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Indonesian Perspective: Identification of Stevia Plant (*Stevia Rebaudiana* Bertoni M.) as Medicine Prospects

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HIGHLIGHTS

- Description of Stevia Plant (*Stevia Rebaudiana* Bertoni M.)
- Content of Bioactive Compounds of Stevia Plant (*Stevia Rebaudiana* Bertoni M.)
- Plant Pest Organisms on *Stevia Rebaudiana* Plants
- How to Use The Stevia Plant Folk Recomend by Medicine of Indonesian Indigenous Tribes

Abstract

Stevia plant has the potential for development as a source of natural sweeteners, a plant from South America and indigenous to Paraguay, has shown several advantages including the level of sweetness that reaches 100-200 the sweetness of sugar cane and low calorie also constituting a source of many substances with a nutritional effect on the human beings. Folk medicine of Indonesian indigenous tribes recommends it particularly as a substance strengthening the heart, the circulatory system and regulating blood pressure. It exhibits antibacterial, antifungal and anticaries properties. This stevia study aimed to educate people about the efficacy and safety of the stevia plant as a sweetener to replace sugar and medicines by diabetic patients as a part of Indonesia perspective the aims also to enrich information about the stevia plant which has the potential for development as a source of natural sweeteners, and as a medicine for diabetes with a bright prospects in the future.

Keywords: Identification of Stevia Plant; *Stevia Rebaudiana* Bertoni M; Medicine Prospects

1. Introduction

Sugar is a strategic commodity because it is consumed by all levels of society whose exploitation comes from on-farm to off-farm and is multi-dimensional regarding technical, social, economic, and political interests. Indonesian national sugar demand in 2014 reached 5.7 million tonnes. Sugar consumption for 2022/23 is expected to increase to 7.8 MMT of raw sugar equivalent from 7.6 MMT in 2021/22. In line with population growth and expected recovery of demand from the food and beverage industry, 2023/24 sugar

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consumption is forecast to reach 7.9 MMT of raw sugar equivalent. The Indonesian government is pursuing a National Sugar Self sufficiency Program (Director General of Plantations of Indonesia 2013); to meet the demand for sugar by looking for alternatives to other natural sweeteners that are safer than synthetic sweeteners to meet local needs.

Sugar is a sweetener for food and beverages. Based on the manufacturing process, sugar is divided into two categories, synthetic sugar and natural sugar. Synthetic sugar is artificial sugar, for example saccharin and cyclimate, while natural sugar is processed and obtained from plants that contain sweeteners, like sugarcane, coconut, palm, and stevia.

Annual non-calorie plant Stevia (*Stevia rebaudiana* Bertoni M.) based sugar contains glycoside, glycosides, steviosides, steviolbiosides, rebauldiosides A and B and several other sweetening ingredients in diterpenes as aglucon groups which can be used as an alternative source of sweetening in Indonesia (Directorate of Various Plants 2000). It has approved for use on the European Union (EU) list of alternative sugars. Stevia is mostly cultivated in South America but most of the world's commercial sales and production are made in Asia (IFST 2012).

Chemical analysis has shown that the stevia plant sweetener is a mixture of glycoside compounds. Several studies on stevia sugar have found that stevia sugar contains protein, fiber, carbohydrates, zinc, vitamin A, vitamin C, sodium, and magnesium. Its use in herbal form, replace sugar. Moreover, stevia has anti-fungal and anti-bacterial functions, which reduce flu symptoms, and is good as a skin care ingredient that can treat digestive disorders.

The cultivation and processing of stevia plants have developed rapidly in Indonesia, seen from the increasing area of stevia plantations and the increasing variety of uses of stevia products. Stevia products can be found both in the form of dry leaves and powder. Stevia products can be found both in the form of dry leaves and powder. Seed, stem cuttings, tillers, or tissue culture methods in large quantities in Indonesia can do stevia propagation

Therefore this stevia study aimed to educate people about the efficacy and safety of the stevia plant as a sweetener to replace sugar and medicines by diabetic patients as a part of Indonesia perspective. This review article could enrich information about the stevia plant which has the potential for development as a source of natural sweeteners, and as a medicine for diabetes with a bright prospects in the future.

2. Stevia Plant Description and Propagation

The stevia plant (Stevia rebaudiana Bertoni M.) was first discovered in the border area between Paraguay and Brazil, South America in 1887 by the American taxonomist Antonio Bertoni and named it Eupatorium rebaudianum Bertoni. Allegedly more than 80 types of stevia species grow wild in North America and 200 species naturally in South America, but only Stevia rebaudiana is used as a sweetener. It is commonly known as sweet leaf, sugar leaf, or simply stevia. It is used as sweetner in Japan since 1970 (Raini and Isnawati 2011). Indonesian local residents use this plant as a sweetener in food and drinks. The stevia plant is estimated to have entered Indonesia in 1977 on the cooperation of Japanese and Indonesian entrepreneurs, since then the stevia plant has become a commodity that has opportunities to be cultivated locally (Rukmana 2003).

According to Syamsuhidayat and Hutapea (1991) stevia plants are classified as following:

Kingdom : Plantae

Division : Spermatophyta

Sub-division : Angiospermae

Class : Dicotyledonae

Ordo : Campanulatae

Family : Compositae

Genus : Stevia

Species : Stevia rebaudiana Bertoni M.

Syn Eupatorium rebaudianum

The stevia plant is an annual shrub with a plant height that can reach 90 cm. The stem is round, fluffy, segmented, and forms many branches. Stevia has a single leaf, the leaves sit opposite each other, the leaves are oval and have fine hairs. Leaves 2-4 cm long and 1-5 cm wide. The stevia has a shallow taproot system with hairy roots that grow in the soil as a thicket. Stevia plants have compound flowers, in the form of panicles that grow at the ends of the stems and axils of the leaves. Stevia fruit is box-shaped, brown, and surrounded by hairs. Stevia seeds are dirty white and needle-shaped (Suhendi 1987). The following shows the shape of the stevia plant, which can be seen in Figure 1.

Figure 1. Stevia Plants

Source: (https://plants.ces.ncsu.edu/plants/stevia-rebaudiana/)

The stevia plant has a strong regeneration capacity and is resistant to pruning. Young stevia shoots will emerge from the base of the stem if pruned. Young shoots also emerge during degeneration at the end of the reproductive phase. Harvesting stevia is done by pruning the stems and leaving only the base. Pruning can continue until the plants are 3 to 4 years old.

Stevia plants can adapt well to various growing environments. Mubiyanto (1990) has mentioned that stevia plants can grow in areas with an altitude of 200-1500 meters above sea level, air temperature between 14°C-27°C, precipitation of 1600-1850 mm/year and 2-3 dry months. Infertile soil can be used to grow stevia provided enough available water. In general the soil should be fertile has loose, lots of humus, with good aeration and drainage, pH 4-5, with sufficient soil water contents between 43%-47%. Soil that is too wet will facilitate the spread of root by soil-borne pathogens.

Stevia propagation can be done generatively using seeds or vegetatively using stem cuttings, shoot cuttings, of shoots, and also plant tissue culture. The stem and shoot cuttings originating from the primary branch should have 3-4 nodes. Propagation of stevia by seeds is difficult because stevia seeds have a very low germination rate of 11% (Goettemoeler and Ching 1999).

The first propagation of stevia stem cuttings was carried out in the greenhouse of the Bogor Plantation Research Institute Indonesia in February 1983, the experimental results showed that the top of the stevia stem, both from the scion and its branches, was the best material for propagating stevia by stem cuttings.

Plant propagation by cuttings can be defined as a process of propagation using vegetative parts which then grow to perfection. Based on the part used as propagation material, there are 3 types of cuttings, namely root cuttings, stem cuttings (shoot cuttings are stem cuttings), and leaf cuttings (Hartmann et al. 1997).

In stem cuttings, the part of the plant taken as material for cuttings can determine success in cutting. The apical part has a higher success rate than the basal part of the plant. Good cuttings can be taken from young, woody stems. Woody cuttings are more resistant to unfavorable environmental conditions. Vegetative propagation basically forms adventitious organs that do not yet exist in cuttings. In stem cuttings, the adventitous roots that are formed, while potential shoots (not adventitious) already exist. Stem cuttings must immediately form roots so that the water supply to the canopy occurs immediately (Hartmann et al. 1997).

The process of forming adventitious roots consists of three stages, namely (1) cell differentiation followed by the formation of meristematic cells (root initiation), (2) differentiation of meristematic cells until root primordia are formed, and (3) emergence of new roots (Ashari 1995).

Vegetative propagation through stem cuttings, and root growth is an important factor during plant growth because they promote shoots induction and grow after the roots. Cuttings taken from an ancient material are unsuitable because they are not prone to rooting. Young cuttings are better because the roots can be induced rapidly (Wudianto 1993).

Vegetative propagation has many advantages, including being able to produce perfect plants with roots, stems, and leaves in a relatively short time, are true to type, fast. Factors that influence the success of cutting can be classified into three, namely plant factors, environmental factors, and implementation factors. Plant factors include the type of cutting material, age of cutting material, food content, water content and growth regulators. Environmental factors include growth media, humidity, temperature, and light, while implementation factors include the time of taking cuttings and treatment with growth regulators (Rochiman and Harjadi 1973).

Propagation of stevia using tissue culture technique, explants. 2mm long shoots were, cultured on Linsmainer and Skoog medium amended with 10 mg/l kinetin, for 50 days. The induced shoots were separated into several clusters, consisting of 2-4 shoots and subcultured. After 30 days, the growing shoots were separated to shoot elongation medium containing namely Linsmainer and Skoog media amended with 1 mg/l kinetin. The shoots that reached 3-5 cm in length, were rooted on Linsmainer and Skoog medium added with 0.1 mg/l NAA (Gunawan 1992).

3. Content of Bioactive Compounds

Stevia leaves contain apigenin, austroinulin, avicularin, beta-sitosterol, caffeic acid, campesterol, caryophyllene, sentaureidin, chlorogenic acid, chlorophyll, cosmosiin, synanoside, daukosterol, diterpene glycosides, dulcosides A-B, funikulin, formic acid, gibberellic acid, gibberellins, indole-3-acetonitrile, isoquercithrin, isosteviol, jihanol, kaempferol, kaurene, lupeol, luteolin, polystacoside, quercitrin, rebaudiosid A-F, scopoletin, sterebin A-H, steviol, steviolbioside, steviolmonosida, stevioside, stevioside a-3, stigmasterol, umbelliferon, and santofil (Raini and Isnawati, 2011). The main content of stevia leaves is steviol derivatives, especially stevioside (4-15%), rebaucide A (2-4%) and C (1-2%) and dulcoside A (0.4-0.7%). (Directorate General XXIV Consumer Policy and Consumer on Health Protection, Scientific Committee on Food in Raini and Isnawati, 2011).

4. Similarities with Other Plants

The stevia plant has similar secondary metabolite groups to the gotu kola plant. *Centella asiatica* can also be an alternative to preventing and treating diabetes. *Centella asiatica* contains asiaticoside compounds. Asiaticoside compounds in gotu kola plants can also improve memory, concentration and alertness. This is possible because asiaticoside can help smooth the circulation of oxygen and nutrients and protect brain cells from oxidative damage by free radicals. After all, the fatty acid content is very high and easily oxidized (Bermawi et al. 2005).

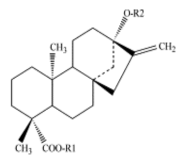
The chemical constituents of *Centella asiatica* leaves include a triterpenoid glycoside compound called asiaticoside (a heteroside compound), which is a secondary metabolite compound belonging to the terpene group which is efficacious for accelerating wound healing, asiaticic acid and madekasat (Haralampidis et al. 2002). Phillips et al. (2006) suggested that these terpenes are fats synthesized from the primary metabolite Acetyl CoA via the Mevalonic Acid (MAP) pathway or the basic intermediates of glycolysis via the Methylerythritol Phosphate (MEP) pathway. Three Acetyl CoA molecules combine to form mevalonic acid. This 6-carbon intermediate compounds undergoes pyrophosphorylation, carboxylation and dehydration to form Isopentenyl pyrophosphate (IPP). IPP is a terpene 5 C block precursor. IPP can also be formed from glycolysis intermediates or carbon reduction cycles in the photosynthetic process (Taiz and Zeiger 2002).

5. Stevioside biosynthetic pathway

Primary metabolite biochemical compounds play a role in the plant bodys nutrition and main metabolic processes. In contrast, secondary metabolites (including the active ingredient in stevioside compounds in the stevia plant) influence the ecological interactions between plants and their environment. In each plant, even between plant organs, biosynthesis of secondary metabolites occurs which varies depending on the environmental factors in which the plant grows. Plant secondary metabolites can be grouped into 3 main groups: terpenes or terpenoids, alkaloids or secondary products containing nitrogen, phenylpropanoids, and other phenolic compounds.

Steviosides are natural compounds belonging to the terpene group. This compound has a very sweet taste, 250-300 times sweeter than sucrose (cane sugar), and is low in calories (Chatsudthipong 2009). Steviosides from the stevia plant have greater potency, function, and sweetener characteristics than other sweeteners. In addition, stevioside also has hypoglycemic properties (Djas 2005), so it can be used as an alternative for preventing and treating *Diabetes mellitus*.

The structure of the stevia sweetener components, especially the steviosides contained in the leaves, can be seen in Figure 2.



	Compound name	R1	R2
1	steviol	H	H
2	steviolbioside	H	β-Glc-β-Glc(2→1)
3	stevioside	β-Glc	β-Glc-β-Glc(2→1)
4	rebaudioside A	β-Glc	β-Glc-β-Glc(2→1) β-Glc(3→1)
5	rebaudioside B	H	β-Glc-β-Glc(2→1) β-Glc(3→1)
6	rebaudioside C (dulcoside B)	β-Glc	β-Glc-α-Rha(2→1) β-Glc(3→1)
7	rebaudioside D	β-Glc-β-Glc(2→1)	β-Glc-β-Glc(2→1) β-Glc(3→1)
8	rebaudioside E	β-Glc-β-Glc(2→1)	β-Glc-β-Glc(2→1)
9	rebaudioside F	β-Glc	β-Glc-β-Xyl(2→1) β-Glc(3→1)
10	dulcoside A	β-Glc	β-Glc-α-Rha(2→1)

Figure 2. Stevioside structure and compound bonds. Rebaudiosides D and ER R1 contain 2-β-Glc- β-Glc-(2→1). Rebaudiosides A, B, C, D, E and F in group R2 are added 3 carbons with the prefix β-Glc. Rebaudioside F one β-Glc replaced with β-Xyl.

The formula of stevioside ent-kaurene and gibberellins (GAs) is formed via the 2-C-Methyl-D-erythritol-4-phosphate(MEP) pathway (Totte et al. 2000). The enzymes catalyzing the first two pathways namely 1-deoxy-D-Xylulose-5-phosphate (DXS) synthase and 1-deoxy-D-Xylulose-5-phosphate reductoisomerase (DXR) were cloned using transcriptase-PCR. DXS and DXR from the stevia plant contained N-base plastid sequences and showed high similarity to other plants. In addition, it was shown through Escherichia coli functional clones of cDNAs coding proteins (Totte et al. 2003). Kim et al. (1996) found that the highest HMG-CoA reductase activity was the main enzyme of the mevalonic acid (MVA) pathway to IPP that occurs in the chloroplasts of the stevia plant. It is suspected that steviol is synthesized via the mevalonic acid (MVA) pathway, but no evidence supports this claim.

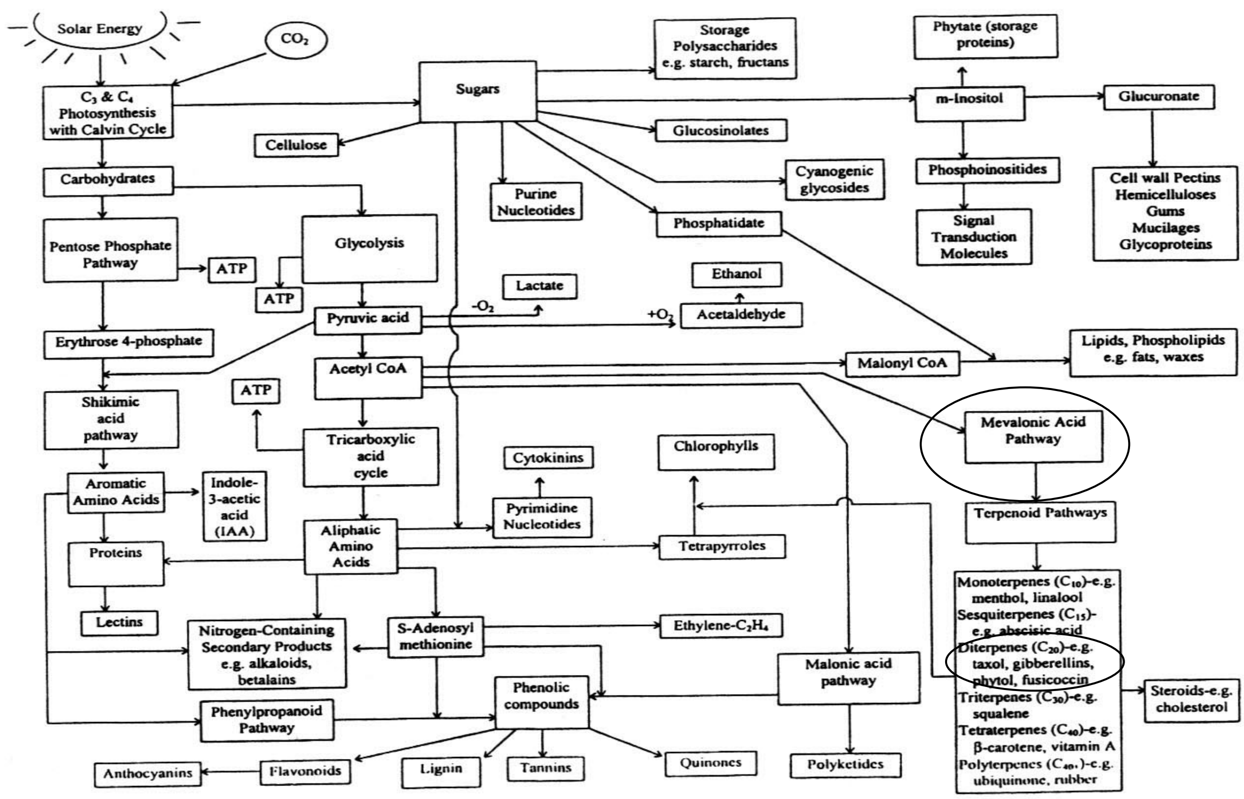


Figure 3. Pathways of stevioside biosynthesis

6. Use of The Stevia Plant

Stevia leaf is used as a sweetner by the Indonesian people. Stevia grown in Indonesia comes from Japan, Korea and China. These plant materials come from seeds so that the growth of stevia plants in the field is very diverse. The quality of stevia leaves is influenced by many environmental factors such as soil type, irrigation, lighting and air circulation. It is also affected by bacterial and fungal disorders. The quality of stevia sweetener is based on its aroma, taste, appearance and level of sweetness. Unlike other sweeteners, stevia doesn't give off a bitter after taste. The secret to stevia's sweetness lies in its complex molecule called stevioside which is a glycoside composed of glucose, sophorose and steviol (Raini and Isnawati 2011).

7. Mechanism of Action of Stevioside Compounds

Steviosides are hydrolyzed to steviol, before being absorbed in the small intestine. The absorption of stevioside and rebaudioside A was deficient, with a permeability coefficient of 0.16. 10-6 and 0.11. At 10-6 cm/sec, steviol at a concentration of 100 mmol/l is absorbed more effectively with a very high permeability coefficient of 44.5. 10-6 cm/sec while in secretory 7.93. 10-6 cm/second (Geuns et al. 2003 in Raini and Isnawati 2011). The absorption of the steviol aglycone in its single form (steviol) is better than in the mixed form of stevia (rebaudioside A, rebaudioside C, stevioside and dulcoside A), more than 93% remains in the mucosal fluid and 76% of steviol is absorbed in both the Duodenum-jejunum and ileum (Koyama et al. 2003 in Raini and Isnawati 2011).

Research conducted by Wang et al. (2004) and Raini and Isnawati 2011 showed that low levels of steviol were found in plasma after 8 hours post oral administration of 0.5 g/kg of steviosida (95% purity). Research to determine the bio-transformation of stevioside was carried out by incubating 50 mg/l stevioside (purity> 96%) in chicken excreta under anaerobic conditions for 24 hours, the result showed that 20% of stevioside hydrolyzed to steviol (Geuns et al. 2003 and Raini and Isnawati 2011).

Another study was carried out by incubating 40 mg of stevioside (85% purity) and 40 mg of rebausid A (90% purity) in faeces derived from 11 volunteers under anaerobic conditions for 72 hours. Steviosides are hydrolyzed to steviol aglycones within 10 hours and rebaudiosides within 12 hours. Steviol remained unchanged for 72 hours, indicating that bacterial enzymes could not break down the steviol structure (Gardana et al. 2003, Raini and Isnawati 2011).

Research on the metabolism of steviol in rats and humans was carried out using human liver microsomal preparations derived from 10 donors and rat liver microsomal preparations. The metabolite profile obtained from human liver microsomes was similar to that of mice, mass spectroscopic analysis showed the presence of 2 dihydroxy metabolites and 4 monohydroxy metabolites. One additional mono hydroxy metabolite was present in the rat preparations. Liver microsomal clearance of steviol in humans is 4 times lower than in mice (Wang et al. 2004 in Raini and Isnawati 2011).

8. Plant Pest Organisms on *Stevia rebaudiana* plants

Pests that commonly attack stevia plants include: aphids (*Aphis* sp.), armyworm (*Heliothis* sp.), grasshoppers, and caterpillars. While the diseases that are often found include: root rot, *Sclerotium rolfsiii wilt disease, Alternaria alternata* leaf spot, and *Fusarium* sp.

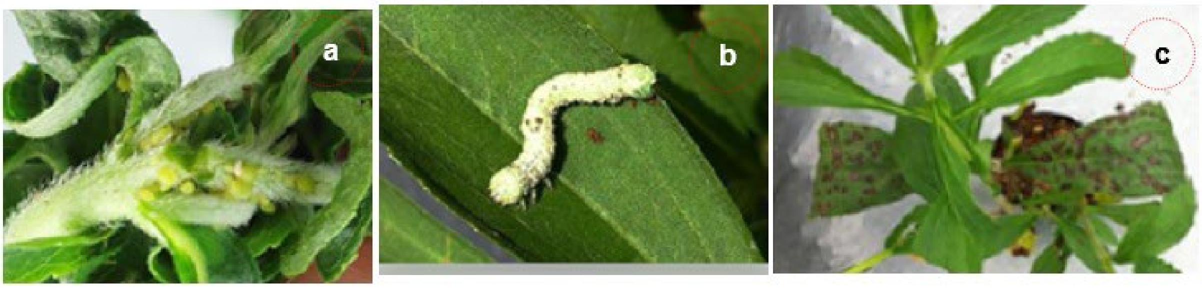


Figure 4. (a) *Aphis* sp., (b) *Heliothis* sp., and (c) leaf spot

Source: https://ditjenbun.pertanian.go.id/mengenal-stevia-pemanis-pengganti-gula-dari-tanaman-stevia-rebaudiana-dan-pengendalian-opt-secara-pht/

8.1 Control by technical culture

Control by technical culture can be done by garden sanitation and fertilizer application. Garden sanitation is carried out through manual weed control or by installing plastic mulch. *Stevia rebaudiana* plants are known to be very weak in competing with weeds, especially at the start of growth. Weed control should be done before weeds flower and seed to reduce weed seed reserves in the soil. Weed growth decreases after the *Stevia rebaudiana* plant canopy covers the soil surface. Garden sanitation is accompanied by applying urea, TSP, and KCL fertilizers at a dose of 1 g each per plant after one week of planting. Fertilization is repeated every time after harvest.

8.2 Mechanical control

Mechanical control can be done by pruning and manual control. Pruning the *Stevia rebaudiana* plant is done when it is about 2 weeks old by pruning each end of the plant so that branches form and produce more leaves. Pruning is also done on the leaves attacked by plant pest oganisms. Control is done manually by taking pests or affected plant parts, then destroying them so they do not spread to other healthy plants.

8.3 Biological control

The type of disease that causes many stevia plants to wilt is the fungus *Poria hypolateria*. Priority control uses biological control agents (APH) or APH secondary metabolites.

8.4 Control with vegetable pesticides

The most common pests that attack stevia plants are aphids (*Aphis* sp.) which damage leaf shoots and caterpillars *Heliothis* sp. eat leaves. Both types of pests can be controlled with vegetable pesticides in the form of neem seed extract.

9. Uses of the Stevia Plant

Stevia has many health benefits that more than 500 studies have proved; It does not affect blood sugar levels, is safe for people with diabetes, prevents tooth decay by inhibiting the growth of bacteria in the mouth, helps improve digestion, and relieves stomach pain. It is good for managing weight, to limit high-calorie sweet foods (Raini and Isnawati 2011). In addition, Kiat (2013) added that the benefits of stevia are that it contains zero calories, loses weight because insulin regulates the body stores less fat, improves digestive function, is good for children with special needs (autism), lowers blood pressure, and reduces inflammation.

Studies in Indonesia have shown that stevia does not break down at high temperatures as saccharin or aspartame. Steviosides are heat resistant up to 200°C (392°Fahrenheit), so they can be used in almost all food recipes (Raini and Isnawati 2011).

Natural sweeteners derived from stevia are safe for health. This is evidenced by reports of no adverse effects on the people of Paraguay who have been using stevia leaves as a sweetener in their drinks and beverages for more than one hundred years. Research in Japan reported that rabbits and rats given stevia leaf extract or pure stevioside did not cause negative effects on growth, behavior, reproduction, and other characteristics (Adinegoro 1986).

10. How to Use The Stevia Plant

According to Kiat (2013), Stevia leaves can be directly used as a sweetener. The way to use it is by drying it. The drying process does not require high heat. It is enough to dry in the sun for about 12 hours on a household scale. Drying it more will reduce the stevioside levels by drying the stevia leaves in the microwave for 2 minutes, then pulverizing them. This powder can be directly consumed as a food sweetener.

Stevia sweetener can also be made in liquid form, namely by soaking it for 24 hours and then storing it in the refrigerator. The ratio of water to stevia is 1:4. Do not use stevia directly if the leaves are exposed to pesticides or other chemicals. It is better to wash it thoroughly before soaking it so that it is not contaminated with substances harmful to health.

11. Stevia leaf drying and storage process:

People in Indonesia cut stevia branches 10-15 cm high from the ground, then pick off the leaves. They do not use Stevia leaves contaminated with pesticides or chemical fertilizers.

- They wash and rinse the stevia leaves under running water until clean.
- They dry the stevia leaves with a clean towel or tissue, or simply drain until the water is gone.
- They place the leaf in direct sunlight.

• They let the stevia leaves dry but remain green in color, crunchy, and crumble to the touch. Approximately it takes 2-3 days for stevia leaves to dry. Do not dry it too long because the leaves turn brown and will yield low.

• They crush the dried stevia leaves using a coffee grinder, or you can also crush them using the back of a spoon by placing the dried leaves in a bowl or crushing them with a mortar.

• They store stevia leaf powder in a glass bottle with a lid in a cool and dry place.

12. Conclusion

Stevia has many health benefits, does not affect blood sugar levels, is safe for people with diabetes, prevents tooth decay by inhibiting the growth of bacteria in the mouth, helps improve digestion and relieves stomach pain. Good for managing weight, to limit high-calorie sweets. Apart from that, other benefits of stevia are that it contains zero calories, loses weight because insulin regulates the body stores less fat, improves digestive function, is good for children with special needs (autism), lowers blood pressure, and reduces inflammation. Stevia plant has the potential for development as a source of natural sweeteners, and as a medicine for diabetes, with bright prospects in the future.

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