuizen, B.W. Dijkstra, Structure of cyclodextrin glycosyltransferase complexed with a maltononaose inhibitor at 2.6 angstrom resolution. Implications for product specificity, Biochem. 35 (1996) 4241–4249.
[149] S. Strompen, A. Miranda-Molina, A. López-Munguía, E. Castillo, G. Saab-Rincón, Acceptor-induced modification of regioselectivity in CGTase-catalyzed glycosylations of p-nitrophenyl-glucopyranosides, Carbohydr. Res. 404 (2015) 46–54.
[150] D. Svensson, P. Adlercreutz, Immobilisation of CGTase for continuous production of long-carbohydrate-chain alkyl glycosides. Control of product distribution by flow rate adjustment, J. Mol. Catal. B Enzym. 69 (2011) 147–153.
[151] D. Svensson, S. Ulvenlund, P. Adlercreutz, Efficient synthesis of a long carbohydrate chain alkyl glycoside catalyzed by cyclodextrin glycosyltransferase (CGTase), Biotechnol. Bioeng. 104 (5) (2009a) 854–861.
[152] D. Svensson, S. Ulvenlund, P. Adlercreutz, Enzymatic route to alkyl glycosides having oligomeric head groups, Green Chem. 11 (8) (2009b) 1222–1226.
[153] Y. Tachibana, Y. Suzuki, T. Yamamoto, S. Fujiwara, Purification and characterization of an extremely thermostable cyclomaltodextrin glucanotransferase from a newly isolated purification and characterization of an extremely thermostable cyclomaltodextrin glucanotransferase from a newly isolated hyperthermophilic archaeon, a *Thermococcus sp*, Appl. Environ. Microbiol. 65 (5) (1999) 1991–1997.
[154] A. Tai, Y. Iwaoka, H. Ito, Highly efficient and regioselective production of an erythorbic acid glucoside using cyclodextrin glucanotransferase from *Thermoanaerobacter sp.* and amyloglucosidase, J. Mol. Catal. B Enzym. 92 (2013) 19–23.
[155] P.W. Tardioli, G.M. Zanin, F.F.D. Moraes, Production of cyclodextrins in a fluidized-bed reactor using cyclodextrin-glycosyl-transferase, Appl. Biochem. Biotechnol. 84–86 (1-9) (2000) 1003–1019.
[156] V. Thiemann, C. Dönges, S.G. Prowe, R. Sterner, G. Antranikian, Characterisation of a thermoalkali-stable cyclodextrin glycosyltransferase from the anaerobic thermoalkaliphilic bacterium *Anaerobranca gottschalkii*, Arch. Microbiol. 182 (2–3) (2004) 226–235.
[157] K. Tomita, M. Kaneda, K. Kawamura, K. Nakanishi, Purification and properties of a cyclodextrin glucanotransferase from *Bacillus autolyticus 11149* and selective formation of beta-cyclodextrin, J. Ferment. Bioeng. 75 (2) (1993) 89–92.
[158] A. Tonkova, Bacterial cyclodextrin glucanotransferase, Enzym. Microb. Technol. 22 (8) (1998) 678–686.
[159] P. Torres, A. Poveda, J. Jimenez-Barbero, J.L. Parra, F. Comelles, A.O. Ballesteros, F.J. Plou, Enzymatic synthesis of α-glucosides of resveratrol with surfactant activity, Adv. Synth. Catal. 353 (7) (2011) 1077–1086.
[160] J.C.M. Uitdehaag, G.J.W.M. Van Alebeek, B.A. Van Der Veen, L. Dijkhuizen, B.W. Dijkstra, Structures of maltohexaose and maltoheptaose bound at the donor sites of cyclodextrin glycosyltransferase give insight into the mechanisms of transglycosylation activity and cyclodextrin size specificity, Biochem. 39 (26) (2000) 7772–7780.
[161] C. Urbach, S. Halila, C. Guerreiro, H. Driguez, L.A. Mulard, S. Armand, CGTase-catalysed cis-glucosylation of L-rhamnosides for the preparation of shigella flexneri 2a and 3a Haptens, Chembiochem 15 (2) (2014) 293–300.
[162] B.A. Van der Veen, H. Leemhuis, S. Kralj, J.C.M. Uitdehaag, B.W. Dijkstra, L. Dijkhuizen, Hydrophobic amino acid residues in the acceptor binding site are main determinants for reaction mechanism and specificity of cyclodextrin-glycosyltransferase, J. Biol. Chem. 276 (48) (2001) 44557–44562.
[163] B.A. Van der Veen, J.C.M. Uitdehaag, B.W. Dijkstra, L. Dijkhuizen, The role of arginine 47 in the cyclization and coupling reactions of CGTase from *Bacillus circulans* strain 251. Implications for product inhibition and product specificity, Eur. J. Biochem. 267 (12) (2000a) 3432–3441.
[164] B.A. Van Der Veen, J.C.M. Uitdehaag, D. Penninga, G.J.W.M. Van Alebeek, L.M. Smith, B.W. Dijkstra, L. Dijkhuizen, Rational design of cyclodextrin glycosyltransferase from *Bacillus circulans strain 251* to increase α-cyclodextrin production, J. Mol. Biol. 296 (4) (2000b) 1027–1038.
[165] B.A. Van Der Veen, G.J.W.M. Van Alebeek, J.C.M. Uitdehaag, B.W. Dijkstra, L. Dijkhuizen, The three transglycosylation reactions catalyzed by cyclodextrin glycosyltransferase from *Bacillus circulans* (strain 251) proceed via different kinetic mechanisms, Eur. J. Biochem. 267 (3) (2000c) 658–665.
[166] L.H.M. Vargas, A.C.S. Pião, R.N. Domingos, E.C. Carmona, Ultrasound effects on invertase from *Aspergillus niger*, World J. Microbiol. Biotechnol. 20 (2) (2004) 137–142.
[167] A. Vassileva, N. Atanasova, V. Ivanova, P. Dhulster, A. Tonkova, Characterisation of cyclodextrin glucanotransferase from *Bacillus circulans* ATCC 21783 in terms of cyclodextrin production, Ann. Microbiol. 57 (4) (2007) 609–615.
[168] I.F.D.S. Videira, D.F.L. Moura, S. Magina, Mechanisms regulating melanogenesis, An. Bras. Dermatol. 88 (1) (2013) 76–83.
[169] J. Vrba, V. Kren, J. Vacek, B. Papouskova, J. Ulrichova, Quercetin, quercetin glycosides and taxifolin differ in their ability to induce AhR activation and CYP1A1 expression in HepG2 cells, Phytother Res. 26 (11) (2012) 1746–1752.
[170] L. Wang, Z. Yang, F. Lu, J. Liu, Y. Song, D. Li, Cucurbitane glycosides derived from mogroside IIE: structure-taste relationships, antioxidant activity, and acute toxicity, Molecules 19 (8) (2014) 12676–12689.
[171] L.X. Wang, W. Huang, Enzymatic transglycosylation for glycoconjugate synthesis, Curr. Opin. Chem. Biol. 13 (5–6) (2009) 592–600.
[172] Q. Wang, J.S. Dordick, R.J. Linhardt, Synthesis and application of carbohydrate-containing Polymers, Chem. Mater. 14 (2002) 3232–3244.
[173] Y. Wang, B. Feng, H. Huang, L. Kang, Y. Cong, W. Zhou, P. Zou, Y. Cong, X. Song, B. Ma, Glucosylation of steroidal saponins by cyclodextrin glucanotransferase, Planta Med. 76 (15) (2010) 1724–1731.
[174] C.A. Weijers, M.C. Franssen, G.M. Visser, Glycosyltransferase-catalyzed synthesis of bioactive oligosaccharides, Biotechnol. Adv. 26 (5) (2008) 436–456.

[175] R.D. Wind, W. Liebl, R.M. Buitelaar, D. Penninga, A. Spreinat, L. Dijkhuizen, H. Bahl, Cyclodextrin formation by the thermostable α-amylase of *Thermoanaerobacterium thermosulfurigenes EM1* and reclassification of the enzymes as a glycosyl transferase, Appl. Environ. Microbiol. 61 (4) (1995) 1257–1265.

[176] R.D. Wind, J.C.M. Uitdehaag, R.M. Buitelaar, B.W. Dijkstra, L. Dijkhuizen, Engineering of cyclodextrin product specificity and pH optima of the thermostable cyclodextrin glycosyltransferase from *Thermoanaerobacterium thermosulfurigenes EM1*, J. Biol. Chem. 273 (10) (1998) 5771–5779.

[177] U. Wolwer-Rieck, The leaves of Stevia rebaudiana (Bertoni), their constituents and the analyses thereof: a review, J. Agric. Food Chem. 60 (4) (2012) 886–895.

[178] L. Xu, T. Qi, L. Xu, L. Lu, M. Xiao, Recent progress in the enzymatic glycosylation of phenolic compounds, J. Carbohydr. Chem. 35 (1) (2016) 1–23.

[179] S. Yadav, S. Yadava, K.D.S. Yadav, Purification and characterization of α-l-rhamnosidase from *Penicillium corylopholum* MTCC-2011, Process Biochem. 48 (9) (2013) 1348–1354.

[180] D.G. Yim, H.H. Sato, Y.H. Park, Y.K. Park, Production of cyclodextrin from starch by cyclodextrin glycosyltransferase from *Bacillus firmus* and characterization of purified enzyme, J. Ind. Microbiol. Biotechnol. 18 (6) (1997) 402–405.

[181] S.H. Yoon, J.F. Robyt, Addition of maltodextrins to the nonreducing-end of acarbose by reaction of acarbose with cyclomaltohexaose and cyclomaltodextrin glucanyltransferase, Carbohydr. Res. 337 (6) (2002) 509–516.

[182] S. Yoshikawa, Y. Murata, M. Sugiura, T. Kiso, M. Shizuma, S. Kitahata, H. Nakano, Transglycosylation of mogroside V, a triterpene glycoside in siraitia grosvenori, by cyclodextrin glucanotransferase and improvement of the qualities of sweetness, J. Appl. Glycosci. 52 (2005) 247–252.

[183] K. Yoshinaga, J.I. Abe, T. Tanimoto, K. Koizumi, S. Hizukuri, Preparation and reactivity of a novel disaccharide, glucosyl 1,5-anhydro-D-fructose (1,5-anhydro-3-O-α-glucopyranosyl-D-fructose), Carbohydr. Res. 338 (21) (2003) 2221–2225.

[184] X. Yu, J. Yang, B. Li, H. Yuan, High efficiency transformation of stevioside into a single mono-glycosylated product using a cyclodextrin glucanotransferase from *Paenibacillus sp.* CGMCC 5316, World J. Microbiol. Biotechnol. 31 (12) (2015) 1983–1991.

[185] Z.C. Zhang, J.H. Li, L. Liu, J. Sun, Z.Z. Hua, G.C. Du, J. Chen, Enzymatic transformation of 2-O-α-D-glucopyranosyl-L-ascorbic acid (AA-2G) by immobilized α-cyclodextrin glucanotransferase from recombinant *Escherichia coli*, J. Mol. Catal. B Enzym. 68 (3-4) (2011) 223–229.