



# Energy Drink Ingredients and their Effect on Endothelial Function: A Review

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## Introduction

It is an age-old idea to try to boost one's performance in order to achieve an elusive goal or conquer an obstacle. Many energy products, especially energy drinks (ED) are now marketed to this need, and examples include Red Bulls' 'Gives You Wings,' as well as Monster Energy's 'Unleash the Beast' advertising campaigns [1,2].

In the light of ED consumption recently being associated with high risk behaviors, unhealthy habits, and some deaths in adolescents and young adults, especially when consumed while exercising, the Food and Drug Agency and the scientific community is now asking for more evidence as to whether these EDs work, what is in them, who should use them, and what if any is a safe dose [3-6].

Studies on the effects of EDs to improve one's physical or cognitive performance have yielded mixed results [7-12]. In a systematic review of the ED ingredients that examined them alone or in combination with caffeine to assess the claims of enhancing physical and cognitive performance, 32 articles found some evidence, albeit weak, to support the claims for glucose and guarana [13]. As for the other common ingredients of taurine, ginseng, B vitamins, glucuronolactone and others, there was an overwhelming lack of evidence for their enhancing physical and cognitive performance [13]. Clearly, more studies that are well designed to examine the effects of EDs and their components are needed to clarify their effects.

The consumption of EDs before or during exercise might be linked to an increased risk for myocardial ischemia in association with endothelial dysfunction [14]. A case report suggested that abnormal vascular function, specifically coronary artery spasm, may have been the result of the high levels of taurine and caffeine in the ED [15]. Several studies have noted reduced endothelial cell function (ECF) following ED consumption [14,16,17]; others have shown no difference [10]. In addition, caffeine, which is often present in high concentrations in EDs, has been associated with reduced myocardial blood flow during exercise [18].

It has been commonly accepted that ECF is closely related to cardiovascular risk, with impairment being involved in the pathogenesis of atherosclerosis and coronary artery disease (CAD) [19,20]. Impairment of ECF is also related to a decrease in the

bioavailability of nitric oxide, a vasodilator and inhibitor of platelet aggregation, which also has anti-inflammatory and anti-proliferative properties [19]. ECF is commonly measured indirectly by flow-mediated dilatation (FMD) in the brachial artery, which is well validated, and serves as a strong predictor of cardiovascular events [19,20]. Due to the various uses of tracking ECF in the process of CAD and other diseases, it is important to determine what effects the various components of ED have on ECF alone or in combination as part of an ED. The goal of this review is to summarize the known effects of the individual ingredients of ED have on ECF.

## Methods

A search of the English-language scientific literature was performed primarily by searching MEDLINE, PubMed, EMBASE, The Cochrane Library, CINAHL Plus, Google Scholar for the time period 1976 through September 2014. Keywords used in the search included the name of each ingredient e.g. 'L-carnitine' AND 'endothelial function'. The bibliographies of articles from the above searches were also explored for relevant articles, and links on websites containing published papers were searched for pertinent information. The final results were pared down to include only human trials and *in vivo* studies.

## Results

### L-carnitine

L-carnitine (LC) is synthesized in the body from lysine and methionine [21]. It serves as a carboxylic acid that plays a vital role in the transport of fatty acids into mitochondria for  $\beta$ -oxidation, while also preventing accumulation of toxic acyl-CoA [13]. Currently there is no experimental evidence to support claims of improvement in physical or cognitive improvements from LC supplementation. One study investigated LC on vascular function in diabetes and heart disease by testing volunteer subjects after free fatty acid elevations both with and without LC supplementation [22]. They found that LC may in fact attenuate free fatty acid induced and obesity associated endothelial dysfunction. Limits of the study include that the delivery of LC was intravenous, the subjects were healthy, and effects of LC supplementation were examined in the short term only. Another study observed the effects of LC during three weeks of 2 g/day

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supplementation and observed the postprandial FMD after a high fat meal at baseline and after supplementation in healthy individuals [23]. They found a significant improvement in FMD after the healthy subjects were given a high fat meal, and determined the effects were probably independent of postprandial lipemic response.

Another review focused on carnitine, specifically the isomer Propionyl-L-carnitine (PLC), which exhibits high affinity for both skeletal and cardiac muscle, and is rapidly converted to LC when given exogenously [24]. They noted improvement of endothelial-dependent dilation in endothelial dysfunction when subjects were given PLC supplementation. Other effects included decreased body weight and abdominal adiposity, decreased vascular inflammation, triglycerides, low-density lipoprotein cholesterol, atherosclerotic lesions, lipid peroxidation, improved peripheral arterial disease symptoms, and possible improvement in myocardial function after ischemia. A further study also showed the benefit of PLC in improving ECF and pain management in critical limb ischemia in the end processes of peripheral arterial disease [25]. They suggested the beneficial effect of PLC on the arterial wall occurred through anti-proliferative, as well as pro-apoptotic effects on smooth muscle cells, leading to functional improvement in the peripheral arterial disease.

### **Guarana**

Guarana (*Paullinacupana*) is a plant from Brazil whose caffeine concentrations is 2-15% of its dry weight (about twice that of coffee beans), and it exhibits antioxidant effects and can decrease platelet aggregation [13,26]. There has been inconsistent evidence for its improvement in cognitive function due to the effects of the ingredients other than caffeine, and no experimental evidence for improvement in physical performance [3,27]. No studies showed any effect of guarana on ECF, whether alone or in conjugation with another substance.

### **Glucuronolactone**

Glucuronolactone is a naturally occurring metabolite in liver derived from glucose that serves as a precursor for ascorbic acid synthesis, an antioxidant, and as a structural component of connective tissues [13]. One study evaluating glucuronolactone as a component of an ED showed reduced ECF and platelet function from the ED, but it did not specifically test the glucuronolactone component separately [16]. Though endothelial dysfunction and platelet impairment has been found to be associated with increased glucose levels, given glucuronolactone is a glucose metabolite, it may also result in detrimental effects on ECF and platelet function [13].

### **Taurine**

Taurine is a non-essential amino acid that is found in high concentrations in the brain, heart, and skeletal muscle [13]. It is involved in the process of conjugating bile acids with chenodeoxycholic acid and cholic acid. In toxicology studies, there have been no adverse effects of taurine supplementation with levels up to 1,000 mg per kilogram of body weight when dosing. There has been mixed results regarding the benefits of use before and during exercise on improving physical performance; in addition, it is also unlikely that increased plasma taurine levels would alter brain levels and neurotransmitters in young adults [13].

A study of taurine and vitamin C supplementation in young smokers noted protective effects on ECF when exposed to pro-inflammatory insults [28]. The study found that taurine and vitamin C may restore the ECF in the young smokers by modifying monocyte-endothelial interactions and thus attenuating impairment of FMD. While vitamin C supplementation did improve FMD, its effect was not as great as taurine. The study also found no adverse effects of taurine supplementation, and that a taurine dose equivalent to 100g of fresh fish would likely reduce risk of coronary artery disease [28].

Taurine, by potentiating the effect of insulin and insulin receptors may benefit diabetic patients' blood glucose levels, which may then improve ECF [29]. In a study of males less than 30 years of age with type

I diabetes mellitus, after two weeks supplementation with taurine, the FMD of the subjects improved. However, another study found large quantities of taurine as part of an ED resulted in detrimental effects on platelet function and ECF [16]. They also reported a significant increase in mean arterial pressure, a significant increase in platelet aggregation, and a significant decrease in ECF. Although taurine was found in high levels in platelets, its exact function on platelets remains unknown. Further, due to previously reported beneficial effects of taurine, the authors speculated that it was unlikely that the negative effects of ED on platelets and ECF were due to the taurine component [16]. However, they could not rule out some interaction effect from between taurine and the other components resulting in worsening of ECF.

### **Ginseng**

There has been no experimental evidence to support any benefit in enhancing physical or cognitive performance from ginseng being added to an ED [13]. Ginseng is available in various forms and types: root, powdered form, Korean and American red ginseng. One study examined the effects of Korean Red Ginseng (KRG) and its metabolites on arterial stiffness in healthy individuals [30]. The augmentation index and blood pressures were measured at baseline and every hour for three hours after treatment with a 3 g KRG dose. An increase in the augmentation index is known to unfavorably affect ventricular after load and compromise coronary perfusion. It was found that the acute consumption of KRG resulted in significant reduction of the augmentation index and also it did indeed cause vasodilation via increases in nitric oxide levels in healthy individuals [30]. The authors suggested that the increase in vasodilation, as well as other effects including inhibition of platelet adhesion, and stimulation of nitric oxide release, were likely attributed to ginsenosides, a class of steroid glycosides, found exclusively in the plant genus *Panax* (ginseng).

KRG was also studied to determine its effect on arterial stiffness in those with hypertension. In contrast to the former study, after receiving a dose of 3 g per day for 3 months, KRG did not result in a significant decrease in blood pressure nor did it improve atherosclerosis [31]. In contrast, a study using American Red Ginseng (ARG) on arterial stiffness in those with type 2 diabetes mellitus with concomitant hypertension showed significant benefit [31]. They noted that ARG improved ECF and arterial stiffness in healthy, those with hypertension, and even type 2 diabetes mellitus by increasing nitric oxide bioavailability. ARG was found to have significantly lower radial augmentation index and systolic blood pressure. However, the true physiologic effects of ARG may not be known due to the many different marketed preparations; further, when whole ARG was tested, it only showed neutral effects on blood pressure and ECF both in the acute and long term setting. Further testing and stricter parameters need to be defined in relation to the exact preparations of ginseng, and evaluation in long-term studies before any recommendations for adjunct treatment can be made [32].

### **B Vitamins**

Many manufacturers tout their complexes of B vitamins as a major contributor to the energy enhancing abilities of their EDs. This section will cover riboflavin (B2), niacin (B3), pyridoxine (B6), inositol (B8), folate (B9), and cobalamin (B12) in respect to ECF. As far as their effect in improving physical and cognitive performance, there has been no evidence supporting the addition of B vitamins to ED that explain improved effects beyond those of caffeine alone.

#### **Riboflavin (Vitamin B2)**

Articles reviewed only addressed riboflavin's use in possible ophthalmological treatments in certain diseases of the cornea, or its effect in promoting lung cancer progression in high doses [33]. No papers addressed its effects on the vascular system.

#### **Niacin (Vitamin B3)**

Niacin was studied in several different populations concerning its effects on vascular function. Niacin still serves as the most potent

therapy to increase high-density lipoprotein cholesterol, and studies on statin-naïve patients show improvement in ECF [34]. Extended release niacin given to metabolic syndrome patients was found to cause a regression in carotid intima-media thickness, improving high-density lipoprotein cholesterol, reducing low-density lipoprotein cholesterol and triglyceride levels, improving ECF, and decreasing vascular inflammation as measured by a decrease in C-reactive protein levels [35]. The improvement in ECF with niacin was consistent with previous studies that showed similar improvement after three months of treatment [35]. Another study evaluated the effect of niacin in coronary artery disease (CAD) patients and endothelial dysfunction and found an improvement in FMD, though only in patients with low high-density lipoprotein cholesterol at baseline [36]. However, no effect on glucose metabolism or inflammatory markers was found in this study [36].

Another study evaluating niacin therapy for twelve months also showed a significant decrease in carotid intima-media thickness as well as an improvement in ECF [37]. In patients with diabetes mellitus type 2 already on statin therapies, addition of niacin was also found to significantly improve brachial FMD and small artery compliance [38]. Niacin was studied to determine its effects on FMD in patients already on high dose statin therapy for CAD. After three months, niacin therapy was still able to significantly improve lipid profiles, but had no observed improvements in FMD [39]. The study further clarified that the low-density lipoprotein cholesterol levels in the subjects were significantly below target levels which may have influenced the effects shown on FMD with extended-release-niacin treatment.

#### **Pyridoxine (Vitamin B6), Folate (Vitamin B9), and Cobalamin (Vitamin B12)**

Studies usually group these vitamins so they will be discussed together.

One study evaluated the possible benefits of homocysteine (HCY) lowering treatment with pyridoxine and folate therapy, and found both improved HCY levels and ECF in those with hyperhomocysteinemia (HHC) [40]. Another study also examined pyridoxine and folate therapy on HHC patients after three months of treatment, but found only significant improvement in biomarkers of ECF after a pyridoxine load at baseline, not after the test period [41]. An additional study was done to investigate the effects of pyridoxine supplementation in cardiac transplant patients, as HHC is common and associated with transplant CAD that can be predicted by endothelial dysfunction [42]. Although no significant change in plasma HCY levels was seen, there was a significant association between pyridoxine and improved ECF. In addition, pyridoxine deficiency is linked to premature CAD and impaired oxidative defense mechanisms due to a reduction in the ratio of reduced to oxidized glutathione, as reduced glutathione itself improves ECF [42].

A two year trial looked at the effects of folate and pyridoxine treatment and determined the only significant associations were with lower systolic and diastolic pressures, but no effects could be demonstrated with the HCY lowering treatment on brachial FMD or carotid artery stiffness in healthy individuals [43]. One study evaluated the use of folate, pyridoxine and cobalamin administration on endothelial dysfunction induced by post-methionine load HHC finding a significant improvement of FMD with the short term vitamin administration [44]. Another similar combination study found significant decreases in HCY levels, improved endothelium dependent dilation, and improved exercise performance while decreasing exercise induced ischemia in patients with CAD and HHC [45]. Yet another group using the folate, pyridoxine and cobalamin showed no effect on the markers of ECF in healthy volunteers [46]. Two further studies using this combination in patients with recent myocardial infarctions or with previous TIAs or stroke found no benefits in markers of inflammation or ECF [47,48]. One additional study on stroke patients explored the effects of long term combination therapy on lowering HCY levels and on carotid intima-media thickness and FMD [49]. The subjects had a mean treatment

period of four years and while the treatment group had significantly lowered its plasma HCY levels, and there was no significant difference in carotid intima-media thickness or FMD. They also conducted a meta-analysis as a part of their study that suggested combination treatment would actually decrease carotid intima-media thickness and increase FMD. While these effects were significant in the short term studies, over a long-term treatment period, combination therapy did not significantly improve FMD or carotid intima-media thickness in patients with a history of stroke [50].

Cobalamin and folate were studied in patients with CAD after eight weeks of treatment and showed improved FMD, significant lowered levels of total plasma HCY, protein bound HCY, and free HCY [50]. This research was unique in that it studied the different ways HCY levels can be measured and the subsequent effects of treatment with B vitamins have on them. It was found that the FMD correlated closely with reduction in free HCY, independent of protein bound HCY, folate or cobalamin levels. They postulated that the improved FMD in ECF of patients with CAD was mediated via this decrease in free HCY. After two months of treatment with folate and cobalamin, patients with metabolic syndrome were found to have significant decreases in HCY and insulin levels, while exhibiting significant improvements in ECF [51]. Another study examined the effects of cobalamin deficiency in subjects with a homozygous mutation, but with no symptoms of coronary, brain or peripheral artery disease and determined that these individuals had high HCY levels, severe forearm endothelial dysfunction and a high prevalence of cobalamin deficiency [52]. They noted that cobalamin therapy was able to normalize ECF.

#### **Inositol (Vitamin B8)**

Inositol which is a component of phosphatidylinositol lipids, also serves as a second messenger, where it triggers release of calcium in cells and transmission of messages between neural cells, and facilitates transport of fat within cells [53]. Currently, there are no studies examining the effects of inositol on ECF alone, or even in conjugation with other compounds in either healthy or diseased states.

#### **Glucose**

Glucose has been found to extend endurance exercise as long as it is consumed at regular intervals in fluids at levels of 6-8% of content rather than the 11-12% that is commonly found in ED that can slow gastric emptying [13]. The combination of glucose and caffeine may enhance cognitive performance in sleep deprived individuals for 30-60 minutes post ingestion, though with inconsistent evidence causing improvements in physical or cognitive improvement on its own. A study exploring the relation of plasma glucose levels on ECF in those without diabetes found that FMD significantly decreased in those with impaired fasting glucose [54]. Thus hyperglycemia plays a significant role in the pathogenesis of vascular dysfunction at different stages of diabetes mellitus development, while also playing an important role in the development of atherosclerosis even in pre-diabetics. Children with type 1 diabetes mellitus also show endothelial dysfunction when compared to controls [55].

The effect of the glucose spike and peak during an oral glucose tolerance test was studied to verify the effect of spike compared to peak on ECF and the possible involvement of oxidative stress [56]. It was found that the incremental increase in glucose correlated with a decrease in ECF, that the glucose spike may be a stronger predictor of carotid intima-media thickness, and that oxidative stress works as an integral part in changes of ECF and can be mediated by vitamin C supplements. Another strategy to assess hyperglycemia effects on vascular function was to examine glycemic variability in those with metabolic syndrome and diabetes mellitus type 2 [57]. These researchers found that FMD decreased while carotid intima-media thickness increased across groups with increase glycemic variability. This increase in variability may precede established hyperglycemia and be associated with endothelial dysfunction. Another study of obese children and adolescents and the effect of postprandial hyperglycemia on ECF, inflammation and oxidative stress determined

**Table 1:** Effects of Energy Drink Ingredient of Endothelial Function.

Ingredient	Effect on Endothelial Function	Therapy	Comments
L-Carnitine	Increase	*PAD	Further long term studies needed & which isomer would be most effective
Guarana	NF	NR	-
Inositol	NF	NR	-
Glucuronolactone	NF	NR	-
Taurine	Increase	*DM1	Further elucidation for mechanism of action in DM1 patients and protective effects in pro-inflammatory states
Ginseng	Increase / no effect	*DM2/HTN	Delineation between KRG and ARG to determine which has greater potential for therapy; also what are the active compounds in the marketed preparations
Glucose	Decrease	NR	All advocated a decrease in serum levels of glucose being beneficial to patients
Caffeine	Decrease	NR	Possible use in coronary artery disease since a study showed improvement after purified caffeine pills
Riboflavin	NF	NR	-
Niacin	Increase / no effect	CAD/DM2/MS/HLD	Clarification on beginning treatment on statin therapy and at what levels of high-density lipoprotein cholesterol
Pyridoxine	Increase / no effect	*HHC/CAD	Studies on healthy, without folate, and long-term studies with HHC
Cyanocobalamin	No effect	*HHC/MS	Studies without folate and role in HHC therapy

NF: No articles Found; NR: No Recommendations at this time; \*: Possible role in therapy; PAD: Peripheral Arterial Disease; HTN: Hypertension; DM: Diabetes Mellitus; HLD: Hyperlipidemia; HHC: Hyperhomocysteinemia

that an acute oral glucose load did not reduce ECF or increase levels of inflammation or oxidative stress [58]. Thus, the arteries may be able to retain their ability to regulate blood flow and dilatory capacity within a postprandial setting during childhood, even in the content of obesity [58].

Low versus high glycemic indices during hypocaloric diets were tested for three months in overweight and obese adults without diabetes, yet at increased risk for CAD, and showed improved ECF and glycemic variability in those relegated to a low glycemic index hypocaloric diet [4]. Post-prandial hyperglycemia was found to transiently decrease FMD responses in healthy individuals, while those with impaired glucose tolerance, or even overt diabetes mellitus had a more pronounced response [59]. Post-prandial hyperglycemia appears to impair vascular function in an oxidative stress dependent manner, likely from inducing peroxidation of lipids. In subjects with normal glucose tolerance, it was found that post-prandial hyperglycemia effects on ECF was associated with short term decreases in FMD; those with insulin resistance also showed short term impairment in ECF [60]. Improvement of the fasting FMD correlated with an improvement of insulin resistance [60].

**Caffeine**

Pure caffeine and its effect on ECF are different to those of caffeine when consumed as coffee or as part of an ED [18]. Indeed, coffee and EDs contains substances other than caffeine that are known to have antioxidative effects and may improve ECF [18].

When studied in healthy subjects who were regular non-heavy coffee drinkers, caffeinated coffee showed a decrease in FMD, whereas decaffeinated coffee showed no significant difference in FMD [61]. The unfavorable effects of coffee on ECF in healthy adults lasted up to an hour. When testing a load of 300 mg of oral caffeine, a significant increase was found in both diastolic and systolic blood pressures, but no alterations were found in heart rate or forearm blood flow in healthy subjects [62]. Though caffeine ingestion did not increase forearm blood flow directly, it did seem to increase forearm blood flow response to acetylcholine in a significant manner suggesting that caffeine augments endogenous nitric oxide production by agonist stimulation, even though simultaneously causing vasoconstrictive effects as an adenosine receptor antagonist [62].

A study that evaluated healthy and diabetic women showed those diabetics who had caffeinated coffee had decreased levels of inflammatory markers, while the healthy subjects had the same effect but with decaffeinated coffee [63]. Additionally, with either the caffeinated or decaffeinated coffee, no detrimental effects were observed on ECF. One study tried to address this discrepancy by trying to determine whether caffeine or the antioxidants in the coffee

determined the type of change in FMD [64]. What was determined was that antioxidant levels were higher in the caffeinated coffee, and thus responsible for the increase in FMD. Though the detrimental effects of caffeine on FMD cannot be blunted solely by antioxidants, further studies are needed to evaluate the long term effects of coffee in relation to caffeine and antioxidant consumption. Another study with decaffeinated versus caffeinated coffee in healthy subjects showed a significant, acute progressive decrease in FMD after caffeinated, but no change with decaffeinated coffee [65]. A final study studied caffeine ingestion in patients with and without CAD noted that acute caffeine ingestion significantly increased FMD and decreased C-reactive protein in comparison to placebo group [66]. These results were seen in the CAD subjects and subjects without CAD after ingesting 200 mg of purified caffeine in a capsule instead of a drink. This was the first study to test caffeine this way, and the first to show improved brachial ECF and decreased inflammatory markers in patients with CAD [66].

Table 1 summarizes the effects of the various components of EDs on ECF.

**Discussion**

While many ingredients in ED have the potential to effect ECF, more research is needed to determine their specific effects alone and in combination with other ingredients. Researchers have only begun research on guarana, inositol, glucuronolactone and riboflavin using strict protocols with enough power to produce recommendations for therapy if beneficial results are found. Most of the results with LC suggest the compound may provide some benefits in a diseased state.

Further research for taurine should be directed at elucidating its real function in platelets, and like LC, how it works in healthy individuals and what goals can be deemed acceptable for use in therapies. The next step for ginseng, is to determine the ideal preparation that can be used to garner positive effects in the healthy and diseased individuals, since its two most popular forms, KRG and ARG, have yielded mixed results.

Niacin is the only one of the ED ingredients that is used as pharmacologic therapy, with recent evidence supporting its benefits. Further studies will help clarify to what point niacin as an adjunct therapy will be beneficial to the patient, and if there is any benefit to using niacin for therapy alone or for possible disease prevention, especially with respect to improvement in ECF. Pyridoxine and cobalamin need further studies examining them without folate, to determine their effects not only in individuals with HHC, but if there is any added benefits to supplementation in healthy and/or those at increased risk for disease.

Abnormally high levels of glucose are generally detrimental to

ECF [67]. More research on the types of glucose lowering treatment, and how much they improve ECF when preventing disease is needed.

Finally, caffeine may be the most controversial of all the ingredients since there are many studies with coffee exhibiting mixed results. The next step in research should focus on purified capsules of caffeine at different doses, and studying their effects on vascular function to determine recommendations on safe daily amounts of ingestion.

## Conclusion

While some components of ED's may have been shown to improve ECF, some appear to be detrimental, while others have just not been studied. Further, the popular EDs mix together glucose, high levels of caffeine, glucose, B-vitamins, L-Carnitine, Guarana, Glucuronolactone, Taurine, Ginseng and other components as part of an energy blend. In order to better understand the effect of consumption of these drinks on ECF, it is likely that an approach will be required which evaluates each of the components of the EDs separately as well as their effect in combination, both at rest and during exercise. Specifically, we need to determine if there is an interaction between the ingredients of EDs that may result in an acute adverse effect on ECF, which could possibly result in adverse effects. In addition, more research is required to determine what, if any, are safe levels of consumption of EDs, and whether they are efficacious with respect to improving performance as their manufacturers claim i.e. safety and efficacy studies are needed. Given the associations between ED consumption and reported adverse events and deaths, it behooves us to study EDs further and if needed, regulate them appropriately to protect vulnerable populations from their adverse events.

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