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REVIEW

Stevia rebaudiana as a nutraceutical for COVID-19 patients with no sugar diet during recovery and its nanoparticle application

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Abstract

Introduction: Some patients with comorbidity such as diabetes are at risk of worsening after being infected with the COVID-19 and they usually adjust their diet during the recovery process. **Aim:** To explore the use of *Stevia rebaudiana* leaves as a natural sweetener recommended for COVID-19 patients and the nanoparticle approach of S. rebaudiana extract to improve the efficacy. **Methods:** Four electronic databases (Google Scholar, PubMed, Scopus, and ScienceDirect) were used with specified inclusion and exclusion criteria set. **Results:** The glycosides produced by *S. rebaudiana* are 300 times sweeter than sucrose, low in calories, and can control blood sugar levels and increase insulin secretion. The application of nanoparticles in *S. rebaudiana* extract is a new step to maximise efficacy, increase stability and solubility. **Conclusion:** *S. rebaudiana* can be used as an alternative diet for COVID-19 diabetes patients. The application of the nanoparticles can increase the stability and solubility, thus improving the efficacy.

Introduction

The coronavirus disease known as COVID-19 is a respiratory infectious disease caused by the severe acute syndrome coronavirus-2 (SARS-CoV-2) (Nugraha *et al.*, 2020). The first case has been reported to have occurred in Wuhan, China, in December 2019 and has spread to Indonesia. The Indonesian government reported 2,983,830 confirmed cases, 77,583 COVID-19 related deaths reported, and 2,356,553 patients have recovered on 21 July 2021 (WHO, 2021). Some patients mostly have co-morbidities when they get infected and may worsen their condition, such as hypertension (52.1%), diabetes mellitus (33.6%), and other cardiovascular diseases (20.9%). The rate of hospital admission and self-quarantine for diabetic patients became 2% (Karyono and Wicaksana, 2020). Researchers have identified that poor glucose homeostasis and inflammation were the cause of worsened patient outcome, thus increasing the risk of extended hospital stay and ICU admission (Roncon *et al*., 2020). COVID-19 patients with diabetes still need to maintain their diet by consuming more nutritious foods during the recovery period. The use of artificial sweeteners such as aspartame, saccharin, sucralose, and acesulfame have a variety of adverse effects including a negative taste profile, increased risk of metabolic syndrome and obesity, changes in the gut microbiota, neurotransmitter disturbances, and negative pregnancy outcomes (Ray *et al*., 2020). This paper is a review on the use of *S. rebaudiana* as a natural sweetener for COVID-19 patients. The study explores the pharmacological effect that accelerate healing of COVID-19 theraphy in comorbidity patients, and nanoparticle application in *S. rebaudiana.*

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Methods

The reference data used in this review were obtained from journals regarding the potential of *Stevia rebaudiana* Bertoni leaves as a natural sweetener for COVID-19 patients who have diabetes mellitus through websites that provide online journals (Google Scholar, PubMed, Scopus, and ScienceDirect). The search strategy included the following terms: *Stevia rebaudiana*, natural sweetener, sweet herb, *Stevia*, Stevioside, rebaudioside A, chemical composition, covid-19, diabetes mellitus, insulin, nanoparticle, pharmacology, nutritional value. Any indexed terms equivalent to "*Stevia rebaudiana*", "Nutritional Value", "COVID-19", "nanoparticle", "pharmacology" were also searched to extend the search coverage. Determination of inclusion criteria are data in the form of national and international journals, textbooks or scientific articles, including *S. rebaudiana* as an application of natural sweetener and nanoparticle. The exclusion criteria are data obtained from invalid sources such as the websites without the authors or theses, journals both national and international, textbooks, scientific articles and also data containing specific species of other species in the same genus. The selected references are journals released in the last ten years (2011 to 2021).

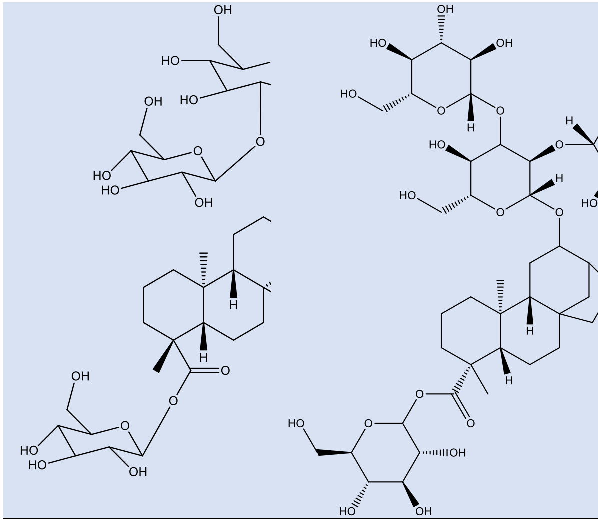
Results

The search strategy identified 85 articles from Google Scholar (30), PubMed (19), Scopus (15), ScienceDirect (21) databases. Forty (40) articles were excluded because they did not conform to the combination of the descriptor, whereas eight (8) were excluded due to duplication. Thirty-seven (37) articles were used in the present review, and all articles meet the categories.

Botanical description

S. rebaudiana (Figure 1) is a source of natural sweetener that has a sweetness level of 200-300 times sweeter than cane sugar. Stevia can provide a way out for consumers who cannot or should not consume sugar/cane sugar, especially patients infected with COVID-19 and diabetes mellitus, because stevia sugar is safer than artificial sweeteners. This sweet taste is produced from the leaves of the stevia plant due to the glycoside content (stevioside and rebaudioside A) in the stevia leaves (Figure 2) (Permatasari *et al*., 2018; Salehi *et al*., 2019). This glycoside is a compound consisting of sugar and non-sugar moiety (aglucon) (Widodo *et al*., 2015). Additionally, *stevia* is also reported to have an antihyperglycemic and anti-inflammatory effect that shows great promise for use in the diet of COVID-19 diabetic patients during recovery (Boonkaewwan & Burodom, 2013; Sing *et al.,* 2013).

Figure 1: *Stevia rebaudiana* (Hossain *et al.*, 2017)



A. Stevioside B. Rebaudioside A

Figure 2: Chemical structure of glycosides in *S. rebaudiana*

Stevia is a shrub from the sunflower family (Asteraceae), has a genus of about 240 species, and is native to South America. Of the 240 species, only *S. rebaudiana* is used as a sweetener, so it is known as "the sweet herb of Paraguay" (Limanto, 2017). The plant is a perennial herb with a wide root system, fragile stem and weak pubescent hairs at the bottom, producing small oval leaves. It grows 65 cm to 1 m high. The leaves are sessile, 3-4 cm long, slender lanceolate to oblanceolate, the leaves are blunt-pointed, with serrated edges from the middle to the tip. The upper surface of the leaf is slightly granular. The rhizome has slightly branched roots (Zlabur *et al*., 2013; Alahmad, 2018).

Chemical composition

Known as 'the sweet herb of Paraguay', *S. rebaudiana* was first scientifically coined by Moises S. Bertoni (Table I) (Lemus-Mondaca *et al*., 2018).

Table I: Research results from several journals related to the bioactive composition contained in *S. rebaudiana*

Description	Component	Reference
Chemical composition of dry stevia leaves	Protein, Fats, Ash, Carbohydrates, Dietary fibre and Reducing sugars	(Gupta *et al*., 2013; Gasmalla *et al*., 2014)
Amino acid composition of stevia leaves	Arginine, Lysine, Histidine, Phenylalanine, Leucine, Methionine, Valine, Threonine and Isoleucine	(Li *et al*., 2011; Gupta *et al*., 2013)
The composition of fatty acids in oil from stevia leaves	Palmitic acid, Oleopalmitic acid, Stearic acid, Oleic acid, Linolic acid and Linolenic acid	(Atteh *et al*., 2011 ; Gupta *et al*., 2013)
Contents of water-soluble vitamins in *Stevia rebaudiana*	Vitamin C, Vitamin B2, Vitamin B6, Folic acid, Niacin and Thiamine	(Kim *et al*., 2011)
Contents of minerals in dried leaves of Stevia rebaudiana	Calcium, Phosphorus, Sodium, Potassium, Iron, Magnesium and Zinc	(Atteh *et al*., 2011)
Contents of glycosides in leaves of *Stevia rebaudiana*	Stevioside, Steviolbioside, Rebaudioside A, Rebaudioside B, Rebaudioside C, Rebaudioside D, Rebaudioside F and Dulcoside	(Ashwell, 2015)
Contents of polyphenols and flavanols in stevia extract	Polyphenols and flavonoid	(Mutmainah *et al*., 2019)

Pharmacological activities

Anti-hyperglycemia

Research conducted by Singh and colleagues in 2013 showed that stevia significantly reduced the average serum glucose levels in mice induced by alloxan. The 21-day treatment with *stevia* leaf extract caused a significant decrease in sugar content of 39.84% (193.0 ± 63.57 to 116.1 ± 41.03) in the treatment group (Singh *et al*., 2013). Stevia is also able to increase insulin secretion, which has been proven by Philippaert and colleagues in the transient receptor potential cation channel subfamily melastatin 5 (TPRM 5). These receptors are involved in taste perception and insulin secretion from the pancreas. The whole-cell patch-clamp technique was used to measure the current through the TRPM5 channel and found that in the presence of steviol and stevioside, there was an increase in the frequency of Ca^{2+} oscillations in the cells and a delay in the inactivation of Ca^{2+}-activated TRPM5 current (Philippaert *et al*., 2017).

Anti-inflammatory

Administration of stevioside to insulin-resistant mice showed a decrease in the regulation of the NF- kB pathway, an increase in insulin sensitivity, the degree of the glucose-lowering effect of insulin, and the rate of glucose infusion. In addition, there was a significant downregulation of TNFα expression (a proinflammatory cytokine that contributes to decreased insulin sensitivity) and IL-6, IL-10, and IL 1β expression. It can reduce inflammation through down-regulation of TNFα in adipose tissue by stevioside to reduce insulin resistance in diabetic patients (Wang *et al.*, 2012).

Anti-hyperlipidemic

Research conducted by Ray and the authors in 2020 showed that stevioside could significantly reduce total cholesterol, triglyceride, LDL-C significantly in 20 hypercholesterolemic women, while an increase in HDL-C was noted, which is desirable (Ray *et al.*, 2020). Stevioside decreased triglyceride levels through stimulation of lipase enzyme activity produced by the liver, which resulted in lipid catabolism as well as increased excretion of triglycerides through faeces. Decreased LDL levels from stevioside are explained through the mechanism of increasing LDL receptors and modulating cholesterol metabolism (Aghajanyan *et al*., 2017; Ahmad *et al.*, 2018; Latarissa *et al*., 2020).

Stevia and Nutraceutical

Nutraceutical, which consists of nutrient or nutritive and pharmaceutical, are understood as foods of food ingredients that help prevent or treat illness. Nutraceuticals can be classified into two categories: natural or traditional and unnatural or non-traditional (Shinde *et al.,* 2014; Nwosu and Ubaoji, 2020). Traditional nutraceuticals are natural products such as omega-3 in fish, saponins in soybeans, and flavonoids in oranges. Herbal nutraceuticals have the function of promoting health and preventing chronic disease. Some examples are alliin and allicin in garlic which have anti-inflammatory, antibacterial, and anti-gout effects. Zingiberene and gingerol in ginger are useful as stimulants, chronic bronchitis, and hyperglycemia (Chauhan *et al*., 2013).

Stevia has been useful as a neutraceutical for a long time. The newest status of stevia from the Joint FAO/WHO Expert Committee on Food Additives (JECFA) is a dietary supplement (an artificial sweetener with relatively low side effects (ADI: 4 mg/kg body weight) (Chughtai *et al*., 2020). Stevia leaves are classified as low-calorie sweeteners with a high sweetness intensity compared to other low-calorie sweeteners. The Stevia leaf's protein content can be obtained around 10 - 20.4 grams/100 grams of products. There are seventeen amino acids found in stevia leaves which include lysine, glutamic acid, serine, aspartic acid, alanine, tyrosine, L-isoleucine, proline, methionine, etc. Stevia leaves also contain micronutrients such as calcium, sodium, potassium, magnesium, iron, and zinc. Researchers have reported that vitamin C can be found in its leaves, with levels ranging around 14.98 mg/100 grams of water extract. The folic acid content is known to be 52.18 mg/100 grams of its water extract (Kristanto & Hartono, 2021).

Nanoparticles application

Basically, the use of natural ingredients directly for treatment has drawbacks, such as frequent failures in the clinical phase due to low bioavailability, causing the drug to undergo morphological damage and biological aspects that can reduce concentration and solubility. Therefore, the nanoparticle-based drug delivery system becomes a new strategy in delivering drugs, especially intracellular delivery. With the nanotechnology system, the drug will be protected by encapsulating it to keep the drug during drug delivery to the target and also provide improvements to the stability and solubility as well as the pharmacokinetic profile of these drugs. This will ensure that dosage forms with controlled small molecule drug delivery devices that have high sensitivity and low toxicity are produced (Martien *et al*., 2012).

Stevioside has proven to be a potent antidiabetic, anti-inflammatory, and antihyperlipidemic agent but has several disadvantages such as insufficient intestinal absorption, which reduces its bioavailability, low persistence, and degradation in metabolism. According to Barwal and his colleagues, stevioside can improve intestinal absorption and bioavailability by formulating it into nanoencapsulation using Pluronic-F-68-PLA nanoparticles (Barwal *et al*., 2013). Stevioside-loaded Pluronic-F-68-PLA nanoparticles had encapsulation efficiency, and drug load were 64.4% and 16.32%, respectively. The size of this nanoparticle was 132 ± 10 nm according to Scanning Electron Microscopy (SEM) analysis, and the Transmission electron microscopy (TEM) showed a diameter of 125 ± 8 nm. The in-vitro release of stevioside-loaded Pluronic-F-68-PLA nanoparticles showed initial burst and then sustained release with half burst in 25 ± 4 hours and full burst in 200 ± 10 hours (Barwal *et al*., 2013).

In a study done by Bujak and the authors, the DPPH method showed that the antioxidant activity of the extract of Silver nanoparticles (AgNPs) was higher than that of the Stevia extract alone (Bujak *et al*., 2015). Another study conducted by Majlesi and his colleagues also showed significant changes observed in glycosides in plants under the treatment of synthesized and commercially available AgNPs, which can be used to make plants with higher glycosides useful for pharmaceutical purposes (Majlesi *et al*., 2018). There was also another study conducted by Srihasam and authors regarding the generation of phytogenic nanoparticles using Stevia leaf extract and the in-Vitro evaluation of antioxidant and antimicrobial properties. The prepared nanoparticles strongly inhibit gram-negative bacteria, which are campers with gram-positive bacteria and fungi. In addition, it performs effective in-vitro activity through DPPH reduction (Srihasam *et al*., 2020).

Conclusion

Stevia is good for use in humans, especially in COVID-19 patients with diabetes mellitus. There are therapeutic benefits such as antihyperglycemic anti-inflammatory, and its nutritional benefits could help the patient recover from the disease while maintaining the diet. The nanoparticle encapsulation system can provide improvements in the stability and solubility as well as the pharmacokinetic profile of *S. rebaudiana,* which has drawbacks in direct use.

Conflict of interest

The authors have no conflict of interest associated with the material presented in this paper.

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