UNIVERSITI PUTRA MALAYSIA

IDENTIFICATION AND FUNCTIONAL ANNOTATION OF GENIC SIMPLE SEQUENCE REPEATs FROM LEAVES TISSUE TRANSCRIPTOME DATASET OF Stevia rebaudiana Bertoni

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By

AZRUL AFIQ BIN AZMI MURAD

Thesis Submitted to School of Graduate Studies, Universiti Putra Malaysia, in Fulfilment of the Requirements for the Degree of Master of Science

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Abstract of thesis presented to the Senate of Universiti Putra Malaysia in fulfilment of the requirement for degree of Master of Science

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June 2021

Chair : Christina Yong Seok Yien, PhD
Faculty : Science

Stevia rebaudiana is an important agricultural crop that yields diterpenoid steviol glycosides (SGs) commonly used to substitute sugar in food products and nutraceuticals. Despite the increasing demand for Stevia leaf and Stevia-based products, the genetic background of this crop remains poorly elucidated. The genetic markers available for this species are also extremely lacking. The current study investigated an in-house leaf tissue transcriptome dataset of *Stevia rebaudiana* and developed genic-SSR markers for the species using *in silico* approaches. In total, 103,890 *de novo* assembled contig sequences were analysed. Out of that, 8,065 contigs containing 8,789 genic-SSR loci were unearthed via MIcroSAtellite identification (MISA) tool. From the 8,065 contigs containing genic-SSR (CCGS) found, 7,400 CCGS contained single genic-SSR per locus; while 665 CCGS contained multiple SSR per locus (ML). Furthermore, amongst the 8,789 genic-SSR, 8,302 were identified as pure genic-SSRs, 105 were complex genic-SSRs and the remaining 382 were compound genic-SSRs. From the functional annotation of the 8,065 CCGS identified, 6,447 CCGS were annotated with functional genes; while remaining 1,618 CCGS were unannotated. Out of 6,447 annotated CCGS, 5,494 CCGS matched significantly to protein sequences of various plant species with an *E*-value cut off at $1.0E^{-15}$. Among the 5,494 CCGS, 3,069 CCGS were annotated with known functional genes and containing only single pure genic-SSR per locus. Pure trinucleotide genic-SSRs (52.66%) were the predominant repeats. This was followed by pure di- (35.32%), hexa- (6.48%), penta- (3.84%) and tetranucleotides (1.69%). Microsatellite di- and trinucleotides are preponderant in *S. rebaudiana* leaf transcriptome. Repeat motif AT/TA (50.28%) was the most abundant among the dinucleotides, and the repeat motif GAT/ATC (12.87%) was predominant among the trinucleotides. From the 3,069 annotated CCGS, 1,617 were mapped to proteins available in the Kyoto Encyclopaedia of Genes and Genomes (KEGG) database. The biosynthesis pathways with the highest number of annotated CCGS mapped to them were the metabolic pathways, secondary metabolite

biosynthesis pathway, and antibiotics biosynthesis pathway. Most studies on *S. rebaudiana* focused on the biosynthesis of secondary metabolites with a particular interest in SGs that contribute to the natural sweetness of Stevia. In this study, a total number of 14 genic-SSR loci associated with genes involved in the SGs biosynthesis pathway were identified. In addition, twenty pairs of genic-SSR primers were also designed and further validated in this study. From the 20 primer pairs, 17 (85.00%) were successfully cross-amplified in three different varieties of *S. rebaudiana* (SweetStevia, UKMB408 and AKHL1 var.). Three out of 17 loci screened were found to be polymorphic as revealed by polyacrylamide gel electrophoresis and confirmed by bidirectional amplicon sequencing of the PCR products. In conclusion, the transcriptome dataset has served as an excellent resource for the discovery of genic-SSRs in *Stevia rebaudiana*, and it also shows promising potential to develop polymorphic genic-SSR markers. As DNA markers available for this species is still very limited, the genic-SSR loci identified in this study will contribute substantially to the development of more DNA markers for the species, which may be applied in population and functional studies in the future. It may also be used as the baseline data towards developing DNA markers for selective breeding in the future.

Abstrak tesis yang dikemukakan kepada Senat of Universiti Putra Malaysia sebagai memenuhi keperluan untuk Ijazah Master Sains

IDENTIFIKASI DAN PENGANOTASIAN BERFUNGSI JUJUKAN ULANGAN RINGKAS GEN DARI DATASET TRANSKRIPTOM TISU DAUN *Stevia rebaudiana* BERTONI.

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Stevia rebaudiana merupakan tanaman pertanian penting yang menghasilkan diterpenoid steviol glikosida (SGs) yang biasa digunakan untuk menggantikan gula dalam produk makanan dan nutraseutikal. Walaupun permintaan untuk daun Stevia dan produk yang berasaskan Stevia meningkat, latar belakang genetik tanaman ini masih kurang difahami. Penanda genetik yang ada untuk spesies ini juga amat kurang. Kajian ini dilakukan adalah untuk mengkaji set data transkriptom dari tisu daun *Stevia rebaudiana* dan mencari penanda gen-SSR bagi spesies tersebut dengan menggunakan pendekatan berkomputasi. Sejumlah 103,890 jujukan kontig terkumpul dianalisis secara baharu. Daripada jumlah itu, 8,065 kontig mengandungi 8,789 lokus gen-SSR ditemui menggunakan alat MIcroSAtellite identification (MISA). Dari 8,065 kontig yang mengandungi gen-SSR (CCGS) yang dijumpai, 7,400 CCGS mengandungi hanya satu gen-SSR bagi satu lokus; manakala 665 CCGS mengandungi gen-SSR berganda bagi satu lokus (ML). Selanjutnya, di antara 8,789 gen-SSR, 8,302 dikenal pasti sebagai gen-SSR tulen, 105 adalah gen-SSR kompleks dan lebihan 382 adalah gen-SSR sebatian. From the functional annotation of the 8,065 CCGS identified, 6,447 CCGS were annotated with functional genes; while remaining 1,618 CCGS were unannotated. Dari 8,065 CCGS yang digunakan untuk kajian penganotasian berfungsi, 6,477 CCGS dikenal pasti beranotasi dengan gen berfungsi; sementara baki 1,618 CCGS tidak beranotasi. Dari 6,447 CCGS yang beranotasi, 5,494 CCGS sepadan ketara dengan urutan protein dari pelbagai spesies tumbuhan dengan nilai-*E* penggal pada $1.0E^{-15}$. Di antara 5,494 CCGS, 3,069 adalah beranotasi dengan gen berfungsi dan mempunyai hanya satu gen-SSR bagi satu lokus. Gen-SSR trinukleotida tulen (52.66%) adalah ulangan terbanyak. Ini diikuti oleh di- (35.32%), hexa- (6.48%), penta- (3.84%) dan tetranukleotida (1.69%) tulen. Mikrosatelit di- dan trinukleotida adalah dominan dalam transkriptom daun *S. rebaudiana*. Motif ulangan AT / TA (50.28%) adalah yang paling banyak di antara dinukleotida, dan motif ulangan

GAT / ATC (12.87%) adalah yang utama di antara trinukleotida. Dari 3,069 CCGS beranotasi, 1,617 dipadankan dengan protein yang terdapat dalam pangkalan data Kyoto Encyclopaedia of Genes and Genomes (KEGG). Laluan biosintesis dengan jumlah CCGS beranotasi tertinggi yang dipetakan adalah laluan metabolik, laluan biosintesis metabolit sekunder, dan laluan biosintesis antibiotik. Sebilangan besar kajian mengenai *S. rebaudiana* difokuskan pada biosintesis metabolit sekunder dengan tumpuan diberikan terhadap SGs yang menyumbang kepada kemanisan semula jadi Stevia. Dalam kajian ini, sejumlah 14 lokus gen-SSR dikenal pasti berkaitan dengan gen yang terlibat dalam laluan biosintesis SGs. Tambahan lagi, dua puluh pasang primer gen-SSR juga direka dan disahkan lebih lanjut dalam kajian ini. Dari 20 pasangan primer, 17 (85.00%) berjaya teramplifikasi pada tiga variasi *S. rebaudiana* yang berbeza (SweetStevia, UKMB408 dan AKHL1 var.). Tiga daripada 17 lokus yang disaring didapati polimorfik didedahkan oleh elektroforesis gel poliakrilamida dan disahkan dengan cara penjujukan dua-arah menggunakan produk PCR. Kesimpulannya, kumpulan data transkriptom telah berfungsi sebagai sumber yang sangat baik untuk pencarian gen-SSR pada *Stevia rebaudiana*, dan ia juga berpotensi untuk membina penanda gen-SSR polimorfik. Oleh kerana penanda DNA yang tersedia untuk spesies ini masih sangat terhad, lokus gen-SSR yang dikenal pasti dalam kajian ini akan memberikan sumbangan besar kepada pembangunan penanda DNA untuk spesies ini, yang mungkin boleh diaplikasikan dalam kajian populasi dan kajian berfungsi pada masa akan datang. Ia juga dapat digunakan sebagai data asas untuk pembangunan penanda DNA untuk pembiakan pilihan dalam jangka panjang.

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Declaration by Members of Supervisory Committee

This is to confirm that:

- the research conducted and the writing of this thesis was under our supervision;
- supervision responsibilities as stated in the Universiti Putra Malaysia (Graduate Studies) Rules 2003 (Revision 2012-2013) are adhered to.

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LIST OF ABBREVIATIONS

°C	Degree Celcius
µl	Microlitre
µM	Micromolar
3'	Three Prime
5'	Five Prime
A	Adenine
AKF	Annotated Known Function
AUF	Annotated Undefined Function
bp	Base Pair
c	Compound
C	Cytosine
c*	Complex
CAGR	Compound Annual Growth Rate
CCGS	Contigs Containing Genic-SSR
CCS	Chosen Contig Sequences
cDNA	Complementary DNA
CDS	Coding Sequence
CID	Contigs Identifier
cm	Centimeter
COVID-19	Coronavirus Disease 2019
CTAB	Cetyl Trimethylammonium Bromide
DNA	Deoxyribonucleic Acid
e.g.	*Exempli Gratia* (For Example)

EDTA	Ethylenediaminetetraacetic Acid
ent	Enantiomer
EST	Expressed Sequence Tag
EtOH	Ethanol
E-value	Expect value
FASTA	Fast Adaptive Shrinkage Threshold Algorithm
FELDA	Federal Land Development Authority
G	Guanine
Gb	Gigabase pair
ISSR	Inter-Simple Sequence Repeat
KAAS	KEGG Automatic Annotation Server
kb	Kilobase Pair
kcal	Kilocalorie
KEGG	Kyoto Encyclopedia of Genes and Genomes
KID	KAAS Identifier
LAI	Leaf Area Index
lncRNA	Long Non-Coding RNA
m	Meter
M	Molar
MAS	Marker-assisted Selection
Mb	Megabase Pair
mg	Milligram
MID	MISA Identifier
MISA	MIcroSAtellite Identification Tool

mL	Millilitre
ML	Multiple SSR per Locus
mm	Millimetre
mM	Millimolar
mRNA	Messenger RNA
n	Number
ng	Nanogram
NGS	Next Generation Sequencing
nm	Nanometer
nr	Non-redundant
nt	Nucleotide
ORF	Open Reading Frame
p2	Pure Dinucleotide
p3	Pure Trinucleotide
p4	Pure Tetranucleotide
p5	Pure Pentanucleotide
p6	Pure Hexanucleotide
PAGE	Polyacrylamide Gel Electrophoresis
PCR	Polymerase Chain Reaction
PGR	Plant Growth Retardant
pH	Potential of Hydrogen
Pte Ltd	Private Limited
QTL	Quantitative Trait Locus
RNA	Ribonucleic Acid

rRNA	Ribosomal RNA
ScL	Single Complex/Compound SSR per Locus
Sdn. Bhd.	*Sendirian Berhad*
seq	Sequencing
SGs	Steviol Glycosides
siRNA	Short Interfering RNA
SL	Single SSR per Locus
SpL	Single Pure SSR per Locus
SSR	Simple Sequence Repeat
T	Thymine
TAE	Tris-Acetate-EDTA
TBE	Tris-Borate-EDTA
T_m	Melting Temperature
tRNA	Transfer RNA
u	Unit
USD	United States Dollar
UTR	Untranslated Region
UV	Ultraviolet
V	Volt
v/v	Volume/Volume
var.	Variety
w/v	Weight/Volume
x	Times
β	Beta

ΔG	Gibbs Energy
λ	Lambda

CHAPTER 1

INTRODUCTION

The increasing statistics of diabetic patients encourage people to take less sugar in their diets. Approximately 463 million adults (20-79 years old) were suffering from diabetes worldwide in 2019 (International Diabetes Federation, 2019). The number of people afflicted is predicted to rise up to 700 million by 2045 according to International Diabetes Federation (2019). As sugar substitutes, artificial sweeteners such as acesulfame-K, aspartame, cyclamate, neotame, saccharin and sucralose are used to curb the problem of high sugar intake in daily life. However, there have been reports that these artificial sweeteners have some toxic side effects (Whitehouse et al., 2008).

Stevia rebaudiana or commonly known as the sweet leaves, honey herbs, or sweet herbs (Joshi et al., 2006) is found to have great potential to replace sucrose as a zero-caloric and healthier natural sweetener in recent years (Putnik et al., 2020; Madan et al., 2010). Japan was the pioneer in the commercialisation of Stevia sweetener and the Japanese have been using Stevia-based products as a sweetener since the 1970s (Hossain et al., 2017; Kinghorn and Soejarto, 1985). The sweetness of Stevia is attributed by its diterpenoid steviol glycoside constituents, mainly the stevioside and rebaudioside A (Parris, 2016). Both of these constituents, which have now been commercialised worldwide as hypocaloric bio-sweeteners, have been shown to possess anti-hyperglycaemic effects (Radzman et al., 2013). Stevioside is 250-300 times sweeter than sucrose but it has a bitter aftertaste (Brandle et al., 1998). On the other hand, rebaudioside A is sweeter than stevioside but it has no bitter aftertaste (Wang et al., 2016a; Brandle et al., 1998). This makes Stevia plant containing higher proportion of rebaudioside A highly desirable by planters and producers. Nutrition and toxicity studies have also shown that neither stevioside nor rebaudioside A pose health threats in various animals' trials, if consumed at a fixed amount daily; no more than 4mg per kg (Lohner et al., 2017; Toskulkao et al., 1997). Furthermore, clinical studies have demonstrated that by consuming Stevia, can significantly lower insulin levels and postprandial glucose in humans, as compared to sucrose (Apaicio et al., 2017; Anton et al., 2010; Geeraert et al., 2010).

The worldwide demand for *S. rebaudiana* leaf and purified steviol glycosides has increased steadily over the years, with the growing awareness for a healthier diet among consumers (Tavarini et al., 2018). The market value of Stevia had increased consistently from USD 490.08 million in year 2017 to USD 536.64 million in year 2018 and USD 587.62 million in year 2019 (Stevia's global market value, 2017-2022 | Statista, 2021; Shahbandeh, 2018). However, the global market for Stevia and Stevia-based products had decreased slightly to USD 520.32 million in 2020, because the markets and consumer purchase behaviours of the products were affected by the global COVID-19 pandemic (Global Stevia

Market Report and Forecast 2021-2026, 2021). As a result, the global market production of *S. rebaudiana* products (includes: powder, liquid, leaf; by end product: beverages, food products, sweetener and pharmaceuticals) in the year 2020 was lower. Nevertheless, the market value is expected to grow with a Compound Annual Growth Rate (CAGR) at 8.4%, with the market value predicted to reach USD 844.20 million by 2026 (Global Stevia Market Report and Forecast 2021-2026, 2021).

Although the global size of the Stevia market is characterized by rapid progress, agricultural production of this crop remains challenging and inadequate to support the increasing global demand. Stevia yield remains unstable and low due to deficiency of varieties that can suitably adapt to different environments, inadequate cultivation expertise, lack of irrigation and poor disease control (Tavarini et al., 2018). It is important to produce enhanced, higher-performing and yield Stevia crops that are more resistant to abiotic and biotic stresses to improve the competitiveness of Stevia production. Therefore, genetic approach aims at developing better Stevia plant variety with higher leaf and steviol glycosides yield are the main goals in Stevia breeding. The development of genic microsatellite or simple sequence repeat (genic-SSR) may contribute to development of functional marker in *S. rebaudiana* that is currently limited.

Genic-SSR that is derived from the transcribed region of the DNA possesses the advantages of being co-dominant, allowing genotype and allele frequencies determination at a specific locus, and also its association with functional genes. Genic-SSR can be applied in gene tagging analysis that is useful for marker-trait associations (MTAs), which may be used for the improvement of *S. rebaudiana* varieties. Genic-SSR marker can be across-amplified in different Stevia varieties, as well as other closely related species in the Asteraceae family (such as *Helianthus annuus*, *Lactuca sativa* and *Cynara cardunculus*), as it has higher transferability compared to genomic-SSR. However, the available genic-SSR for *S. rebaudiana* is still very limited. To date, only one reported study in 2015, which identified 168 expressed sequence tag SSR (EST-SSR) from 5,548 *S. rebaudiana* EST sequences are available in the public database (Kaur et al., 2015). However, the EST-SSRs related to candidate genes such as those involved in the biosynthesis of steviol glycoside are still extremely lacking.

Therefore, to fill in the above-mentioned information gap, the current study was focused on the identification of genic-SSRs associated with functional genes, particularly those that are involved in the biosynthesis of secondary metabolites such as the steviol glycosides. In order to achieve this, this study has four specific **objectives:**

1. To identify and characterize genic-SSR from a *Stevia rebaudiana* leaves tissue transcriptome dataset.
2. To correlate the contigs containing genic-SSR with functional genes.

3. To develop primers containing pure dinucleotides and trinucleotides associated with known functions gene.
4. To validate the genic-SSR primers on three different *Stevia rebaudiana* varieties (SweetStevia var., AKHL1 var. and UKMB408 var.).

Hypothesis:

It is hypothesized that trinucleotide genic-SSRs are the predominant motif types in the transcriptome of *S. rebaudiana* and genic-SSR associated with functional genes can be identified from the transcriptome dataset. It was also hypothesized that the genic-SSR can be cross-amplified in different varieties of *S. rebaudiana* (SweetStevia var., AKHL1 var. and UKMB408 var.) and polymorphisms among the three varieties can be identified.

Significance of the study:

The genic-SSRs associated with functional genes identified in this study may serve as an excellent baseline data to develop SSR panels for this species. The SSR markers may be applied in large scale population screening to assist in seedlings/plantlets selection in marker-assisted selection (MAS). The genic-SSR markers linked with desirable traits may also be useful for functional and quantitative trait locus (QTL) analyses. Furthermore, the SSR markers can also be applied to study the genetic variations of different Stevia varieties, as well as among different Stevia species. This study confirmed the efficiency of transcriptome-derived genic SSR markers for *S. rebaudiana*, in which the markers are highly useful to generate more genetic information about the species. With more information available, it is anticipated to assist in producing better planting material with a higher yield to support market demand.

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