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REVIEW

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Is the consumption of energy drink beneficial or detrimental to health: a comprehensive review?

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Abstract

Background: Energy drinks (EDs) are a type of beverage that mostly contains caffeine and other dietary supplements (if present) and does not contain any alcohol in the ingredients. The products in this category include Red Bull, Redline, Monster, Full Throttle, and others. They are claimed to help in boosting energy, stamina, sports performance, and concentration among individuals. This article focused on the review of the benefits and disadvantages of consumption of energy drinks to health and well-being. ED provides health benefits effects such as improved physical performance, mood and attitude, cognition, and weight loss. Some adverse negative health challenges have been linked to consumption of ED. Therefore, this review is a wholistic appraisal of benefits or detriments of consumption of energy drink to our health and suggestions to curtail the excesses of ED consumption.

Main body: Energy drink has been around since 1950, and it is marketed as energy booster and comes in different types, energy shots, fruit-based, non-fruit-based (regular), sugar-free, and plant-based. These products are marketed as a low-calorie "instant" energy drink that can be consumed in a single sip, or bottle to boost energy or to boost the nutritional value of conventional products. Many of them contain different ingredients such as caffeine, guarana, ginseng, yerba mate, acai berry, ginkgo biloba, methylxanthines, sugar, glucuronolactone, taurine, maltodextrin, B vitamins. Vitamin B2 (riboflavin), B3 (niacin), B6 (pyridoxine, pyridoxal, and pyridoxamine), Inositol B8 and B12, vitamin C and vitamin D; calcium, Iron, chromium, zinc, manganese, molybdenum; artificial sweeteners, aspartame, and sucralose. Health benefits such as improved physical performance, improved mood and attitude, improved concentration, and memory, good source of vitamin B and weight loss have been reported. Negative impact on health such as adverse cardiovascular effect, headaches, epileptic seizures, ischemic stroke, hallucinations, muscular twitching, restlessness, sleeplessness, anxiety, depression, gastrointestinal effect, renal effects, dental effects, obesity and type II diabetes, cancer, and caffeine toxicity has been reported.

Conclusions: Most of the health detriments caused because of consumption of energy drink is mostly due to the presence of excess quantity of caffeine and sugar. If the quantities of caffeine and sugar content in energy drink are kept at FDA- and WHO-recommended daily consumption amount, then it will not be present any problem to health. Consumption of energy drink that contains natural ingredients such as yerba mate, acai berry, ginkgo biloba, methylxanthines, amino acid, guarana, and ginseng with moderate FDA- and WHO-approved daily consumption of caffeine and sugar is not detrimental to health.

Keywords: Energy drinks, Micro/macronutrients, Natural ingredients, Health benefits, Diseases

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Background

Energy drinks (EDs) are a type of liquid beverage that contains caffeine and may or may not contain other dietary supplements (Alsunni 2015). They are

non-alcoholic drinks that claim to boost energy, stamina, sports performance, and concentration (Al-Shaar et al. 2017). Energy drinks use a combination of stimulants and energy boosters to give the consumer an "energy boost." Caffeine is the main ingredient in most energy drinks. They typically have 80–150 mg of caffeine per 8 oz, which is about the same as 5 oz of coffee or two 12-oz cans of caffeinated soda (Alsunni 2011). Most brands on the market are high in glucose, while some do provide artificially sweetened variants. The common ingredients used in ED are being classified into 4 different categories: natural extracts (ginseng, guarana, yerba mate, acai, caffeine, and ginkgo biloba), macronutrients (carbohydrates and protein), micronutrients (vitamins and minerals), and artificial sweeteners (aspartame and sucralose).

Manufacturers recently have shifted their consumer focus from athletes to young people. Energy drinks are aggressively marketed in places popular with teens and young adults. The capability of EDs to control mood, increase alertness, reduce fatigue, improve athletic performance (Giles et al. 2012), and lower high levels of perceived stress has been promoted aggressively among college students (Pettit and DeBarr 2011).

Currently, there are major concerns about the safety of these products. There have been several reports linking energy drinks to negative health effects. Despite this, energy drink manufacturers believe that their products are safe and appropriate for customers. Scientists are conflicted on whether energy drinks have negative health impacts. There are only a few extensive reviews of the literature evaluations that show the acceptability and safety of energy drink intake, especially among young individuals.

Main text

Methods

Article was obtained through online database search from Mendeley, Science direct, Scopus, PubMed, Google Scholar. Search was limited between 2001 and 2021.

Brief introduction of ED

Japan was the first country to invent the energy drink. Amphetamines were immensely popular in the postwar period until legislation was implemented in the 1950s to restrict their usage. Then, in 1962, Taisho released Lipovitan D shown in Fig. 1A, a legal, stimulating tonic packaged in minibar-size bottles. By the 1980s,

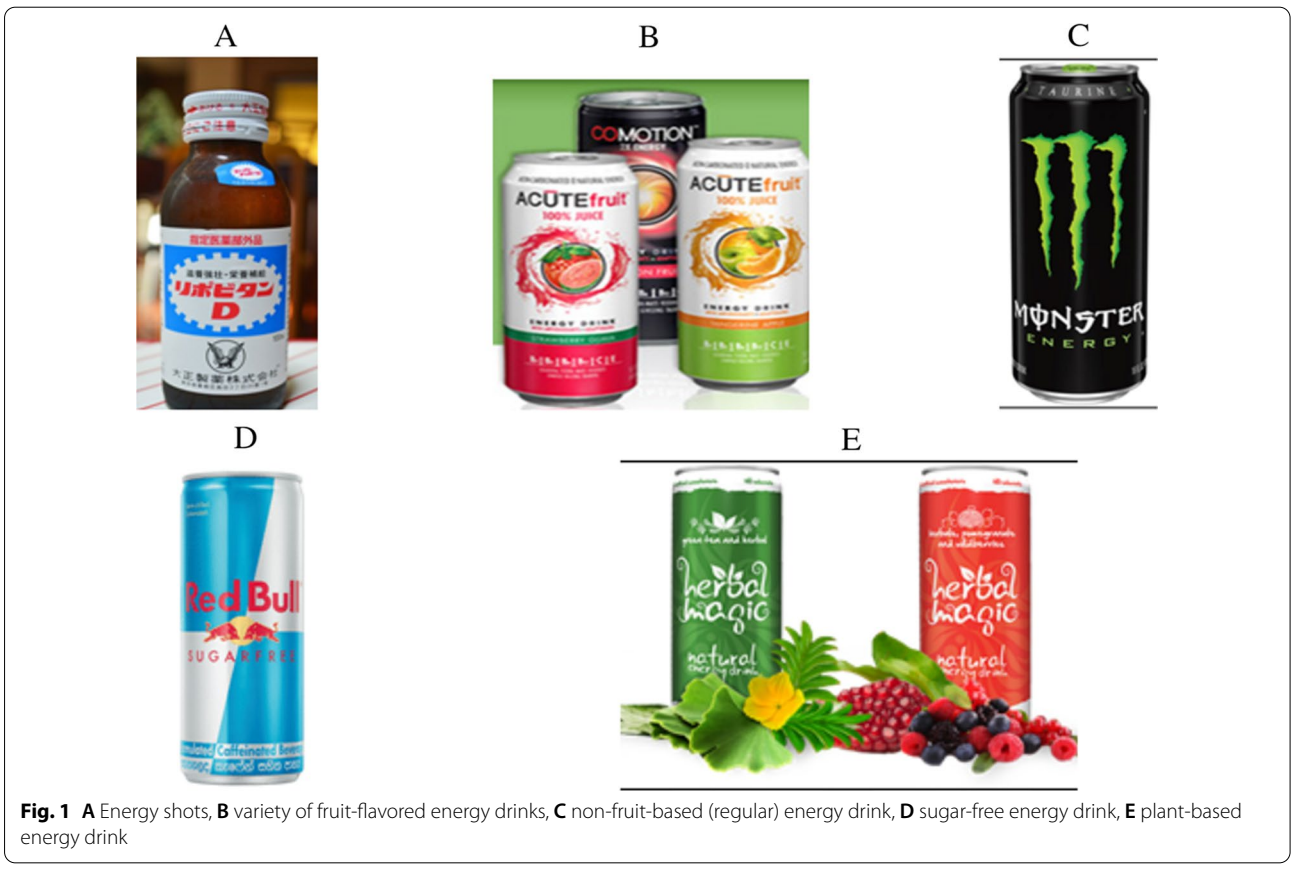

Fig. 1 **A** Energy shots, **B** variety of fruit-flavored energy drinks, **C** non-fruit-based (regular) energy drink, **D** sugar-free energy drink, **E** plant-based energy drink

Table 1 Caffeine content of a representative sample of caffeinated beverages (adapted from O'Mathúna 2012)

Name	Bottle/can volume (oz)	Caffeine concentration (mg/oz)	Total caffeine (mg) per serving size listed in second column
Full Throttle	16	9	144
Monster	16	10	160
Powershot	1	100	100
Red Bull	8.3	9.6	80
Redline Power Rush	2.5	140	350
Wired X505	24	21	505
Coca-Cola Classic	12	3	34.5
Mountain Dew	12	4.5	54
Coffee, Starbucks brewed	12	20	240
Coffee, generic brewed	12	16	195 (range 150–300)
Tea, brewed	12	6	76 (range 60–180)

Japanese businessmen tried to push the frequent consumption of fortified vitamins and extra-caffeinated drinks (Engber 2013). The first energy drink appeared in the USA in 1949 and was marketed as "Dr. Enuf." They were originally introduced in Europe in 1987, and the market quickly spread across the globe with the introduction of Red Bull in 1997 (Zucconi et al. 2013). Since then, the energy drink market has grown rapidly, with several new brands hitting the markets across the world. In 2013, energy drinks were consumed in more than 160 countries for a total of 5.8 billion liters (Bailey et al. 2014). In 2017, energy drinks accounted for 30% of all packaged beverages sold in convenience stores in the USA in terms of dollar sales. According to energy drink sales data, the global market for energy drinks was worth $53 billion in 2019 (Edgson 2021).

Types of ED

Energy shots

There are two types of energy drinks on the market. One is marketed in bottles the same size as regular soft drinks, such as a 16-oz bottle. The other type, known as "energy shots," comes in little bottles that hold 2 to 212 oz of concentrated drink (NCCIH 2021). Energy shots can contain the same total amount of caffeine, vitamins, or other functional ingredients as their larger versions and may be considered concentrated forms of energy drinks. Energy shots are typically marketed as a low-calorie "instant" energy drink that can be consumed in a single sip (or "shot"), as opposed to energy drinks that encourage users to drink a full can, which can have 250 cal or more (We-energy 2015). An example of energy shots of ED (Lipovitan D brand) is shown in Fig. 1A.

Fruit-based

The development of blended drinks is a successful way to boost the nutritional value of conventional products or to overcome the problems associated with current products (Márquez Cardozo et al. 2017). Several researchers have created alternatives to energy drinks based on fruits. For example, Márquez Cardozo et al. (2017) formulated mango energy drinks containing caffeine at a concentration of 30 mg/100 mL, though Nowak and Goslinski (2020) evaluated various fruit energy drinks containing pineapple, apple, strawberry, raspberry, carrot, and pomegranate juice. An example of a variety of fruit-based energy drinks is shown in Fig. 1B.

Non-fruit-based (regular)

Regular or non-fruit-based EDs are beverages that contain large doses of caffeine, sugar, and a variety of other stimulants and substances such as guarana, taurine, or vitamins (Higgins et al. 2010). Examples include ED brands such as Red Bull, Rockstar, Monster, Full Throttle ED, and NOS. Figure 1C shows the non-fruit-based (regular) ED of Red Bull brand (Table 1).

Sugar-free

In recent years, consumption of sugar-free energy drinks has increased possibly because of the low-calorie, refined sugar content. The main active ingredient in sugar-free energy drinks such as Red Bull is caffeine. Caffeine is one of the most widely used ergogenic aids, with acute caffeine ingestion increasing aerobic exercise endurance and reducing fatigue. Although they are claimed as sugar-free, artificial sweeteners are heavily used as the ingredients such as Aspartame (Null Chiropractic LLC n.d.). It is also known as non-nutritive sweeteners which are high-intensity sweeteners that are used in small amounts

to reduce the caloric and sugar content of food and beverages (Choudhary and Pretorius 2014). An example of a sugar-free energy drink is shown in Fig. 1D.

Plant-based

Most energy drinks incorporate additional artificial mood enhancers, synthetic caffeine, and a huge amount of sugar. Plant-based energy drinks, on the other hand, contain only natural caffeine, electrolytes, vitamins, and antioxidants, as well as a blend of natural caffeine, electrolytes, vitamins, and antioxidants. An example of plant-based energy drinks is shown in Fig. 1E.

Major ingredients and constituents of ED

Natural extracts

Natural ED may get a boost from the antioxidants, vitamin, minerals, and naturally occurring caffeine derived from the fruits, herbs, and plants. The natural extracts found in various types of ED are summarized in Table 2.

Caffeine Caffeine concentration in ED varies significantly, ranging from 47 to 80 mg per 8 oz to 207 mg per 2 oz, and comes from a variety of sources (Generali 2013), while moderate caffeine consumption (up to 400 mg per day) is usually regarded as safe and even beneficial to adults' well-being (McLellan et al. 2016). Caffeine is a stimulant that antagonizes adenosine receptors and stimulates dopamine neurotransmission in the central and peripheral nervous systems. Interactions with various receptors result in a variety of outcomes. O'Mathúna (2021) stated that moderate acute dosages (200–350 mg) reduce heart rate and raise blood pressure in adults, while also enhancing emotions of well-being, focus, and arousal.

Guarana Reports on other constituents of ED are relatively limited. Guarana is a plant extract native to South America which contains a significant amount of caffeine, with 1 g of guarana equivalent to 40 mg of caffeine (Al-Shaar et al. 2017). Guarana is frequently added as an ingredient in ED for its stimulatory impact due to its high caffeine content (Heckman et al. 2010). The effects of guarana are currently unknown. It is uncertain whether it has an additional or synergistic impact when coupled with caffeine. However, it has been found that guarana can act as an antioxidant, traditional medicinal, and an effective stimulant. It can also treat fatigue and depression related to cancer treatment (Moustakas et al. 2015). The amount of guarana in a 16-oz energy drink can range from 1.4 to 300 mg. Although there are no standard quantities, the FDA considers guarana to be safe. It is also unclear how much guarana is in each drink because many manufacturers do not specify the milligram value. As a result, it is safe to believe that the amount of caffeine in the products is higher than the amount listed, especially if guarana is present (Schimpl et al. 2013).

Ginseng Ginseng has been used as a medicinal herb for ages and is claimed to boost energy, reduce fatigue, relieve stress, and improve memory. It is also claimed to activate the hypothalamus and pituitary glands, which subsequently release an anti-inflammatory hormone called adrenal corticotropic hormone. Normal ginseng-incorporated energy drink appears to have a regular amount of 200 mg per day, although most people can safely take up to 2700 mg through supplementation (Caffeineinformer n.d). However, there are several adverse effects caused by ginseng abuse which include maniac episodes, uterine bleeding, gynecomastia, long QT syndrome, atrial fibrillation with bradycardia, hypertensive crisis, and acute lobular hepatitis (Ratan et al. 2021).

Yerba mate Yerba mate is derived from the *Ilex paraguariensis* plant, which is native to South America and is mostly used to make yerba mate tea. Yerba mate tea has historically been a popular beverage in South American countries; however, its global appeal is growing due to its high concentration of bioactive components such as polyphenols, xanthines, flavonoids, saponins, amino acids, minerals, and vitamins (Valenca et al. 2013). Yerba mate has anti-inflammatory and anti-diabetic effects, as well as functioning as an oxidative stress regulator. Furthermore, yerba mate has demonstrated in vitro cytotoxicity to cancer cells as well as inhibition of Topoisomerase II, which is involved in cell division and hence inhibits cancer cell proliferation; however, further in research is needed (Heckman et al. 2010). Both in vivo and in vitro yerba mate has a beneficial effect on the management of obesity. In both normolipidemic and dyslipidemic people, yerba mate consumption improved blood lipid markers considerably. Additionally, yerba mate assisted in the decrease in LDL cholesterol levels in people who were taking statins (Yunusa and Ahmed 2011).

Acai berry Acai berry is an ingredient that is increasingly appearing in energy drinks. The acai berry is produced by the Acai Palm tree, which is native to South America. Antioxidants are abundant in the berries, but not as much as in a concord grape or blueberry (Yunusa and Ahmed 2011). Most acai berry advantages are unproven and linked to marketing hype. It contains a high number of oxidants, nutrient dense, has anticancer properties, and helps to lower cholesterol levels (Arakelyan 2020).

Ginkgo Biloba The ingredient ginkgo biloba is named after the unique tree from which it derives. It is associated with improvement of memory retention, focus, and circu-

Table 2 Summary of ingredient's information, health benefits, side effects of the ED that are available in the market according to the types of natural extracts

Classes of nutrients	Ingredient's name	Examples of ED containing the ingredient	Information on ingredients	Health benefits	Side effects	References
Natural extracts	Caffeine		Moderate caffeine consumption (up to 400 mg per day) is usually regarded as safe and even beneficial to adults' well-being (McLellan et al. 2016), and it comes from a variety of sources (Generali 2013)	Reduce heart rate and raise blood pressure in adults, while also enhancing emotions of well-being, focus, and arousal (O'Mathúna 2012)	Adverse cardiovascular effect such as increased in systolic and diastolic blood pressure, heart rate, and cardiac output (Grasser et al. 2014)	McLellan et al. (2016), Generali (2013), O'Mathúna (2012), Grasser et al. (2014)
	Guarana		Guarana is a plant extract native to South America which contains a significant amount of caffeine, with 1 g of guarana equivalent to 40 mg of caffeine (Al-Shaar et al. 2017)	Acts as antioxidant, traditional medicinal, and an effective stimulant. It can also treat fatigue and depression related to cancer treatment (Moustakas et al. 2015)	N/A	Al-Shaar et al. (2017), Moustakas et al. (2015)
	Ginseng		Normal ginseng-incorporated energy drink appears to have a regular amount of 200 mg per day, although most people can safely take up to 2700 mg through supplementation (Caffeineinformer n.d)	Boost energy, reduce fatigue, relieve stress, and improve memory. It is also claimed to activate the hypothalamus and pituitary glands, which subsequently release an anti-inflammatory hormone called adrenal corticotropic hormone (Caffeineinformer n.d)	Adverse effects caused by ginseng abuse include maniac episodes, uterine bleeding, gynecomastia, long QT syndrome, atrial fibrillation with bradycardia, hypertensive crisis, and acute lobular hepatitis (Ratan et al. 2021)	Caffeineinformer n.d, Ratan et al. (2021)
	Yerba mate		Yerba mate is derived from the *Ilex paraguariensis* plant, which is native to South America and is mostly used to make yerba mate tea (Valenca et al. 2013)	Yerba mate has anti-inflammatory and anti-diabetic effects, as well as functioning as an oxidative stress regulator. Also, yerba mate assisted in the decrease in LDL cholesterol levels in people who were taking statins (Yunusa and Ahmed 2011)	N/A	Valenca et al. (2013), Yunusa and Ahmed (2011)
	Acai berry		The acai berry is produced by the Acai Palm tree, which is native to South America. Antioxidants are abundant in the berries, but not as much as in a concord grape or blueberry (Yunusa and Ahmed 2011)	Contain a high number of oxidants, nutrient dense, have anticancer properties, and help to lower cholesterol levels (Arakelyan 2020)	N/A	Yunusa and Ahmed (2011), Arakelyan (2020)

Table 2 (continued)

Classes of nutrients	Ingredient's name	Examples of ED containing the ingredient	Information on ingredients	Health benefits	Side effects	References
	Ginkgo biloba		The ingredient ginkgo biloba is named after the unique tree from which it derives. A normal supplemental dose is 60 mg (Yunusa and Ahmed 2011)	Improvement of memory retention, focus, and circulation, as well as acting as an antidepressant and showing indications of aiding persons with Alzheimer's disease. It is recognized by the German government as a treatment for memory loss, attention problems, and depression	Blood thinning, nausea, vomiting, diarrhea, headaches, dizziness, heart palpitations, and restlessness are some of the other side effects of ginkgo (Yunusa and Ahmed 2011)	Yunusa and Ahmed (2011)
	Methylxanthines		Methylated xanthines (methylxanthines) are produced by a large number of different plant species. They are commonly found in regular diet, as well as in a variety of incredibly common beverages and meals. Caffeine, theophylline, and theobromine are the most common methylxanthines found in nature	Methylxanthines have been linked to a number of other health benefits, including neurodegenerative disorders, cardio protection, diabetes, and fertility (Monteiro et al. 2019)	When concentrations of methylxanthines are below 20 mcg/ml, milder side effects such as nausea, vomiting, increased stomach acid secretion (and subsequent gastroesophageal reflux), polyuria, sleeplessness, palpitations, headaches, and tremors are more common (Gottwalt and Tadi, 2021)	Monteiro et al. (2019), Gottwalt and Tadi (2021)

lation, as well as acting as an antidepressant and showing indications of aiding persons with Alzheimer's disease. It is recognized by the German government as a treatment for memory loss, attention problems, and depression. A normal supplemental dose is 60 mg. Most energy drinks, on the other hand, do not contain enough ginkgo to be beneficial. Blood thinning, nausea, vomiting, diarrhea, headaches, dizziness, heart palpitations, and restlessness are some of the other side effects of ginkgo (Yunusa and Ahmed 2011).

Methylxanthines Methylated xanthines (methylxanthines) are produced by many different plant species.

They are commonly found in regular diet, as well as in a variety of incredibly common beverages and meals. Caffeine, theophylline, and theobromine are the most common methylxanthines found in nature. Methylxanthines have a long history of usage as therapeutic agents in a diverse variety of medical applications. Methylxanthines have been/were utilized in medicine as CNS stimulants, bronchodilators, coronary dilators, diuretics, and anticancer adjuvant therapies. Aside from these uses, methylxanthines have been linked to several other health benefits, including neurodegenerative disorders, cardio protection, diabetes, and fertility (Monteiro et al. 2019). However, methylxanthines have a limited therapeutic spectrum and, as a result, a high rate of side effects. When concentrations of methylxanthines are below 20 mcg/ml, milder side effects such as nausea, vomiting, increased stomach acid secretion (and subsequent gastroesophageal reflux), polyuria, sleeplessness, palpitations, headaches, and tremors are more common (Gottwalt and Tadi 2021).

Macronutrients

Breakdown of macronutrients such as carbohydrates and proteins will contribute to the major sources of energy. Different classes of macronutrients are summarized in Table 3.

Carbohydrates

Sugar Simple sugars (such as sucrose, fructose, or beet sugar) are a fast-acting source of energy and are used in energy drinks to boost cognitive performance. Sugar content in drinks is normally around 27 g per 8 oz. Energy drinks with a higher volume surpass the daily sugar limit of 32 g (Rath 2012). The amount of sugar in one can of ED (500 mL or 16.9 oz) is usually around 54 g (Higgins et al. 2010). Due to the strong significant evidence linking added sugar consumption to poor health, many institutions, including the World Health Organization, have advised limiting sugar intake (WHO 2015).

Glucuronolactone The human body produces glucuronolactone (DGL) when glucose is broken down by the liver.

This component is found in all connective tissue. DGL is believed to help with detoxification, the release of hormones and other compounds, and vitamin C production. It is included in energy drinks because it claimed to help with glycogen depletion by preventing other compounds from depleting muscle glycogen stores. (Yunusa and Ahmed 2011).

Protein

Taurine A semi-essential amino acid that is not involved in protein synthesis and is abundant in mammalian tissues is known as taurine (2-aminoethanesulfonic acid). It is naturally found in human bodies, mostly in the brain, eyes, heart, and muscles (Beyranvand et al. 2014). Taurine is also naturally found in protein sources such as milk, meat, and fish. It is a common ingredient in sports supplements, energy drinks, dietary supplements, and non-caffeinated energy drinks. It has also been proved to help athletes perform better. Taurine is normally included in levels of 1–2 g per serving in products that specify the amount of taurine contained (Childs 2014). Taurine has been recommended as a treatment for epilepsy, heart failure, cystic fibrosis, and diabetes due to its anti-inflammatory properties (Caine and Geracioti 2016). Taurine may help to manage blood sugar levels and fight diabetes. Without any modifications in food or exercise, long-term supplementation reduced fasting blood sugar levels in diabetic rats used in research labs (Chauhan and Piracha 2021). According to some animal studies, increasing taurine intake can help prevent type 2 diabetes by lowering blood sugar levels and insulin resistance (Ito et al. 2012). However, additional research is required before any conclusions can be drawn.

Maltodextrin Maltodextrins ($C_6H_{10}O_5$) n·H_2O are saccharide polymers composed mostly of glucose units linked by -1,4 glucosidic boundaries. Maltodextrins are produced by enzymatic hydrolysis with or without acid, although only to a lesser amount than starch syrups (Klinjapo and Krasaekoopt 2018). Commercially accessible, typically white powders with excellent purity and microbiological safety are utilized in a wide range of food and beverage products, including baked goods and sports drinks (Hofman et al. 2016). Maltodextrins are known for their relatively high molecular weights and limited reducing power. Maltodextrin solutions have low osmotic pressures, high viscosities, and little or no sweetness due to their high molecular weights (Featherstone 2018). Maltodextrins, like any other carbohydrate, were found to reduce net glycogen breakdown during long-duration

Table 3 Summary of ingredient's information, health benefits, and side effects of the ED that are available in the market according to the classes of macronutrients (carbohydrates and proteins)

Classes of nutrients	Nutrients	Ingredient's name	Examples of ED containing the ingredient	Information on ingredients	Health benefits	Side effects	References
Macronutrients	Carbohydrates	Sugar		Simple sugars (such as sucrose, fructose, or beet sugar) are a fast-acting source of energy and are used in energy drinks to boost cognitive performance. Sugar content in drinks is normally around 27 g per 8 oz. Energy drinks with a higher volume surpass the daily sugar limit of 32 g (Rath 2012)	N/A	Excessive consumption of high-energy drinks may raise the risk of obesity and type 2 diabetes (Bedi et al. 2014)	Rath (2012), Bedi et al. (2014), Greenblum et al. (2012)
		Glucuronolactone		The human body produces glucuronolactone (DGL) when glucose is broken down by the liver. This component is found in all connective tissue	DGL is believed to help with detoxification, the release of hormones and other compounds, and vitamin C production. It is included in energy drinks because it claimed to help with glycogen depletion by preventing other compounds from depleting muscle glycogen stores. (Yunusa and Ahmed 2011)	N/A	Yunusa and Ahmed (2011)

Table 3 (continued)

Classes of nutrients	Nutrients	Ingredient's name	Examples of ED containing the ingredient	Information on ingredients	Health benefits	Side effects	References
	Protein	Taurine		A semi-essential amino acid that is not involved in protein synthesis and is abundant in mammalian tissues is known as taurine (2-aminoethanesulfonic acid). It is naturally found in human bodies, mostly in the brain, eyes, heart, and muscles (Beyranvand et al. 2011)	Taurine has been recommended as a treatment for epilepsy, heart failure, cystic fibrosis, and diabetes due to its anti-inflammatory properties (Caine and Geracioti 2016). Taurine may help to manage blood sugar levels and fight diabetes. Without any modifications in food or exercise, long-term supplementation reduced fasting blood sugar levels in diabetic rats used in research laboratories (Chauhan and Piracha 2020)	N/A	Beyranvand et al. (2011), Caine and Geracioti (2016), Chauhan and Piracha (2020)
		Maltodextrin		Maltodextrins ($C_6H_{10}O_5$) n·H_2O are saccharide polymers composed mostly of glucose units linked by -1,4 glucosidic boundaries. Maltodextrins are produced by enzymatic hydrolysis with or without acid, although only to a lesser amount than starch syrups (Klinjapo and Krasaekoopt 2018)	Maltodextrins, like any other carbohydrate, were found to reduce net glycogen breakdown during long-duration exercise while maintaining a high whole-body glucose oxidation rate (Hofman et al. 2016)	N/A	Klinjapo and Krasaekoopt (2018), Hofman et al. (2016)
		Carnitine		L-Carnitine is an amino acid produced mostly by the liver and kidneys that aids in metabolism and energy production (Yunusa and Ahmed 2011)	Carnitine acts as antioxidant and anti-inflammatory compound. Thus, it may reduce the exercise-induced muscle damage (Sawicka et al. 2020)	Nausea, vomiting, abdominal pain, and diarrhea are examples of rare adverse effects (Yunusa and Ahmed 2011)	Yunusa and Ahmed, (2011), Sawicka et al. (2020), Yunusa and Ahmed (2011)

exercise while maintaining a high whole-body glucose oxidation rate (Hofman et al. 2016).

Micronutrients

Many EDs are fortified with various types of vitamins and minerals. The purpose of the micronutrients (vitamins and minerals) improves person's emotion and increases the alertness and focus. The health benefits and side effects of the micronutrients in different types of ED are summarized in Tables 4 and 5.

Vitamins

Vitamin B A group of eight water-soluble vitamins that play a significant role in cell function is referred to as B vitamins. Vitamin B_2 (riboflavin), B_3 (niacin), B_6 (pyridoxine, pyridoxal, and pyridoxamine), inositol B_8 and B_{12} are the most common B vitamins added to ED (Heckman et al. 2010). Considering the significance of B vitamins as coenzymes in many metabolic processes, most people in the USA already consume the necessary daily quantity, and thus, any additional B vitamins added to ED are often lost in the urine, with no further health benefits (Heckman et al. 2010). Other additives including l-carnitine, d-glucuronolactone, and inositol have less research on their composition and function, with just a few studies showing minimal advantages (Yunusa and Ahmed 2011).

Riboflavin (B_2) Riboflavin, often known as crucial vitamin B2, is a heat-stable water-soluble vitamin. The flavoenzymes of the respiratory chain require riboflavin (B2), which facilitates energy metabolism involving lipids, carbs, and proteins (Yunusa and Ahmed 2011). It is also an important vitamin for a variety of physiological functions in the body, such as lowering migraines and boosting the immune system (Suwannasom et al. 2020). Riboflavin levels taken orally in a diet or from most multivitamin supplements rarely give side effects or toxicity (Pinto and Zempleni 2016).

Niacin (B_3) Niacin is used to make the reduced form of nicotinamide adenine dinucleotide (NADH) (vitamin B3). This coenzyme is necessary for supplying protons for oxidative phosphorylation and is important for cell energy production. It also raises the production of l-dopa, dopamine, serotonin, and norepinephrine, among other neurotransmitters (Yunusa and Ahmed 2011). Niacin dosage, either alone or in addition with statins and/or bile acid sequestrants, was reported to significantly improve markers of atherosclerosis, such as carotid intima-media thickening and stenosis incidence and balance out the ratio of HDL/LDL cholesterol in patients with dyslipidemia (Meyer-Ficca et al. 2016). The characteristics including skin flushing and itching were reported in clinical trials, as well as more significant disorders such as gastrointestinal and musculoskeletal issues, heart failure, diabetic complications, and new-onset diabetes (Meyer-Ficca and Kirkland 2016).

Pyridoxine (B_6) Vitamin B6 (pyridoxine hydrochloride) is a coenzyme that plays a role in amino acid and homocysteine metabolism, glucose and lipid metabolism, neurotransmitter generation, and DNA and RNA synthesis. Pyridoxine hydrochloride is involved in protein and red blood cell metabolism, as well as immune system function and the conversion of tryptophan to niacin (Yunusa and Ahmed 2011). It also works to utilize a protection reaction against chronic diseases including cardiovascular diseases (CVD) and diabetes by inhibiting inflammation, inflammasomes, oxidative stress, and carbonyl stress (Thanutchaporn et al. 2020). However, vitamin B6 can be toxic if its concentration inside the body is too high, resulting in sensory neuropathy with no apparent cause. Degeneration of peripheral nerve sensory fibers and myelin, as well as the dorsal columns of the spinal cord, results in bilateral loss of peripheral sensation or hyperesthesia, as well as limb pain, ataxia, and loss of balance (Abosamak and Gupta 2021).

Inositol (B_8) Inositol (previously vitamin B8, but no longer considered a vitamin because it is produced by the human body) comes in nine different stereoisomers, the most common of which being myoinositol. It is a component of cell membranes, aids in the digestion of fats by the liver, and aids muscle and nerve function (Higgins et al. 2010). The consumption of inositol may also help in preventing the development of chronic diseases—including obesity, diabetes, polycystic ovary syndrome (PCOS), metabolic syndrome, cardiovascular diseases, and cancer (Dinicola et al. 2017).

Cyanocobalamin B_{12} Cyanocobalamin is a vitamin B12 synthetic compound used to treat vitamin B12 deficiency. It is involved in several methylation reactions in the human body. In the body, it functions as a cofactor in the conversion of homocysteine to methionine as methylcobalamin, and as adenosylcobalamin in the conversion of methylmalonyl-CoA to succinyl-CoA as adenosylcobalamin. Cell division and expansion rely on both responses (Vasavada and Sanghavi 2020). This vitamin also aids nerve cell function, is required for DNA creation, and is necessary for red blood cell formation.

Vitamin C Vitamin C is required for the body's basic physiological activities. It aids in tyrosine, folic acid, and tryptophan synthesis and metabolism, as well as the hydroxylation of glycine, proline, lysine, carnitine, and

Table 4 Summary of ingredient's information, health benefits, and side effects of the ED that are available in the market according to the classes of micronutrients (vitamins)

Class of nutrients	Nutrients	Ingredient's name	Examples of ED	Information on ingredients	Health benefits	Side effects	References
Micronutrient	Vitamins B	Riboflavin (B_2)		Riboflavin, often known as crucial vitamin B2, is a heat-stable water-soluble vitamin. The flavoenzymes of the respiratory chain require riboflavin (B2), which facilitates energy metabolism involving lipids, carbs, and proteins (Yunusa and Ahmed 2011)	It is also an important vitamin for a variety of physiological functions in the body, such as lowering migraines and boosting the immune system (Suwannasom et al. 2020)	Riboflavin levels taken orally in a diet or from most multivitamin supplements rarely give side effects or toxicity (Pinto and Zempleni, 2016)	Yunusa and Ahmed (2011), Suwannasom et al. (2020), Pinto and Zempleni (2016)
		Niacin (B3)		Niacin is used to make the reduced form of nicotinamide adenine dinucleotide (NADH) (vitamin B3). This coenzyme is necessary for supplying protons for oxidative phosphorylation and is important for cell energy production (Yunusa and Ahmed 2011)	Significantly improve markers of atherosclerosis, such as carotid intima-media thickening and stenosis incidence and balance out the ratio of HDL:LDL cholesterol in patients with dyslipidemia (Meyer-Ficca and Kirkland 2016)	Skin flushing and itching were reported in clinical trials, as well as more significant disorders such as gastrointestinal and musculoskeletal issues, heart failure, diabetic complications, and new-onset diabetes (Meyer-Ficca and Kirkland 2016)	Yunusa and Ahmed (2011), Meyer-Ficca and Kirkland (2016)
		Pyridoxine (B_6)		Vitamin B6 (pyridoxine hydrochloride) is a coenzyme that plays a role in amino acid and homocysteine metabolism, glucose and lipid metabolism, neurotransmitter generation, and DNA and RNA synthesis. Pyridoxine hydrochloride, in particular, is involved in protein and red blood cell metabolism, as well as immune system function and the conversion of tryptophan to niacin (Yunusa and Ahmed 2011)	Utilize a protection reaction against chronic diseases including cardiovascular diseases (CVD) and diabetes by inhibiting inflammation, inflammasomes, oxidative stress, and carbonyl stress (Thanutchaporn et al. 2020)	However, vitamin B6 can be toxic if it's concentration inside the body are too high, resulting in sensory neuropathy with no apparent cause. Degeneration of peripheral nerve sensory fibers and myelin, as well as the dorsal columns of the spinal cord, results in bilateral loss of peripheral sensation or hyperesthesia, as well as limb pain, ataxia, and loss of balance (Abosamak and Gupta 2021)	Yunusa and Ahmed (2011), Thanutchaporn et al. (2020), Abosamak and Gupta (2021)

Table 4 (continued)

Class of nutrients	Nutrients	Ingredient's name	Examples of ED	Information on ingredients	Health benefits	Side effects	References
				Inositol (previously vitamin B8, but no longer considered a vitamin because it is produced by the human body) comes in nine different stereoisomers, the most common of which being myoinositol. It is a component of cell membranes, aids in the digestion of fats by the liver, and aids muscle and nerve function (Higgins et al. 2010)	The development of chronic diseases—including obesity, diabetes, polycystic ovary syndrome (PCOS), metabolic syndrome, cardiovascular diseases, and cancer, can be prevented by consuming this vitamin (Dinicola et al. 2017)	N/A	Higgins et al. (2010), Dinicola et al. (2017)
		Cyanocobalamin B_{12}		Cyanocobalamin is a vitamin B12 synthetic compound used to treat vitamin B12 deficiency. It is involved in a number of methylation reactions in the human body. In the body, it functions as a cofactor in the conversion of homocysteine to methionine as methylcobalamin, and as adenosylcobalamin in the conversion of methylmalonyl-CoA to succinyl-CoA as adenosylcobalamin. Cell division and expansion rely on both of these responses (Vasavada and Sanghavi 2021)	This vitamin also aids nerve cell function, is required for DNA creation, and is necessary for red blood cell formation	N/A	Vasavada and Sanghavi (2021)

Table 4 (continued)

Class of nutrients	Nutrients	Ingredient's name	Examples of ED	Information on ingredients	Health benefits	Side effects	References
		Vitamin C		Vitamin C is required for the body's basic physiological activities. It aids in tyrosine, folic acid, and tryptophan synthesis and metabolism, as well as the hydroxylation of glycine, proline, lysine, carnitine, and catecholamine (Chambial et al. 2013)	It promotes cholesterol conversion to bile acids easier, decreasing blood cholesterol levels. Vitamin C also improves iron absorption in the intestines by converting ferric to ferrous. It protects the body from the harmful effects of free radicals, pollution, and poisons as an antioxidant (Chambial et al. 2013)	Although large doses of vitamin C are considered to be safe, there have been reports that they can induce hemolytic anemia in individuals who have glucose-6-phosphate dehydrogenase deficiency (Unlu et al. 2016)	Chambial et al. (2013), Chambial et al. (2013), Unlu et al. (2016)
		Vitamin D		Vitamin D is exceptional that it can be produced in the skin as a result of sun exposure (Nair and Maseeh 2012). Vitamin D is both a vitamin and a hormone produced by our bodies. It is a fat-soluble vitamin that has long been recognized to aid in the absorption and retention of calcium and phosphorus, both of which are essential for bone formation (Nair and Maseeh 2012)	Vitamin D may help prevent cancer, heart disease, fractures and falls, autoimmune illnesses, influenza, type 2 diabetes, and depression, according to recent studies (Nair and Maseeh 2012)	However, a higher possibility of exogenous hypervitaminosis D with symptoms of hypercalcemia also known as vitamin D toxicity (VDT) is caused by excess intake or overdose of vitamin D (Marcinowska-Suchowierska et al. 2018)	Nair and Maseeh, (2012), Nair and Maseeh (2012), Marcinowska-Suchowierska et al. (2018)

Table 5 Summary of ingredient's information, health benefits, and side effects of the ED that are available in the market according to the classes of micronutrients (minerals), examples of ED available in market containing each ingredient, its health benefits, and side effects

Classes of nutrients	Nutrients	Ingredient's name	Examples of ED containing the ingredient	Information on ingredients	Health benefits	Side effects	References
Micronutrients	Minerals	Calcium (Ca)		Calcium is most typically associated with the development and metabolism of bone as a nutrient. Calcium is required for vascular contraction and vasodilation, muscular function, neuronal transmission, intracellular interaction, and hormone production in the circulatory system, extracellular fluid, muscle, and other tissues (Ross et al. 2011)	The prevention of hypertensive disorders of pregnancy and blood pressure reduction has not only been linked to a sufficient of dietary calcium consumption but also with low-density lipoprotein (LDL) cholesterol levels and prevention of osteoporosis and colorectal adenomas (Cormick and Belizan 2019)	Excess consumption of calcium might lead to increase in the incidence of constipation, severe diarrhea, and abdominal pain (Li et al. 2018a, b)	Ross et al. (2011), Cormick and Belizan, (2019), Li et al. (2018a, b)
		Iron (Fe)		Iron is a vital element for practically all living creatures since it is involved in a range of metabolic activities such as oxygen transport, DNA synthesis, and electron transport (Abbaspour et al. 2014)	To prevent iron deficiency anemia especially to pregnant mothers and women during menstruation	For the adverse effects associated with oral iron intake, it is frequently reported to be gastrointestinal side effects which include nausea, flatulence, abdominal pain, diarrhea, constipation, and black or tarry stools (Tolkien et al. 2015)	Abbaspour et al. (2014), Tolkien et al. (2015)
		Chromium (Cr)		Chromium is a trace mineral that can help with insulin sensitivity as well as protein, carbohydrate, and lipid metabolism (Wilson and Ware 2017)	The exact mechanism by which chromium improves the body is unknown, and human insufficiency reports are uncommon (Wilson and Ware 2017)	N/A	Wilson and Ware (2017)
		Zinc (Zn)		Chromium is a trace mineral that can help with insulin sensitivity as well as protein, carbohydrate, and lipid metabolism (Wilson and Ware 2017)	The exact mechanism by which chromium improves the body is unknown, and human insufficiency reports are uncommon (Wilson and Ware 2017)	N/A	Wilson and Ware (2017)

Table 5 (continued)

Classes of nutrients	Nutrients	Ingredient's name	Examples of ED containing the ingredient	Information on ingredients	Health benefits	Side effects	References
		Manganese (Mn)		Manganese (Mn) is a mineral that is mostly derived from food and water in the human body. Mn is absorbed by the gastrointestinal system and subsequently delivered to mitochondria-rich tissues (the liver, pancreas, and pituitary, in particular), where it is rapidly concentrated	Regulation of cellular energy, bone and growth of connective tissue, blood clotting and improve brain development (Avila et al. 2013)	Increased in oxidative stress, a well-established molecular mechanism of Mn-induced toxicity (Avila et al. 2013)	Avila et al. (2013)
		Molybdenum (Mo)		Molybdenum is a crucial trace element for microorganisms, plants, and mammals. Molybdenum (Mo) is required in extremely small amounts by the human body (usually 100 mg per day1), as opposed to macronutrients such as nitrogen, phosphorus, salt, calcium, magnesium, potassium, chlorine, and others, which are required in larger amounts (Sabatino et al. 2018)	It helps break down toxic sulfites and prevents toxins from building up in the body by activating enzymes (Sabatino et al. 2018)	N/A	Sabatino et al. (2018)

catecholamine. It promotes cholesterol conversion to bile acids easier, decreasing blood cholesterol levels. Vitamin C also improves iron absorption in the intestines by converting ferric to ferrous. It protects the body from the harmful effects of free radicals, pollution, and poisons as an antioxidant (Chambial et al. 2013). Although large doses of vitamin C are safe, there have been reports that they can induce hemolytic anemia in individuals who have glucose-6-phosphate dehydrogenase deficiency (Unlu et al. 2016).

Vitamin D Vitamin D is exceptional that it can be produced in the skin because of sun exposure (Nair and Maseeh 2012). Vitamin D is both a vitamin and a hormone produced by our bodies. It is a fat-soluble vitamin that has long been recognized to aid in the absorption and retention of calcium and phosphorus, both of which are essential for bone formation. Vitamin D may help prevent cancer, heart disease, fractures and falls, autoimmune illnesses, influenza, type 2 diabetes, and depression, according to recent studies (Nair and Maseeh 2012). However, a higher possibility of exogenous hypervitaminosis D with symptoms of hypercalcemia also known as vitamin D toxicity (VDT) is caused by excess intake or overdose of vitamin D (Marcinowska-Suchowierska et al. 2018).

Minerals

Calcium (Ca) Calcium is most typically associated with the development and metabolism of bone as a nutrient. Calcium hydroxyapatite ($Ca_{10}[PO_4]_6[OH]_2$) makes up almost 99% of total body calcium and is found in bones and teeth, where it gives hard tissue its strength. Calcium is required for vascular contraction and vasodilation, muscular function, neuronal transmission, intracellular interaction, and hormone production in the circulatory system, extracellular fluid, muscle, and other tissues. Through the process of bone remodeling, bone tissue serves as a calcium storage and supplier for these key metabolic demands (Ross et al. 2011). The prevention of hypertensive disorders of pregnancy and blood pressure reduction not only been linked to a sufficient of dietary calcium consumption but also with low-density lipoprotein (LDL) cholesterol levels and prevention of osteoporosis and colorectal adenomas (Cormick and Belizan 2019). However, excess consumption of calcium might lead to increase in the incidence of constipation, severe diarrhea, and abdominal pain (Li et al. 2018a, b).

Iron (Fe) Iron is a vital element for practically all living creatures since it is involved in a range of metabolic activities such as oxygen transport, DNA synthesis, and electron transport (Abbaspour et al. 2014). The most important health benefits that this nutrient provides are to prevent iron deficiency anemia especially to pregnant mothers and women during menstruation. As for its adverse effects associated with oral iron intake, it is frequently reported to be gastrointestinal side effects which include nausea, flatulence, abdominal pain, diarrhea, constipation, and black or tarry stools (Tolkien et al. 2015).

Chromium (Cr) Chromium is a trace mineral that can help with insulin sensitivity as well as protein, carbohydrate, and lipid metabolism. The exact mechanism by which chromium improves the body is unknown, and human insufficiency reports are uncommon. A deficit could be linked to a variety of health issues. Impaired glucose tolerance leads to poor blood sugar management in persons with type 2 diabetes, and ineffective cholesterol control, which increases the risk of atherosclerosis and heart disease. However, there is insufficient evidence to back up either the advantages of chromium or the risks associated with a deficiency (Wilson and Ware 2021).

Zinc (Zn) Zinc is an essential nutrient, which means that your body cannot make or store it. It is an essential trace mineral for maintaining good health and is only second to iron in terms of body content among the trace minerals. It is present in every cell of the body, and it is required for the normal functioning of the body's defensive (immune) system. Zinc can be present in a wide range of foods, both plant and animal. Breakfast cereals, snack bars, and baking flour are typically fortified with synthetic forms of zinc because they do not naturally contain the mineral. Cell division, cell development, wound healing, and glucose digestion are all facilitated by this protein. The senses of smell and taste require zinc as well. The body requires zinc to grow and develop normally during pregnancy, infancy, and childhood. Zinc also helps insulin perform better (MedlinePlus n.d.). There are several adverse effects for excessive intake of zinc which includes immediate symptoms such as abdominal pain, nausea, and vomiting (Plum et al. 2010).

Manganese (Mn) Manganese (Mn) is a mineral that is mostly derived from food and water in the human body. Mn is absorbed by the gastrointestinal system and subsequently delivered to mitochondria-rich tissues (the liver, pancreas, and pituitary, in particular), where it is rapidly concentrated. Mn is also involved in the synthesis and activation of many enzymes (e.g., oxidoreductases, transferases, hydrolases, lyases, isomerases, and ligases); glucose and lipid metabolism; protein, vitamin C, and vitamin B synthesis; hematopoiesis catalysis; endocrine regulation; and immune function improvement (Li and Yang 2018). The health benefits for the consumption of manganese in our diet include regulation of cellular

energy, bone and growth of connective tissue, blood clotting and improve brain development. However, there are also adverse effects in Mn which includes the increase in oxidative stress, a well-established molecular mechanism of Mn-induced toxicity (Avila et al. 2013).

Molybdenum (Mo) Molybdenum is a crucial trace element for microorganisms, plants, and mammals. It can be found in large amounts in legumes, grains, and organ meats. It helps break down toxic sulfites and prevents toxins from building up in the body by activating enzymes. Mo is required in extremely small amounts by the human body (usually 100 mg per day1), as opposed to macronutrients such as nitrogen, phosphorus, salt, calcium, magnesium, potassium, chlorine, and others, which are required in larger amounts (Sabatino et al. 2018).

Artificial sweeteners

The role of artificial sweeteners is to provide sweetness to ED without adding extra calories and glucose. They may also aid in controlling blood glucose level and thus reduce the risk of obesity and diabetes. The health benefits and side effects of the artificial sweeteners in different types of ED are summarized in Table 6.

Aspartame Aspartame (E951) is a dipeptide-based synthetic sweetener that is nearly 180–200 times sweeter than sucrose while having a low calorific value. The consumption of regular sugar is restricted in diabetics who have trouble controlling their blood sugar levels. This is caused by diabetics' insufficient amounts of insulin, a hormone that regulates sugar absorption in the bloodstream. Aspartame helps to restrict sucrose intake by acting as a sugar substitute and release a very small amount of energy. Since it is digested more slowly than sucrose, blood sugar levels stay steadier over time. After swiftly absorbing glucose into the bloodstream, people with reactive hypoglycemia produce an excess of insulin (Zafar et al. 2017). Aspartame metabolites may also be a primary cause for adverse effects, such as headache, compromised memory, mood changes, and depression and others which are not being identified yet (Lindseth et al. 2014). Aspartame's metabolic metabolites (aspartic acid, phenylalanine, and methanol) have been determined to be more toxic to the body than the original chemical. After ingesting aspartame, both normal persons and phenylketonurics saw a significant increase in plasma phenylalanine levels (Stegink et al 1977; Koch et al 1976). Many studies have linked aspartame consumption to health implications. There could be a link between aspartame consumption and the development of diabetes mellitus (DM) and type 2 diabetes (T2D), as well as effects on obesity levels, glucose and insulin intolerance, and alterations in the microbiota of rats' offspring. In humans, there have been reports of premature birth, allergic reactions, and weight gain in newborns, increased risk of early first menstruation (11 years), mood disorders, mental stress, and depression, autism development in children, neurodegeneration, modification of neuronal cell functions, disruption of homeostasis, learning, and memory. Aspartame, whose metabolite is phenylalanine, is a common food additive that is particularly toxic to those with phenylketonuria. Aspartame releases 50% of its mass as phenylalanine after digestion, resulting in an increase in phenylalanine levels in the blood. Although the genotoxicity of aspartame is unknown, it has been shown to promote proliferation and slow apoptosis in test cells, suggesting that it may have carcinogenic qualities. Increases in the markers Ki 67, PCNA, and bcl-2 were also seen. The markers c-myc, Haras, and the p53 suppressor gene have all increased significantly. Females who are exposed to aspartame from a young age are more likely to develop lymphomas and leukemias. P27 and H-ras expression has also been found to be higher in studies. There is no evidence of a link between aspartame and pancreatic, gastric, or endometrial cancer. Aspartame's consumption has been linked to free radical generation and decrease in antioxidant enzyme activity (Mohammad et al. 2017; Ab Qayoom et al. 2018; Zafar et al. 2017; Czarnecka et al. 1957; Iman 2011). Table 7 shows effects of aspartame in various diseases.

Sucralose Sucralose is a modified version of ordinary sugar (sucrose) with the E number E955 attached to it. It is typically available in granular, liquid, or mini-tablet form under the brand name "Splenda," or as individual Canderel yellow packets (no other versions of Canderel as they contain different sweeteners). Sucralose has no calories, but because it is so sweet (about 600 times sweeter than sugar), it is frequently blended with other sweetening substances like maltodextrin in granulated form. This adds volume and texture while diluting the strong sweetness. These, on the other hand, are not calorie-free, and a teaspoon has roughly 2–4 cal in it. This is roughly 20% of the sugar calories that the granulated product is supposed to (British Dietetic Association 2018). The health benefits for sucralose as a beverage sweetener include improvement in weight loss, as well as prevention of tooth decay, diabetes, and reactive hypoglycemia. Safety concerns regarding sucralose were mostly related to the fact that it comes from a class of chemicals called organic chlorides, some types of which are known as toxic or carcinogenic; however, the chlorine presence in an organic compound does not guarantee its toxicity (Lindseth et al. 2014). Thus, there is lack of evidence or study regarding the toxicity and carcinogenic effect of sucralose consumption.

Table 6 Summary of ingredient's information, health benefits, and side effects of the ED that are available in the market according to the classes of artificial sweeteners

Classes of nutrients	Ingredient's name	Examples of ED containing the ingredient	Information on ingredients	Health benefits	Side effects	References
Artificial sweeteners	Aspartame		Aspartame (E951) is a dipeptide-based synthetic sweetener that is nearly 180–200 times sweeter than sucrose while having a low calorific value	Restrict sucrose intake by acting as a sugar substitute and release a very small amount of energy. Since it is digested more slowly than sucrose, blood sugar levels stay steadier over time	Aspartame metabolites may also be a primary cause for adverse effects, such as headache, compromised memory, mood changes, and depression and others which are not being identified yet (Lindseth et al. 2014)	Lindseth et al. (2014)
	Sucralose		Sucralose is a modified version of ordinary sugar (sucrose) with the E number E955 attached to it. It is typically available in granular, liquid, or mini-tablet form under the brand name "Splenda," or as individual Canderel yellow packets (not other versions of Canderel as they contain different sweeteners). Sucralose has no calories, but because it is so sweet (about 600 times sweeter than sugar)	Improvement in weight loss, as well as prevention of tooth decay, diabetes and reactive hypoglycemia (Lindseth et al. 2014)	There is lack of evidence or study in regards to the toxicity and carcinogenic effect of sucralose consumption	Lindseth et al. (2014)

Table 7 Effects of aspartame in various diseases

Type of disease	Influence of Aspartame
Obesity	It is unclear if obesity is associated with the consumption or products containing aspartame
Diabetes mellitus	The connection between aspartame and TD2 risk is unclear
Impact on children and fetus	Aspartame may have influence on children and fetuses
Genotoxicity	Aspartame may have genotoxic properties
Behavioral disorders	Aspartame can cause long-term changes in behavior
Autism	Aspartame itself does not trigger autism
Neurodegeneration	Aspartame cause mental stress, affects learning skills and memory. Aspartame is also amyloidogenic
Neurotransmission	Aspartame reduces catecholamine levels
Hormones	Aspartame elevates plasma corticosterone level and plasma adrenocorticotropic level
Allergies and skin problems	Aspartame can induce systemic contact dermatitis (in huge daily doses which lead to formaldehyde accumulation). 0.5 μg kg^{-1} and 0.5 mg μg kg^{-1} doses of aspartame reduces some atopic dermatitis symptoms
Phenylketonuria	Aspartame intake rises plasma Phe level. People suffering from phenylketonuria should avoid products containing aspartame
Cancer	Aspartame may have carcinogenic properties but further studies are needed
Inflammation	Aspartame caused neurotoxicity, oxidative stress, and inflammation in rat brain tissue
Preterm birth and maternity problem in women	aspartame increased risk of preterm birth, allergic reactions, weight growth in babies, early first menstruation, aspartame is linked to autism in children
Reduction of antioxidant enzyme activity	Aspartame use lowers hepatic tissue SOD, CAT, activity in renal tissue, and GSH levels while increasing GST activity in liver tissue

Health benefits of ED

Improved physical performance

Walsh et al. (2010) investigated the effects of energy drinks on treadmill exercise time to exhaustion. During a moderate-intensity endurance run, they noticed a significant increase in time to exhaustion, as well as improvements in perceived feelings of focus, energy, and tiredness (Walsh et al. 2010). Another research examined how caffeinated energy drinks affected acceleration tolerance and strength when subjected to a "G" load. Energy drinks improved relaxed G tolerance and increased strength but did not influence acceleration tolerance duration, according to the findings (Walker et al. 2010). According to the findings of a recent study, caffeinated energy drinks containing around 3 mg/kg of caffeine greatly increased the physical performance of female volleyball players (Perez-Lopez et al. 2015).

Improves mood and attitude

Taurine is found in ED ingredients and plays a role in metabolic processes. Amino acids are often added to energy drinks and supplements because they are the building blocks of proteins and precursors of neurotransmitters. The assumption is that enhanced amino acid availability will improve protein synthesis and neurotransmitter reserve, influencing consumer mood (Childs 2014). Another research found that 50 mg of guarana in EDs given twice daily for 21 days improved fatigue and tiredness ratings without affecting anxiety or depression in people receiving systemic chemotherapy. Prolonged treatment sessions did not create any noticeable mood effects in healthy participants (e.g., 360 mg 3 times daily for 3 days) or in people undergoing radiation therapy (75 mg daily for 28 days) (Silvestrini et al. 2013).

A range of automated memory and attention tests were used to examine cognitive performance, while the mood was assessed using a variety of questionnaires such as the Profile of Mood States (POMS), Bond–Lader, and Chalder Fatigue Scales. Both cognitive function and mood were dramatically enhanced in partially sleep-deprived persons who drank energy drinks, according to the findings. They were able to maintain their initial levels of attention for six hours, but the placebo group was unable to do so (Wesnes et al. 2013).

Improved concentration and memory

Only a few randomized controlled trials (RCTs) on energy drinks have been reported. 5-way crossover research with 20 college students (mean age 21 years) was conducted in one of the studies. They drank 250 mL of either flavorants (not expected to have physiological effects), the energetic drink (glucose, caffeine, ginseng, and gingko), or a placebo consisting of the medium used for the other drinks. The energy drink considerably increased "secondary memory" ($P=0.007$) and "speed of attention" ($P=0.044$) when compared to the placebo (O'Mathúna 2021).

Other studies involving Red Bull energy drink and sports performance have also been documented, in which participants were given either Red Bull or a placebo drink to drink. The Red Bull groups improved their aerobic endurance by 9% ($P < 0.05$), as well as their anaerobic performance by up to 24% ($P < 0.05$). Significant improvements also occurred in mental performance, including choice reaction time, concentration, and memory (O'Mathúna 2021).

Good source of vitamin B

Energy drinks frequently include significant amounts of B-group vitamins, often at higher doses than the daily recommended requirement for healthy people. High dietary folate and vitamin B6 intakes have been related to a lower risk of death from stroke, coronary heart disease, and heart failure, according to studies (Cui et al. 2010). B vitamins have also been proven to lower homocysteine levels, which have been associated with a variety of comorbidities, including pregnancy problems, cognitive impairment and mental illnesses, and cardiovascular risks. Although B vitamin supplementation lowered homocysteine levels and has a significant protective impact against stroke, there was no advantage in reducing cardiovascular disease, myocardial infarction, coronary artery disease, cardiovascular death, or all-cause mortality, according to a meta-analysis (Huang et al. 2012).

Weight loss

Energy drinks have been shown to be relatively useful in stimulating metabolic alterations in various studies (Jeffers et al. 2014). Caffeine in energy drinks may accelerate metabolism by fewer than 100 cal per day, which might burn around 1 pound of fat in a month. Caffeine's weight loss effect is dose-dependent, according to Tabrizi et al. 2019. Repeated energy drinks in a day, on the other hand, can have major health and well-being effects. Nevertheless, there is a lack of evidence and study investigating the effects of energy drinks on weight loss endeavors (Jeffers et al. 2014).

Health disadvantages of ED

Adverse cardiovascular effect

Several researchers have examined the short-term effects of ED on the cardiovascular system, focusing on caffeine and sugar (38–40). Consuming 355 mL of ED raised systolic and diastolic blood pressure, heart rate, and cardiac output according to a recent randomized crossover study on healthy adults (Grasser et al. 2014). A meta-analysis of 15 studies published in 2016 found that acute ED consumption led to higher systolic and diastolic blood pressure across the pooled results (Shah et al. 2016). Aspartame administration (54.87.3 mg kgG1 b.wt. day) resulted in elevated blood pressure, increased body weight, and a short-term increase in blood pressure, plasma glucose and triglyceride values, as well as a transitory reduction in plasma urea, all of which could affect cardiovascular risk factors (Martinez-Morales et al 2015). When compared to a control group, aspartame (40 mg kgG1 b.wt.) causes a rise in blood glucose, cholesterol, and triglycerides (Prokic et al 2014).

Caffeine toxicity is assumed to cause at doses higher than 400 mg per day for adults, 100 mg per day for adolescents (12–18 years), and 2.5 mg per kilogram of body weight for children (< 12 years), with serious symptoms often linked to cardiovascular consequences (Seifert et al. 2013). The US National Poison Data System received 4,854 ED-related calls between October 2010 and September 2011, including significant adverse events like seizure, dysrhythmia, and tachypnea (Seifert et al. 2013). In addition to palpitations, agitation, and tremor, data from Australian poison control centers indicate these primary symptoms of recreational or accidental ED consumption among children and adolescents (Gunja and Brown 2012). Considering that these data are based on self-reported signs and symptoms, and most consumers may not recognize ED as a toxin, ED-related toxicity concerns are likely to be underestimated.

Neurological effect

Headaches Caffeine causes a pro-nociceptive condition of cortical hyperexcitability, which is connected to acute and recurrent daily headaches (Espinosa and Sobrino 2017). Using a statistical model, Mostofsky et al. 2019 determined that drinking one or two caffeinated beverages did not alter the likelihood of getting a migraine headache on the same day. The probabilities were much higher when the volunteers took three or more caffeinated drinks. There was a nonlinear relationship between caffeinated beverage consumption and the likelihood of a migraine headache on that day in this study. This shows that excessive consumption of caffeinated beverages on that day may be a migraine trigger (Mostofsky et al. 2019).

Epileptic seizures Caffeine has been shown to cause seizures in people who are sensitive to it, especially when they are sleep-deprived. There has been no conclusive evidence of a relationship between seizures and energy drinks. Nonetheless, after drinking a lot of energy drinks, some people started having new adult-onset seizures without any signs of intracranial abnormalities or electroencephalography (Dikici et al. 2013). In kainic acid-induced seizure models in rats, long-term administration of taurine in drinking water increases seizure susceptibility and reduces clonic seizure latency. Caffeine is also

a natural stimulant that can be found in coffee and tea. Caffeine overdose has been linked to seizures in humans (Dikici et al. 2013).

Ischemic stroke In young- and middle-aged adults, alcohol misuse is also an independent risk factor for ischemic stroke. Rapid absorption and the resulting increase in the CNS may cause more negative effects when high-volume energy drinks are consumed with vodka on an empty stomach (Dikici et al. 2013). According to Steinke et al., after consuming 500 mL of energy drink on a weekly basis, heart rate increased 5 to 7 beats per minute, and maximum mean systolic blood pressure increased 10 mm Hg. On an empty stomach, drinking a high-energy drink with vodka may contribute to ischemic stroke by raising blood pressure and heart rate. In addition, the patient has hemorrhoid-related iron deficiency anemia. Anemia due to iron deficiency may play a role in ischemic stroke (Dikici et al. 2013). In Syrian weanling hamsters, aspartame increased appetite and weight gain and caused histological alterations in brain and liver cells, while aspartame metabolites, aspartic acid, phenylalanine, and diketopiperazine are responsible for neuron and astrocyte degeneration (Hassan 2016; Rycerz and Jaworska-Adamu 2013).

Hallucinations Hallucinations may occur in people who consume more than 300 mg of caffeine per day. High levels of cortisol can be caused by caffeine consumption, which could explain the above. Cortisol amplifies the physiological effects of stress, increasing the risk of hallucinations (Crowe et al. 2011).

Physiological effect

Muscular twitching Caffeine overdose can result in muscle twitching, which can be caused by minor muscle contractions or uncontrollable twitching in muscle groups controlled by motor nerve fibers. Dietary deficiencies, medication side effects, and strenuous exercise are all possible causes.

Muscle twitching can be caused by stress or anxiety, or it can indicate a nervous system disorder (MedlinePlus 2021).

Restlessness Energy drinks significantly increased the odds of insomnia and jitteriness/activity when compared to the control group (P 0.05), according to a meta-analysis. Caffeine intoxication, a clinical syndrome described in the Diagnostic and Statistical Manual of Mental Disorders, fifth edition, is linked to many of the negative effects of energy drinks. Caffeine intoxications are typically indicated by restlessness. (Nadeem et al. 2021).

Sleeplessness There is currently inadequate research evaluating how these substances function alone or in combination to produce mental health issues. It is possible that caffeinated and sugary EDs influence sleep behavior (i.e., the sleep–wake cycle) by stimulating the adrenergic system, which could contribute to poor psychological distress management and mental health issues (Kaur et al. 2020).

Psychological effect

Anxiety According to report from Hofmeister et al. (2010), in two samples of students, anxiety levels were found to be higher in energy drink consumers compared to non-consumers. Nevertheless, in one of the two groups, anxiety was only higher among regular users compared to nonregular users, making it difficult to say whether the association was dosage-dependent or not. In addition, another study found that energy drink use was associated with anxiety in a large sample ($N=4957$) of Turkish 10th grade students; anxiety scores were higher in those who had used the products once in their lifetime, once to three times a month, once to five times a week, and every day, compared to nonusers in the previous year. However, at the multivariate level, the impacts were no longer significant (Evren and Evren 2015).

Depression Over a two-year period, this study discovered strong positive relationships between ED use and depression, anxiety, and stress symptoms in young adult males (but not females). Males who switched from non-ED to ED use experienced greater depression and stress symptoms over time. The findings backed up previous research that found a link between ED use and sadness and stress symptoms. Males are more likely than females to have these relationships, according to cross-sectional studies (Kaur et al. 2020). Consumption of aspartame has been linked to mood problems, mental stress, and sadness. Long-term aspartame usage affects the cerebral and cerebellar cortex, causing neurodegeneration, altering neuronal cell activities, and disrupting homeostasis, learning, and memory (Czarnecka et al. 1957).

Gastrointestinal effect A case with a woman that presented with jaundice, abdominal pain, and highly increased liver enzymes was reported following energy drink overconsumption (Vivekanandarajah et al. 2011). The same result was reported by Huang et al. in a 36-year-old man (Huang et al. 2014). More research is needed to determine which people are particularly vulnerable and the mechanism by which energy drinks cause hepatic injury.

Renal effects

EDs are not the same as "sports drinks," which provide hydration and electrolyte replenishment. EDs are rich in carbohydrates, which influence fluid absorption and cause gastrointestinal distress, as well as caffeine, which tends to cause diuresis, which results in greater urinary output and natriuresis rather than hydration (Higgins et al. 2010). Excessive Red Bull consumption has been linked to a variety of effects, including acute renal failure, greater systolic and diastolic blood pressure, heart rate, and even decreased blood supply to the brain (Greene et al. 2014). According to Schöffl et al. (2011), after consuming 750 mL of energy drink, this patient developed acute kidney failure with tubular necrosis and rhabdomyolysis. Due to its potential to change renal blood flow and regulate osmolarity in the renal medulla, the authors speculated that excessive intake of taurine may be implicated in the development of kidney injury; however, this role has yet to be proven (Chesney et al. 2010). Nephrotoxicity is caused by the ingestion of aspartame (Martins et al 2007; Bahr and Zaki 2014).

Dental effects

There is growing evidence that the intake of possibly erosive beverages is on the rise. Also, there has been a significant correlation discovered between the consumption of energy drinks and the deterioration of teeth (Hasselkvist et al. 2010). The consumption of ED was linked to a 2.4-fold rise in tooth deterioration. This has been related to energy drinks' low pH and high sugar content (Li et al. 2012). The sugars in drinks are metabolized by plaque microorganisms to generate organic acids that bring about demineralization (Li et al. 2012). Pinto et al. have discovered that drinking energy drinks can cause cervical dentin hypersensitivity by eliminating the smear layer of the teeth (Pinto et al. 2013).

Obesity and type II diabetes

Energy drinks often have high sugar content, ranging from 21 to 34 g per ounce. Sucrose, glucose, and high-fructose corn syrup are the main sources of sugar. As a result, excessive consumption of high-energy drinks may raise the risk of obesity and type 2 diabetes (Bedi et al. 2014). Furthermore, the amount of sugar in energy drinks may decrease intestinal bacteria activity, variety, and gene expression, increasing the risk of obesity and metabolic syndrome (Greenblum et al. 2012). Acute caffeine consumption reduces insulin sensitivity, which may justify the spike in blood glucose levels observed in some studies after energy drink consumption (Ragsdale et al. 2010). Caffeine intake lowers insulin sensitivity in a dose-dependent approach, with a 5.8% increase in insulin for each mg/kg increase in caffeine (Beaudoin et al. 2012). There may be a link between aspartame consumption and the development of diabetes mellitus (DM) and type 2 diabetes (T2D), and it was found to be dangerous to mice in terms of behavior and biochemical analysis parameters when used as a food additive (Czarnecka et al. 1957; Abu-Taweel 2016; Zafar et al. 2017; Collison et al. 2012). When C57BL/6J mice are exposed to chronic aspartame treatment beginning in utero, it causes changes in blood glucose levels, spatial learning, and memory, as well as weight growth (Collison et al 2013).

Cancer

The link between sugary drinks and cancer risk has received far less attention. Nevertheless, because of its mechanical plausibility, this potential relationship raises growing concern. Sugary drinks are, in fact, strongly linked to the development of obesity, which is now identified as a major risk factor for several cancers. Besides obesity and adiposity, insulin resistance induced by high glycemic index or glycemic load, which has been linked to breast cancer, hepatocellular cancer, and diabetes-related carcinomas, could be a mechanism behind a link between sugary drinks and cancer. Chemical compounds in sugary drinks, such as 4-methylimidazole in drinks containing caramel colorings (described as possibly carcinogenic to humans by the International Agency for Research on Cancer, IARC), pesticides in fruit juices, and artificial sweeteners like aspartame, could all play a role in cancer development (Chazelas et al. 2019). Another study revealed that a combination of caffeine, taurine, and guarana may stimulate and increase apoptosis by lowering superoxide dismutase and catalase activity in human neuronal SH-SY5Y cells in vitro (Zeidán-Chuliá et al. 2013). In both male and female rodents, aspartame ingestion has been shown to be a carcinogenic and angiogenic agent. The markers Ki 67, PCNA, and bcl-2 all showed an increase. According to rat studies, 200 mg/kg body weight caused a considerable surge in the markers c-myc, Ha-ras, and the p53 suppressor gene in rats. Females who are exposed to aspartame from a young age are more likely to develop lymphomas and leukemias. P27 and H-ras expression has also been found to be higher in studies (Czarnecka et al. 1957; Soffritti et al 2010; Alleva et al 2011; Gombos et al 2007; Martins et al 2007).

Caffeine toxicity

Caffeine is a stimulant that has been used for ages around the world because of its ability to increase mental alertness. Caffeine lethal dosages have been reported at blood concentrations of 80 to 100 μg/ml, which can be achieved with a dose of 10 g or more. Caffeine overdoses in adults are uncommon, but when

they do occur, they are frequently triggered by an intentional overdose of medications (Murray and Traylor 2020). Four caffeine-induced psychiatric disorders have been classified by the Diagnostic and Statistical Manual of Mental Disorders. Caffeine intoxication, anxiety, sleep disturbance and other related disorders are all examples of caffeine related disorders (Juliano et al. 2012). Caffeine intoxication symptoms are most common in individuals who consume 200 mg or more of the stimulant. Anxiety, insomnia, gastrointestinal problems, muscle twitching, restlessness, and spells of exhaustion are just a few of the symptoms (Bedi et al. 2014).

Combined effects of alcohol Underage and younger consumers enjoy alcohol combined with energy drinks, and the beverage industry has benefited on this dynamic trend by aggressively marketing to teenagers and young adults. Nonetheless, there have recently been concerns about the combination's potential public health implications. Consequently, the FDA issued warning letter to manufacturers, effectively banning the manufacture and sale of pre-mixed caffeinated alcoholic beverages (CABs); however, consumers continue to combine energy drinks with alcohol by hand (e.g., Red Bull and vodka, Jaeger Bomb) (Heinz et al. 2013). CAB use is linked to problematic alcohol use and harmful alcohol-related effects. In a large multi-site survey, college students who consumed alcohol mixed with energy drinks reported more alcohol-related risk behaviors (e.g., riding in a car with a drunk driver, being hurt or injured, sexually exploiting another student, being taken advantage of sexually) than students who consumed alcohol alone. Furthermore, students who drink caffeine–alcohol combination drink more alcohol and engage in riskier drinking behaviors (e.g., binge drinking) than students who solely consume alcohol (Heinz et al. 2013).

Reduction of antioxidant enzyme activity Aspartame use lowers hepatic tissue superoxide dismutase (SOD), superoxide dismutase SOD and catalase CAT activity in renal tissue, and glutathione (GSH) levels while increasing glutathione S-transferase (GST) activity in liver tissue. This could be due to the creation of methanol or other metabolites, as aspartame is metabolized into aspartic acid, phenylalanine, and methanol in the ratio of 50:40:10, as well as a little quantity of aspartyl phenylalanine diketopiperazine, especially when heated (Abhilash et al 2011; Iman 2011; Prokic et al 2014; Choudhary and Devi 2014; Alwaleedi 2016; Adaramoye and Akanni 2016; Iyyaswamy and Rathinasamy 2012).

Inflammation Aspartame caused neurotoxicity, oxidative stress, and inflammation in rat brain tissue, as well as a large increase in protein carbonyl content and a significant drop in reduced glutathione concentration. Also, a significant increase in brain interleukin-1 (IL-1) and tumor necrosis factor- "(TNF-)" production was accompanied by a significant reduction in brain-derived neurotropic factor (BDNF), serotonin, and acetylcholine esterase (AchE) activity, as well as a substantial increase in acetylcholine (Ach) accumulation in brain homogenates (Lindseth et al 2014; Kamel 2015).

Preterm birth and maternity problem in women Intake of artificially sweetened drinks containing aspartame as one of the ingredients has been associated with an increased risk of premature birth in both normal-weight and overweight women, indicating that aspartame intake and use, particularly during pregnancy, may have detrimental consequences (Halldorsson et al 2010; Czarnecka et al. 1957; Martins et al 2007; Czarnecka et al. 1957). There have been instances of allergic reactions, and weight growth in babies in humans. Aspartame has been proven to enhance the probability of an early first menstruation (11 years) in females aged 9–10. Aspartame absorption by mothers during pregnancy is linked to autism in children. Maternal absorption of aspartame during pregnancy correlates with autism in children (Halldorsson et al 2010; Czarnecka et al. 1957; Martins et al 2007).

Discussion

This review has given a lot of insight into the benefits and detriments of the consumption of energy drink to human health. The author's view is that the ingredient type and the amount contained in the energy drink determine to a major extent the effect on health. The presence of caffeine in ED is not a threat to health; rather a moderate acute dose ranging from 200–350 mg reduces heart rate and raise blood pressure in adults, while also enhancing emotions of well-being, focus, and arousal. Moderate caffeine consumption of up to 400 mg per day is usually regarded as safe and even beneficial to adults' well-being. Guarana has been reported to possess antioxidant, effective stimulant and may be effective in treatment of fatigue and depression related to cancer treatment. A 16-oz energy drink can range from 1.4 mg to 300 mg and is considered safe by Food and Drug Administration (FDA). Ginseng is useful in boosting energy, reducing fatigue, relieving stress, and improving memory and anti-inflammatory activity through activation of corticotropic hormone release from hypothalamus and pituitary glands, and consumption of regular amount of 200 mg per day is considered

safe. However, the consumption of more than 2700 mg per day may pose a threat to health such as maniac episodes, uterine bleeding, gynecomastia, long QT syndrome, atrial fibrillation with bradycardia, hypertensive crisis, and acute lobular hepatitis.

Yerba mate and acai berry possess useful pharmacological such as anti-inflammatory, anti-diabetic, antioxidant, in vitro anticancer, inhibition of topoisomerase II, anti-obesity and reduces LDL cholesterol levels. Ginkgo biloba has good health benefits, a normal supplemental dose of 60 mg per day present biological effect such as improvement of memory retention, focus, enhanced blood circulation, and antidepressant. However, consumption of ginkgo biloba maybe poses health discomfort of blood thinning, nausea, vomiting, diarrhea, headaches, dizziness, heart palpitations, and restlessness. Methylxanthines act as CNS stimulants, bronchodilators, coronary dilators, diuretics, and anticancer adjuvant therapies, aside from treatment of neurodegenerative disorders, cardio protection, diabetes, and fertility. Consumption of methylxanthines at lower dose may pose milder side effects such as nausea, vomiting, increased stomach acid secretion, polyuria, sleeplessness, palpitations, headaches, and tremors which are more common.

Energy drink that contains sugar concentration of 500 mL or 16.9 oz usually around 54 g maybe detrimental to health, strong evidence has associated sugar consumption to poor health, and many institutions, including the World Health Organization, have advised limiting sugar intake. This is because the consumption of regular sugar for diabetics who have trouble controlling their blood sugar levels causes insufficient amounts of insulin that regulates sugar absorption in the bloodstream. Consumption of ED that the sugar content is above the daily sugar limit of 32 g for sure will be detrimental to health and Rath 2012 reported that energy drinks with a higher volume usually surpass the daily sugar limit of 32 g. Glucuronolactone is useful in detoxification, the release of hormones and vitamin C production, and protection of muscle glycogen stores. Taurine is associated with treatment of epilepsy, heart failure, cystic fibrosis, and diabetes; however, additional research is required before any conclusions can be drawn. Carnitine acts as antioxidant and anti-inflammatory compound and may reduce the exercise-induced muscle damage. Maltodextrins reduce net glycogen breakdown during long-duration exercise while maintaining a high whole-body glucose oxidation rate. Artificial sweeteners such as aspartame and sucralose are added in energy drink to replace sugar and restrict absorption of sugar. Aspartame helps to restrict sucrose intake by acting as a sugar substitute and releases a very small amount of energy. Aspartame metabolites may also be a primary cause for adverse effects, such as headache, compromised memory, mood changes, and depression and others which are not being identified yet.

The presence of vitamins such as vitamin B, riboflavin (B2), niacin (B3), pyridoxine (B6), inositol (B8), cyanocobalamin B12, vitamin C and vitamin D in energy drink has various health benefits. B vitamins as coenzymes in many metabolic processes facilitate energy metabolism involving lipids, carbs, and proteins, boast immune system, oxidative phosphorylation, and cell energy production; amino acid and homocysteine metabolism, glucose and lipid metabolism, neurotransmitter generation, and DNA and RNA synthesis. The consumption of inositol (former B8) is reported to assist in preventing the development of chronic diseases, including obesity, diabetes, polycystic ovary syndrome (PCOS), metabolic syndrome, cardiovascular diseases, and cancer. Incorporation of mineral such as calcium, iron, chromium, zinc, manganese, and molybdenum is very useful to health. Most of the minerals are useful for vascular contraction and vasodilation, muscular function, neuronal transmission, intracellular interaction, and hormone production in the circulatory system, extracellular fluid, muscle, and other tissues. Oxygen transport, DNA synthesis, and electron transport prevent iron deficiency anemia, protein, carbohydrate, and lipid metabolism. They help in glucose and lipid metabolism; protein, vitamin C, and vitamin B synthesis, hematopoiesis catalysis, endocrine regulation, regulation of cellular energy, bone and growth of connective tissue, blood clotting, improvement of brain development, and immune function improvement (Li and Yang 2018); consumption of aspartame and the development of diabetes mellitus (DM) and type 2 diabetes (T2D), obesity, changes in the microbiota of the offspring of rats. In humans, there has been evidence of premature birth, allergic reactions, weight gain in the newborns, increase in the risk of an early first menstruation, mood disorders, mental stress, and depression, development of autism in children, neurodegeneration, modification of the functions of neuronal cells, interruption of homeostasis, learning and memory, harmful people with phenylketonuria, free radical generation, impairment of antioxidant enzymes and carcinogenic.

Consumers should be aware of the potential side effects of aspartame, notwithstanding the lack of solid clinical data on those side effects. The author concludes that the oral treatment with a high dose of aspartame used in those animal trials was rare in humans. Future epidemiological studies and clinical trials are needed to look at the long-term effects of aspartame use at the recommended daily amount. The position of aspartame has remained controversial due to the lack of scientific data supporting and opposing its use. The negative side effects of aspartame ingestion, on the other hand, are extensively

documented in human and animal studies. Investigations in similar fresh avenues are strongly urged to cover existing research gaps and put an end to the debate regarding aspartame use. The critical assessment of the literature supporting aspartame use appears to be affected in part by interest groups. The authors propose that bias-free comprehensive trials be used to investigate the safety of aspartame in a variety of groups with varying clinical circumstances. As a result, authorities such as the US Food and Drug Administration (FDA), the European Food Safety Authority (EFSA), the Agence Française de Sécurité Sanitaire des Aliments (AFSSA), the FSSAI (Food Safety and Standard Authority of India), and the Joint FAO/WHO Expert Committee on Food Additives (JECFA) should reconsider the acceptable daily intake (ADI) of aspartame among the public.

In the food and pharmaceutical industries, aspartame is a common sweetener; therefore, it is critical to understand the benefits and drawbacks of aspartame to determine the danger of negative health effects. Based on current knowledge, the benefits of using aspartame outweigh the risks of adverse effects, and thus, this artificial sweetener will continue to be a common ingredient in products. Given the widespread use of aspartame as an artificial sweetener, it appears reasonable to continue study into its safety. Nonetheless, whether aspartame is the direct cause of sickness is unknown.

Conclusions

Most of the health detriments caused because of consumption of energy drink is mostly due to the presence of excess quantity of caffeine and sugar, and presence of aspartame. Scientific reports from in vitro and in vivo have linked aspartame to many detrimental health issues. The presence of aspartame in the energy drink may pose a health risk to consumers. However, if the quantities of caffeine and sugar content in energy drink are kept at FDA- and WHO-recommended daily consumption amount, and no aspartame content, then it may not present any problem to health. Consumption of energy drink that contains natural ingredients such as yerba mate, acai berry, ginkgo biloba, methylxanthines, amino acid, guarana, and ginseng with moderate FDA- and WHO-approved daily consumption of caffeine and sugar is not detrimental to health.

Abbreviations

ED: Energy drinks; B2: Riboflavin; B3: Niacin; B6: Pyridoxine; B8: Inositol; B12: Cyanocobalamin; Vit C: Ascorbic acid; Vit D: Cholecalciferol; D2: Ergocalciferol; D3: Cholecalciferol; WHO: World Health Organization; DGL: Glucuronolactone; C6H10O5: Maltodextrins; B2: Riboflavin; B3: Niacin; B6: Pyridoxine; CVD: Cardiovascular diseases; B8: Inositol; B12: Cyanocobalamin; Ca: Calcium; LDL: Low-density lipoprotein; Fe: Iron; Cr: Chromium; Zn: Zinc; Mn: Manganese; Mo: Molybdenum; RCTs: Randomized controlled trials; IARC: International Agency for Research on Cancer; CABs: Caffeinated alcoholic beverages; FDA: Food and Drug Administration; PCOS: Polycystic ovary syndrome; RNA: Ribonucleic acid; CNS: Central nervous system; DNA: Deoxyribonucleic acid; LDL: Low-density lipoprotein; SOD: Superoxide dismutase; CAT: Catalase; GSH: Glutathione; GST: Glutathione *S*-transferase; DM: Diabetes mellitus; T2D: Type 2 diabetes; MKI 67: Marker of proliferation Ki-67; Bcl-2: B-cell lymphoma 2; c-myc: C-myelocytomatosis; p53: Tumor suppressor protein; p27: Cyclin-dependent kinase inhibitors; EFSA: European Food Safety Authority; AFSSA: Agence Française de Sécurité Sanitaire des Aliments; FSSAI: Food Safety and Standard Authority of India; JECFA: Joint FAO/WHO Expert Committee on Food Additives; ADI: Acceptable daily intake.

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Author contributions

PNO conceptualized the project and reviewed and supervised the writing of the manuscript, and CPN assisted with review and supervised the writing of the manuscript project. HA searched for materials and wrote the manuscript, assisted by XQC. All authors read and approved the final manuscript.

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Availability of data and materials

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Declarations

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Not applicable.

Consent for publication

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Competing interests

We, the authors (Hani' Ariffin, Xiu Qing, Dr. Chong, Chong Pei Nee, and Dr. Patrick Nwabueze Okechukwu), declare that we do not have any conflict of interest with any one with respect to our manuscript entitled "Is the Consumption of Energy Drink Beneficial or Detrimental to Health: A Comprehensive Review?".

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