Cognitive Vitality Reports® are reports written by neuroscientists at the Alzheimer's Drug Discovery Foundation (ADDF). These scientific reports include analysis of drugs, drugs-in-development, drug targets, supplements, nutraceuticals, food/drink, non-pharmacologic interventions, and risk factors. Neuroscientists evaluate the potential benefit (or harm) for brain health, as well as for age-related health concerns that can affect brain health (e.g., cardiovascular diseases, cancers, diabetes/metabolic syndrome). In addition, these reports include evaluation of safety data, from clinical trials if available, and from preclinical models.

Stevia

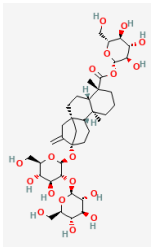
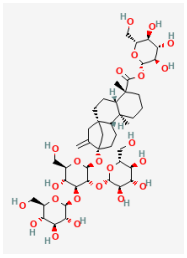
Evidence Summary

Stevia is a low-calorie natural sweetener with a strong safety profile. It doesn't impact glucose tolerance at recommended doses in most people, but chronic use may impact metabolism via the microbiome.

Neuroprotective Benefit: Stevia consumption can potentially impact memory by affecting the microbiome, but there is no clear evidence of this in humans to date. Chronic stevia use may alter reward signaling to sweet taste.

Aging and related health concerns: At recommended dose ranges, stevia can induce sweet tastes without glycemic effects as a sugar substitute. At higher doses, stevia extracts may induce hypoglycemic and hypotensive effects in some populations.

Safety: Highly purified steviol glycosides are non-toxic natural sweeteners at recommended doses. Chronic consumption of stevia may be more likely to affect metabolism and sweet preferences in children relative to adults.

Availability: OTC	**Dose**: Acceptable daily intake as a food additive sweetener 4 mg/kg bw	**Stevioside** **Chemical formula:** $C_{38}H_{60}O_{18}$ **MW**: 804.9 g/mol  Source: PubChem **Rebaudioside A** **Chemical Formula**: $C_{44}H_{70}O_{23}$ **MW**: 967.0 g/mol  Source: PubChem
Half-life: ~ 14 hours	**BBB**: Steviol glycosides are not penetrant. The penetrance of steviol metabolites is unclear.	
Clinical trials: Steviol glycosides have primarily been tested in small trials (n= 10s-100s) examining their metabolic/glycemic effects in healthy individuals and those with metabolic diseases.	**Observational studies**: *Stevia* leaves have been used as part of traditional medicine for cardiovascular effects in South America for thousands of years.	

What is it?

Stevia is a low-calorie sweetener approved for use as a food additive [1]. *Stevia* refers to a genus of shrubs and herbs in the Asteraceae family, which is related to asters and chrysanthemums. Only 18 of the over 200 varieties of *Stevia* are sweet, with *Stevia rebaudiana* (Bertoni), which is endemic to South America, particularly Paraguay and Brazil, as the sweetest variety. *Stevia* leaves have been cultivated for thousands of years for use in traditional herbal medicine. *Stevia* extracts have been reported to have anti-diabetic and anti-microbial properties. The sweetness of *Stevia* leaves stems from the presence of steviol glycosides. Stevioside and rebaudioside A are the major glycosides, though the glycoside profile varies depending on the species and the growing conditions. Stevioside is 300-fold sweeter than sucrose

(0.4% solution) and rebaudioside A is 450-fold sweeter than sucrose. At low levels, they have a cleanly sweet taste, but at higher levels they can have a bitter aftertaste. Highly purified steviol glycosides (>95%) have been approved for use as natural sweeteners. Steviol glycosides are popular substitutes for sugar because they contribute sweetness without adding calories or contributing to the development of dental caries. *Stevia* leaves contain a variety of bioactive compounds, including phenols, such that the pharmacological profiles of *Stevia* leaf preparations and purified steviol glycosides are likely to differ. The impacts of steviol glycosides on metabolic and cardiovascular parameters have been investigated in clinical studies. The use of steviol glycosides within the approved acceptable daily intake (ADI) level of 4 mg/kg body weight (bw) has largely been found to be physiologically neutral in healthy people, while much higher doses have shown evidence of glycemic and hypotensive effects in some populations. Steviol glycosides do not have a direct effect on the body; they are metabolized by the gut microbiome. They may exert effects via the modulation of the microbiome [2], and high levels of the steviol metabolites may have physiological effects.

Neuroprotective Benefit: Stevia consumption can potentially impact memory by affecting the microbiome, but there is no clear evidence of this is humans to date. Chronic stevia use may alter reward signaling to sweet taste.

Types of evidence:

- 1 clinical trial on stevia consumption and neurological function
- 1 clinical brain imaging study following stevia consumption
- Numerous laboratory studies

Human research to suggest prevention of dementia, prevention of decline, or improved cognitive function:

Stevia has been shown to influence brain activity in brain regions associated with taste perception and reward [3], but there is currently no clear evidence to indicate that stevia consumption influences cognitive function in humans. One study assessing the impact of daily consumption of 4 grams per day of commercially available steviol glycosides sweetener for six weeks found no effect on overall memory score or executive function using the Neuropsi test battery, though there was a trend toward better encoding memory score ($p = 0.0466$) in a cohort of 39 healthy, normal weight young adults (age 18-35) [4]. Additionally, there were no significant differences in brain activity based on quantitative EEG.

Human research to suggest benefits to patients with dementia:

Stevia has not been clinically tested in dementia patients, so it is unclear if the pharmacological profile would be affected. Studies suggest that the impacts to metabolic function are largely a function of the composition of the microbiome [2]. Since the microbiome has been found to be altered in the context of various neurodegenerative diseases [5], stevia consumption may potentially affect the composition of microbial-derived metabolites, including those with psychoactive properties, in a different manner than in healthy adults.

Mechanisms of action for neuroprotection identified from laboratory and clinical research:

Modulation of microbiome: Clinical and preclinical studies have found that stevia can influence the composition of the microbiome, which, in turn, can potentially impact metabolism and cognitive function by altering the composition of gut derived metabolites. This appears to be most impactful during development, although some preclinical studies have found that chronic use can also affect these parameters in adult animals. A high *Bacteroidetes* and low *Firmicutes* ratio in the gut microbiome has been associated with features of metabolic syndrome, such as insulin resistance, obesity, and inflammation [6]. The microbiome composition, including the balance between *Bacteroidetes* and *Firmicutes*, was found to be altered in the male offspring of rats fed a high-stevia diet during gestation and lactation [7]. This shift was associated with worse performance on the Barnes maze, a measure of learning and memory. Similarly, rats fed a stevia-enriched diet (~4 mg/kg) during adolescence showed contextual episodic memory deficits on a hippocampal dependent task [8]. Spatial memory deficits were also observed in the males. Chronic low-dose consumption of rebaudioside A starting at three weeks of age altered the gut microbiome composition of male rats, reducing the abundance of some beneficial species, and altered the profile of microbiota-derived short chain fatty acids in a manner associated with obesity [9]. Chronic (18 weeks) consumption of a stevia-enriched diet (3.4 mg/kg/day), which is within the acceptable daily intake (ADI), led to a reduction in performance on measures of long-term memory in adult male rats [10]. The stevia fed rodents also showed an increase in systolic blood pressure and circulating blood lipids, including total cholesterol, LDL-cholesterol, and triglycerides. Since the effects on memory appear to be dependent on alterations to the microbiome, the potential impacts of stevia consumption are likely to be highly variable across individuals depending on their baseline microbiome composition, diet, and level of stevia consumption.

Synaptic plasticity: Preclinical studies suggest that stevia may be able to influence neuronal activity. Stevia leaf extract has been shown to exert anti-inflammatory and antioxidant activity [1]. Treatment with stevia leaf powder (20 mg/kg) was found to protect rats against altered plasticity in the entorhinal-hippocampus-amygdala cortical network related to a high-fructose diet [11]. The protective effects appear to be mediated by its anti-inflammatory activity, which is likely related to compounds in the leaf extract other than the steviol glycosides.
Similar to sugar, stevia has been shown to alter activity in the nucleus accumbens, in both rodents and humans [3; 12]. Preferences for sweet taste are altered in rodents in response to chronic consumption of non-nutritive sweeteners during adolescence, which may be related to altered taste receptor expression and glutamatergic plasticity in the nucleus accumbens, suggestive of altered reward signaling [8].

APOE4 interactions: Not established.

Aging and related health concerns: At recommended dose ranges, stevia can induce sweet tastes without glycemic effects as a sugar substitute. At higher doses, stevia extracts may induce hypoglycemic and hypotensive effects in some populations.

Types of evidence:

- 4 meta-analyses of RCTs testing steviol glycosides
- 6 clinical trials testing steviol glycosides
- Numerous laboratory studies

Diabetes: POTENTIAL BENEFIT AT DOSES ABOVE ACCETABLE DAILY INTAKE (ADI)
Stevia leaf has long been used for its anti-hyperglycemic properties as part of traditional medicine in South America. Steviol glycosides do not raise blood sugar levels, and have been shown to promote insulin sensitivity in some diabetic populations and animal models. Meanwhile clinical studies suggest that they do not significantly impact glucose homeostasis parameters in healthy normoglycemic individuals. Whether stevia has a hypoglycemic or neutral effect depends on the preparation, dose, and the population. Studies have generally shown that the consumption of steviol glycosides has a neutral effect on glycemic parameters in normoglycemic individuals and a potentially stabilizing effect in diabetic populations. Some studies using whole leaf preparations, as would be used in traditional medicine, have shown hypoglycemic effects, which may be related to some of the other compounds in the plant. Additionally, the doses of stevia used as herbal medicine are far higher than would be

consumed as a sweetener. Overall, the replacement of dietary sugar with stevia may help prevent the exacerbation of metabolic dysfunction in diabetics, but would not be expected to have a therapeutic effect. There is currently no established preparation or dose of stevia leaves with clinically meaningful anti-diabetic properties.

A systematic review and network meta-analysis of 36 clinical trials testing non-nutritive sweetened beverages in 472 predominantly healthy participants examined postprandial glycemic and endocrine responses [10]. Non-nutritive sweetened beverages showed no significant acute effects on postprandial glucose or insulin responses, with postprandial GLP-1, GIP, PYY, ghrelin, and glucagon responses showing a similar profile to water controls.

A meta-analysis of nine RCTs including 462 participants examining the impact of steviol glycosides on biomarkers of type 2 diabetes found trends toward reductions, but no significant effects on levels of glycated hemoglobin (HbA1c), total cholesterol, fasting blood glucose, or body mass index (BMI) [13]. Differences in the utilization of concomitant anti-diabetic medications complicates the interpretation of these studies. While most studies did not show significant reductions in glycemic parameters, several showed evidence for stabilization. Several studies showed no change from baseline for HbA1c or fasting glucose with steviol glycoside preparations, but an increase in these glycemic measures in the placebo group. No changes in glycemic parameters, such as HbA1c, were seen in an open-label study of 45 overweight adults, 21 of which were prediabetic, after replacing dietary added sugar with a stevia-based sweetener for 90 days [14]. In the SWEET beverages trial (NCT04483180) (n=60), consumption of a stevia rebaudioside A- thaumatin based sweetener blend resulted in lower 2-hour area under the curve measures for blood insulin and glucose, relative to a sucrose (8%) sweetened beverage [15]. Meanwhile, a study testing 1 gram per day of *Stevia* leaf powder for 60 days in patients with type 2 diabetes (n=20) saw significant reductions in fasting blood glucose (123.55 ± 22.94 mg/dL vs. 155.29 ± 36.54 mg/dL) and postprandial blood glucose (200.60 ± 43.80 mg/dL vs. 228.35 ± 9.82 mg/dL) relative to the control group [16]. Notably, a chemical analysis of the *Stevia* leaf powder indicated that it contained a variety of potentially bioactive chemical compounds in addition to the glycosides, such as labdanediterpenes, triterpenes, stigmasterol, tannins, and volatile oils. A meta-analysis of nine preclinical studies found that stevia leaf doses of 200, 300, and 400 mg/kg reduced blood glucose levels in rodents, though there was a high degree of heterogeneity across studies [17].

Stevia contains a variety of glycosides, which may differ in their anti-diabetic properties. A study in rodent models of diabetes found that the anti-hyperglycemic properties of steviol glycosides were more prominent in compounds with fewer glucosyl moieties attached to the steviol glycone [18]. The anti-diabetic performance followed the order of steviol > steviol glucosyl ester > steviolbioside > rubusoside > stevioside > rebaudioside A, which is generally in reverse order of sweetness. This suggests that

steviol, which is the common metabolite of all steviol glycosides, may be the primary mediator of the anti-diabetic effects of steviol glycosides *in vivo*.
Preclinical studies have identified several potential mechanisms by which *Stevia* may exert its anti-diabetic effects. Stevia extract and stevioside have been shown to activate PPARα-mediated lipophagy in hepatic cells, and enhance mitochondrial activity in the skeletal muscle cells of diabetic (db/db) mice [19; 20]. Steviol glycosides have also been shown to stimulate insulin secretion from pancreatic β-cells *in vitro* [21].

Hypertension: POTENTIAL HYPOTENSIVE EFFECT AT DOSES ABOVE ADI
Stevia leaf preparations have shown hypotensive effects in animal models and in the context of traditional medicine, however, the effects have been less consistent in clinical trials [22]. This may be related to the use of different preparations, as clinical trials typically use highly purified components rather than whole leaf extracts, as well as differences in dose. Additionally, the hypotensive effects appear most prominently in hypertensive individuals relative to normotensive individuals. A significant reduction was seen in systolic blood pressure relative to placebo (Mean Difference [MD]: −6.32 mm Hg, 95% Confidence Interval [CI] −10.17 to −2.46; p = 0.001), in a meta-analysis of nine RCTs (n=462) testing steivol glycosides, including both diabetic and non-diabetic populations, but the effect was only significant in non-diabetic individuals [13]. In a study including 168 patients with mild essential hypertension, supplementation with 500 mg capsules of stevioside powder three times per day for two years was associated with reductions in systolic blood pressure from 150± 7.3 to 140 ± 6.8 mm Hg and diastolic blood pressure from 95 ± 4.2 to 89 ± 3.2 mm Hg, which were significant reductions relative to placebo [23]. A placebo controlled RCT including 106 adults with hypertension found significant reductions in both systolic blood pressure from 166.5 ± 7.4 to 152.6 ± 6.8 mm Hg and diastolic blood pressure from 102.1 ± 4.0 to 90.3 ± 3.6 mm Hg with 250 mg stevioside three times per day for three months [24]. Significant reductions were seen within two weeks and remained throughout the duration of the year-long trial. In a three-month RCT (n=76) testing 250 mg of stevioside three times per day, there was a small reduction in systolic blood pressure (108.3 ± 3.0 to 105.7 ± 2.8 mm Hg) in participants with type 1 diabetes (n=16), but no significant effects on systolic or diastolic blood pressure in participants with type 2 diabetes (n=30) or non-diabetics (n=30) in response to stevioside [25]. In contrast, hypotensive effects have not been seen in clinical trials testing purified rebaudioside A [22]. The difference in the anti-hypertensive potential of the steviol glycosides may be related to differences in the production of downstream metabolites, steviol and steviol glucuronide [21]. Steviol glycosides are metabolized into steviol in the colon by gut microbiota, which is then absorbed into the blood and rapidly converted to steviol glucuronide in the liver. A pharmacokinetics study in healthy adult men

found that rebaudioside A led to approximately 22% lower levels of steviol glucuronide in the plasma compared to stevioside [26].

Lipidemia: NO CLEAR EFFECT

Various clinical and preclinical studies have found small alterations to the circulating lipid profile in response to stevia consumption, though generally under the thresholds for statistical or clinical significance.

A meta-analysis of 14 RCTs, including five studies using stevia-based sweeteners (n=509), assessing the impact of non-nutritive sweeteners on the lipid profile found no significant effects on total cholesterol, LDL, HDL, or triglycerides [27]. In a subgroup analysis, a small increase in LDL was seen in individuals with normal (<100 mg/dL) LDL levels (weighted mean difference [WMD]: 4.23 mg/dL, 95% CI 0.50 to 7.96 mg/dL). A meta-analysis of nine RCTs (n=462) found non-significant trends toward reductions in total cholesterol and HDL-cholesterol, as well as non-significant trends toward increases in LDL-cholesterol and triglycerides in response to consumption of steviol glycosides ranging from three months to two years [13]. The SWEET beverages trial (n=60) showed a 3% increase in LDL-cholesterol following consumption of a rebaudioside A- thaumatin sweetened beverage relative to a sucrose sweetened beverage [15].

Discrepancies across studies may depend on the type and purity of the stevia extract used. A hypolipidemia effect was only seen in one clinical study using a stevia leaf extract, whereas studies using highly purified steviol glycosides, such as those approved for use as natural sweeteners, have been more likely to show no effect or even a slight hyperlipidemic effect. The study found that 20 mL/day of a stevia leaf extract reduced levels of total cholesterol, LDL-cholesterol, and triglycerides, while raising HDL-cholesterol in 20 women with hypercholesteremia [28]. Hypolipidemic effects have also been seen in some preclinical studies using *Stevia* leaf extracts [22]. This suggests that components in the *Stevia* leaves other than the glycosides, such as its phenolic components, may be responsible for the potential hypolipidemic effects, such that consumption of stevia as a natural sweetener is unlikely to have a significant effect on the blood lipid profile in the majority of people.

Obesity: POTENTIAL BENEFIT FOR WEIGHT MANAGEMENT

As a non-nutritive sweetener, replacement of sugar (i.e. sucrose) with stevia has been proposed as a strategy for weight management. The majority of clinical studies examining the effect of stevia consumption have found little to no effect on anthropometric indices. A meta-analysis of 20 RCTs testing non-nutritive sweeteners, including eight studies with stevia (n=591 participants), found that there were small effects on the reduction of body weight (WMD: -1.02 kg, 95% CI -1.57 to -0.46 kg), fat mass (WMD:

-1.09 kg, 95% CI -1.90 to -0.29 kg), and free fat mass (WMD: -0.83 kg, 95% CI -1.42 to -0.23 kg), but no significant effects on (WMD: -0.16 kg/m^2, 95% CI -0.35 to 0.02 kg/m^2), waist circumference (WMD: -1.03 cm, 95% CI -2.77 to 0.72 cm), or serum leptin levels (WMD: -2.17 ng/mL, 95% CI -4.98 to 0.65 ng/mL) [29]. There is a high degree of heterogeneity across studies due to variation with the particular sweetener and the study design.

Some cohort studies have found increases in weight with chronic consumption of non-nutritive sweeteners, though there is a high risk for confounding, as individuals with pre-existing metabolic dysfunction may increase consumption of non-nutritive sweeteners as part of a weight management strategy. Nevertheless, there is evidence to suggest that non-nutritive sweeteners, including stevia, could potentially influence food consumption and weight by increasing cravings for sweet foods and altering the gut microbiome. Steviol glycosides can activate the T1R2/T1R3 sweet taste receptor [21]. Brain imaging indicates that consumption of a stevia-sweetened beverage activates both gustatory and reward areas of the brain [3]. A study in 33 women with insulin resistance found that although consumption of a preload of stevia did not impact serum glucose levels following an oral glucose load, it did significantly increase levels of C-peptide, a marker of insulin production, consistent with the insulinotropic effect of stevia [30]. While the acute consumption of food was not affected, which is consistent with other studies finding that stevia produces an acute satiety response, the participants who received stevia reported a delayed greater desire to eat several hours later.

The potential metabolic impact to chronic consumption of stevia or other non-nutritive sweeteners appears to be largely a function of the microbiome. As a result, the effects are highly individualized. While low levels of consumption tend to be metabolically neutral for most people, it may be metabolically beneficial or harmful in subsets depending on their overall diet, the baseline composition of their microbiome, and how the sweetener alters the microbiome. An RCT in 120 healthy adults examined the impact of non-nutritive sweeteners on the microbiome and glycemic parameters. The study used 180 mg stevia per day, which is lower than the approved acceptable daily intake (ADI) level [2]. The study found that the sweeteners induced person-specific, microbiome-dependent glycemic effects. Plasma insulin levels increased in response to stevia, similar to those consuming glucose. While stevia was not associated with altered glucose tolerance overall, there were sensitive individuals. The impact on glucose tolerance was associated with changes in the composition of the gut microbiome in these individuals. The transfer of the microbiomes from these individuals into mice replicated the glycemic effects, suggesting that it was related to the alteration of the microbiome. Metabolites increased in response to stevia consumption included the amino acids lysine and serine, as well as the arginine-derived metabolites, ornithine and citrulline.

Chronic kidney disease: POTENTIAL BENEFIT AT DOSES ABOVE ADI
Stevioside (250 mg capsules, twice per day) has been tested in an RCT in patients with Stage I to Stage III chronic kidney disease (n=97) for nine months in conjunction with their standard antihypertensive and antidiabetic medications [31]. In a three-month interim assessment, there were significant changes in serum creatinine, serum uric acid, fasting blood sugar, postprandial blood sugar, and microalbumin with stevioside [31]. Significant reductions in systolic blood pressure and diastolic blood pressure were also seen during the six-month follow-up [32].

Cancer: POTENTIAL BENEFIT (Preclinical)
Stevia leaf extracts or glycosides have not yet been clinically tested in cancer patients, however, there have been a variety of preclinical studies showing anti-cancer properties [33]. Steviol glycosides have been shown to be cytotoxic in numerous cancer cell lines. In addition to their direct effects on cell survival and proliferation, the steviol glycosides show indirect anti-cancer effects through their antioxidant and lipid regulating activities. While the majority of steviol glycosides appear to be non-toxic toward normal cells, steviolbioside has shown toxicity in normal cells in vitro, suggesting it is not a good candidate for clinical use.

Safety: Highly purified steviol glycosides are non-toxic natural sweeteners at recommended doses. Chronic consumption may be more likely to affect metabolism and sweet preferences in children relative to adults.

Types of evidence:

- 4 meta-analyses of RCTs testing steviol glycosides
- 3 clinical trials assessing the safety of steviol glycosides
- 3 safety reviews
- Numerous laboratory studies

Stevia leaf preparations have been safely used as traditional herbal medicine in South America for over 1500 years [21]. The safety of crude *Stevia* leaf extracts has not been well characterized, and crude extracts have not been approved for human use by regulatory agencies. Potential reproductive toxicity in rodents has been seen with high doses of crude extracts, which may be related to the presence of impurities [21]. Only highly purified extracts (>95%) of steviol glycosides are currently approved for human consumption, in the form of food additives. In animal toxicology studies, steviol glycosides have shown no evidence of teratogenic, reproductive toxicity, mutagenic, or carcinogenic effects [1; 21]. The

NOAEL of rebaudioside A in Wistar rats was determined to be 50,000 ppm, which is the daily equivalent of 4.161 and 4.645 mg/kg bw in males and females, respectively [21]. An analysis examining over 900 mechanistic endpoints concluded that steviol glycosides lack carcinogenic or genotoxic activity [34].

The majority of clinical studies testing steviol glycosides report the absence of adverse events, including those at doses two or three times higher than the ADI for periods ranging from months to years [1; 13; 21]. Side effects are primarily limited to mild gastrointestinal events.
A pharmacokinetic study testing single oral doses of 5 mg/kg rebaudioside A and 4.2 mg/kg stevioside in healthy men (n=8), found no consistent effects on laboratory measures or vital signs [26]. Similarly, a study testing 750 mg (250 mg capsules/3X per day) of stevioside for three days found no effects on blood pressure, blood glucose, insulin, blood biochemical parameters, 24-hr urinary volume, or urinary excretion of electrolytes in healthy volunteers (n=10) [35]. At doses over 250 times the average human consumption level (1.5 g/day), stevioside showed evidence of nephrotoxicity in rats, based on elevated plasma glucose and creatinine levels, though no evidence of impaired renal function has been detected in human studies conducted thus far [1].
Steviol glycosides cannot be metabolized by digestive enzymes in the human body, but are instead metabolized into steviol by the gut microbiota, which is excreted in the feces [21]. Steviol can be absorbed into the blood in the lower intestine and then converted to steviol glucuronide in the liver, which is then excreted in the urine.

While some studies have found that *Stevia* extracts may have mild hypoglycemic and hypotensive effects in diabetic and hypertensive populations, respectively, these have only been seen at doses exceeding the approved ADI for steviol glycosides [22].

Due to its metabolism by the microbiome, chronic use of steviol glycosides can potentially alter the composition and functional profile of the microbiome [2]. The potential downstream effects, such as altered metabolism, are highly individualized depending on the baseline composition of the microbiome and dietary patterns.

Studies in animals suggest that chronic consumption of stevia during pregnancy and early developmental periods could influence the physiology of the offspring by shaping the microbiome and metabolic responses to sweet taste [7; 8].

Drug interactions: Stevia has been safely used in conjunction with both antihypertensives and antidiabetics in clinical trials [13; 22; 31], but could potentially interact in some patients. Due to potential diuretic effects, stevia may interact with the metabolism of lithium (WebMD).

Sources and dosing:

Stevia, in the form of steviol glycosides, is available for purchase as a natural sweetener, and is also found as a non-nutritive sweetener food additive in a variety of foods. Many brands contain blends with other non-nutritive sweeteners, such as erythritol or monk fruit extract.
Steviol glycosides with >95% purity were approved as sweeteners by the Joint FAO/WHO Expert Committee on Food Additives (JECFA) in 2007 [1]. The acceptable daily intake (ADI) was originally set at 0-2 mg/kg bw, but was revised upwards to the current ADI of 0-4 mg/kg bw (JECFA). Steviol glycosides were certified as a food additive with an ADI of 4 mg/kg in 2011 [1]. Stevia leaf extract was granted GRAS status by the FDA in 2018.

Research underway:

According to Clinicaltrials.gov, there are currently 23 active clinical trials involving stevia. These include trials assessing changes to the oral microbiome, glycemic effects, brain effects, metabolic effects, impacts to the gut microbiome, blood lipids, appetite hormones, blood pressure, and non-alcoholic fatty liver disease.

There are efforts underway to develop new formulations of steviol glycosides with an improved sensory sweet profile relative to stevioside and rebaudioside A, which can have a bitter taste at high doses. Cargill has entered a joint venture with DSM Nutritional Products called Avansya to develop EVERSWEET™, a natural sweetener including yeast-derived steviol glycosides rebaudiosides M and D. The EFSA has declared that the metabolism of glucosylated steviol glycosides is comparable enough to steviol glycosides, that the same ADI (4 mg/kg) can be applied to these stevia derivatives as well [36].

Search terms:
Pubmed, Google: Stevia, Steviol glycosides

- Alzheimer's disease, dementia, cognition, brain, lifespan, cardiovascular, diabetes, cancer, clinical trial, meta-analysis, safety

Websites visited for Stevia:

- Clinicaltrials.gov
- Examine.com
- Drugs.com
- WebMD.com
- PubChem
- DrugBank.ca (Stevioside)
- ConsumerLab.com

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