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Original Article

Bioinformatics analysis and pharmacological effect of *Stevia rebaudiana* in the prevention of type-2 diabetes

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ABSTRACT

Different groups of enzymes and regulatory elements are involved in the synthesis of Ribodioside A, which is one of the most important sweetening compounds in stevia. The UGT family (UDP-glycosyltransferase) is a group of regulatory genes that are very effective in converting steviol glycoside to Ribodioside A. Bioinformatics analyses on this gene family, which included the *UGT74G1*, *UGT76G1*, and *UGT85C2* genes, showed that the protein encoded by these genes had a UDPGT protected protein domain. Also, the study of the secondary structure of these proteins showed that the total corrosion of these proteins is mainly from alpha-helix and random screws or loops that are connected with linear strands. Also, the study of the secondary structure of these proteins showed that the total corrosion of these proteins is mainly from alpha-helix and random screws or loops that are connected with linear strands. The results of studying the three-dimensional structure of the studied proteins confirmed the previous findings of high genomic similarity between these proteins. The results of the ProtScale program showed that the abundance of amino acids with negative hydropathicity in the sequence of these proteins is high, which is effective in creating plant resistance to drought stress. Finally, the codon preference trend of these proteins was investigated using the sequence manipulation suite database. This information can be used for other research, including the transfer of these proteins.

1. Introduction

Sweeteners are compounds that have sweetening properties and are divided into two categories of natural and artificial sweeteners[1]. In recent years, the development of natural sweeteners has greatly increased, especially natural sweeteners containing sucrose that is not absorbed in the digestive system and is not caloric, and are suitable for diabetes and obese people [2-4]. One of these promising natural sweeteners is steviol glycosides (SGs). SGs are extracted from stevia leaves. Steviosides and ribodioside A are most abundant in leaf extract[5].

SGs are glycoside diterpene and have been identified in the extract of various components of the stevia plant body and contain various compounds[6]. Among these compounds, ribodiozide A is more commercially important and the UGT family (UDP-glycosyltransferase) and especially the genes *UGT85C2*, *UGT74G1*, and *UGT76G1* play an effective role in the conversion of SGs to ribodioside A [7]. Figure 1 shows the common skeletal structure of stevia glycosides with the structure of ribodioside A [8, 9]. In Stevia, in addition to Rebaudioside A, there are other types of Rebaudioside, such as Rebaudioside E, Rebaudioside D and Rebaudioside M [10,

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11]. *UGT76G1* is a key enzyme in the production of Rebaudioside. Research has shown that a single-point saturation mutation in the *UGT76G1* gene converts Rebaudioside M to Rebaudioside E, which improves its performance and sweetening properties by 2 times [12].

So far, more than 60 different steviolglycosyl and 68 different putative *UGTs* have been identified in stevia rebaudiana, which helps us better understand this key family in improving the sweetening properties of this plant [13]. The latest medical research has shown that blood sugar can be treated with the use of stevia. It has also been found that the therapeutic effects of this plant are due to the presence of phenolic compounds in different parts of this plant, especially in the leaves and calluses, and have considered anti-cancer effects and treatment of diseases related to hypertension and hypoglycemia due to their free radical scavenging and antioxidant properties[14, 15]. Studies have shown that stevia has an antiviral effect, prevents high blood pressure and blood sugar, and is beneficial for patients with diabetes. Clinical trials have shown that the use of this plant and its extract as a real medicine is effective for patients with hypoglycemia.[16-18]. This study aimed to compare the encoded regions, study the similarities and differences, and bioinformatics of *UGT85C2*, *UGT74G1*, and *UGT76G1* genes in stevia to identify possible differences related to different reactions.

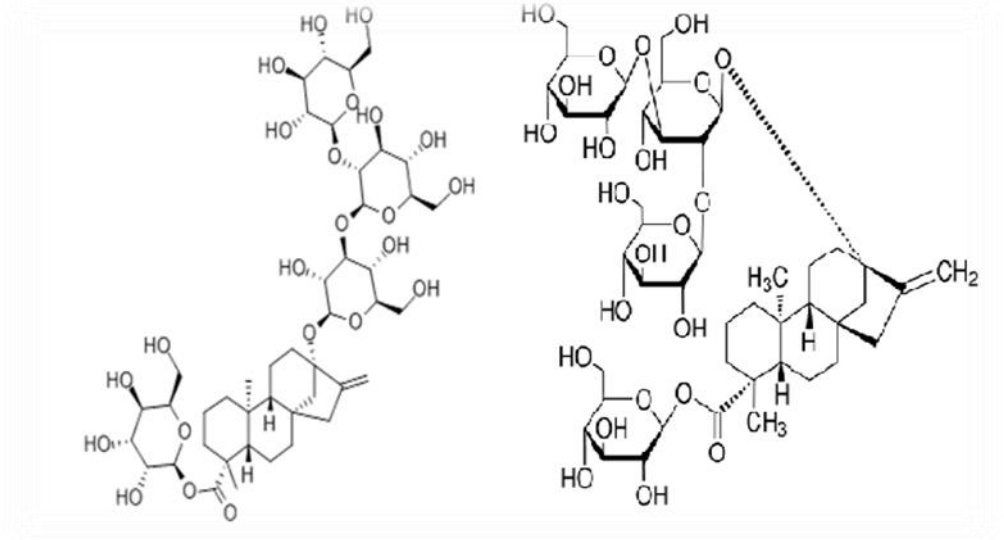

Fig. 1. The image on the right shows the common skeleton structure of stevia glycosides and the image on the left shows the chemical structure of ribodioside A.

2. Materials and methods

First, the protein sequences of *UGT85C2* (AY345978.1), *UGT76G1* (KC631816.1), and *UGT74G1* (AY345982.1) genes in stevia were obtained from NCBI (http://www.ncbi.nlm.nih.gov/). The lengths of these proteins were 528, 538, and 518 amino acids, respectively. Then these sequences were aligned using Vector-NTI software and protein domains in amino acid sequences of genes were identified using the Pfam database. The secondary protein structure of each sequence was determined using the SOPMA database and the three-dimensional structure of the proteins was determined using the MBC database. Hydropathicity analysis and determination of molecular weight and isoelectric point of proteins were performed using the ProtScale database. The codon preference trend of these proteins was investigated using the sequence manipulation suite database. Then the promoter region of the genes was analyzed using the PlantCARE database to identify putative CREs.

3. Results

The sequential results of protein sequences of *UGT85C2* (AY345978.1), *UGT76G1* (AY345974.1), and *UGT74G1* (AY345982.1) genes in stevia showed that these sequences are very similar in primary structures Table 1. The percentage similarity of amino acid sequences is shown in Table 2.

Table 1. Genes sequence results of *UGT85C2*, *UGT76G1*, and *UGT74G1* in stevia rebaudiana

Name	ORGANISM	Gene ID	creation location in cellular organ	Accession number nucleotide	Accession number protein	Nucleotide length	Protein length
UGT74G1	Stevia rebaudiana	37993668	leaf	AY345982.1	AAR06920.1	1555 bp	460aa
UGT76G1	Stevia rebaudiana	37993652	leaf	AY345974.1	AAR06912.1	1616 bp	458aa
UGT85C2	Stevia rebaudiana	37993660	leaf	AY345978.1	AAR06916.1	1586 bp	481aa

Table 2. Percentage similarity of *UGT85C2*, *UGT76G1*, and *UGT74G1* amino acid sequences using Vector-NTI software.

	UGT74G1	*UGT76G1*	*UGT85C2*
UGT74G1		49	49.7
UGT76G1			47.9
UGT85C2			

3.1. Secondary structure

Search results on the Pfam database indicate the presence of a common UDPGT protein domain in the *UGT85C2*, *UGT76G1*, and *UGT74G1* sequences, indicating that the UDPGT protein domain is highly conserved in the UGT family. Also, the secondary structure of these sequences was very close to each other. Studies from the SOPMA database have shown that *UGT74G1*, *UGT76G1*, and *UGT85C2* proteins are generally alpha-helix and random screws or loops associated with linear strands. Also, these proteins contain beta-helix, which effectively stabilizes the structure of these proteins.

3.2. Three-dimensional structure

Molecular homologation modeling using SWISS-MODEL server in Expasy resulted in a three-dimensional structure of *UGT85C2*, *UGT76G1*, and *UGT74G1* proteins based on sample 1a02 with the highest similarity, which these results it was consistent with previous findings of the high genomic similarity of these proteins (Figure 2).

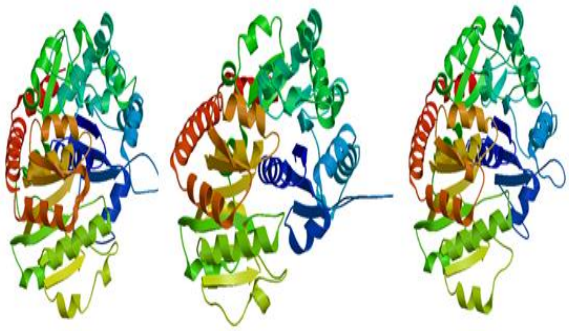

Fig. 2. The image on the right shows the three-dimensional structure of the *UGT74G1* protein, the middle image shows the three-dimensional structure of the *UGT76G1* protein, and the image on the left shows the three-dimensional structure of the *UGT85C2* protein.

3.3. Molecular weight, Isoelectric point and Hydropathicity

Also, determine the molecular weight (kDa), isoelectric point and hydropathicity analysis of these amino acid sequences were performed using the ProtScale program (Table 3). It was also found that due to the abundance of amino acids with negative hydropathicity in the sequences of *UGT85C2*, *UGT76G1*, and *UGT74G1*, these proteins are hydrophilic and are effective in creating resistance to drought stress.

Table 3. Determination of molecular weight (kDa), isoelectric point, and hydropathicity evaluation of *UGT85C2*, *UGT76G1*, and *UGT74G1* proteins using the ProtScale program.

	Molecular weight (kDa)	Isoelectric point	Hydropathicity min	Hydropathicity max
UGT74G1	41/51	91/5	889/2–	211/2
UGT76G1	04/52	28/6	589/2–	000/2
UGT85C2	47/54	24/6	867/2–	844/1

3.4. Analysis of *UGTs* promoter

A different group of transcription factors and their cis-element regulators have been determined in response to stress. The promoter region of the *UGTs* gene was analyzed using the PlantCARE database to identify putative CREs. A total of 89 CREs from 29 different types within the *UGT74G1* promoter sequence, 79 CREs from 27 different types within the *UGT76G1* promoter sequence and 106 CREs from 24 different types within the *UGT85C2* promoter sequence were identified (Table 4-6). *UGTs* promoter contained several hormone-responsive CREs associated with activity and regulation of abscisic acid and auxin implying that *UGTs* may be involved in hormone crosstalk. Moreover, a number of putative CREs involved in tissue-specificity, endosperm, and light response were found in the *UGTs* promoter. The existence of cis-acting elements involved in light responsiveness shows that the *UGTs* genes can reduce evapotranspiration by reducing light contact with stomata by reducing leaf area and thus increasing drought stress resistance in plants. Also, CREs related to responses to salinity stress (MeJA motifs like the CGTCA-motif and TGACG-motif) were detected in the *UGTs* promoter, indicating that the gene is involved in plant responses to salinity stress.

Table 4. The most important cis-elements in the promoter region of the *UGT74G1* gene in *Stevia rebaudiana*

CRE	sequence	Number of occurrences	Function
ABRE	ACGTG	2	cis-acting element involved in the abscisic acid responsiveness
AAAC-motif	CAATCAAAACCT	1	light-responsive element
ARE	AAACCA	3	cis-acting regulatory element essential for the anaerobic induction
AT-rich element	ATAGAAATCAA	1	binding site of AT-rich DNA binding protein (ATBP-1)
AuxRR-core	GGTCCAT	1	cis-acting regulatory element involved in auxin responsiveness
Box 4	ATTAAT	2	part of a conserved DNA module involved in light responsiveness
CAAT-box	CAAT CCAAT CAAAT	19 2 7	common cis-acting element in promoter and enhancer regions
CCAAT-box	CAACGG	2	MYBHv1 binding site
CGTCA-motif	CGTCA	1	cis-acting regulatory element involved in the MeJA-responsiveness
G-Box	CACGTT	2	cis-acting regulatory element involved in light responsiveness
LAMP-element	CTTTATCA	1	part of a light-responsive element
LTR	CCGAAA	4	cis-acting element involved in low-temperature responsiveness
MBS	CAACTG	1	MYB binding site involved in drought-inducibility
TATA-box	TATAAA ATATAA TATAA TATA	1 1 2 3	core promoter element around -30 of transcription start
TATC-box	TATCCCA	1	cis-acting element involved in gibberellin-responsiveness
TCA-element	TCAGAAGAGG	1	cis-acting element involved in salicylic acid responsiveness
TGA-element	AACGAC	1	auxin-responsive element
TGACG-motif	TGACG	1	cis-acting regulatory element involved in the MeJA-responsiveness
circadian	CAAAGATATC	1	cis-acting regulatory element involved in circadian control

Table 5. The most important cis elements in the promoter region of the *UGT76G1* gene in *Stevia rebaudiana*

CRE	sequence	Number of occurrences	Function
ABRE	ACGTG	1	cis-acting element involved in the abscisic acid responsiveness
ACE	GCGACGTACC	2	cis-acting element involved in light responsiveness
AE-box	AGAAACTT	2	part of a module for light response
ARE	AAACCA	1	cis-acting regulatory element essential for the anaerobic induction
Box 4	ATTAAT	1	part of a conserved DNA module involved in light responsiveness
CAAT-box	CAAT	11	common cis-acting element in promoter and enhancer regions
	CCAAT	4	
	CAAAT	5	
CCAAT-box	CAACGG	2	MYBHv1 binding site
CGTCA-motif	CGTCA	2	cis-acting regulatory element involved in the MeJA-responsiveness
G-box	CACGTC	1	cis-acting regulatory element involved in light responsiveness
GARE-motif	TCTGTTG	1	gibberellin-responsive element
GT1-motif	GGTTAAT	1	light-responsive element
	GGTTAA	1	
P-box	CCTTTTG	1	gibberellin-responsive element
TATA-box	CCTATAAAAA	1	core promoter element around -30 of transcription start
	TATA	1	
	TACAAAA	1	
TCT-motif	TCTTAC	2	part of a light-responsive element
TGA-element	AACGAC	2	auxin-responsive element
TGACG-motif	TGACG	1	cis-acting regulatory element involved in the MeJA-responsiveness

Table 6. The most important cis-elements in the promoter region of the *UGT85C2* gene in *Stevia rebaudiana*

CRE	sequence	Number of occurrences	Function
ABRE	ACGTG	1	cis-acting element involved in the abscisic acid responsiveness
	AACCCGG	1	
	ACGTG	1	
ARE	AAACCA	3	cis-acting regulatory element essential for the anaerobic induction
CAAT-box	CAAT	21	common cis-acting element in promoter and enhancer regions
	CCAAT	5	
	CAAAT	6	
CAT-box	GCCACT	1	cis-acting regulatory element related to meristem expression
CGTCA-motif	CGTCA	5	cis-acting regulatory element involved in the MeJA-responsiveness
G-box	CACGTC	1	cis-acting regulatory element involved in light responsiveness
G-box	CACGTC	1	cis-acting regulatory element involved in light responsiveness
GATA-motif	GATAGGG	1	part of a light-responsive element
GCN4_motif	TGAGTCA	1	cis-regulatory element involved in endosperm expression
I-box	GTATAAGGCC	1	part of a light-responsive element
	AAGATAAGGCT	1	
MBS	CAACTG	1	MYB binding site involved in drought-inducibility
O2-site	GATGA(C/T) (A/G)TG(A/G)	1	cis-acting regulatory element involved in zein metabolism regulation
TATA-box	ATTATA	2	core promoter element around -30 of transcription start
	ATATAA	1	
	TATA	4	
	TATAA	1	
	TAAAGATT	1	
	TATATA	1	
	TACATAAA	1	
TGA-element	AACGAC	1	auxin-responsive element
TGACG-motif	TGACG	4	cis-acting regulatory element involved in the MeJA-responsiveness

3.5. Phylogenetic tree

Analysis of the phylogenetic tree of the *UGTs* family showed that genes *UGT74G1* and *UGT85C2* are most similar. Also, the similarity of *UGTs* genes in stevia is much greater than the genes of this family in other plants such as *Triticum aestivum* (Figure 3).

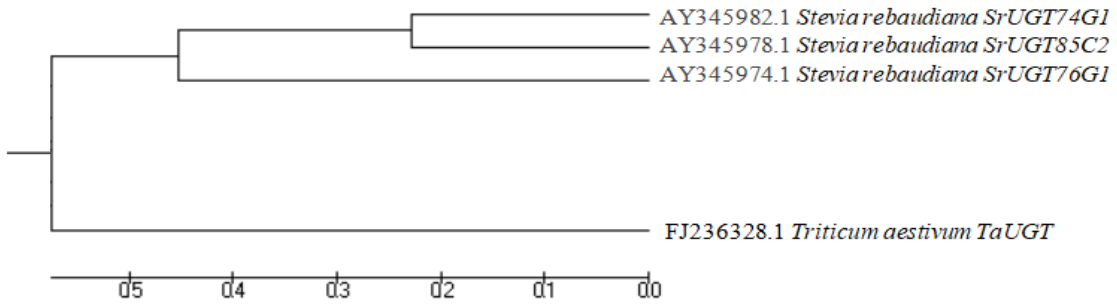

Fig. 3. Neighbour-joining phylogenetic tree based on aligned amino acid sequences deduced from *SrUGT74G1*, *SrUGT76G1*and *SrUGT85C2* genes from *Stevia rebaudiana* and *Triticum aestivum TaUGT*. Values at the nodes indicate bootstrap support (%) out of 1000 replicates.

3.6. Codon usage

The codon preference trend of these proteins was investigated using the sequence manipulation suite database, the results for *UGT85C2*, *UGT76G1*, and *UGT74G1* genes are shown in the Table 7 to 9. This information can be used for other research, including transferring these proteins. Also, we can use codon usage to assess whether a sequence shows a preference for particular synonymous codons (Table 7-9).

Table 7. Results of codon usage for gene *UGT74G1* (Results for 1555 residue sequence " *UGT74G1*" starting "ATGGCGGAAC")

AmAcid	Codon	Number	/1000	Fraction	AmAcid	Codon	Number	/1000	Fraction	AmAcid	Codon	Number	/1000	Fraction
Ala	GCG	3	5.79	0.12	Asn	AAT	13	25.1	0.54	Lys	AAG	19	36.68	0.49
Ala	GCA	12	23.1	0.48	Asn	AAC	11	21.24	0.46	Lys	AAA	20	38.61	0.51
Ala	GCT	8	15.4	0.32	Pro	CCG	1	1.93	0.06	Leu	TTG	15	28.96	0.29
Ala	GCC	2	3.86	0.08	Pro	CCA	8	15.44	0.47	Leu	TTA	14	27.03	0.27
Cys	TGT	5	9.65	0.56	Pro	CCT	6	11.58	0.35	Leu	CTG	1	1.93	0.02
Cys	TGC	4	7.72	0.44	Pro	CCC	2	3.86	0.12	Leu	CTA	7	13.51	0.13
Asp	GAT	20	38.6	0.8	Gln	CAG	5	9.65	0.26	Leu	CTT	11	21.24	0.21
Asp	GAC	5	9.65	0.2	Gln	CAA	14	27.03	0.74	Leu	CTC	4	7.72	0.08
Glu	GAG	12	23.1	0.33	Arg	AGG	0	0	0	Met	ATG	11	21.24	1
Glu	GAA	24	46.33	0.67	Arg	AGA	6	11.58	0.46	Tyr	TAC	4	7.72	0.33
Phe	TTT	19	36.68	0.7	Arg	CGG	3	5.79	0.23	Trp	TGG	10	19.31	1
Phe	TTC	8	15.44	0.3	Arg	CGA	3	5.79	0.23	Thr	ACA	10	19.31	0.37
Gly	GGG	4	7.72	0.12	Arg	CGT	1	1.93	0.08	Thr	ACT	6	11.58	0.22
Gly	GGA	13	25.1	0.38	Arg	CGC	0	0	0	Thr	ACC	10	19.31	0.37
Gly	GGT	14	27.03	0.41	Ser	AGT	7	13.51	0.2	Val	GTG	5	9.65	0.11
Gly	GGC	3	5.79	0.09	Ser	AGC	4	7.72	0.11	Val	GTA	12	23.17	0.27
His	CAT	10	19.31	0.71	Ser	TCG	4	7.72	0.11	Val	GTT	21	40.54	0.48
His	CAC	4	7.72	0.29	Ser	TCA	12	23.17	0.34	End	TGA	0	0	0
Ile	ATA	10	19.31	0.24	Ser	TCT	4	7.72	0.11	End	TAG	1	1.93	0.33
Ile	ATT	18	34.75	0.43	Ser	TCC	4	7.72	0.11	End	TAA	2	3.86	0.67
Ile	ATC	14	27.03	0.33	Thr	ACG	1	1.93	0.04					
Tyr	TAT	8	15.44	0.67	Val	GTC	6	11.58	0.14					

Table 8. Results of codon usage for gene *UGT76G1* (Results for 1616 residue sequence " *UGT76G1*" starting "CTTGCGTGTA")

AmAcid	Codon	Number	/1000	Fraction	AmAcid	Codon	Number	/1000	Fraction	AmAcid	Codon	Number	/1000	Fraction
Ala	GCG	4	7.43	0.17	Lys	AAG	11	20.45	0.37	Arg	CGT	5	9.29	0.17
Ala	GCA	8	14.87	0.33	Lys	AAA	19	35.32	0.63	Arg	CGC	4	7.43	0.14
Ala	GCT	10	18.59	0.42	Leu	TTG	20	37.17	0.33	Ser	AGT	9	16.73	0.18
Ala	GCC	2	3.72	0.08	Leu	TTA	11	20.45	0.18	Ser	AGC	10	18.59	0.2
Cys	TGT	4	7.43	0.8	Leu	CTG	4	7.43	0.07	Ser	TCT	15	27.88	0.3
Cys	TGC	1	1.86	0.2	Leu	CTA	7	13.01	0.11	Ser	TCC	2	3.72	0.04
Asp	GAT	16	29.74	0.62	Leu	CTT	9	16.73	0.15	Thr	ACG	4	7.43	0.2
Asp	GAC	10	18.59	0.38	Leu	CTC	10	18.59	0.16	Thr	ACA	5	9.29	0.25
Glu	GAG	11	20.45	0.29	Met	ATG	15	27.88	1	Thr	ACT	5	9.29	0.25
Glu	GAA	27	50.19	0.71	Asn	AAT	9	16.73	0.47	Thr	ACC	6	11.15	0.3
Phe	TTT	16	29.74	0.57	Asn	AAC	10	18.59	0.53	Val	GTG	10	18.59	0.23
Phe	TTC	12	22.3	0.43	Pro	CCG	8	14.87	0.32	Val	GTA	6	11.15	0.14
Gly	GGG	8	14.87	0.28	Pro	CCA	9	16.73	0.36	Val	GTT	24	44.61	0.56
Gly	GGA	8	14.87	0.28	Pro	CCT	6	11.15	0.24	Val	GTC	3	5.58	0.07
Gly	GGT	10	18.59	0.34	Pro	CCC	2	3.72	0.08	Trp	TGG	10	18.59	1
Gly	GGC	3	5.58	0.1	Gln	CAG	6	11.15	0.33	Tyr	TAT	5	9.29	0.36
His	CAT	7	13.01	0.54	Gln	CAA	12	22.3	0.67	Tyr	TAC	9	16.73	0.64
His	CAC	6	11.15	0.46	Arg	AGG	1	1.86	0.03	End	TGA	2	3.72	0.29
Ile	ATA	11	20.45	0.32	Arg	AGA	10	18.59	0.34	End	TAG	2	3.72	0.29
Ile	ATT	13	24.16	0.38	Arg	CGG	4	7.43	0.14	End	TAA	3	5.58	0.43
Ile	ATC	10	18.59	0.29	Arg	CGA	5	9.29	0.17					
Ser	TCG	8	14.87	0.16	Ser	TCA	6	11.15	0.12					

Table 9. Results of codon usage for gene *UGT85C2* (Results for 1586 residue sequence " *UGT85C2*" starting "ATGGATGCAA")

AmAcid	Codon	Number	/1000	Fraction	AmAcid	Codon	Number	/1000	Fraction	AmAcid	Codon	Number	/1000	Fraction
Ala	GCG	1	1.89	0.04	Lys	AAA	21	39.77	0.62	Ser	AGT	7	13.26	0.18
Ala	GCA	10	18.94	0.43	Leu	TTG	19	35.98	0.35	Ser	AGC	6	11.36	0.15
Ala	GCT	10	18.94	0.43	Leu	TTA	5	9.47	0.09	Ser	TCG	5	9.47	0.13
Ala	GCC	2	3.79	0.09	Leu	CTG	3	5.68	0.05	Ser	TCA	10	18.94	0.26
Cys	TGT	10	18.94	0.77	Leu	CTA	4	7.58	0.07	Ser	TCT	9	17.05	0.23
Cys	TGC	3	5.68	0.23	Leu	CTT	15	28.41	0.27	Ser	TCC	2	3.79	0.05
Asp	GAT	14	26.52	0.58	Leu	CTC	9	17.05	0.16	Thr	ACG	4	7.58	0.14
Asp	GAC	10	18.94	0.42	Met	ATG	16	30.3	1	Thr	ACA	6	11.36	0.21
Glu	GAG	11	20.83	0.32	Asn	AAT	10	18.94	0.5	Thr	ACT	8	15.15	0.28
Glu	GAA	23	43.56	0.68	Asn	AAC	10	18.94	0.5	Thr	ACC	11	20.83	0.38
Phe	TTT	10	18.94	0.36	Pro	CCG	8	15.15	0.29	Val	GTG	4	7.58	0.14
Phe	TTC	18	34.09	0.64	Pro	CCA	11	20.83	0.39	Val	GTA	5	9.47	0.18
Gly	GGG	9	17.05	0.26	Pro	CCT	7	13.26	0.25	Val	GTT	10	18.94	0.36
Gly	GGA	14	26.52	0.4	Pro	CCC	2	3.79	0.07	Val	GTC	9	17.05	0.32
Gly	GGT	8	15.15	0.23	Gln	CAG	5	9.47	0.36	Trp	TGG	12	22.73	1
Gly	GGC	4	7.58	0.11	Gln	CAA	9	17.05	0.64	Tyr	TAT	7	13.26	0.64
His	CAT	10	18.94	0.48	Arg	AGG	5	9.47	0.31	Tyr	TAC	4	7.58	0.36
His	CAC	11	20.83	0.52	Arg	AGA	5	9.47	0.31	End	TGA	2	3.79	0.25
Ile	ATA	11	20.83	0.28	Arg	CGG	1	1.89	0.06	End	TAG	3	5.68	0.38
Ile	ATT	18	34.09	0.45	Arg	CGA	2	3.79	0.13	End	TAA	3	5.68	0.38
Ile	ATC	11	20.83	0.28	Arg	CGT	2	3.79	0.13					
Lys	AAG	13	24.62	0.38	Arg	CGC	1	1.89	0.06					

4. Discussion

UGTs genes constitute a large and important gene family in Stevia[19]. Careful study of the structure and function of these genes is an essential step for a further in-depth understanding of plant regulatory pathways. In this study, secondary structures, three-dimensional structures, and codon analyzes were performed to investigate the similarities and differences between these genes. Understanding these helps us better understand the transfer of these genes and other genetic analyzes. Examination of the three-dimensional structure of the *UGTs* genes

showed that these structures contained a set of proteins bound to the active site with UDP and rebaudioside A, which also confirmed Lee et al evidence for the *UGT76G1* gene [20]. On the other hand, *UGTs* genes are very effective due to their significant effect on the synthesis of glycosides in plant sweetness, and understanding their structure is very important. Also, the close phylogenetic relationship between *UGT74G1* and *UGT85C2* genes showed that the structural similarities between these genes are very high. The promoter analysis suggested that *UGTs* gene expression is regulated by modulators, such as phytohormones, light, meristem, endosperm, and drought. In addition, the UGTs gene with diversified CREs may play a mediator to link different signaling pathways. Finally, we can say the careful study of these structures provides insight into glycosylation and a suitable model for steviol biosynthesis engineering.

5. Conclusion

In general, clinical results show that stevia consumption reduces blood sugar by increasing insulin sensitivity. A natural substance with antioxidant properties is effective in reducing and preventing kidney and liver damage in diabetic patients. Therefore, the consumption of stevia as a blood sugar controller and antioxidant is recommended for diabetic patients.

Abbreviation

SGs: Steviol glycosides

UGT family: UDP-glycosyltransferase

Conflict of Interests

All authors declare no conflict of interest.

Ethics approval and consent to participate

No human or animals were used in the present research.

Consent for publications

All authors read and approved the final manuscript for publication.

Availability of data and material

All the data are embedded in the manuscript.

Authors' Contribution

All authors had an equal role in study design, work, statistical analysis and manuscript writing.

Informed Consent

The authors declare not to use any patients in this research.

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