THE CARB-APPROPRIATE REVIEW

A MONTHLY RESEARCH REVIEW BY

CLIFF HARVEY PHD

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ABOUT CLIFF

Cliff Harvey PhD is an author, clinician, and researcher. He was one of the first clinical nutritionists to begin working with ketogenic and low-carb diets, way back in the 1990s and is also considered a pioneer in the area of mind-body integrative healthcare.

Cliff's early post-graduate work was in mind-body healthcare, while his master's research focussed on the use of medium-chain triglycerides to mitigate 'keto-flu' and encourage faster induction of nutritional ketosis.

His doctoral thesis continued to investigate keto-flu and ketogenesis, and the effects of different types of low-carbohydrate diets along with the individualisation of dietary prescription and how 'carbohydrate tolerance' varies from person-to-person.

He is a former world champion strength athlete, submission grappler, and author of several best-selling books, including *The Carbohydrate Appropriate Diet*, *Carb-Appropriate 101*, *Time Rich Cash Optional* and *The Credo.*

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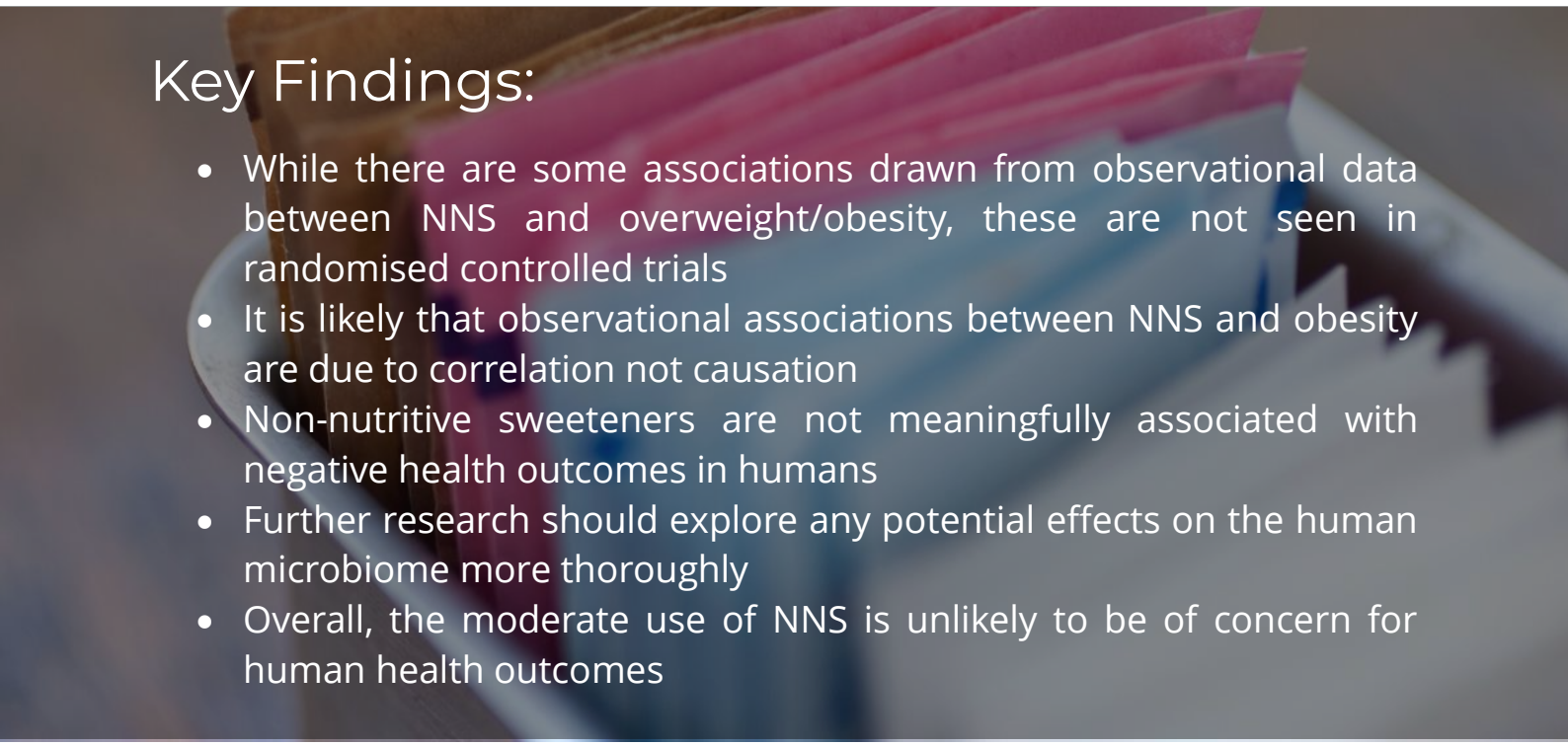
THE IMPACT OF NON-NUTRITIVE SWEETENERS ON HEALTH



Key Findings:

- While there are some associations drawn from observational data between NNS and overweight/obesity, these are not seen in randomised controlled trials
- It is likely that observational associations between NNS and obesity are due to correlation not causation
- Non-nutritive sweeteners are not meaningfully associated with negative health outcomes in humans
- Further research should explore any potential effects on the human microbiome more thoroughly
- Overall, the moderate use of NNS is unlikely to be of concern for human health outcomes

The topic of artificial, or more commonly called 'non-nutritive sweeteners' (as many common sweeteners such as stevia leaf are 'natural'), and health is a controversial one. Overall, there is no conclusive proof that non-nutritive sweeteners are beneficial to weight management or blood sugar control, but similarly, there is no conclusive evidence that they increase the risk of cancer, diabetes, obesity, or increase habituation to 'sweetness',[1] all claims that are commonly made in popular media.

Some observational studies have suggested an association between non-nutritive sweeteners and the development of metabolic diseases or obesity;[2] however, while sweeteners are associated with higher body weight and metabolic disease in observational studies, randomised controlled trials demonstrate that non-nutritive sweeteners may support weight loss, particularly when used alongside behavioural support.[3, 4] This suggests that the observed association between sweeteners and obesity is one of correlation not causation. Similarly, consumption of NNS during childhood and adolescence is associated with significant increase in BMI

of around 15% (OR 1.15, 95% CI 1.06-1.25),[5, 6] however, this association is unclear as the use of non-nutritive sweeteners is common amongst those with higher BMI wanting to lose weight and there might be a greater effect of 'sweet' sensitivity in those with existing or underlying metabolic disorders.

> The observed association between sweeteners and obesity is one of correlation not causation

Exposure levels to non-nutritive sweeteners may also play a role in their effects on the human body. It has been observed that lower doses of non-nutritive sweeteners are associated with reduced weight gain compared to higher doses (but this result is also unclear and lacking clinical meaningfulness). This review also found no evidence of any effect of sweeteners on overweight or obese adults or children actively trying to lose weight, and in children, a smaller increase in body mass index was observed when sweetener intake was compared with sugar.[7]

The effect of non-nutritive sweeteners on glucose metabolism is also unclear. Experimental animal studies show that consumption of these can induce glucose intolerance, increase food consumption and weight gain, possibly due to disturbances of the gut microbiome, inhibition of protective intestinal enzymes, and increased appetite. The evidence from human studies is more controversial. Meta-analyses have suggested that non-nutritive sweeteners have little or no effect on blood glucose control in humans,[8] and the results of clinical trials are contradictory and are not comparable because of significant differences in methodology.[9]

> Meta-analyses have suggested that non-nutritive sweeteners have little or no effect on blood glucose control in humans

While further research is needed to evaluate the effect of non-nutritive sweeteners on the gut biome (and on non-alcoholic fatty liver disease), [10] It has been suggested that they do not lead to clinically relevant changes in gastrointestinal health. In a recent review, Bryant and Mclaughlin, [11] reported that exposure to non-nutritive sweeteners "fails to replicate any of the effects on gastric motility, gut hormones or appetitive responses evoked by caloric sugars." Likewise the majority of animal research shows no clinically meaningful changes in gastrointestinal hormones associated with taste receptor activation by 'sweet' and furthermore, research demonstrates that overall, non-nutritive sweeteners are safe and with few robust

and verifiable negative functional effects on the human gut having been observed.[11]

> Non-nutritive sweeteners are safe and with few robust and verifiable negative functional effects on the human gut

A question of taste?

The question of 'taste is an interesting one...

Taste has important implications for human health because we do not exist in a vacuum and our relationship with food is determined by not only its chemical makeup, but also by taste and sensory pleasure and psychosocial associations with particular foods, tastes, textures, and other aspects of foods. Furthermore, activation of sweet taste receptors triggers physiological responses which modulate glucose homeostasis. However, non-nutritive sweeteners activate receptors but do not improve glucose homeostasis.[12]

Summary of potential adverse effects

from *Adverse effects of the consumption of artificial sweeteners - systematic review*; Bernado et al., 2016 [13]:

1. Daily consumption of artificially sweetened soft drinks by pregnant women can increase the likelihood of prematurity.
2. The consumption of artificially sweetened drinks by pregnant women may be associated with the diagnosis of asthma in their children up to the age of 7 years.
3. There is no association between aspartame consumption during pregnancy, lactation or by the child and brain tumours in childhood and adulthood.
4. There is no association between aspartame consumption and risk of hematopoietic cancer.
5. There is no association between the consumption of sugar or other sweeteners, particularly aspartame, and the development of cancer in the digestive and reproductive systems.
6. Consumption of artificial sweeteners is not associated with the development of kidney or bladder cancer in humans.
7. The association between intake of artificially sweetened drinks and type 2 diabetes is uncertain.
8. There is no association between the consumption of cyclamate and male infertility.

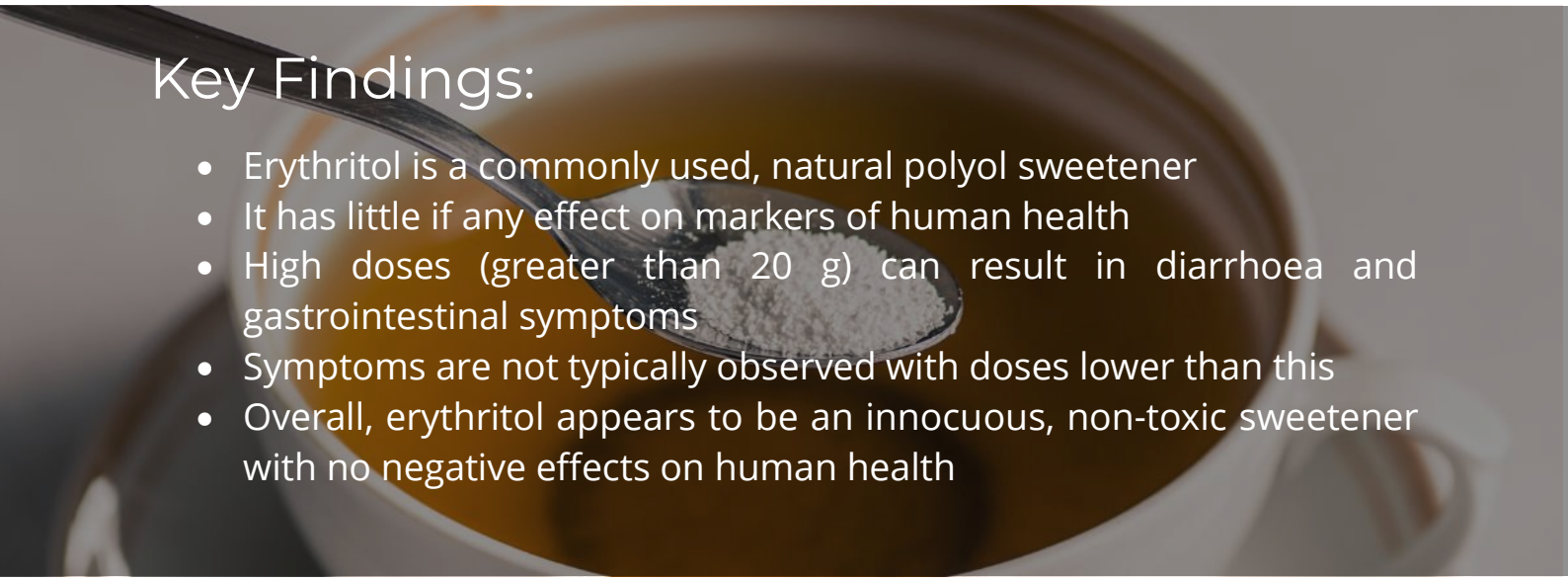
Conclusion

While there are associations between artificial or non-nutritive sweeteners overall and some health outcomes (premature birth, overweight and obesity) these associations are unclear, and are seen in observational research but not backed up by RCT evidence, which instead show a benefit to weight-loss from moderate use of non-nutritive sweeteners. The results of observational studies are likely to be confounded by pre-existing or latent metabolic syndrome, and overweight/obesity, and psychosocial impactors of diet.

> It seems unlikely that moderate use of artificially sweetened foods and beverages poses any meaningful human health risk

Overall, it seems unlikely, based on the evidence, that occasional and moderate use of artificially sweetened foods and beverages poses any meaningful human health risks.

IS ERYTHRITOL SAFE TO USE?



Key Findings:

- Erythritol is a commonly used, natural polyol sweetener
- It has little if any effect on markers of human health
- High doses (greater than 20 g) can result in diarrhoea and gastrointestinal symptoms
- Symptoms are not typically observed with doses lower than this
- Overall, erythritol appears to be an innocuous, non-toxic sweetener with no negative effects on human health

Erythritol is a 'sugar alcohol' (polyol) used as a sugar substitute in foods and beverages. It is approximately 60-70% as sweet as table sugar, yet is functionally non-caloric and greater than 82% is excreted in the urine.[14] Erythritol is classed as a natural sweetener as it naturally in some foods and beverages such as wine, beer, mushrooms, pears, grapes, and soy sauce,[15, 16] and the majority of erythritol used in products comes from yeast fermentation of glucose.

Are there any health effects?

Erythritol and glucose control

While some animal models of diabetes have shown effects such as reduced post-meal blood glucose, increased muscle glucose uptake and reduced intestinal glucose absorption,[17] in non-diabetic human subjects there has been demonstrated to be no significant effect on blood glucose, insulin, or blood lipids.[17] It does not appreciably affect blood glucose, insulin, water consumption, diuresis or electrolyte balance, at 0.4 and 0.8 g per kilogram of body weight per day (the equivalent of 68 g for me!).[18] Additionally, gut responses and tolerance were equivalent to sugar of the same dosage.[18] A 20 g single dose of erythritol resulted in no change in glucose or insulin levels. When this dose was repeated daily for 14 days, there were reductions in fasting glucose and HbA1c, with no change in markers of kidney function.[14]

In human subjects there has been no significant effect on blood glucose,

insulin, or blood lipids

Erythritol and the gut microbiome

Erythritol does not appear to be fermentable by colonic bacteria and is unlikely to have any effect on the gut microbiome.[19]

Erythritol and cardiovascular health

There is some suggestion that chronic, high-dose intake of erythritol might be associated with higher uric acid levels and triglycerides but human studies have shown there to be no effect from acute, sub-chronic or chronic exposure to erythritol.[17]

In a study of (24) patients with type 2 diabetes, 36 g of erythritol per day (in an orange-flavoured beverage) for 4 weeks, and a single dose of 24 g at baseline and post-study actually resulted acutely in improved endothelial function (measured by fingertip peripheral arterial tonometry [0.52 ± 0.48 to 0.87 ± 0.29 au, $p = 0.005$]). Chronic erythritol decreased central pulse pressure (47 ± 13 to 41 ± 9 mmHg, $p = 0.02$) and tended to decrease carotid-femoral pulse wave velocity ($p = 0.06$). It was concluded that erythritol consumption acutely improved small vessel endothelial function, and chronic treatment reduced central aortic stiffness.[20]

Is it safe?

Animal studies in rats, mice, rabbits and dogs have shown no significant or meaningful adverse effects in doses up to 5g/kg per day or up to 10% of food volume in studies lasting over two years and up to two generations of animals.[21-26] In mice, doses of 45 g/kg per day (for 90 days) did not result in any symptoms of toxicity.[27]

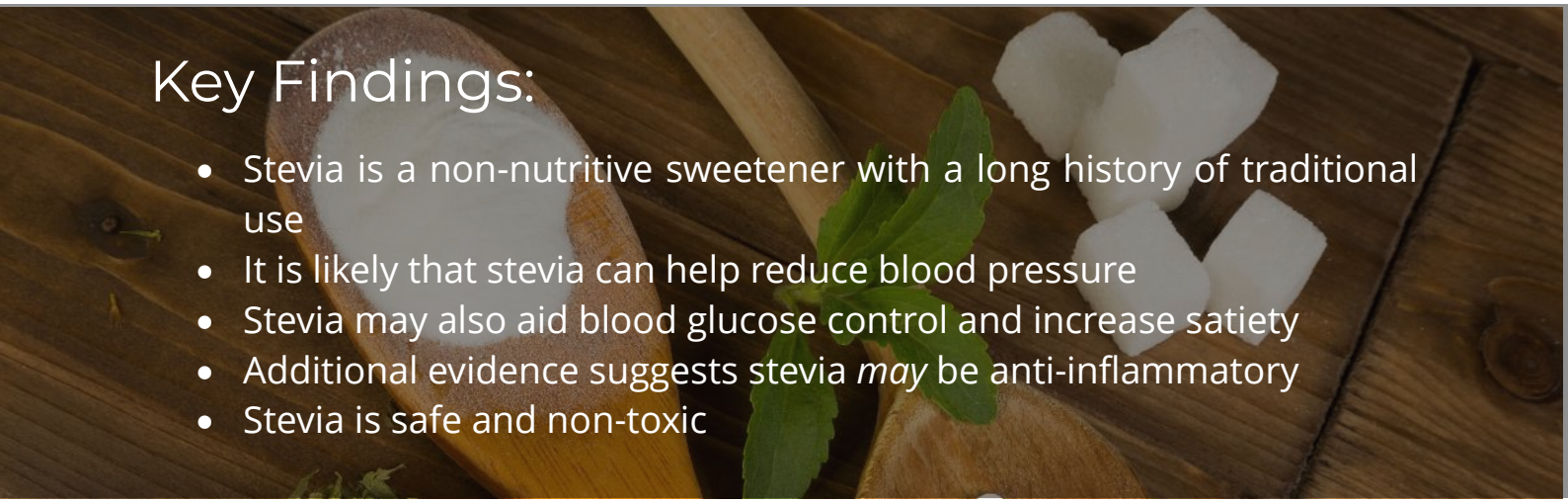
In humans, erythritol is considered to be non-toxic

In humans, erythritol is considered to be non-toxic.[28, 29] At high oral doses, approximately 90% is excreted in the urine.[29] However, doses of 20 g or more result in significantly greater episodes of diarrhoea and gastrointestinal symptoms (pain, bloating etc.) than 5-15 g (which do not produce these effects).[30] The estimated average daily intake of erythritol is 1.24 g.[31]

Conclusion

Based on the evidence, erythritol appears to be a fairly innocuous sweetener with no negative effects on any parameter of human health. The only caution would be high doses in the range of greater than 4 tsp. of erythritol sweetener per day due to an increased risk of GI distress and diarrhoea.

ALL YOU NEED TO KNOW ABOUT: STEVIA



Key Findings:

- Stevia is a non-nutritive sweetener with a long history of traditional use
- It is likely that stevia can help reduce blood pressure
- Stevia may also aid blood glucose control and increase satiety
- Additional evidence suggests stevia *may* be anti-inflammatory
- Stevia is safe and non-toxic

Stevia (*Stevia rebaudiana* is a perennial shrub, originally native to Paraguay and Brazil in South America. The plant has been used traditionally for more than 1,500 years by the Guaraní peoples of South America who called it ka'a he'ê ("sweet herb"), and more widely for the last several hundred years in both Brazil and Paraguay. The leaves have been used to sweeten local teas, foods, and medicines, and as a sweet treat and medicine on their own. The herb was first described for botanical and medicinal purposes in the 19th century by the Swiss botanist Moisés Santiago Bertoni, and in the 20th century, the sweet-tasting *glycosides* that give stevia its sweet taste were isolated.

What's in Stevia?

The active compounds in stevia are steviol glycosides; mostly stevioside and rebaudioside A but also including more than 30 additional steviol glycosides, along with nonglycoside diterpenes, flavonoids, chlorogenic acids, and vitamins, many of which have antioxidant properties.[32] These steviol glycosides are approximately 30 to 300 times sweeter than sugar, depending on the particular glycoside,[33] and because the body does not metabolise these glycosides, stevia is considered to be a zero-calorie sweetener.

Stevia has been used traditionally for more than 1,500 years by the Guaraní people

What are the benefits of Stevia?

While stevia is most commonly known as a non-calorific sweetener, it is also an herb with a long history of use for medicinal purposes particularly as an antihypertensive (reducing blood pressure) and anti-hyperglycaemic agent (to reduce blood sugar). Stevia is purported to also have a range of other health effects, ranging from anti-microbial, including anti-fungal, anti-viral, and anti-bacterial actions, to antioxidant actions,[34, 35] and its therapeutic effects might have implications for the treatment of cancer, diabetes, hypertension, cystic fibrosis, obesity, and tooth decay.[33, 36, 37]

> Stevia preparations have exhibited anti-inflammatory, and cancer-protective effects

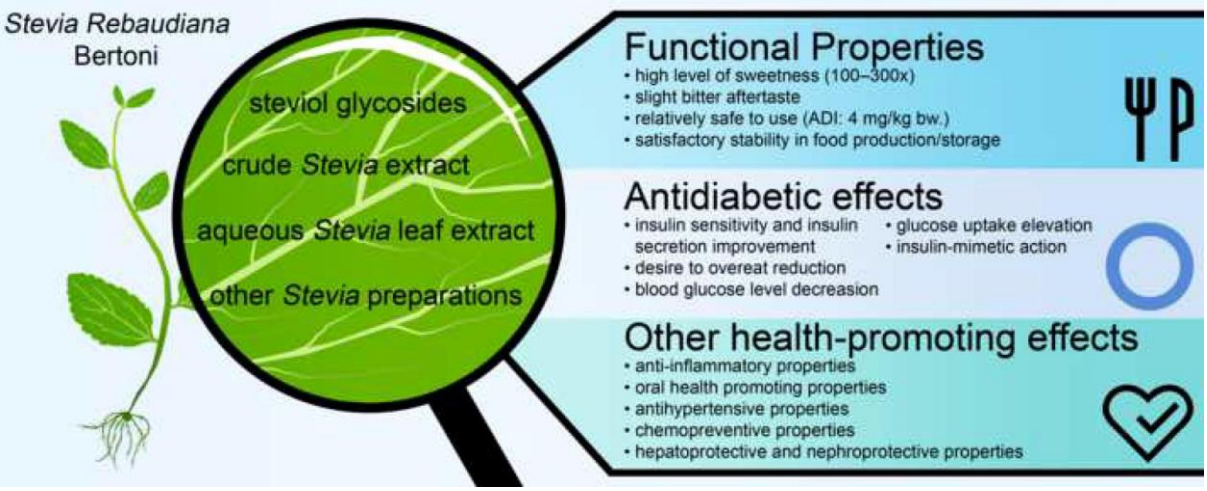
Stevia preparations have exhibited anti-inflammatory, oral health-promoting, antihypertensive, and cancer-protective effects and they might help to regulate blood glucose through some combination of improved glucose uptake, and possibly by improving insulin sensitivity.[38]

Evidence-based benefits of stevia

A thorough review by *The Natural Standard Research Collaboration* ranked the scientific evidence as 'good' ('B') for the use of stevia for hypertension (high blood pressure) and 'Unclear' ('C') for hyperglycaemia (high blood sugar).[39]

Other reviews of clinical trials have yielded additional benefits:

- Anti-inflammatory (reduced TNF-α, interleukin 6, interleukin 1β, and interleukin 10)[40]
- Improved blood glucose control (improved post-meal glucose levels when the meal contained stevia)[40]
- Improved satiety (patients do not compensate with more calories, versus when fed with sugar)[40]
- Significant improvements in systolic blood pressure[41]
- Significant improvements in diastolic blood pressure[42]



From: The functional and health-promoting properties of *Stevia rebaudiana* Bertoni and its glycosides with special focus on the antidiabetic potential – A review. Jakub Michał Kurek & Zbigniew Krejpcio https://doi.org/10.1016/j.jff.2019.103465

Implications for oral health

Stevia is also anti-bacterial, and this could have implications for oral health. While sweeter than sugar, stevia offers a non-calorie sweetening option free-from sugar and other carbohydrates that can feed pathogenic bacteria. *In vitro* research has shown that stevia extracts have antibacterial activity against *Streptococcus mutans*, *Streptococcus sobrinus* and *Lactobacillus acidophilus*, which are associated with tooth decay. Stevia might also help to reduce plaque formation by helping to inhibit bacterial biofilm formation.[43] Thus, stevia is considered to be a non-cariogenic sweetener (i.e. does not increase dental decay).[44]

Is Stevia safe?

Perhaps the most interesting observation to have been reported is that there have been no adverse effects recorded over the many hundreds of years of use by Paraguayans.[45]

> There have been no adverse effects recorded over the many hundreds of years of use by Paraguayans

On a biochemical level, the various steviol glycosides (i.e. stevioside, rebaudioside A and rebaudioside C) are metabolised and essentially leave the body without accumulation. Studies have

shown that steviol glycosides found in Stevia are not teratogenic, mutagenic or carcinogenic and cause no acute and subacute toxicity.[33, 46, 47]

> Steviol glycosides are not teratogenic, mutagenic or carcinogenic and cause no acute and subacute toxicity

Some earlier *in vitro* research had suggested that there might be some genotoxic (DNA damage) effects from stevia. However, the vast majority of scientific findings show no evidence of genotoxic activity and stevioside has not been shown to react directly with DNA or demonstrate genotoxic damage relevant to human risk.[48] The mutagenic activity of steviol and some of its derivatives, that had been demonstrated in a particular strain of bacteria (*Salmonella typhimurium* TM677),[49] was not reproduced in the same bacteria having normal DNA repair processes. The only positive *in vivo* study showing DNA damage in Wistar rat tissue by stevioside was not confirmed in subsequent experiments and appears to be a result of differing measurements rather than actual damage to DNA.[48]

In any event, steviol and steviosides do not produce chromosomal damage or effects even at extremely high dose levels *in vivo* reviews of the potential genotoxicity of stevia have concluded that it does "not pose a risk of genetic damage following human consumption".[48]

Scientific analyses have also shown that daily oral intakes of 5 mg/kg of body weight are safe, non-toxic and neither carcinogenic (cancer-causing) nor mutagenic.[45] Safety assessment in a review by *The Natural Standard Research Collaboration* suggested that 750-1500 mg per day were likely to be safe in healthy and hypertensive adults. And only due to insufficient evidence, caution was suggested for those with kidney disease, hypotension (low blood pressure), hypocalcaemia (low blood calcium levels), and hypoglycaemia (low blood glucose levels), although evidence is similarly lacking for any harm resulting from stevia for these conditions.[39] Note: Stevia is also stable at temperatures up to 200◦ Celsius.[35]

> Stevia does "not pose a risk of genetic damage following human consumption"

Is there an allergy risk?

Because stevia arises from the *Asteracae/Compositae* (daisy) family, those with known allergies to daisies and related plants should exercise caution with its use.[39] However, reviews have also shown that there have been no reports of allergy from stevioside use.[46]

Conclusions

Stevia has a very long history of use both as a sweetener and as a medicine in its own right with no adverse effects having been reported over thousands of years of use, and no toxicity demonstrated in modern, scientific trials.

Stevia is non-cariogenic and non-calorific and so, offers benefits when compared to other sweeteners for both oral health and for healthy weight management. While further research needs to be performed on the medicinal properties of stevia it appears likely that there are (albeit small) benefits to blood pressure and perhaps to other realms of health.

Overall, based on the evidence, stevia is a safe and effective non-calorie sweetener that might also offer some health benefits.

Stevia is a safe and effective non-calorie sweetener that might also offer some health benefits

ARE LOW-CARB AND KETO DIETS 'BAD' FOR OVARIAN CANCER?

Key Findings:

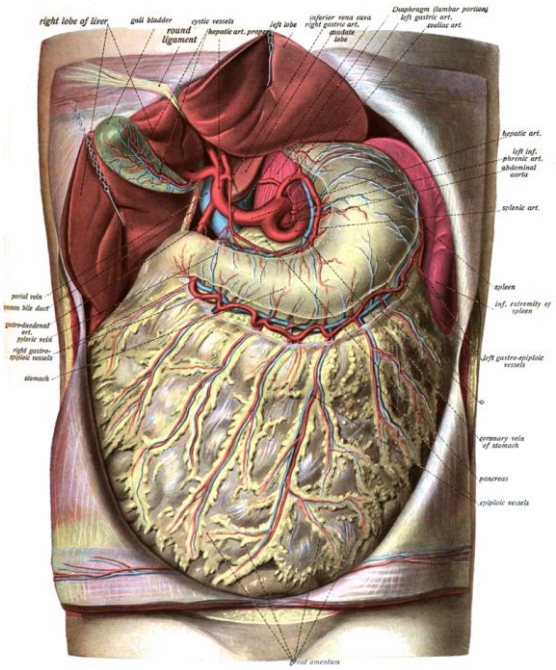
- Ovarian cancer cells are known to migrate to the omentum
- These cells 'co-opt' fatty acids for use as fuel from adipocytes
- Ketogenic diets do not worsen blood lipids in ovarian cancer patients
- Ketogenic diets reduce total and visceral fat more than standard-care cancer diets
- When compared to standard-care diet, a keto-diet might reduce cravings for fast food, sugar, and starch
- Greater intakes of fat do not necessarily result in greater availability of fatty-acid fuels to cancers favouring this fuel-type
- Dietary interventions should focus on reducing total fuel availability to cancer cells and also on reducing known drivers of cancer growth and proliferation
- Low-carbohydrate and ketogenic diets that do not result in increased free fatty-acids or excessive serum ketone levels are likely to help reduce total fuel availability to ovarian cancer cells

There has recently been significant discussion in clinical circles about the appropriateness of the ketogenic diet for the treatment of ovarian cancer. There is, as with most cancer forms and their most appropriate dietary treatment, vociferous debate between advocates of low-carbohydrate and ketogenic diets, and those more inclined towards higher-carbohydrate approaches. There is also a lot of complexity due to the very diverse nature of cancers and cancer cells, even within an individual. In this article, I summarise the available research on ketogenic diets and ovarian cancer to shed some light on whether it is or isn't appropriate...

Ovarian cancer, the omentum and metastasis

Tumours of the abdomen, including ovarian cancer, are characterised by widespread and rapid metastases in the peritoneal cavity.[50] In particular, they have a clear predilection to metastasis to the omentum (a large 'apron-like' fold of peritoneum that hangs down from the stomach). It has been demonstrated that adipocytes (fat cells) of the omentum promote migration and invasion by ovarian cancer cells and that these processes are mediated by inflammatory adipokines including interleukin-8 (IL-8). In addition, *in vitro* and *in vivo* analysis has shown that ovarian cancer cells induce lipolysis in adipose tissue and increased β-oxidation in the cancer cells, suggesting that adipocytes are used as a source of fatty-acid-derived energy to fuel cancer growth. It is thought that this occurs due to upregulation of adipocyte Protein 2 (a fatty-acid carrier protein) in omental metastases compared to primary ovarian tumours.[51] Ovarian cancer cells co-cultured with primary human omental adipocytes also express high levels of the fatty-acid receptor, CD36, which imports fatty acids into the cell for use.[50]

Adipocytes (fat cells) of the omentum promote migration and invasion by ovarian cancer cells



Anatomical illustration from Sobotta's Human Anatomy (1908) showing the omentum.

These findings taken together, suggest that ovarian cancer cells, when migrated to areas with a relative abundance of adipocytes (like the omentum) can induce adipose tissue to release fatty-acids and that this can be used efficiently as a fuel.

Ovarian cancer cells can induce adipose tissue to release fatty-acids and this can be used efficiently as a fuel

Is a low-carb or ketogenic diet inappropriate for Ovarian Cancer?

In Ovarian Cancer patients, no difference in blood lipids was seen between a ketogenic diet and low-fat diet after 12 weeks.[52] Furthermore, in another randomised, controlled trial, after 12 weeks, those following a ketogenic diet, compared to the American Cancer Society diet had lower total fat mass (35.3 compared with 38.0 kg, $p < 0.05$) and a greater change in visceral fat mass (–21.2% compared with –4.6%, $p < 0.05$), with no difference in lean mass. In addition, the ketogenic diet group had lower fasting insulin (7.6 compared with 11.2 μU/mL, $p < 0.01$), and β-hydroxybutyrate had a significant *inverse* association with IGF-I concentration (r = –0.57; P < 0.0001), i.e. greater βOHB (the main 'fuel' ketone) levels were associated with lower levels of IGF-1, a known driver of cancer growth.

The authors concluded "elevated serum β-hydroxybutyrate may reflect a metabolic environment inhospitable to cancer proliferation".[53]

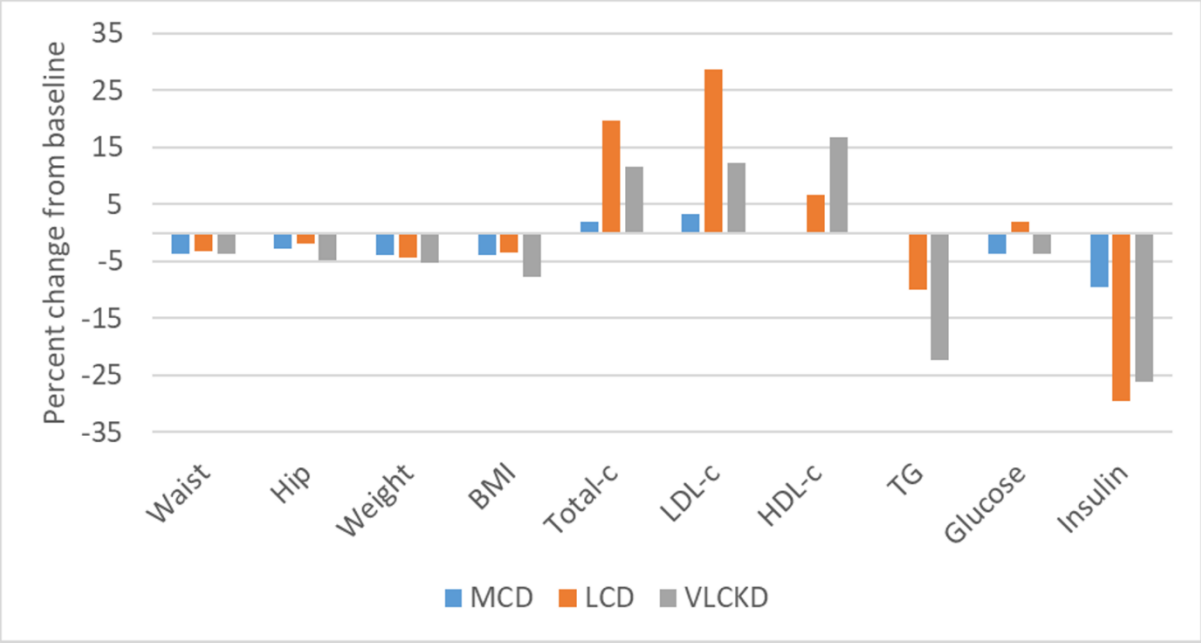
Those following a ketogenic diet, had lower total fat mass and a greater change in visceral fat mass compared to patients following the American Cancer Society diet

In another trial comparing the American Cancer Society diet to a ketogenic diet, ketogenic diet participants reported a significant reduction in fatigue ($p < 0.05$). There were no significant between-group differences in mental function, hunger, or appetite. However, the ketogenic diet group exhibited significantly fewer cravings for starchy foods and fast food fats at 12 weeks ($p < 0.05$). The authors concluded; "in women with ovarian or endometrial cancer, a ketogenic diet does not negatively affect quality of life and in fact may improve physical function, increase energy, and diminish specific food cravings."[54]

In women with ovarian cancer, a ketogenic diet may improve physical function, increase energy, and diminish specific food cravings

Conclusions

Serum fatty acids and triglyceride levels are often tightly linked. It has been demonstrated on countless occasions that low-carbohydrate and ketogenic diets reduce triglycerides more than other diets. In fact, in the only study to date which has compared different lower-carbohydrate diets, differing in the magnitude of carbohydrate restriction, we demonstrated that the greatest change in triglyceride levels occurred in the very-low-carbohydrate, ketogenic diet,[55] with no change seen in the moderate carbohydrate group (25% of TE from carbohydrate). This suggests that despite there being a potential (but not necessarily excessive) increase in fat intake on a low-carbohydrate or ketogenic diet, this does not lead to greater levels of fatty acid availability to cells.



It must also be considered that ovarian cancer cells do not simply take up fatty acids alone or in isolation. They are flexible cancer cells that can utilise a variety of substrates, including (and probably most prominently) glucose. In addition, ovarian cancer metastasis through the abdominal cavity and elsewhere and can induce the liberation of fatty acids from adipocytes (and also become more efficient at using that fuel source). But, perhaps most importantly, this process does not relate to the fatty acid quotient of the diet *per se*, but instead to the presence of ovarian cancer cells, adjacent adipocytes AND to the fatty acid balance of the adipocytes and the metabolic status of the individual.

Dietary interventions should focus on reducing total fuel availability to cancer cells and on reducing known drivers of cancer growth and proliferation.

Dietary interventions should focus on reducing total fuel availability to cancer cells and on reducing known drivers of cancer growth and proliferation

So, it is known that low-carbohydrate diets reduce cancer drivers such as IGF-1, reduce average glucose and insulin levels, and do not predispose to greater triglyceride/fatty acid availability. Furthermore, ketone levels (βOHB) do not need to be excessively high, and for the purposes of ovarian cancer treatment, a modified ketogenic diet approach, rich in phytonutrients, sufficient in protein (to reduce muscle-wasting), and not excessively high in fat (so as to allow for sufficient fuelling without excessive βOHB levels) is likely to be both safe and, based on the extant literature, may also improve cancer outcomes versus standard care.

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APPENDICES

Structure, ADI, and biological effects of natural and synthetic sweeteners

Sweetener	ADI, mg/kg/d	Structure	Biological effects
Acesulfame K (E-950)	15	$C_4H_4KNO_4S$	Acesulfame K undergoes metabolization by the human body, which the majority of studies describe as innocuous. No effects on body weight or glucose tolerance.
Aspartame (E-951)	40	$C_{14}H_{18}N_2O_5$	Aspartame, a combination of amino acids, namely L-phenylalanine and L-aspartic acid, and connected through methyl ester bonds, is rapidly absorbed. This compound is safe and without toxicity in gene mutations.
Neotame (E-961)	2	$C_{20}H_{30}N_2O_5$	Neotame is a sweetener with a very similar structure to aspartame. It is safe for patients with phenylketonuria, but also safe for diabetics. With regard to its metabolization, half of the ingested neotame is not absorbed and excreted through the feces, whereas the other half is excreted in the urine as de-esterified neotame.
Advantame (E-969)	5	$C_{24}H_{30}N_2O_7$	Advantame is obtained through chemical synthesis from aspartame and isovanillin and is a source of phenylalanine. This compound is nontoxic or carcinogenic and there are no risks of its consumption as a food additive.
Cyclamate (E-952)	11	$C_6H_{12}NNaO_3S$	Cyclamate is prepared by the sulfonation of cyclohexylamine (toxic compound). The EU has approved its use in food, although the FDA removed its GRAS status in 1969 and completely banned it in 1970. No effects on body weight or glucose tolerance.

Sweetener	ADI, mg/kg/d	Structure	Biological effects
Saccharin (E-954)	5	$C_7H_5NO_3S$	Saccharin is excreted through urine and is not metabolized in the body, although it can cross the placenta and can be transferred through breast milk. Its consumption is not recommended for pregnant or breastfeeding women.
Sucralose (E-955)	5	$C_{12}H_{22}O_{11}$	Sucralose is obtained by substitution of the 3-hydroxyl groups in sucrose. Approximately 11–27% of ingested sucralose is absorbed from the gut and is excreted in the kidneys. Sucralose is safe.
Steviol glucosides (E-960)	4	Variable	Steviol glycosides are molecules extracted from the leaves of *Stevia rebaudiana* Bertoni. Colonic bacteria converts them into steviol glucoronides to finally be excreted through urine. The consumption of these molecules is safe.
Glycyrrhizin	NA	$C_{42}H_{62}O_{16}$	Glycyrrhizin is a triterpenoid saponin that is obtained from the roots and rhizome of *Glycyrrhiza glabra.* In the EU, its consumption is considered safe with a limit of 100 mg/d, given the glucocorticoid effects in the glycyrrhetinic acid present in the extract.
Neohesperidine dihydrochalcone (E-959)	4	$C_{28}H_{36}O_{15}$	Neohesperidin dihydrochalcone is a seminatural sweetener that comes from the skin of the immature fruits of *Citrus aurantium* L. Approved in the EU since 1994 but not in the United States.
Thaumatin (E-957)	50	—	Thaumatin is a mixture of compounds extracted from the *Thaumatococcus danielli* Bennett plant. As a sweetener, it is approved both in the EU and the United States, where it is considered GRAS.

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ADI, Acceptable Daily Intake; EU, European Union; GRAS, Generally Recognized as Safe; NA, not available.

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Effects of synthetic sweeteners on gut microbiota

	Model	Dose tested	Method of analysis	Main outcomes	Magnitude of change
Acesulfame K (E-950)					
Pfeffer et al. (22)	Rats	3% acesulfame	Inhibitory activity in cecal content	Acesulfame K might act on glucose transport systems.	Marginally inhibited
Frankenfeld et al. (23)	Human trial	1.7–33.2 mg · kg^{-1} · d^{-1}	16S rRNA	Consumption was not associated with the functional capability of the gut microbiota.	Reduction in bacterial diversity from 24 to 7 phyla
Uebanso et al. (24)	Mice	15 mg · kg body weight^{-1} · d^{-1}	PCR denaturing gradient gel electrophoresis	Scarce effects on the gut microbiota and its metabolism.	Marginal changes
Bian et al. (25)	Mice	37.5 mg · kg body weight^{-1} · d^{-1}	16S rRNA and GC	The population of *Bacteroides* was highly increased in acesulfame K–treated male mice, with significant changes in the *Anaerostipes* and *Sutterella* populations. Conversely, in female mice, acesulfame K decreased the *Lactobacillus* and *Clostridium* populations.	The bacterial genera increased or decreased more than twice

	Model	Dose tested	Method of analysis	Main outcomes	Magnitude of change
Aspartame (E-951)					
Horwitz et al. (26)	Human trial	400 mg	Ingestion and analysis of AUC	Plasma glucose declined and the peak insulin concentrations in subjects treated with aspartame, no effects on gut microbiota.	No changes
Tordoff and Alleva (27)	Human trial	590 mg	Ingestion and dietary record	Aspartame reduced sugar intake, no effects on gut microbiota.	No changes
Palmnäs et al. (28)	Rats	60 mg/L drinking water	qRT-PCR analysis	Increased numbers of Enterobacteriaceae and *Clostridium leptum.*	More than 10% increase
Suez et al. (15)	Mice	4% aspartame	16S rRNA	No change in the intestinal microbiota.	No changes
Cyclamate (E-952)					
Drasar et al. (38)	Rats	100 mg calcium cyclamate	^{14}C-analysis	No effects on the gut microbiota.	No changes
Mallett et al. (39)	In vitro	25–75% cyclamate concentration in medium	Two-stage continuous culture system	No effects on the gut microbiota.	No changes

	Model	Dose tested	Method of analysis	Main outcomes	Magnitude of change
Pfeffer et al. (22)	In vitro	5% cyclamate	Inhibitory activity in cecal content	Cyclamate decreased glucose fermentation.	Marginally inhibited
Saccharin (E-954)					
Anderson et al. (41)	Rats	7.5% sodium saccharin	Enzymatic activity and microbiology analyses	Saccharin did not alter the total numbers of anaerobic microbes but deleted a specific anaerobic microbe in the cecal contents.	Marginally inhibited
Naim et al. (42)	Rats	2.5% sodium saccharin	Enzymatic activity and microbiology analyses	Saccharin inhibited the growth of 3 *Lactobacillus* strains and 3 *Escherichia coli* strains.	Almost 40% of growth inhibition
Pfeffer et al. (22)	In vitro	0.5% saccharin	Inhibitory activity in cecal content	Saccharin inhibited glucose fermentation by the gut microbiota in Cara rats.	Marginally inhibited
Daly et al. (43)	Piglets	0.015% (wt:wt) saccharin and neohesperidin dihydrochalcone	16S rRNA	Neohesperidin dihydrochalcone/saccharin increased the cecal populations of *Lactobacillus* and the intraluminal lactic acid concentration.	Increased by 3 times the lactobacilli population
Daly et al. (44)	Piglets	0.015% (wt:wt) saccharin and neohespe	16S rRNA	Saccharin caused significant shifts in microbial composition.	Increased lactobacilli twice and decreased *Ruminococceae* and *Veillonellaceae* by almost 50%

	Model	Dose tested	Method of analysis	Main outcomes	Magnitude of change
		ridin dihydrochalcone			
Suez et al. (15)	Mice/human trial	120 mg saccharin	16S rRNA	Alterations in metabolic pathways linked to glucose tolerance and dysbiosis in healthy human subjects.	The magnitude of the difference was >30%
Labrecque et al. (45)	Mice	0.066% (wt:vol) saccharin in water	qRT-PCR analysis	*Eubacteria* were increased in the pregnant group that received ethanol plus saccharin and the presence of saccharin reduced *Clostridium* counts.	Reduction in *Clostridium* was almost 50%
Bian et al. (46)	Mice	0.3 mg/mL in drinking water	16S rRNA	Altered gut bacterial genera were associated with the saccharin-induced liver inflammation.	iNOS and TNF-α increased by 3 and 2 times, respectively. Intestinal microbiota changes were observed in *Ruminococcus*, *Adlercreutzia*, *Dorea*, *Corynebacterium*, *Roseburia*, and *Turicibacter*, increasing by more than twice
Neotame (E-961)	—	—	—	No effects on gut microbiota.	No changes
Advantame (E-969)	—	—	—	No effects on gut microbiota.	No changes
Sucralose (E-955)					

	Model	Dose tested	Method of analysis	Main outcomes	Magnitude of change
Abou-Donia et al. (48)	Rats	100, 300, 500, or 1000 mg/kg	Bacteriological analyses	The consumption of sucralose decreased the total anaerobes and aerobic bacteria, bifidobacteria, lactobacilli, *Bacteroides*, and *Clostridium*.	The decrease was >2-fold
Uebanso et al. (49)	Mice	15 mg · kg body weight^{-1} · d^{-1}	PCR denaturing gradient gel electrophoresis	Sucralose administration produced modifications in *Clostridium* cluster XIVa.	The inhibition was >50%

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iNOS, inducible NO synthase; 16S rRNA, 16S ribosomal RNA.[31]

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