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Review Article

Substances Containing Caffeine–Friend or Foe: A Review

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Abstract: Caffeine is the most widely used and commercialized pharmacological active substances in the world. It is found in common beverages such as; coffee, tea, energy drink and even drugs. Performance benefits attributed to intake of caffeine include; physical endurance, reduction of fatigue, and enhancing mental alertness and concentration, and it has been believed by many researchers that moderate consumption of substance containing stimulants is considered safe and its uses as food ingredient within certain/control limits, by many regulatory agencies around the world but despite all the benefits attributed to caffeine, the potential side effects of excessive intake of substances containing caffeine should also be considered, particularly among children and pregnant women which is why this research gives a comprehensive review into the composition, consumption, safety and regulatory measures of commercially sold substances containing caffeine.

Keywords: Stimulants, Mental Alertness, Beverages, Commercial, Caffeine

1. Introduction

Caffeine has been used for thousands of years and is one of the most widely consumed active food ingredient throughout the world. It is found in common beverages including coffee, tea and soft drinks, as well as products containing cocoa or chocolate, and a variety of medications and dietary supplements [1] [2]. Caffeine, the common name for 1, 3, 7-trimethylxanthine, was derived from the German word kaffee and the French word caf˝ e, each meaning coffee.

Historians suggest that caffeine was consumed as far back as 2737 BC when Chinese Emperor Shen Nung drank an infusion of leaves from a nearby bush, creating a pleasant aroma [3]. Coffee originated many years later in the 9th century in Ethiopia when a shepherd began consuming wild coffee berries after observing that his goats had increased energy after eating them [4]. It was not until the late 1800's that caffeinated soft drinks began appearing with the introduction of Dr. Pepper, followed by Coca-Cola and then Pepsi Cola [5]. The caffeinated soft drink market grew enormously during the 2nd half of the 20th century with increased popularity occurring among the beverages containing higher amounts of caffeine. The increased popularity inspired the products of energy drinks, which have become very prevalent. Today, approximately 80% of the world's population consumes a caffeinated product every day and 90% of adults in North America consume caffeine on a daily basis [6]. The attractiveness and recognition of these beverages are due to the effect which caffeine has on the body and mind. It has properties that aids staying awake and improving mental alertness after fatigue [7]. In addition, other findings reveals that caffeine can be a potential contributor to reducing risk factors involved in the metabolic syndrome, including type 2 diabetes mellitus (DM) and obesity [8] [9]. Due to the popularity and wide consumption of caffeinated beverages, the objective of this review was to compile and comprehensively analyze updated scientific information about dietary caffeine, including its consumption, health related

functionality, safety and regulations.

2. Materials and Methods

The method involves the review of several research materials and online data relating to the research interest and a comprehensive and detailed review was done to ascertain the composition, effects, and regulatory measures with regards to intake of substances containing caffeine.

2.1. Energy Drinks

Energy drinks are non-alcohol beverages, marketed as increasing energy levels and wakefulness or boosting attention span [10]. Caffeine is the main functional ingredient of energy drinks, but they may also contain a wide variety of other natural substances, many derived from plants and herbs, with claimed stimulant properties [11-13]. Many energy drinks have similar ingredient profiles [14] and some group certain ingredients together as part of an "energy blend", rather than listing them individually [15], so the exact concentrations used may not be apparent.

Energy drinks often contain the following ingredients: Caffeine, Guaraná (which is an independent source of caffeine), Taurine, Ginseng, B vitamins, Sugars or sweeteners, Glucuronolactone (an organic metabolite with claimed detoxifying properties)

The caffeine content of energy drinks ranges from 30–505mg per can or bottle, in serving sizes of 250–500ml, but typically falling between 80 and 141 mg caffeine per serving [11, 16-18]. For comparison, the caffeine content of a cup of brewed coffee may fall between 100 mg and in excess of 500 mg, depending on strength and serving size, with instant coffee and brewed tea containing approximately 75 mg and 50 mg, respectively [17] [19]. In soft drinks, caffeine levels are typically 100 mg/l – equivalent to 25 mg in a 250 ml serving – but can be as high as 200 mg/l in some products [20].

Information on energy drink consumption practices varies considerably. In the USA, there has been a particular focus on college-aged students [21], with more than 50% reporting regular consumption of energy drinks in some surveys [11] [22]. However, energy drink consumption is not limited to young adults. A recent, large-scale European study looked at a wider population and found 68% of adolescents reporting Energy Drink consumption in comparison to 30% of adults, but no difference between the two age categories in high, chronic ED consumption (12% in adults and adolescents) or high, acute Energy Drink consumption (11% for adults, 12% for adolescents) [18]. Considering mean daily intake of energy drinks, the Scientific Committee on Food of the European Commission [29], has classified consumption into "mean chronic" (125 ml/day), "high chronic" (350 ml/day) and "acute" (750 ml/day). For a typical ED product containing 320 mg/l of caffeine, these classifications would equate to 40 mg, 112 mg and 240 mg of caffeine per day.

2.2. Caffeinated Alcohol Beverages

Caffeinated alcohol beverages are premixed, ready-to-drink products that contain alcohol and other stimulants similar to those used in energy drinks [23]. Some malt-based products or "caffeinated beers" may contain added caffeine and fruit flavorings, but not necessarily other ingredients typically found in energy drinks.

There has been relatively little research on caffeinated alcohol beverages consumption as opposed to alcohol mixed with energy drinks. One recent study of undergraduate students [24] reported 68% prevalence of alcohol mixed with energy drinks consumption in the last month in comparison to 29% of Caffeinated alcohol beverage consumption, suggesting that alcohol mixed with energy drinks consumption plays a larger role in increased risk than premixed caffeinated alcohol beverages.

2.3. Guaraná

Guaraná (*Paullinia cupana*) is a rainforest vine that grows in the Brazilian Amazon. It has a long history of use in Brazil as the active component of tonic sodas, but in the last 20 years it has emerged globally as a key ingredient in nutraceutical and energy drinks [25]. Guaraná seed extracts contain caffeine (known as 'guaranine' in this context) at concentrations between 2% and 15% of dry weight [26-29], as well as saponins and tannins [30], which have antioxidant properties [31], and flavonoids, which can reduce blood platelet aggregation [32].

Guaraná has been suggested to improve cognitive performance, mental fatigue, and mood at physiologically relevant dosages [33] [34], and in animal studies, it has been shown to exert no toxic effects when consumed in acute high dosages as well as in chronic lower dosages [31]. Given that caffeine is the primary active component of guaraná, much of the research relating to caffeine is pertinent. However, there are some points of difference. For example, caffeine from guaraná is reported to be released more slowly than pure caffeine, providing a more subtle and prolonged stimulatory effect [34]. It is also believed to have a potentially longer half-life, because of interactions with other compounds in the plant, according to some reports [29].

Caffeine derived from guaraná should be considered part of the total caffeine content of premixed beverages with added caffeine.

2.4. Yerba Mate

Yerba mate comes from the *Ilex paraguariensis* plant which is native to South America where its main function is for the production of yerba mate tea [35]. Yerba mate tea is a commonly consumed beverage in South American countries and has been for centuries; however, it is increasing in popularity globally due to its content of a variety of bioactive components including polyphenols, xanthines, flavonoids, saponins, amino acids, minerals, and vitamins [35]. The abundant array of phytochemicals present in yerba mate has been connected to various health benefits. Yerba mate

possesses anti-inflammatory and antidiabetic properties as well as acts as an inhibitor to oxidative stress [36]. Moreover, yerba mate has shown in-vitro cytotoxicity to cancer cells and inhibition against Topoisomerase II, which plays a role in cell division and therefore works to inhibit cancer cell proliferation [35]; however, in vivo studies are needed [39]. Yerba mate also has a positive impact on the management of obesity, both in vivo and in vitro [32]. The consumption of yerba mate significantly improved the serum lipid parameters in normolipidemic and dyslipidemic individuals [38]. Furthermore, yerba mate enhanced the reduction in LDL cholesterol levels in individuals who were also under statin therapy [38]. In addition, yerba mate is a central nervous system stimulant due to its high caffeine concentration, which is the primary reason for yerba mate to be incorporated into energy drink formulations. The caffeine concentration in 1 cup (8 ounce) of yerba mate tea is equivalent to about 78 mg, which is very comparable to 8 ounce of Red Bull, which contains 80 mg [35]. On the other hand, concerns have been raised regarding an association between yerba mate and the occurrence of certain types of cancer, specifically oral, esophageal, lung, bladder, and renal [35]. However, there is no conclusive evidence that this association is a result of the consumption of yerba mate but rather due to various lifestyle choices including smoking and excessive alcohol consumption. In addition, these cases have primarily been reported in certain areas of South America where large amounts of yerba mate are consumed at very hot and damaging temperatures which could lead to increased absorption of carcinogens found in cigarette smoke or other environmental pollutants [35].

2.5. Substances Having Stimulating Properties Relative to Caffeine

2.5.1. Taurine

Taurine (2-aminoethane sulfonic acid) is an amino acid found in high concentrations in heart and muscle tissue and the brain, where it acts as an agonist or a partial agonist at glycine receptors [40] [41]. It also occurs in the human diet and is commonly added to energy drinks at concentrations of around 4 g/l [17] [42]. The mean daily intake of taurine from all sources has been estimated at between 40 and 400 mg (ANZFA, 2001).

Taurine is reported to have physiologically beneficial effects in humans [43] [44], and a literature review conducted by Finnegan in 2003 [45] found no evidence that consumption was a risk to human health. In contrast, McLellan and Lieberman (2012) [13] highlighted flaws in studies often cited to support the addition of taurine to energy drinks [46] [47] [48] and concluded that there is little evidence to support taurine addition for cognitive or physical benefit.

The benefits of taurine supplementation in exercise have been attributed to its antioxidant effects [17]. However, Galloway and colleagues (2008) [49] found that three 1.66 g doses of taurine over seven days significantly increased plasma taurine levels but did not alter resting skeletal muscle taurine content and had no effect on metabolic responses to 120 min of exercise. A dose of 1.66 g would be equivalent to 415 ml of an energy drink containing a typical taurine level of 4 g/l [17] [42].

Beverages containing taurine have been reported to enhance the positive effects of ethanol, possibly by countering its depressant effects [50], although the extent of this effect and the precise role of taurine remain speculative [51]. It has also been reported a major metabolite of taurine, taurocholic acid, can decrease ethanol preference [52].

In 2003, the European Food Safety Authority (EFSA) issued a scientific opinion on the use of taurine in energy drinks [52]. EFSA's Panel on Food Additives and Nutrient Sources added to Food (ANS) concluded that, "a sufficient margin of safety exists for mean and high level regular consumers of energy drinks, drinking on average 125 ml and 350 ml per person per day respectively; hence, exposure to taurine at these levels is not a safety concern." The Panel also considered that cumulative interactions between taurine and caffeine were unlikely. The Committee noted a No Observable Adverse Effect Level (NOAEL) of at least 1,000 mg/kg of taurine per kg body weight per day for pathological changes. For a 60 kg person, this would be 43-fold higher than the estimated 95th percentile for exposure to taurine from energy drinks. In animal studies, evidence was found for some behavioral effects at a level of 300 mg/kg body weight of taurine per day and, whilst that is also much higher than the levels achieved in humans from exposure to energy drinks, it precluded the setting of an upper safe level for daily taurine intake.

Based on current research and regulatory decisions, addition of taurine to beverages at a concentration of up to 4g/l would appear to be safe.

2.5.2. Ginseng

Ginseng is a widely used herbal medicine, derived from any of several species of the genus *Panax* [53]. It contains more than 40 active compounds, including ginsenosides, steroid-like compounds that are also responsible for its bitter taste. Ginseng extract is added to some energy drinks at concentrations of between 100 and 420 mg/l (approximately 25 to 120 mg per serving), and, in terms of flavor profile, the natural bitterness of ginseng is additive to that provided by caffeine, which tends to limit the levels added to such beverages [54].

2.5.3. Methamphetamine

Methamphetamine is a stimulant drug chemically related to amphetamine but with stronger effects on the central nervous system. Street names for the drug include "speed," "meth," and "crank." Methamphetamine is used in pill form or in powdered form by snorting or injecting. Crystallized methamphetamine known as "ice," "crystal," or "glass," is a smokable and more powerful form of the drug.

The effects of methamphetamine use include: euphoria, increased heart rate and blood pressure, increased wakefulness; insomnia, increased physical activity, decreased appetite; extreme anorexia, respiratory problems, hypothermia, convulsions, and cardiovascular problems, which can lead to

death, irritability, confusion, tremors anxiety, paranoia, or violent behavior can cause irreversible damage to blood vessels in the brain, producing strokes.

3. Result

In the USA, the Food and Drug Administration (FDA) has approved caffeine as "Generally Recognized as Safe" (GRAS) for non-alcohol, cola-type beverages, in concentrations no higher than 200 parts per million, or 200 mg/l [55]. Under GRAS guidelines, a manufacturer is obliged to provide proof that an additive is safe for its intended use based on published scientific literature, and that there is a consensus of scientific opinion regarding the safety of the use of the substance [56] [57].

The FDA is reported to be assessing the safety of caffeinated energy drinks. Pertaining to this, in March 2013, a group of scientists concluded, in a letter to FDA Commissioner Margaret A. Hamburg, *"There is no general consensus among qualified experts that the addition of caffeine in the amounts used in energy drinks is safe under its conditions of intended use as required by the GRAS standard"* [58]. In September 2009, some of the same scientists had raised concerns about caffeinated alcohol beverages with the Co-chairs of the National Association of Attorneys General Youth Access to Alcohol Committee [59], who passed on the letter to the FDA, adding their own concerns [60]. The scientists concluded, *"Based on our findings and our comprehensive review of the scientific literature on this topic, we conclude that there is no evidence to support the claim that caffeine is 'generally recognized as safe' ('GRAS') for use in alcoholic beverages."*

In other countries, the maximum permitted caffeine content for cola-type beverages and other soft drinks falls between 145 mg/l and 200 mg/l, which equates to approximately 36–50 mg of caffeine in a 250 ml beverage serving or 72–100 mg in a 500 ml serving? The maximum permitted caffeine content for energy drinks is higher, at between 320 mg/l and 350 mg/l, although in some countries (EU, South Africa, New Zealand) it is specified that beverages containing more than 145/150 mg/l should be labeled "high caffeine content", and one country (Canada) permits concentrations up to 400 mg/l but specifies a cap of 180 mg per serving. These figures equate to 80–88 mg of caffeine in a 250 ml beverage serving or 160–175 mg in a 500 ml serving.

Table 1. *Caffeine Regulatory Dosage and effect.*

Caffeine dose		Description/Definition	Source
12.5–50 mg	LOW	"low doses of caffeine (12.5 to 50 mg) have been found to improve cognitive performance and mood [6]"	[61]
40–60 mg	LOW	"as little as 40–60 mg of caffeine can exert positive effects on cognitive function"	[13]
~ 75 mg	MODERATE	"Evidence suggests that moderate levels of caffeine (about 75 mg) improve several aspects of cognitive performance including attention, visual searching, psychomotor speed, memory, and serial subtraction."	[62]
100–500 mg	NORMAL	"In normal doses (100 – 500 mg), [caffeine] potently stimulates the cerebral cortex, promoting wakefulness and improving some aspects of psychomotor performance."	[63]
210 mg	ADVERSE EFFECTS	"Based on data up to 1999, Smith et al. (2000) concluded an adverse effect level of 210 mg in adults (3 mg/day for a 70 kg adult) based on observations of increased anxiety."	[64]
> 200 mg	HIGHER	"At higher acute doses (> 200 mg), caffeine is more likely to produce negative subjective effects such as anxiety, jitteriness, and gastrointestinal disturbances."	[65]
10,000 mg	LETHAL	"The acute lethal dose in adult humans has been estimated to be 10 g/person."	[66]
10,500– 14,000 mg for a 70 kg person	LETHAL	"Caffeine toxicity is dosed dependent and fatalities have been reported at very high dosages of greater than 150-200 mg/kg" body weight.	[67]

4. Discussion

Considering the mean daily intake of energy drinks, the Scientific Committee on Food of the European Commission [29], has classified consumption into "mean chronic" (125 ml/day), "high chronic" (350 ml/day) and "acute" (750 ml/day). For a typical ED product containing 320 mg/l of caffeine, these classifications would equate to 40 mg, 112 mg and 240 mg of caffeine per day. Referring to the research extracts in Table 1, acute caffeine doses of fewer than 100 mg are generally regarded as low, exerting positive effects on cognitive function and mood, but with no adverse effects. The upper end of that range is also the lowest level at which most people can detect the bitter taste of caffeine and begin to discriminate its presence. Doses of between 100 mg and 200 mg are in the low-to moderate range, still enhancing cognitive performance, but producing positive subjective effects. Moderate doses of between 200 mg and 400 mg are required to elicit positive physical benefits in relation to exercise, but there are some reports of anxiety experienced in this range. At higher doses, above 400 mg, adverse effects begin to emerge, with reports of symptoms such as anxiety, nausea, jitteriness and nervousness. Levels over 500 mg are described as excessive.

5. Conclusion

Substances containing caffeine contain bio-active ingredients that may likely stimulate brain and other vital

organs of their consumers. These stimulatory effects may be positive but sometimes could be detrimental to the health of their consumers. It is therefore, recommended that prescribed doses should be taken as recommended by doctors and researchers in order to maximize the full potential of its activity in human health.

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