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Minireview

Excessive consumption of fructose-containing sugars: An emerging threat for developing nations?

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ABSTRACT

Consumption of sugar sweetened beverages and processed foods has increased in the last decade in developed countries. This has been associated with the prevalence of diet-induced obesity and type-2 diabetes mellitus, albeit a causal relationship has not been proven. Although sugar-sweetened beverages and foods contain both fructose and glucose, it is now clear that fructose poses the highest health risk when consumed excessively. In studies from the United States of America and Australia, hyper-caloric diets with high concentrations of fructose, have been shown to have adverse metabolic effects. At high concentrations, fructose increases plasma triglycerides, stimulates hepatic *de novo* lipogenesis and reduces insulin sensitivity. In developing countries, the consumption of sugar-sweetened beverages and processed foods is on the rise, particularly in the African continent. This review discusses the adverse health effects of excessive consumption of fructose, the increase in fructose consumption in Africa, and the potential threat that increased fructose consumption might have on developing countries such as those found in the African continent. The review further provides recommendations and precautionary measures that could be applied in these countries.

INTRODUCTION

Where did it all begin?

Sucrose contains 50% fructose and 50% glucose, while high fructose corn syrup contains 55-65% fructose and 35-45% glucose (White, 2008; Lim *et al.*, 2012; Mozaffarian *et al.*, 2011; Ford and Mokdad, 2001; Miller *et al.*, 2004; Cao *et al.*, 1998; Miller *et al.*, 1998) . Added dietary sweeteners usually consist of either sucrose or high fructose corn syrup and are routinely used to sweeten and improve the taste of fruit juices, carbonated drinks, yogurts, cereals and baby milk formulae (White, 2008; Lim *et al.*, 2012; Mozaffarian *et al.*, 2011; Ford and Mokdad, 2001; Miller *et al.*, 2004; Cao *et al.*, 1998; Miller *et al.*, 1998) . Prior to 1970 there was no consumption of high fructose corn syrup, however in recent years it has been introduced as a commonly used sweetener with daily consumption increasing across both developed and developing countries (Tappy *et al.*, 2010) . During this same period, there was also an increase in the consumption of sucrose (Tappy *et al.*, 2010) . According to the 2003-2006 US National Health and Nutrition Examination Survey data, approximately a quarter of children (total n=1961, age 2–9 years) consumed fruit juice and soft drinks that were sweetened with high concentrations of fructose corn syrup (DeChristopher *et al.*, 2015) . Although consumption of fructose corn syrup has slightly decreased in the last decade, fructose in the form of sucrose is still being consumed at high levels (Rippe and Angelopoulos, 2013) .

Evidence from numerous studies demonstrate a correlation between the excessive consumption of these sweeteners and their adverse metabolic effects (Lim *et al.*, 2012; Mozaffarian *et al.*, 2011; Stanhope *et al.*, 2015b; Schwarz *et al.*, 2015) . Accordingly, research has been directed towards isolating the metabolic effects of fructose when compared to glucose consumption. Studies by Brown *et al.* (2008) and Stanhope *et al.* (2009) showed that when compared to glucose, fructose is the monosaccharide that has a pathologic nature. Specifically, Stanhope *et al.* (2009) administered glucose or fructose-sweetened beverages

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(providing 25% of energy requirements) to 39 overweight and obese human subjects for ten weeks. After treatment, both groups displayed a similar weight gain but the volume of visceral adipose tissue increased only in subjects who consumed fructose. Hepatic *de novo* lipogenesis and 23 hour postprandial triglycerides increased only in response to fructose consumption. Similarly, markers of altered lipid metabolism and lipoprotein remodeling (including fasting apolipoprotein-B, low density lipoprotein (LDL), small-dense LDL and oxidized LDL) increased in response to fructose but not glucose consumption. Lastly, fasting plasma glucose and insulin increased and insulin sensitivity decreased in subjects consuming fructose but not in those consuming glucose. In a separate study, participants consumed a fructose containing drink (total volume of each drink was 500mL, and the fructose content 60g). After two hours, participants displayed increased blood pressure, heart rate, and cardiac output but not total peripheral resistance (Brown *et al.*, 2008) . These studies suggest that high concentrations of fructose can modulate vascular tone in addition to its metabolic and lipogenic effects.

Additional clinical and experimental evidence suggest that excessive dietary sugar consumption is also strongly associated with increased body mass index, reduced insulin sensitivity, hypertriglyceridemia and hepatosteatosis (Schwarz *et al.*, 2015; Stanhope *et al.*, 2009; Berkey *et al.*, 2004; Forshee *et al.*, 2004; Giammattei *et al.*, 2003; Tordoff and Alleva, 1990; Bremer *et al.*, 2011; Lecoultre *et al.*, 2014; Hokayem *et al.*, 2013; Egli *et al.*, 2013; Brown *et al.*, 2008; Stanhope *et al.*, 2015b) . A recent study by Schwarz *et al.* (2015), placed four healthy males on a weight maintaining diet for nine days (50% complex carbohydrates, 35% fat, 15% protein and 5% fructose) and switched to a high fructose diet for an additional nine days (25% complex carbohydrates, 35% fat, 15% protein and 25% fructose). The switch to a high fructose diet caused insulin resistance, increased hepatic fat content and reduced lipid oxidation. This and other studies (Bhandari *et al.*, 2014; Zomorrodian *et al.*, 2015; Huang *et al.*, 2014; Lakka *et al.*, 2002; Kissebah and Krakower, 1994) show that consumption of excess calorie with high fructose may cause greater adverse health effects compared with consumption of excess calories with low fructose. Hence, there is a strong link between the consumption of excess fructose and adverse health effects. Notably, the consumption of naturally occurring fructose in fruits and vegetables in moderation is considered appropriate due to the added nutrient and fiber value when compared to the consumption of concentrated fructose as an additive in processed foods and beverages (Ford and Mokdad, 2001; Miller *et al.*, 2004; Cao *et al.*, 1998; Miller *et al.*, 1998) .

Metabolism of glucose differs from that of fructose

Tappy and Le (2010) eloquently portrayed the differences between the metabolism and metabolic fates of fructose and glucose in the liver. After the consumption of glucose-containing foods, GLUT-2 transporters facilitate some glucose uptake into hepatocytes and GLUT4 transporters facilitate a large portion into skeletal muscle, cardiac tissue and adiposities. In hepatocytes (see Figure 1), glucose enters a stepwise series of enzymatic reactions, where it is broken down into glucose-6-phoshphate and glucose-1-phosphate, and culminates in glycogenesis. A fraction of the glucose-6-phosphate is also converted to fructose-6-phosphate where it undergoes glycolysis. These metabolic pathways of glucose do not commonly result in pathologic endpoints.

On the other hand fructose is transported from the gut into enterocytes via fructose transporters and diffuses into the portal circulation, predominantly destined for metabolism in hepatocytes (Tappy and Le, 2010; Samuel, 2011) . Only a small percentage of fructose that is released into the blood after digestion is taken up and metabolized in skeletal muscle and other tissues (Ahlborg and Bjorkman, 1990; Tappy and Le, 2010) . In the hepatocytes, fructose is sequentially converted to fructose-1-phosphate, triose-phosphate, glyceraldehyde phosphate and ultimately to acetyl coenzyme-A. A vast number of studies have confirmed that with excessive fructose consumption, the acetyl coenzyme-A from fructose and other substrates are predominantly channeled for *de-novo* lipogenesis (Tappy *et al.*, 2010; Samuel, 2011) due to inhibition of aconitase and other tricarboxylic acid cycle enzymes (Lanaspa *et al.*, 2012b; Lanaspa *et al.*, 2012a) . These lipids accumulate in the liver and disrupt insulin signaling by activating protein kinase C-epsilon, changing the phosphorylation state of the insulin receptor and decreasing insulin stimulated glucose uptake, eventually leading to hepatic insulin resistance (Samuel, 2011; Crescenzo *et al.*, 2013a; Parker *et al.*, 1997; Herzberg and Rogerson, 1988; Carmona and Freedland, 1989) (Figure 1).

There is also evidence that following fructose consumption hepatocytes display impaired lipid oxidation (Lanaspa *et al.*, 2012b; Lanaspa *et al.*, 2012a) . Lipids are released from the liver into circulation in the form of very low density lipoprotein and taken up by skeletal muscle, heart and other organs (Tappy and Le, 2010; Samuel, 2011;Koricanac *et al.*, 2012; Ussher, 2014; Axelsen *et al.*, 2010) . Excess lipid uptake by these tissues have been shown to alter the resident tissue metabolism significantly (Guo and Tabrizchi,

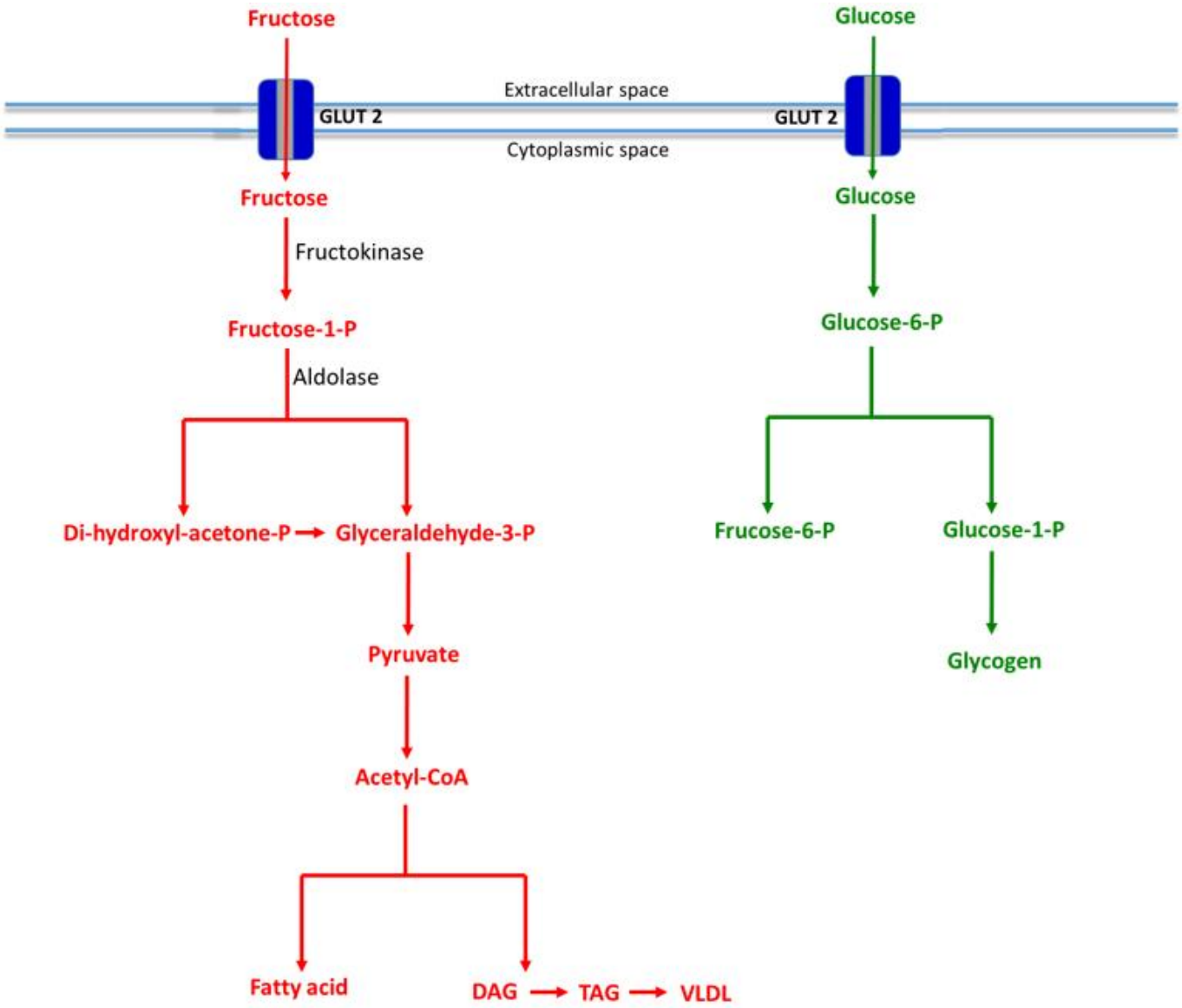

Fig. 1:
A simplified representation of the metabolic pathways for fructose and glucose in the hepatocyte. This figure, which is modified from Tappy and Le (2010) and Samuel (2011) demonstrate that the metabolic fates of these two monosaccharides are different.

2006) . For example, fructose consumption (30% in diet, for 8 weeks) in rats has been shown to increase skeletal muscle triacylglycerol content, lipid peroxidation and insulin resistance; reduce skeletal muscle antioxidant enzyme activity; and impair insulin signaling (Crescenzo *et al.*, 2013b) . These data therefore show that metabolism of fructose results in toxic effects on the liver and culminates in hepatic *de-novo* lipogenesis and insulin resistance.

The underlying mechanisms for the metabolic abnormalities following a high fructose diet appear to be centered on alterations in the mitochondrial milieu. In fructose-fed rats, liver mitochondrial mass, coupling efficiency and lipid peroxidation were perniciously increased (Crescenzo *et al.*, 2013a) . In the same model, fructose caused dysfunctional fatty acid oxidation and a reduction in skeletal muscle mitochondrial respiration when pyruvate was used as a substrate (Warren *et al.*, 2014) . Further evidence demonstrates that high fructose diets a) cause disruptions in the ratios of acetyl coenzyme-A/coenzyme-A and nicotinamide/adenine dinucleotide, b) increase concentrations of mitochondrial reactive oxygen species and c) decreased antioxidant defense (Warren *et al.*, 2014; Crescenzo *et al.*, 2013b; Catena *et al.*, 2003) . This suggests that

excessive concentrations of fructose disrupts liver mitochondrial metabolic properties, impairs fat metabolism and ultimately contributes to lipid accumulation in the liver; which may eventually lead to insulin resistance.

The dose effect of fructose in experimental and clinical studies

The study by Schwarz *et al.* (2015) showed that participants with a diet consisting of 5% calories from fructose did not show signs of adverse metabolic effects in the short term. This could mean that short-term consumption of a 5% fructose diet is relatively safe. The long term (>18 days) effects of such a diet still requires investigation. Metabolic abnormalities were only seen when fructose content reached 25% of the total calorie intake. A recent meta-analysis demonstrates that the average human consumption of fructose is ≤ 49g/day, as opposed to 101.7g/day and 187.3g/day that are often used in clinical studies (Choo and Sievenpiper, 2015) . Administration of such excessive amounts of fructose in clinical studies, has been highly criticized as they tend to exaggerate the adverse metabolic effects (Sievenpiper *et al.*, 2015; Choo and Sievenpiper, 2015; Brown *et al.*, 2015; Chiavaroli *et al.*, 2015) . Because experimental and clinical studies often administer excessive concentrations of fructose (25% or higher) (Hokayem *et al.*, 2013; Lanaspa *et al.*, 2012b; Bremer *et al.*, 2011; Warren *et al.*, 2014; Hecker *et al.*, 2012; Lida *et al.*, 2013; Suwannaphet *et al.*, 2010; Bezerra *et al.*, 2001; Oudot *et al.*, 2009) , results obtained from these studies are a subject of much debate and should be interpreted with caution.

Fructose consumption in developing countries

There is now concern that consumption of fructose sweeteners is also increasing in the developing world including Africa (Steyn *et al.*, 2003b; Kiwanuka *et al.*, 2006; Bankole *et al.*, 2006; MacKeown and Faber, 2005) . It has been reported that almost 78 million daily servings of fructose-sweetened soft drinks are consumed in sub-Saharan Africa which are sold by > 900,000 retail partners (Wojcicki and Heyman, 2010) . In urban Ibadan Nigeria, 16% of children (6 to 18 months) were provided soft drinks at least once a day and 45% of mothers provided infants with sweetened fruit-juices (Bankole *et al.*, 2006) . Twenty four to 37% of school children (aged 10–14 years) in Kampala, Uganda, consumed fructose-laden beverages daily. High consumption of these beverages has also been reported in rural Uganda (Kiwanuka *et al.*, 2006) .

Prior to 2007, Swaziland, Botswana and South Africa had the highest fructose sweetener consumption amongst several Southern African countries (Nnyepi *et al.*, 2015) . Reports have shown that fructose-sweetened carbonated soft drinks were the third most commonly consumed item among urban South African children aged 12–24 months (equating to 54.3 - 86.2g/day/child) (Theron *et al.*, 2007) . Another study showed that children aged 4 to 24 months consumed fructose-sweetened beverages approximately 2-3 times per week in remote rural areas in KwaZulu-Natal province of South Africa (MacKeown and Faber, 2005) . Furthermore, total sugar intake (fructose and glucose) via beverages and processed foods was found to be high (between 50 g/day and 100 g/day) in South African school-aged children (Steyn *et al.*, 2003b; Steyn and Temple, 2012) . A meta-analyses conducted in South Africa showed that between 1983 and 2000 over two thirds of adults consumed sweetened beverages on three or more occasions per week (Steyn *et al.*, 2003a) . Results also showed that added dietary sweeteners, were commonly consumed on a daily basis and these results were similar for South African children between the ages of 1-5 years (Steyn *et al.*, 2003a) . Another meta-analysis by Steyn and Temple (2012) showed that the total sugar intake (fructose and glucose) in South African children is 50g/day and increases to 100g/day in adolescence. Considering the adverse health effects of excess fructose, the above data raise concern because the amount of fructose in these sweetened carbonated soft drinks is as high as 60% (Walker *et al.*, 2014) . The data also attest to the high consumption of sweetened beverages among very young children in certain areas of sub-Saharan Africa at a dose which have previously been reported to induce concerns in experimental and clinical trials.

Small scale studies from developing countries report an association between excessive consumption of fructose and metabolic perturbations (Schwarz *et al.*, 2015; Stanhope *et al.*, 2015a; Cox *et al.*, 2012) . In an African cohort, Vorster and colleagues recently correlated the intake of added fructose sweetener in the form of beverages with risk factors for cardiovascular diseases. This was a five-year follow-up study (recruitment began in 2005) of a cohort of 2000 urban and rural men and women (30–70 years of age at recruitment) from the North West Province in South Africa. Data confirmed that added dietary total sugar intake (fructose and glucose), particularly in rural areas, increased rapidly in the five years. In these areas, the proportion of adults who consumed fructose sweetened beverages approximately doubled (for men: from 25% to 56% and for women: from 33% to 63%). Subjects who consumed more total added sugars (10% energy from fructose and glucose combined) had a higher waist circumference, body mass index and a lower high density lipoprotein, compared with those who consumed less added sweeteners (less than 10% energy

from fructose and glucose combined) (Vorster *et al.*, 2014) . Excessive fructose consumption that coincides with hyper-caloric diets and obesity from a young age is of concern in developing nations (Baleta and Mitchell, 2014; Pienaar, 2015; Lambert and Kolbe-Alexander, 2013; Lundeen *et al.*, 2016; Wand and Ramjee, 2013; Tathiah *et al.*, 2013; Timaeus, 2012; Malaza *et al.*, 2012; Kimani-Murage *et al.*, 2011; Kruger *et al.*, 2005) . However, the isolated metabolic effects of fructose when compared to glucose consumption in the African population is unknown. Thus, future research is required to assess these outcomes in addition to the average fructose consumption in developing nations.

The above statistics from Africa has generated concern because Africa contains a large portion of the global population but has a developing healthcare system which may be unable to cope with the adverse effects that excessive fructose consumption might introduce. Therefore, it is crucial to educate developing nations on the potential adverse effects of excess fructose consumption. Although every developing nation is unique, it is crucial to undertake studies to address these concerns. Given that the largest portion of the developing world population is found in Africa, it is essential to undertake studies specific to the African population in order to address these particular trends (Monyeki *et al.*, 2015; Sedibe *et al.*, 2014; MacKeown and Faber, 2005; Wojcicki and Heyman, 2010; Theron *et al.*, 2007; Bankole *et al.*, 2006; Kiwanuka *et al.*, 2006; Steyn *et al.*, 2003b; Vorster *et al.*, 2014) .

Precautionary measures needed in developing countries

As discussed, populations from developing countries are beginning to increasingly consume fructose-containing sweeteners. Nonetheless, it is unknown whether these dietary changes cause disease or only mild acute metabolic perturbations. Regardless, it may be wise to take precautionary measures to discourage intake of excess fructose or glucose in the form of additive sweeteners. In line with this view, South Africa's Department of Health adopted food-based dietary guidelines stating that foods and drinks containing added sweeteners should be consumed sparingly and not between meals (Steyn *et al.*, 2003b) . Steyn *et al*. (2003a), commenting on the guidelines, have suggested that they should also communicate the potential side-effects of excessively consuming additive dietary sugar. For example, it should inform the public that excessive dietary sugar intake may promote weight gain that could potentially contribute to insulin resistance and type-2 diabetes mellitus. In addition, policies to ensure implementation of dietary guidelines have also been recommended (Tugendhaft *et al.*, 2015) . Others have noted that ultimately, dietary guidelines cannot restrict consumers choice of diet but perhaps commercial restriction of fructose sweeteners in beverages, processed foods and other consumables would be a better option (van Dam and Seidell, 2007; Ventura *et al.*, 2011; Walker *et al.*, 2014; Wojcicki and Heyman, 2010; Malde *et al.*, 2011; Cabrera Escobar *et al.*, 2013) .

Government policies designed to encourage healthier food consumption patterns among the public have been implemented in countries like Hungary and the United States of America (Cabrera Escobar *et al.*, 2013; Holt, 2011) . Cabrera Escobar *et al.* (2013) are of the opinion that in order to address the growing epidemic of non-communicable disease, one would need to combine programs that target individual behavior change with a fiscal policy of taxing beverages. The authors re-evaluated the taxation of fructose sweetened beverages and their potential impact on consumption levels, obesity and body mass index and concluded that future research should be conducted to estimate price elasticity in low- and middle-income countries, identify potential health gains, and pin point the wider impact on food security, jobs, monetary savings to the health sector, implementation costs and government revenue. These recommendations were recently echoed by numerous studies that affirmed the importance of promoting programs that discourage the consumption of foods and beverages high in added sugars and the potential benefits of implementing lifestyle intervention programs in the developing world (Vorster *et al.*, 2014; Simonsen *et al.*, 2015; Akinroye *et al.*, 2014; Draper *et al.*, 2010; Mendham *et al.*, 2014a; Mendham *et al.*, 2014b; Brassai *et al.*, 2015; Wu *et al.*, 2015; Pillay *et al.*, 2015) . Data from these would allow policy makers to assess and implement effective strategies for disease prevention.

CONCLUSION

Epidemiological data display a rise in the consumption of foods and beverages that contain fructose. Excessive consumption of these foods and beverages is also on the rise in the developing world, particularly Africa. Current evidence supports the notion that if consumed in excess, fructose-containing sweeteners have adverse metabolic effects. However, most of the studies are small-scale, use debatable doses of fructose and fail to show long-term effects. Furthermore, the average daily dietary consumption of fructose has been difficult to ascertain since the exact concentration of fructose in foods is often not disclosed; which elicits great concern, as it suggests that people are consuming unregulated amounts of fructose. Restriction of fructose content in beverages and processed foods may provide an alternative to address the health concerns of excess

fructose consumption in both the developed and developing world.

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