ISSN 1949-8462 (online)

World Journal of *Cardiology*

World J Cardiol 2017 November 26; 9(11): 796-812

Published by Baishideng Publishing Group Inc

World Journal of Cardiology

Contents

Monthly Volume 11 Number 9 November 26, 2017

World Journal of Cardiology
Volume 11 Number 9 November 26, 2017

Contents

NAME OF JOURNAL
World Journal of Cardiology

ISSN
ISSN 1949-8462 (online)

LAUNCH DATE
December 31, 2009

FREQUENCY
Monthly

EDITORIAL OFFICE
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World Journal of Cardiology
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7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-2238242
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E-mail: editorialoffice@wjgnet.com
Help Desk: http://www.f6publishing.com/helpdesk
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7901 Stoneridge Drive, Suite 501,
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Help Desk: http://www.f6publishing.com/helpdesk
http://www.wjgnet.com

PUBLICATION DATE
November 26, 2017

INSTRUCTIONS TO AUTHORS
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ONLINE SUBMISSION
http://www.f6publishing.com

World Journal of Cardiology

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World J Cardiol 2017 November 26; 9(11): 796-806

DOI: 10.4330/wjc.v9.i11.796

ISSN 1949-8462 (online)

REVIEW

Effects of energy drinks on the cardiovascular system

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Author contributions: All of the authors contributed to this manuscript.

Conflict-of-interest statement: No conflicts of interest exist for any of the authors with respect to the publication of this article.

Manuscript source: Invited manuscript

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Received: April 21, 2017
Peer-review started: April 21, 2017
First decision: June 12, 2017
Revised: August 4, 2017
Accepted: August 15, 2017
Article in press: August 16, 2017

Published online: November 26, 2017

Abstract

Throughout the last decade, the use of energy drinks has been increasingly looked upon with caution as potentially dangerous due to their perceived strong concentration of caffeine aside from other substances such as taurine, guarana, and L-carnitine that are largely unknown to the general public. In addition, a large number of energy drink intoxications have been reported all over the world including cases of seizures and arrhythmias. In this paper, we focus on the effect of energy drinks on the cardiovascular system and whether the current ongoing call for the products' sales and regulation of their contents should continue.

Key words: Energy drinks; Caffeine; Taurine; Guarana; Cardiovascular effects

Core tip: The last decade has witnessed a great surge in the consumption of energy drinks which coincided with an increased rate of reported cases of intoxications resulting in cardiovascular adverse effects especially arrhythmias, although most of such cases were associated with alcohol, stimulants, or rapid consumption in a short period of time. In our paper, we summarized the research pertaining to the most common components of the energy drinks in an attempt to evaluate whether the call for control of the products is merited, some of which had surprising possible health benefits.

Wassef B, Kohansieh M, Makaryus AN. Effects of energy drinks on the cardiovascular system. *World J Cardiol* 2017;

9(11): 796-806 Available from: URL: http://www.wjgnet.com/1949-8462/full/v9/i11/796.htm DOI: http://dx.doi.org/10.4330/wjc.v9.i11.796

INTRODUCTION

The last decade has witnessed the greatest rise in the consumption of non-steroidal energy supplements for the specific purpose of boosting athletic performance and concentration. For many years, the use of energy drinks (ED) has been perceived as potentially dangerous due to their strong concentration of caffeine and presence of other substances such as taurine, guarana, and L-carnitine amongst others. In France, the use of Red Bull™ was banned at one point until the rule was reversed by the European Union on claims of the lack of evidence for its toxicity. The controversy surrounding energy drinks heightened recently due to the increasing reports of energy drink toxicities, most alarmingly in regard to heart rhythm and central nervous system abnormalities such as atrial fibrillation and seizures, respectively. We aim to focus on the effect of energy drinks on the cardiovascular system and whether the call for the products' sales and regulation of their contents has merit.

SCOPE OF THE ISSUE

In recent years, the market for energy drinks has thrived and after 50 years in the market, the consumption of these beverages has increased exponentially[1]. Along with a growing global market, emergency room visits due to the consumption of energy drinks have increased as well. The Substance Abuse and Mental Health Services Administration revealed that 20783 people visited the emergency department with complaints involving caffeine rich energy drinks in 2011. Over the period from 2007-2011, ED-related emergency department visits in the United States doubled[2]. Due to their high consumption, lack of evidence, and occasional acute adverse health effects, the safety of energy drinks has been called into question. Our review will specifically focus on the cardiovascular effects of the ingredients contained in EDs.

As promisors of prolonged arousal, boosted athletic performance, and increased concentration, energy drinks have become popular supplements in the past few years. A recent study of 1620 nursing students noted 78.1% reported ED use. The students consumed an average of 1.6 cans per week, ranging from 1 to 30 cans per week[3]. Certain ED company claims have been found to be true. One placebo controlled study found that certain important aspects of cognitive function can be improved by a single energy shot. The study was performed on partially sleep-deprived healthy individuals and the effect was noted to last for up to 6 h[4]. Another study found that subjective ratings of vigor and fatigue were improved after the consumption of energy drinks, although, objective performance did not improve and, in fact, seemed to worsen over time[5].

With increased stress to perform academically, athletically, and socially, it is not surprising that most consumers of EDs are teenagers and young male adults[6,7]. It should be noted that ED consumption cannot be looked at as a separate entity as co-ingestion with alcohol, drugs, and other pharmaceuticals has become a widespread practice. A cross-sectional survey conducted in 2012 reported that 85 emergency department patients, that were there for ED related events, showed that illicit stimulants such as cocaine and methamphetamine were often co-ingested[8]. Another study found that males were more likely to co-ingest alcohol or drugs, whereas in females, co-ingestion of other medications was more common[9]. It should be noted that the half-life of caffeine was found to increase by up to 72% with its coingestion with alcohol, thereby enhancing the effects of EDs[10].

PURPORTED EFFECTS OF ENERGY DRINKS AND THEIR CAFFEINE-RELATED CAUSAL ROLES ON THE CARDIOVASCULAR SYSTEM (FIGURE 1)

Physiologic effects on vital signs

Evidence of reported energy drinks-related cardiovascular adverse effects has helped to further raise suspicion of these beverages. It is widely believed that caffeine, particularly at high doses, is associated with multiple cardiac comorbidities including palpitations and a number of arrhythmias such as atrial fibrillation and supraventricular and ventricular ectopy. Caffeine's effect in acutely raising the blood pressure is also thought to stress the cardiovascular system, furthering the likelihood of it causing arrhythmia. Such an elevation in blood pressure has been also shown to be more prominent in the elderly and those with underlying hypertension. A study of 20 young healthy humans explored the effects of Red Bull along with induced mental stress. It was found that compared with the ingestion of water, ingestion of a 355 mL can of Red Bull imposes a cumulative cardiovascular load, increasing systolic BP by about 10 mmHg, diastolic BP by about 7 mmHg, and heart rate by 20 beats/min, and decreasing cerebral blood flow velocity by -7 cm/s[11].

Several studies have found energy drinks have been shown to induce hypertension compared to placebo. A recent study asked fifteen recreational runners to complete five exercise trials. The subjects ingested one of three energy drinks or a placebo one hour prior to testing. Results showed that the fifteen minute systolic BP readings were significantly higher in the three energy drink trials (163.87, 166.47, and

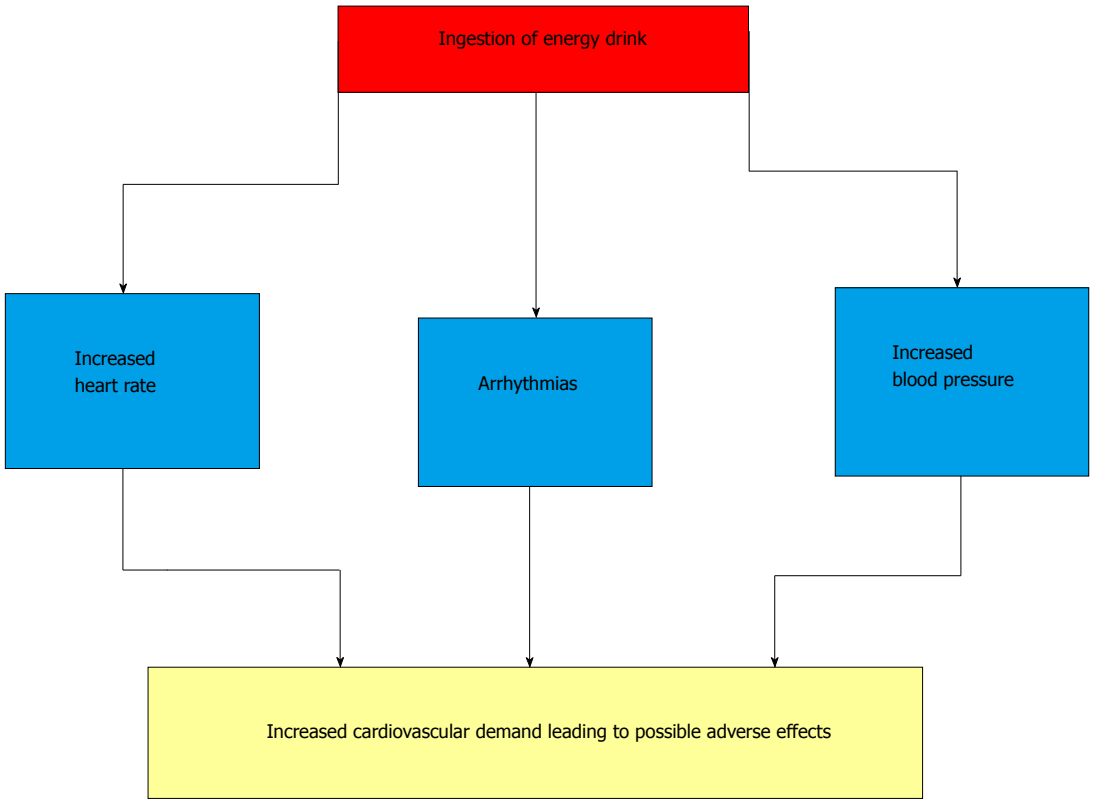

Figure 1 Effects of energy drinks on the cardiovascular system.

165.00) compared to the placebo trials (156)[12]. Other studies have found the same effect as well. Elitok *et al*[13] studied 50 young, healthy subjects and found that 2 h after consumption of 355 mL of Red Bull their systolic blood pressure increased from 112 to 121 mmHg, and diastolic blood pressure 73 to 76 mmHg. Grasser *et al*[14] conducted a randomized crossover study of twenty-five young non-obese and healthy subjects and showed that both systolic and diastolic blood pressure increased as a result of Red Bull consumption. The water control load did not. The study also showed increases in cerebrovascular resistance and breathing frequency, in addition to decreases in cerebral blood flow velocity and end-tidal carbon dioxide[14].

A recent comprehensive and systematic review of case studies related to EDs and their adverse health effects has found that the most common adverse events affect the neurological and cardiovascular systems. The neurological effects were most commonly seizures but also included neuro psychotic agitation, aggressive behavior, and suicidal ideation. That may be because caffeine and taurine are known psychoactive agents. The cardiac related events included reports of: Arrhythmias (highest percent 35% with the others being rare), coronary vasospasm, aortic aneurysm dissection, cardiac arrest, QT prolongation, acute cardiomyopathies, accelerated hypertension, reversible postural tachycardia syndrome, acute coronary thrombosis, and ST-elevation myocardial infarction. The authors attribute the cardiovascular adverse effects to the ingredients in ED, such as caffeine and taurine which have shown to increase platelet aggregation, disturb the endothelial function, and possibly causing vasospasm in association with hypertension[15]. Although there has been a link between energy drink consumption and platelet aggregation and endothelial dysfunction, the exact agent that is causing the effects is still unknown[16]. It should be noted that many of the adverse events described in these case reports have been linked to haphazard use of ED's and ED use combined with alcohol and other substances. Thus, emergency department case reports offer a hurdle to clearly understanding the adverse effects of EDs alone.

Another study was conducted with fifteen healthy adults. Their blood pressures were taken after abstaining from caffeine for 48 h, and, baseline BP, HR, and electrocardiographic (ECG) parameters were measured. Participants were asked to consume 500 mL of an energy drink and measurements were repeated 30 min, 1 h, 2 h, 3 h, and 4 h later, then drank 500 mL of energy drink daily for the next 5 d and measurements taken again on the final day. No significant ECG changes were noted, yet HR and SBP measurements increased by 5-7 beats/min and 10 mmHg, respectively. The cardiovascular effects were greater after five days of consumption than after the first day of consumption[17].

Another study enrolled fourteen volunteers, who completed a three-session study. In each session,

they received a 2oz. 5-h Energy shot, 2oz. Ocean Spray™ Diet Cranberry Juice as the placebo, or no drink with BP readings measured each hour. The energy shot condition showed diastolic BP readings that were significantly higher when compared to both the no drink and placebo drink conditions. Interestingly, it was also significantly higher at 240 and 360 min when compared to 60 min. There was no difference in BP between the placebo and no drink[5].

Physiologic effects on heart rhythm and induction of arrhythmia

A number of documented cases correlated the consumption of energy drinks to the development of atrial fibrillation such as: Atrial fibrillation in a 16-year-old Caucasian boy after consuming an unknown amount of Red Bull™ mixed with vodka[18]. A case of atrial fibrillation in a patient with dilated cardiomyopathy that experienced seizures after the cessation of his excessive caffeine consumption[19], and, atrial fibrillation in a 14-year-old Caucasian boy after an athletic event where he consumed an unknown amount of energy drink. He noted that he felt the same fluttering feeling 5 d before as well when he ingested a Red Bull™[18]. It is noteworthy that in all of such cases, there is a high suspicion for the excessive consumption of the beverages as the causal event.

CAFFEINE CONTENT AND DOSE

The caffeine content of energy drinks has been the center of the controversy, as it is widely believed that most such products contain a significantly higher concentration of caffeine than what is found in an average cup of coffee. The cardiovascular effects of caffeine have been heavily studied. Caffeine's inotropic effect on the heart muscle has been long looked at with suspicion as a possible culprit for heart disease in some people[20]. The last couple of decades saw coffee be linked with various harmful effects such as hypertension, gastric ulcers, palpitations, anxiety, tremulousness, and, ultimately, heart disease[21-23]. Hence, caffeine has an essential role in understanding the possible dangers of energy drinks.

In healthy individuals, caffeine, a methylxanthine, increases sympathetic nerve activity. Caffeine's molecular mechanism lies in its competitive inhibition of phosphodiesterase. This results in an elevation in myocardial cyclic AMP and, as a consequence, the positive inotropic action on the myocardium. On the other hand, the inhibition of adenosine receptors prevents the negative inotropic effect elicited by adenosine, namely, blocking the vasodilatory effect of adenosine and adenosine's inhibitory effects in platelet aggregation, catecholamine levels, renin release, and lipolysis. Thus, acute caffeine administration may increase blood pressure and increase levels of plasma catecholamine, renin, and free fatty acid[24].

As noted above, there is an extensive amount of literature that reveals that caffeine moderately increases blood pressure and heart rate[25-28] and also linked to a drop in myocardial blood flow[29,30]. However, caffeine has also been shown to have some positive benefits as well. One study showed that caffeine consumption was associated with a significant increase in flow-mediated dilation and a decrease in hs-CRP level in healthy volunteers and volunteers with coronary artery disease alike. It is noteworthy that these positive effects in endothelial dysfunction and inflammation were not seen with nitroglycerin application[31]. While these results seem promising, other studies have found negative effects that caffeine may have on endothelial function, such as a study conducted by Papamichael *et al*[32] they found that after ingestion of 80 mg of caffeine by healthy individuals, flow-mediated dilation was decreased in these individuals, most acutely in the first hour after ingestion. These results may not come as a surprise, as caffeine has been known to promote endothelial dysfunction through sympathetic activation[33].

A large prospective study followed 130054 members of a healthcare plan in Northern California gathering subjects from 1978 to 1985 and following them until 2008 to note the amount of coffee consumed by each individual and whether that added a risk for hospitalization for arrhythmias or any other cardiomyopathy. Results showed a strong inverse relationship of coffee consumption to risk of hospitalization for arrhythmia. The inverse relationship was consistent in men, women, whites, blacks, and persons younger or older than 60 years old at baseline[34]. This result shows that participants who consumed more cups of coffee generally were significantly less likely to develop cardiac arrhythmias. This shows the reverse of the idea traditionally held of increased caffeine consumption leading to more cardiac arrhythmias. Additionally, a comprehensive literature review dealing with the effects of habitual caffeine consumption on the cardiovascular system found that moderate consumption resulted in beneficial to neutral effects[35].

There is evidence, however, that point to caffeine's possible adverse effects especially when consumed at high doses. Toxic doses may affect conductance and refractoriness on the heart, which results in the development of various arrhythmias[36]. Symptoms of caffeine overdose also include palpitation, hypertension, irritability, insomnia, tremors, and seizures. In addition, the hypertensive effects of caffeine should not be overlooked as they may lead to hazardous cardiovascular events. The HARVEST study found that when after adjusting for possible confounding variables, cardiovascular events were more common among coffee drinkers than non-coffee drinkers. The authors suggested that hypertensive patients should be discouraged from drinking coffee[6].

Table 1 Caffeine concentration in common drinks

Caffeinated beverage	Amount of caffeine/drink, mg
5-h energy™ bottle	215
Arizona Iced Black Tea (16oz)	30
Bang Energy (16oz)	357
Caffeine Powder (1/16 Tsp.)	200
Coca Cola, Coke Zero, Diet Pepsi (12oz)	34
Dannon Coffee Yogurt (6oz)	30
Dunkin Donuts™ Medium Brewed Coffee (14oz)	178
Dunkin Donuts™ Medium Latte (14oz)	97
FDA official limit for cola and pepper soft drinks(12oz)	71
Herbal Tea (8oz)	0
Lipton Decaffeinated Black Tea (8oz)	5
Maxwell House Decaf Ground Coffee (2 Tbs. makes 12oz)	2-10
Maxwell House Light Ground Coffee (2 Tbs. makes 12oz)	50-100
Monster Energy™ (16oz)	160
Mountain Dew (12oz)	54
Pepsi (12oz)	38
Red Bull™ (8.4oz)	80
Rockstar™ (16oz)	160
Snapple Lemon Tea (16 oz)	37
Starbucks Grande Chai Latte (16oz)	95
Starbucks Hot Chocolate (16oz)	25
Starbucks Refreshers Can (12oz)	50
Starbucks™ Grande Caffe Americano (16oz)	225
Starbucks™ Grande Caffe Mocha (16oz)	175
Starbucks™ Grande Coffee Frapuccino (16oz)	95
Starbucks™ Grande Ice coffee (16oz)	165

There is a widespread belief that caffeine may be arrhythmogenic in those who regularly consume it. However, a large-scale Danish study did not find a higher risk for atrial fibrillation/flutter with different amounts of caffeine consumed[37]. In addition, the stimulant effects of caffeine seems to vary amongst individuals, in fact, the degree of tolerance and dependence to it is likely heritable and may be linked to polymorphisms[38].

Two comprehensive meta-analyses both determined that caffeine is unlikely to promote cardiovascular disease. In fact, the opposite may be true. The first review, conducted by Cheng *et al*[39] found an inverse relation was found between habitual caffeine intake and risk of atrial fibrillation. For every 300 mg per day increment in habitual caffeine intake, incidence of AF was found to drop by 6%. One explanation for these results is caffeine's association with lower risks of obesity, and metabolic disease. Thus, adverse cardiovascular effects of caffeine seem to represent itself with a J-shaped curve, with higher doses increasing the risks of heart disease, and normal doses proving to be beneficial[40].

The discrepancies in these studies can be difficult to reconcile although some of the variation in results may be attributed to differences in study design, varied caffeine dosages administered, and different study cohorts. Most studies do an inclusion criteria exercise for their cohorts. However, many did not take into account the regular coffee consumption of volunteers prior to the study. This is important because coffee metabolism is extremely variable in humans; thus, the effects of caffeine are not uniform. The half-life is 4.9 h, however absorption rates are largely based on the individual's genes, age, sex, liver health, and drug uptake, such as use of oral contraception, antidepressants, and antiarrhythmics, as well as their tolerance to the stimulant[41]. Caffeine is primarily metabolized through the liver's cytochrome P450 1A2 (CYP1A2) enzyme and defects in such an enzyme have been implicated in the population's variation in metabolism and half-life. Hence, genetic polymorphisms in the CYP1A2 pathway may explain some of the inconsistencies in studies of coffee and its effects on health[42].

To examine the caffeine amounts, Table 1 shows the caffeine concentrations of some popular drinks at Starbucks™ and Dunkin Donuts™ along with some of the most popular caffeine containing drinks[43]. Note that all EDs or energy shots surpass the FDA official soft drink concentration limit of 71 mg per twelve-ounce drink, sometimes by over triple the amount. According to the Mayo Clinic and the US food and Drug Administration up to 400 mg of caffeine a day appears to be safe for most healthy adults[44,45]. One study that supports this quantity mentions that maximum safe caffeine intake for pregnant women, children, and those taking medications is still undetermined[9,46]. Unfortunately, proper labeling has also been an issue, with companies reportedly falsely labeling caffeine content on their products, and

misguiding consumers[47].

OTHER ACTIVE INGREDIENTS IN ENERGY DRINKS AND THEIR ADDED EFFECTS

Taurine

Taurine is a derivative of the amino acid cysteine, and is found in high quantities in heart and skeletal muscle[48]. It is added in a large number of energy drinks such as 5-h energy™ and Red Bull™. Although taurine is considered an essential nutrient for humans, clinical studies evaluating the effects of taurine are limited. Taurine has been shown to be beneficial in improving the lipid profile by increasing the transcription of CYP7A1, an important enzyme in bile conjugation[49], as well increasing the liver's LDL uptake and up-regulation of LDL receptors[50]. Its supplementation has also been linked with a decrease in blood pressure possibly through the attenuation of angiotensin Ⅱ, which causes vasoconstriction[51] or by "enhancing" the kinin-kallikrein system, which normally causes vasodilation[52]. An ethnic Chinese study found an inverse correlation between twenty-four hour taurine excretion and diastolic blood pressure in Han (the major Chinese ethnic group) individuals and a decrease in both systolic and diastolic BPs in Tibetan subjects when consumed[53]. Similarly, there was a significant decrease in systolic and diastolic BPs in 19 borderline hypertensive subjects[54].

In addition, taurine deficiency was found to be associated with a decrease in the sensitivity of the cardiac muscle to Ca^{2+}, and, hence, a decreased inotropic capability of the organ[48]. This may be the reason for the supplements alleged boost in physical performance through an improved blood supply to the rest of the organs, specifically the musculoskeletal system. Interestingly, concentration of taurine have been found to be higher in the left ventricular muscle of hearts of patients who died of chronic congestive heart failure than that of patients who died of other causes and had no cardiac pathology[55]. The study hints that taurine may, in fact, have an inotropic effect which may shed some light on the cardiovascular adverse effects of energy drinks.

Certain studies have compared the effects of energy drinks containing just caffeine, and those containing caffeine and taurine. One study randomized nine volunteers to receive either an ED containing 80 mg of caffeine and 1000 mg of taurine or a control that contained 80 mg of caffeine solution in water. They were asked to consume their respective drink every 3-4 h for a single day. Mean 24-h systolic blood pressure, diastolic blood pressure, and mean arterial pressure recordings were significantly higher in the ED group than in the control (123.2 mmHg *vs* 117.4 mmHg, 73.6 mmHg *vs* 68.2 mmHg, 90.1 mmHg *vs* 84.8 mmHg, respectively)[56]. Another study asked 13 athletes to ingest either Red Bull, a similar caffeinated drink without taurine, or a placebo prior to performance of exhaustive endurance exercises. ECGs performed before ingestion, before exercise, after ingestion, during the recovery period showed that the only significant increase in stroke volume during the recovery period was the group that consumed taurine containing Red Bull. This study suggests that taurine and caffeine may interact together to increase cardiac contractility[57]. A third study explored the peak systolic strain in 32 healthy individuals at baseline, and one hour after consumption of an ED containing caffeine and taurine, or just caffeine. While the drink with caffeine did not seem to have any significant cardiovascular effects shown by magnetic resonance imagine, those that ingested the combination of caffeine and taurine had a significant increase in peak systolic strain[58].

Schaffer *et al*[59] conducted a comprehensive literature review regarding the interaction between taurine and caffeine and in agreement with the European Union's Scientific Committee on Food, they concluded that taurine should neutralize several untoward effects of caffeine excess. They noted that the physiological functions of taurine appear to be inconsistent with the adverse cardiovascular symptoms associated with excessive consumption of beverages containing caffeine and taurine.

B vitamins

Referred to as vitamin B complex, the eight B vitamins, thiamine (B1), riboflavin (B2), niacin (B3), pantothenic acid (B5), pyridoxine hydrochloride (B6), biotin (B7), inositol (B8), and cyanocobalamin (B12), act as coenzymes for proper cell function, especially mitochondrial function and energy production. Thus, some believe that B vitamins may increase energy expenditure[60]. One study has shown lower fat mass in men who regularly consumed multivitamins[61]. Energy drinks often contain a large quantity of B-group vitamins, often at larger doses than the recommended daily intake for healthy individuals.

Studies have shown that high dietary intakes of folate and vitamin B6 has been linked with reduced risk of mortality from stroke, coronary heart disease, and heart failure[62]. B vitamins have also been shown to reduce levels of the amino acid homocysteine whose elevation have been linked to numerous comorbidities including pregnancy complications, cognitive impairment and mental disorders, as well as cardiovascular risks[63-65].

A meta-analysis established that while B vitamin supplementation the B vitamin reduced homocysteine levels and has a significant protective effect on stroke, no benefit was found to reduce cardiovascular disease, myocardial infarction, coronary artery disease,

cardiovascular death, or all-cause mortality[66].

Guarana

Paullinia cupana, also known as guarana, is a South American plant that has been mentioned as early as 1872 for the treatment of "Sick-Headache"[67]. The Amazonians have used the seeds of its fruit to increase awareness and energy[68]. Guarana's stimulant effect is due to its similar chemical composition to that of caffeine. There is 2%-4.5% caffeine in the guarana seeds, compared to 1%-2% in the coffee bean[69]. The effect of guarana is not yet known. Whether it is of additive or synergistic effect when combined with caffeine is not clear. Guarana in a 16 ounce energy drink ranges from 1.4 mg to as much as 300 mg. The FDA generally recognizes guarana as safe, although there are no established dosages and it is unclear how much guarana is in each drink because many companies do not list a milligram amount. Therefore, it should be assumed that the amount of caffeine in the products is, in reality, larger than the amount of caffeine noted especially when guarana is present. It is not surprising that young adults have been admitted to emergency departments with cardiovascular adverse effects after excessive ingestion of guarana-based EDs[70].

L-carnitine

A meta-analysis on the effect of the L-carnitine supplement on the cardiovascular system found a 40% reduction in angina (RR, 0.60; 95%CI, 0.50-0.72; $P < 0.00001$; $I^2 = 0\%$). Compared with placebo or control, L-carnitine was found to be associated with a highly significant 65% reduction in ventricular arrhythmias (RR = 0.35; 95%CI: 0.21-0.58, $P < 0.0001$, $I^2 = 0\%$)[71]. An increase in cardiac output after intravenous administration of L-carnitine in normotensive coronary artery disease patients has also been observed[72]. Another study showed that L-carnitine supplementation increased the left ventricular ejection fraction in studied individuals. The mean percent of increase of ejection fraction in the L-carnitine group was 12.5% ± 8.3% ($P < 0.01$), while the control group had an increase of ejection fraction of 6.1% ± 4.3% ($P < 0.01$)[73]. In addition, the supplementation of L-carnitine has been shown to decrease left ventricular remodeling in post-myocardial infarction patients[74]. However, Koeth *et al*[75] recently found a possible link of L-carnitine in red meat with cardiovascular disease through the development of atherosclerosis. This effect may simply be due to the long acknowledged negative effect of red meat on the cardiovascular system instead of L-carnitine itself.

L-carnitine is a naturally occurring amino acid made predominantly by the liver and kidneys. It is involved in B-oxidation of fatty acids and is thus linked to changes in metabolism and energy levels. It is commonly added to energy drinks to help promote muscle function and physical performance. It is found in energy drinks such as Monster™ and Rockstar™ energy drinks.

L-carnitine's popularity in EDs is due to its possible ability to burn more fat and increase endurance during exercise, however, those claims remain elusive. Some data has indicated that L-carnitine plays an important role in the prevention of cellular damage and positively affects recovery from exercise stress. Uptake of L-carnitine by blood cells has been implicated in stimulation of hematopoiesis, a dose-dependent inhibition of collagen-induced platelet aggregation; and the prevention of programmed cell death in immune cells. Carnitine was recently shown to have direct effects in the regulation of gene expression and is potentially involved in modulating intracellular fatty acid concentration. Hence, there is evidence for a positive effect of L-carnitine supplementation. It may be especially beneficial in training and recovery from strenuous exercise[76]. In high doses, L-carnitine has been shown to have a side effect of nausea, vomiting, abdominal pain, and diarrhea; in addition, it has been associated with seizures in patients with no known disease and to increase seizure frequency in patients with seizure disorder[9]. However, as with ginseng, the amount of L-carnitine in energy drinks is likely not high enough to be of concern.

Ginseng

This East Asian herb is one of the most popular herbal supplements in the world and has also been a popular additive in EDs. The claims about ginseng range far and wide-reducing stress, curing diabetes, insomnia, erectile dysfunction, improving memory, and increasing stamina are all purported benefits of the herb. However, very few claims are rooted in scientific research. A recent review concluded that evidence of enhanced physical performance after ginseng administration in well-designed investigations remains to be demonstrated[77].

In 2013, one Mayo Clinic study did show that after eight weeks of taking 2000 milligrams of pure American ginseng root in a capsule, patients undergoing cancer treatment found a sudden jump in the general energy levels reported by the group on ginseng when compared to the placebo control group[78].

Interestingly, several studies in rats have results suggesting that oral administration of ginseng root may increase insulin sensitivity and help with weight loss. Researchers at the University of Chicago administered daily intraperitoneal injections of Panax ginseng berry extract to rats and on day 12, extract-treated *ob*/*ob* mice became normoglycemic and were found to have significantly improved glucose tolerance. A more than twofold increase in the rate of insulin-stimulated glucose disposal in treated *ob*/*ob* mice was noted in hyperinsulinemic-euglycemic clamp study. The mice also lost a significant amount of weight which was

believed to be associated with the reduced food intake and the increase in body temperature and energy expenditure. Other studies revealed that ginsenoside Re plays a significant role in antihyperglycemic action. Interestingly, this antidiabetic effect of ginsenoside Re was not associated with body weight changes, suggesting that other components in the extract have distinct pharmacological mechanisms on energy metabolism. Additionally, plasma cholesterol levels were notably reduced following the treatment with the extract[79].

Excessive amounts of ginseng ingestion may cause diarrhea, vaginal bleeding, headache, vertigo, mania, hypertension, rashes, insomnia, irritability, Stevens-Johnson syndrome, and agranulocytosis. However, some of these symptoms may be related to contaminants, such as phenylbutazone and aminopyrine that are used in its production[6]. However, the amounts of ginseng found in EDs are thought to be less than the amount needed to deliver the suggested therapeutic benefits or cause adverse events[80].

Glucuronolactone

Glucuronolactone is a glucose derivative, metabolized in the liver. In the sixties, the Japanese were particularly interested in its performance enhancing properties. They conducted one published study by injecting glucuronolactone, glucose, glycogen, and some other substances directly into the gut of lab rats, and recording the rats' ability to swim 30 min post injection. They repeated the procedure three times. In two of the three trials, the animals injected with glucuronolactone were able to swim longer than those injected with the other substances. The study also noted that the human equivalent of the dose would be between 1 and 2 g of glucuronolactone compared to the 600 mg found in a can of Red Bull[81]. These results may be due to glucuronolactone detoxification effects as supplementation with glucuronolactone may favor the body's natural defense mechanism for eliminating carcinogens and tumor promoters and their effects[82].

Glucuronolactone has shown to act as an anti-platelet aggregative compound[83], however, this outcome has not been proven to be effective when mixed in energy drinks, as after consumption an overall increase in platelet aggregation appears without any apparent effect of platelet anti-aggregation of the glucuronolactone[16]. There has been minimal suggested significant contribution towards energy by glucuronolactone on humans in the scientific literature and, therefore, no definitive conclusion can be made of its safety[84].

OVERALL ASSESSMENT

The increasing number of energy drink and caffeine-related overdoses clearly shows that there seems to be a real risk for adverse health effects such as arrhythmias. However, under moderate use and without combining other stimulants or alcohol, the lack of a similar number of case reports makes the risk for such side effects seem negligible. It is noteworthy that a large number of serious health risks resulted were due to overconsumption of the products or their ingestion in a short period of time. Therefore, it may well be important for energy drink companies to place warnings on their products to avoid such habits.

The exact amounts and concentrations that are ideal in order to minimize the health risks are largely unknown. Patients with underlying illnesses such as hepatic failure or cardiomyopathy should likely avoid such products or, at least, be cautious by consuming small amounts. In addition, since there seems to be variation amongst individuals in the enzymatic activity of CYP1A2 and since testing for such enzymatic activity is not routinely performed, it is of great importance for each consumer to cease consuming the energy drinks if symptoms of an overdose develop. Producers should place a warning that includes such symptoms.

As for the constituents of the energy drinks themselves, the concentrations of caffeine seem to be comparable or even lower than many popular coffee drinks making the amount of caffeine itself an unlikely reason to not consume the products. In fact, medical research has shown that moderate consumption of caffeine is strongly related to a reduced risk of arrhythmias.

As for taurine and L-carnitine, the medical literature shows an overall positive health effect especially for the cardiovascular system, hence, making it unlikely that they can cause harm to that same system. In fact, it may be reasonable to consider those two compounds for future supplementation to those at risk for hyperlipidemia, hypertension, and cardiomyopathy. Guarana, on the other hand, may have a synergistic caffeine-like effect added to the caffeine already in these products and more information is needed on their combined effect.

CONCLUSION

The last decade has seen an exponential increase in the number of energy drink products as well as the number of reported cases of arrhythmias and other health hazards caused by their consumption. Our review has found that the vast majority of the cases were due to excessive consumption of the drinks in a short period of time or when co-ingested with other stimulants such as alcohol and indicates that such drinks may be relatively safe when consumed moderately and separately. Additionally, the research covering the components of the beverages, such as caffeine, taurine, L-carnitine, glucuronolactone, ginseng, and guarana, seems to have a neutral to positive health effect unlike previously thought. However, it may be important for energy drink

producers to place warning labels of symptoms associated with an overdose in order to promote their recognition. Until the FDA sanctions these energy drink products, it is strongly encouraged that individuals research energy drink consumption and consult their physician in order to ensure safe consumption. Also, those with underlying cardiovascular disease should be careful by limiting the amount consumed or avoiding altogether, as they may be at increased risk for arrhythmias or other cardiovascular events.

With the exception of the effects of caffeine, the ingredients in energy drinks have not been thoroughly studied to confirm the cardiovascular safety or the proclaimed energy-boosting benefits. There is an overwhelming lack of evidence to substantiate claims that components of EDs, contribute to the enhancement of physical or cognitive performance. Additional well-designed, randomized, placebo-controlled studies are needed in order to assess claims made for these products and further elucidate potential adverse effects.

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P- Reviewer: Leone A, Losano G, Patanè S **S- Editor**: Kong JX
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