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Review

Effects of coffee, energy drinks and their components on hemostasis: The hypothetical mechanisms of their action

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ABSTRACT

Hemostasis is a process which encompasses the clotting, fibrinolysis, blood platelet activation and endothelial cell function. Certain dietary components may modulate some elements of hemostasis, particularly blood platelet function, and modify the progression of cardiovascular diseases. The aim of this review paper is to provide an overview of current knowledge of the role of coffee, energy drinks and their bioactive compounds in such modulation. It describes the effect of coffee, energy drinks and their selected components (e.g. caffeine) on hemostasis, especially blood platelets, and their underlying mechanisms. Like coffee, energy drinks may modify platelet reactivity by changing the activity of signaling enzymes, and by modifying cAMP and reactive oxygen species levels. However, the effects of coffee and energy drinks on platelet activation are dependent on a range of factors, including their bioactive components, platelet activators and the methods used for monitoring platelet activation. While some studies (*in vivo* models) indicate that energy drinks have pro-aggregatory affects, which may be associated with an elevated risk of thrombosis, others indicate that coffee in fact reduces platelet activation, which may be beneficial for prophylaxis of thrombosis.

1. Introduction

Since their introduction in the United States in 1997 (Reissing et al., 2009), various energy drinks have been introduced to provide the feeling of an energy boost, or for use as dietary supplements. They can now be found in a wide range of formulations and dosages, from 20 oz beverages to 4 oz "shots". Energy drinks contain high concentrations of various bioactive compounds, including caffeine, carnitine, taurine and ginseng extracts: for example, some energy drinks may contain 50 mg–505 mg of caffeine, compared with the 80 mg found in standard cup of coffee (Griffiths et al., 2003; Reissing et al., 2009; Trabulo et al., 2011); however, the caffeine content of coffee can also vary depending on the type of bean or brew. Energy drinks may also contain inositol, extracts of guarana, carbohydrates such as ribose, fructose or sucrose, B-group vitamins and glucuronolactone (Table 1) (Reissing et al., 2009). Importantly, the US Food and Drug Administration does not require energy drinks to display warnings or limit their caffeine content (Kole and Barnhill, 2013).

With such variety possible in the formulation and individual constituents of energy drinks or coffee, it is difficult to draw firm conclusions regarding their effects on the cardiovascular system. Similarly, the wide variety of study designs (human, *in vivo* and *in vitro* studies etc.) have resulted in them being ascribed both protective and harmful effects. Nevertheless, some reports have found particularly large intakes of energy drinks to be associated with the occurrence of cardiovascular disorders, including acute cardiovascular adverse events (Sanchis-Gomar et al., 2015, 2016), and others report that energy drinks may elevate the risk of cerebrovascular accidents and myocardial infarctions by various mechanisms, such as by increasing blood platelet aggregation and decreasing endothelial functions (Arboix, 2015).

The changes occurring in platelet function depend on the bioactive components of energy drinks, for example caffeine increases the

Abbreviations: ADP, adenosine diphosphate; cAMP, cyclic adenosine monophosphate; COX, cyclooxygenase; DAG, diacylglycerol; ERK2, extracellular signal-regulated kinase 2; GPIIb/IIIa, glycoprotein IIb/IIIa (platelet fibrinogen receptor); IP, prostacyclin (PGI_2) receptor, also termed the prostaglandin I2 receptor; IP3, inositol trisphosphate; LOX, 12-lipoxygenase; MAPK, mitogen-activated protein kinases; MLCK, myosin light-chain kinase; NOX, NADPH oxidase; PDE, phosphodiesterase; PGI2, prostacyclin; PIP2, phosphatidylinositol 4,5-bisphosphate; PKA, protein kinase A; PKC, protein kinase C; PLA_2, phospholipase A_2; PLC, phospholipase C; ROS, reactive oxygen species; TP, thromboxane receptor; TXA_2, thromboxane A_2; unc. eNOS, uncoupled endothelial NO synthase; VASP, vasodilator-stimulated phosphoprotein

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Table 1
Common ingredients in energy drinks, physiological functions and their effect of hemostasis. (Goldfarb et al., 2015; modified). The table gives the approximate content of some compounds, calculated on the basis of data provided by producers (e.g. Monster Beverage Corporation; Red Bull GmbH).

INGREDIENTS	PHYSIOLOGICAL FUNCTION	MODULATION OF HEMOSTASIS
CAFFEINE (~30 MG/100 ML)	various physiological processes	Observed (effect on blood platelet functions, coagulation process and fibrinolysis)
GLUCURONOLACTONE (~240 MG/100 ML)	glucose metabolite	no data
TAURINE (~400 MG/100 ML)	nonessential amino acid	Observed (effect on blood platelet functions, and coagulation process)
GUARANA EXTRACT (~40 MG/100 ML)	source of caffeine and other methylxanthines	Observed (effect on blood platelet functions)
L-CARNITINE	transport of long-chain fatty acids into mitochondria	Observed (effect on blood platelet functions)
GINKGO BILOBA EXTRACT	unknown	Observed (effect on blood platelet functions, and coagulation process)
GINSENG EXTRACT	unknown	Observed (effect on blood platelet functions, and coagulation process)
B-COMPLEX VITAMINS	various physiological processes	Observed (effect on plasma homocysteine levels)

formation of blood platelet microparticles (McEwen, 2014). However, as the roles played by the various chemical components of energy drinks or coffee in the modulation of hemostasis are not always well documented, the scope of this paper is restricted to reviewing the effect of energy drinks or coffee, and some their components, on hemostasis, with a particular focus on blood platelet activation.

Entries earlier than November 2018 in Pubmed, Web of Knowledge and Google Scholar were searched by two investigators. The following terms were used: “energy drink” or “coffee” or “caffeine”) and (“hemostasis” or “blood platelet” or “fibrinolysis” or “thrombosis” or “hemorrhage” or “coagulation”) and “cardiovascular disease” or “CVD”. When possible, these were combined with a sensitive search strategy to identify trials performed in “humans”. In addition, the references from all relevant articles were searched manually.

2. Hemostasis

Hemostatic mechanisms maintain a balance between thrombosis and hemorrhage, and hemostasis may also be defined as a group of mechanisms which prevent the outflow of blood from blood vessels under normal conditions and when damaged while ensuring its liquidity in the vessel. Various elements take part in hemostasis: the wall of the blood vessel (especially the intima), the coagulation and fibrinolysis processes (with various clotting factors, including fibrinogen and thrombin) and the phagocyte system.

Hemostasis is also strongly dependent on the activity of small prokaryotic cells known as blood platelets (Fig. 1), which are found in blood at concentrations of 150–400 $\times 10^9$ per liter (Ryningen and Holmsen, 1999; Nowak et al., 2010). Blood platelets play an important role in both health and disease through their involvement in hemostasis and thrombosis. The process of hemostasis begins with blood platelet adhesion at sites of vascular injury, which is followed by blood platelet activation stimulated by platelet agonists, including thrombin, adenosine diphosphate (ADP) and arachidonic acid. Activation is followed by the secretion of various aggregatory substances and finally the aggregation of blood platelets into a hemostatic plug and thrombus (Ryningen and Holmsen, 1999; Shaturny et al., 2014). In addition, blood platelets can also form aggregates with leukocytes, and it is known that platelet-monocyte aggregates contribute to the initiation and progression of atherosclerosis (Shantsila and Lip, 2009; McEwen, 2014).

During blood platelet activation, two important signal transduction cascades are stimulated: (I) the metabolism of arachidonic acid, associated with the eicosanoid biosynthesis, and (II) phosphoinositide hydrolysis. In addition, blood platelet activation is correlated with elevated intracellular calcium level and free radical generation (Ryningen and Holmsen, 1999; Nowak et al., 2010; Shaturny et al., 2014).

Hemostatic abnormalities can lead not only to thrombosis, but also to bleeding and other cardiovascular diseases. It has been demonstrated that the inhibition of blood platelet activation, by anti-platelet drugs such as aspirin and other non-steroidal anti-inflammatory drugs for example, is an effective strategy to treat various cardiovascular diseases associated with platelet hyperactivation. Such changes in platelet function reduce the risk of thrombosis and adverse cardiovascular events. In addition, while dietary supplements are known to influence hemostasis *in vitro*, it is less certain whether such actions are observed *in vivo*.

However, dietary supplements with anti-platelet and/or anticoagulant activity could be beneficial for the prophylaxis and treatment of cardiovascular diseases (Stanger et al., 2012; Olas, 2018). Other dietary components may also influence hemostasis, and the progression of cardiovascular disorders, particularly blood platelet activation (Olas, 2018). Recent epidemiological studies strongly suggest that coffee may play an important role in modifying some elements of hemostasis, especially blood platelet function, and the progression of cardiovascular diseases. *In vitro* and *in vivo* studies have also found that the phenolic compounds in coffee reduce blood platelet activation, including blood platelet aggregation (McEwen, 2014).

3. Consumption of coffee and energy drinks

Coffee is one of the most popular drinks around the world and is obtained from the roasted beans of *Coffea Arabica* (Arabica coffee) and *Coffea canephora* (Robusa coffee) of the Rubiaceae family. After harvesting, the bean is processed by either a dry or wet technique. Coffee itself may be served by various means, with the most common being with milk or sugar (Montagnana et al., 2012; Park, 2015).

In contrast, the main consumers of energy drinks are younger people, typically those between 18 and 34 years of age (Visram et al., 2016; Reid et al., 2017). The target market for energy drinks includes athletes, students and professionals who need to maintain high concentration levels; however, some young people consume energy drinks in combination with illicit substances, such as marijuana and amphetamines (Bitancourt et al., 2016). A study by Vitiello et al. (2016) describes the energy drink consumption habits among 618 female and 389 male Italian university students, both alone and in combination with alcohol, as well as their food habits and lifestyle. The consumers were divided into two groups: (1) occasional consumers (less than one per week) and (2) habitual consumers (up to three or four times per week). All participants completed a survey comprising 30 different questions. The acquired data was analyzed to determine the following: (I) any differences between the habitual and occasional consumers, (II) the characteristics of energy drink consumers (habitual and occasional), (III) the characteristics of the consumers of cocktails that combine energy drinks and alcohol (energy drink-based cocktails), (IV) gender-related differences in food consumption and lifestyle. The results indicated that 28.6% of the tested students consumed energy drinks when under heavy study load, 17.9% on Saturday evening to stay up late at night, 15.5% before physical activity, 9.5% after physical activity, 3.6% while working and 1.2% while driving. It was also found that 32.5% of the students consumed the drinks for their perceived energizing effects, 18.1% perceived enhanced physical strength and 16.9% observed

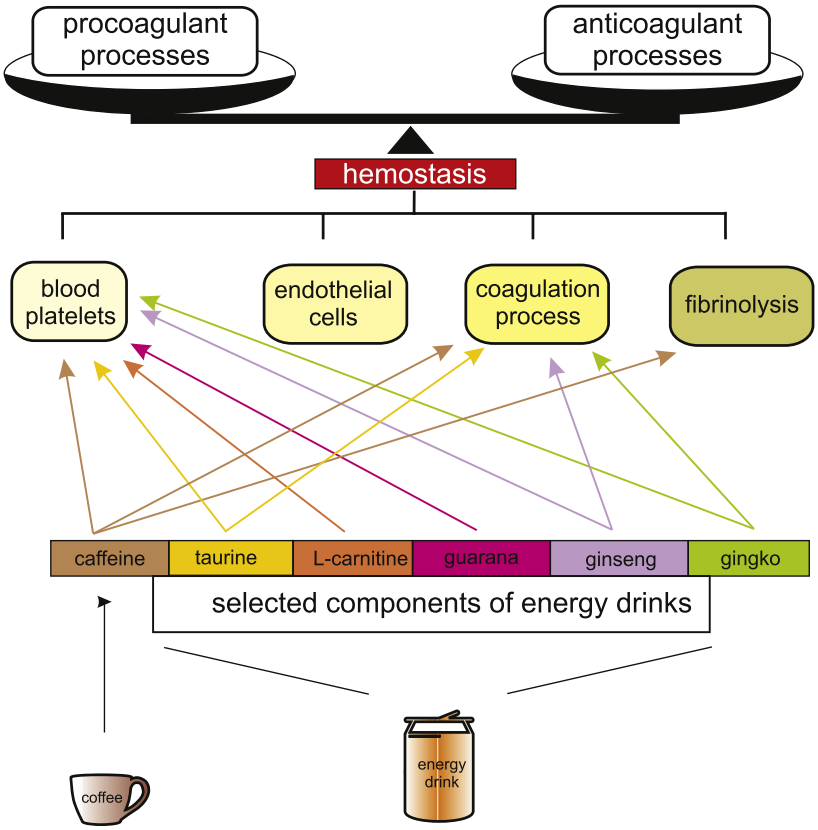

Fig. 1. Endogenous targets of selected components of energy drinks in hemostasis.

enhanced concentration for study. The authors also found that 48% of students tried energy drinks thanks to advertising, 41% following the recommendation of a friend and 11% following the recommendation of a personal trainer (Vitiello et al., 2016).

4. Main bioactive compounds of coffee and energy drinks

Coffee is rich in compounds with high antioxidant activity including phenolic acids such as chlorogenic, caffeic, coumaric, ferulic, isoferulic and hydroxycinnamic acid, but also some which can be potentially negative for health, such as diterpene alcohols, acrylamide and 5-hydroxymethylfurfural. When the green coffee beans are roasted during coffee processing, the high temperature elicits changes in bioactive compounds to produce high molecular weight nitrogenous brown-colored compounds such as melanoidins by the Maillard reaction. Coffee is one of the main sources of melanoidins in the human diet, and several antioxidant, antimicrobial, anticariogenic, anti-inflammatory, antihypertensive and antiglycative activities, have been attributed to coffee melanoidins (Ferruzzi, 2010; Godos et al., 2014).

Energy drinks contain substances that act as bioactive compounds, such as caffeine, taurine, glucuronolactone, L-carnitine, herbal extracts (guarana, ginseng), vitamins, and sugar or sweeteners with purported ergogenic or performance-enhancing effects. All these ingredients create what the manufacturers have called an “energy blend”. Although different brands of energy drinks tend to contain the same ingredients and have similar claims, their precise content may vary (Higgins et al., 2010; McLellan and Lieberman, 2012).

The literature consensus is that caffeine is an adenosine receptor antagonist which stimulates the activity of neuronal control pathways in the central and peripheral nervous systems (Fredholm, 2014; Fredholm et al., 2017). However, a randomized cross-over trial found neither a sugar-free energy drink nor a similar amount of caffeine (120 mg) contained in a water drink to increase heart rate. Caffeine is an ergogenic compound that raises the heart rate and blood pressure (Jones, 2008), which also affects the use of fat resources and stimulates working muscles to use fat as a fuel (Laurent et al., 2000). Caffeine is the main active ingredient of coffee and energy drinks, and it is present in a number of food supplements including those marketed for weight loss and sports performance. It is also an ingredient in a range of products including baked goods, cola-type beverages, ice creams and soft candy. For healthy adults, a caffeine intake of ~400 mg/day is considered safe, while acute clinical toxicity begins at 1 g, and 5 g–10 g is a lethal dose (Seifert et al., 2011; EFSA Journal, 2015). Energy drinks often contain additional amounts of caffeine through additives, such as extracts of guarana, cola nut and yerba mate. Other substances present in energy drinks, e.g. glucuronolactone and taurine, may modify the possible adverse health effects of caffeine and/or the doses at which such adverse effects may occur (Rotstein et al., 2013). More details about the relationship between coffee, caffeine, chlorogenic acid and the purinergic system, including the modulation of P1 and P2 receptors from the central nervous system, are described in a review by Stefanello et al. (2019), which also examines the effect of coffee, caffeine and chlorogenic acid on different components of the antioxidant system and on oxidative stress. For example, Priftis et al. (2019) demonstrate that roasted coffee extract improves blood and tissue redox status in rats through enhancement of glutathione synthesis. The observed increase in glutathione was associated with γ-glutamylcysteine ligase both on the protein and gene levels. In addition, the same authors (Priftis et al., 2018) also observe that roasted and green coffee extracts have antioxidant properties in endothelial cells (in *in vitro* model).

Taurine is a nonproteinogenic β-aminosulfonic acid which regulates muscle contraction and energy levels (Schaffer et al., 2010). Although it has the special property of increasing perceived energy levels, thorough clinical studies have been performed to evaluate its additional effects on the physical, mental and physiological health of humans. However, as the longest study took place over only one year, there is no detailed

evidence of the effect of taurine use beyond this time (Clauson et al., 2008; Ballard et al., 2010).

Glucuronolactone is a naturally-occurring metabolite formed from glucose in the liver. Like glucose and sucrose, glucuronolactone is used to provide immediate energy to the body. There is no experimental evidence suggesting that the addition of glucuronolactone to a caffeinated energy drink will cause greater improvements in physical and cognitive performance than can be attributed to the effects of caffeine alone (McLellan and Lieberman, 2012).

Most energy drinks contain varying amounts of B vitamins and make unsubstantiated claims that these ingredients will increase the perceived energy level of the consumer. However, for most active adults, a balanced nutritious diet will provide sufficient quantities of B complex vitamins without the need for further supplementation. B vitamins aid the conversion from food to energy; however, as the bioavailability of B vitamins is quite low *via* oral administration, consumption of the vitamins in energy drinks may not have much effect (Williams, 2004; Rosenbloom, 2007).

L-carnitine is an amino acid derivative, and its function is to facilitate fatty acid transport into the mitochondria. Dietary supplementation with L-carnitine has been shown to increase maximal oxygen consumption and lower the respiratory quotient, indicating stimulation of lipid metabolism (Higgins et al., 2010). As absorption studies indicate saturation at a dose of 2 g, there appears to be no advantage in giving a greater oral dose at one time (Bain et al., 2006).

Plants from which the extracts are often present in energy drinks are ginseng, guarana, gingko and yerba mate. There are several forms of ginseng, with the most popular being Chinese ginseng (*Panax ginseng* C.A.Mey.), but American (*Panax quinquefolius* L.) or Siberian ginseng [*Eleutherococcus senticosus* (Rupr. & Maxim.) Maxim.] are also often used (McLellan and Lieberman, 2012). This adaptogen, a herb product said to increase resistance to stress, trauma, anxiety and fatigue, is purported to act by stimulating the hypothalamic and pituitary glands to secrete corticotropin. However, the amounts of ginseng found in energy drinks are far below the amounts expected to deliver therapeutic benefits or cause adverse events (Clauson et al., 2008).

Guarana (*Paullinia cupana* Kunth) is a plant that contains caffeine and the stimulants theobromine and theophylline. The caffeine content per gram of guarana is 40–80 mg; however, it has a potentially longer half-life through interactions with other plant compounds (Seifert et al., 2011). Findings from both animal and human studies seem to suggest that guarana extracts can influence behavior and cognitive performance through caffeine-independent mechanisms. However, the possible ergogenic effects of guarana have not been well documented in humans (McLellan and Lieberman, 2012; Higgins, 2013).

Several manufacturers have added ingredients of *Ginkgo biloba* L. to their multivitamin and other multi-component products in amounts that vary from 40 mg to 240 mg a day. Ginkgo extracts can also be found in energy drinks in varying amounts. (Abebe, 2002; Senchina et al., 2011).

Yerba maté (*Ilex paraguariensis* A.St.-Hil.) is a plant native to South America, which is farmed and consumed primarily as a hot or cold drink. Yerba maté leaves contain the methylxanthines caffeine and theobromine, which together comprise approximately 1.2 g/100 g dry weight or about 70 mg/100 ml aqueous extract (Meinhart et al., 2010). However, there is no convincing evidence suggesting that improvements in cognitive performance can be attributed to the effects of ingredients other than the caffeine content of the herbal drink (McLellan and Lieberman, 2012).

5. Energy drinks and coffee - their bioactive compounds and cardiovascular diseases

Many studies have investigated the effects of energy drinks, coffee and their bioactive components on various elements of hemostasis which may be involved in acute cardiovascular effects and cardiovascular diseases. However, a review by Bak and Grobbee (1990) highlights the correlation between coffee consumption and blood pressure, and proposes further research into possible links between coffee and hemostasis or thrombotic tendencies. In addition, different epidemiological studies report a relationship between coffee consumption and both cardiovascular events and mortality (Bhaskar and Rauf, 2010; Naito et al., 2011; Montagnana et al., 2012; Gocken and Sanlier, 2017). However, coffee consumption has been found to have both negative and positive influences on cardiovascular diseases, depending on the particular mechanism (Gocken and Sanlier, 2017). Generally, coffee extracts act as inhibitors of blood platelet aggregation, a critical step of primary hemostasis involved in thrombosis; various studies (Bhaskar and Rauf, 2010; Naito et al., 2011) have found that coffee inhibits the aggregation of blood platelets following stimulation by various agonists, such as epinephrine, ADP, collagen and arachidonic acid.

However, a recent study by Montagnana et al. (2012) suggests that a lower risk of cardiovascular diseases is associated with low (less than one cup of coffee per day) and high (more than or equal to four cups per day) intake, with a higher risk being demonstrated for intermediate consumption of two to four cups per day (Montagnana et al., 2012). It is important to note that most benefits are evident in individuals with a rapid caffeine metabolizer genotype and a low baseline cardiovascular risk. Benefits have also been differentially associated with the type or style of coffee being consumed, e.g. espresso and mocha, filtered coffee or decaffeinated coffee, and the time of coffee consumption, e.g. during breakfast, lunchtime or dinner (Montagnana et al., 2012; Grosso et al., 2017).

Recently, the role of coffee and its components in acute cardiovascular events, particularly the promotion of cardiovascular diseases, has been re-evaluated, as has the effect of energy drinks and their bioactive components on the cardiovascular system: for example increased heart rate, arrhythmias and increased blood pressure (Sanchis-Gomar et al., 2016; Wassef et al., 2017). Busuttil and Willonghby (2016) report that particularly high consumption of energy drinks, e.g. two or more per day, was associated with higher diastolic blood pressure and increased frequency of palpitations, even in healthy people without cardiovascular risk factors. Svatikova et al. (2005) also note that the consumption of energy drinks increased blood pressure in young healthy adults.

Cavka et al. (2015) observed that adrenergic system activation mediates changes in cardiovascular reactions in young individuals after consumption of energy drinks. In this experiment, 38 participants were subjected to four different study protocols in a random order, before consumption of Red Bull (500 ml) and 30 min after. The authors found that the level of glucose and catecholamine in plasma increased after Red Bull consumption, as did heart rate, respiration rate and respiratory flow rate, compared to controls. Similarly, a study of 52 healthy young students by Elitok et al. (2016) found that ingestion of 355 ml of Red Bull increases the heart rate, diastolic and systolic blood pressure, but does not cause alterations in ventricular repolarization. In another study by Grasser et al. (2015), 20 young, healthy subjects ingested 355 ml of Red Bull or water and underwent a 5-min mental arithmetic test 80 min later. The results found the combination of Red Bull and mental stress to be associated with cumulative cardiovascular load and a reduction of cerebral blood flow, even under mental challenge.

Kozik et al. (2016) indicate that in healthy subjects aged 18–40 years who were not energy-drink naive, the consumption of Monster energy drink (a blend of taurine, glucose, *Panax ginseng* extract, L-carnitine, caffeine, guarana extract, inositol, glucuronolactone, vitamins and maltodextrin) also alters repolarization of the cardiac cycle, which may predispose consumers to LQTS (long QT syndrome), increased blood pressure and changes in electrolyte profile.

There are reports about hemorrhages and increased incidence of blood clots occurring following consumption of energy drinks in humans (Benjo et al., 2012; Foran et al., 2012; Unal et al., 2015; Pommerening et al., 2015; Pagano et al., 2017; Venkatraman et al.,

2017; Forward et al., 2018). Pagano et al. (2017) report the case of a 48-year-old man who displayed acute visual loss and intraretinal hemorrhage following the consumption of three large cans (473 ml each) of an energy drink in the course of 30–40 min during a nightshift; however, the authors do not describe the name of the energy drink. Venkatraman et al. (2017) also describe the occurrence of hemorrhagic stroke 1–2 h after the consumption of Redline energy drink, which contains 158 mg of caffeine per serving, or 316 mg per bottle. A recent meta-analysis by Riu et al. (2018) found an association between coffee and hemorrhage, Benjo et al. (2012) report thrombosis in patients after drinking three drinks of vodka mixed with an energy drink and Mattioli et al. (2018) note two cases of atrial fibrillation in young subjects after acute ingestion of energy drinks mixed with alcohol. Other cardiovascular changes associated with energy drinks are described in a review paper by Mangi et al. (2017).

6. The effect of energy drinks, coffee and their bioactive compounds on hemostasis and their mechanisms of action

6.1. Coffee, caffeine and its metabolites

Blood platelet activation, and the consequent alteration of platelet function, plays a specific role in cardiovascular disorders; this is measured by various markers, including platelet aggregate formation and the secretion of ADP, proteins and other compounds from platelet granules. Various *in vivo* studies have examined the effect of coffee on blood platelet functions, especially platelet aggregation.

Natella et al. (2008) examined ten healthy subjects who drank 200 ml coffee, containing 180 mg caffeine, or took a 180 mg capsule of caffeine with 200 ml water as a control. Blood samples were taken at baseline and 30 and 60 min after consumption, and platelet aggregation was induced by three platelet agonists (ADP, collagen or arachidonic acid). The authors observed that blood platelet aggregation induced by collagen and arachidonic acid was significantly reduced after coffee consumption at both the 30 and 60-min time points; however, no statistically significant differences were observed in blood platelet aggregation stimulated by ADP. In addition, no difference in aggregation was observed in the caffeine controls following stimulation by any tested agonist.

An analysis of thromboxane B_2 biosynthesis also found that drinking coffee reduced arachidonic acid metabolism in platelets activated by collagen (Nattela et al., 2008). In contrast, Naito et al. (2011) report that coffee extracts, especially Blue Mountain, Yunnan and Kilimanjaro beans, do not demonstrate anti-platelet aggregation activity, but they do have anti-thrombotic properties.

Natella et al. (2008) suggest that the anti-platelet action of coffee is probably not related to caffeine, but dependent on other bioactive compounds present, particularly phenolic acids: for example, chlorogenic acid may decrease blood platelet aggregation. The concentration of chlorogenic acid in coffee is very similar to that of caffeine; for example, a cup of American coffee contains about 170 mg chlorogenic acid and 180 mg caffeine (Nardini et al., 2000). Moreover, it has been demonstrated that caffeic acid, as with other phenolic acids, is an inhibitor of cyclooxygenase, lipoxygenase and various kinases, which are involved in transduction signaling in blood platelets (de la Puerta et al., 1999; Nardini et al., 2000; Park et al., 2015). Park et al. (2015) report that the chlorogenic acid found in coffee may suppress P-selectin expression on blood platelets by inhibiting cyclooxygenase activity, and may act as an antioxidant.

Interestingly, chicory (*Cichorium intybus* L.) is one of the richest dietary sources of caffeic acid and its derivatives. Schumacher et al. (2011) studied whether chicory coffee consumption may have the potential to prevent thrombus formation. Twenty-seven healthy volunteers consumed 300 ml chicory coffee every day for one week. The results indicate that chicory coffee consumption had an inhibitory effect on blood platelet aggregation, and that this may be dependent on the type of platelet agonist.

Silverio et al. (2013) also observed that decaffeinated coffee samples do not influence hemostasis, e.g. ADP-stimulated blood platelet aggregation, prothrombin time or the activated partial thromboplastin time of plasma, nor hematological parameters such as blood platelet count or lipid profile, e.g. total cholesterol, HDL cholesterol and triglyceride, in normal and hyperlipidemic rats. The study included twelve week-old male Wistar rats which consumed filtered coffee beverages at a dose of 7.2 ml/kg/day, which is equivalent to the daily human consumption of eight 50 ml cups of coffee, for 30 days. The control group received the same dosage of water.

Varani et al. (1999) observed that caffeine administration of 750 mg/day for one week changes the A2A adenosine receptors (up-regulation of these receptors) on human blood platelets. In addition, Varani et al. (2000) showed that intake of caffeine at doses of 400 or 600 mg/day for one week or 400 mg/d for two weeks may lead to up-regulation of A2A adenosine receptors in a time-dependent and dose-dependent manner. Natela et al. (2002, 2008) indicate that caffeine may induce flow-mediated dilatation and fibrinolysis, while Ammaturo et al. (1988) report the release of β-thromboglobulin 1 h after administration of 100 mg of caffeine.

In vitro experiments by Choi and Pai (2003) on the effect of caffeine (770, 1030, 1290 and 1540 μM) on blood platelet aggregation (stimulated by various agonists, including ADP, collagen and epinephrine), and mean platelet volume (MPV) found that caffeine selectively reduces platelet aggregation induced by ADP and epinephrine, and disturbs the release of endogenous ADP from platelet granules in response to exogenous ADP. Watson et al. (2010) also note that caffeine enhanced the effect of ephedrine on blood platelet function, including platelet aggregation.

cAMP (3′, 5′-cyclic adenosine monophosphate) is an important second messenger in blood platelets. For example, the physiological agonist thromboxane A_2 decreases the level of cAMP, which stimulates blood platelet activation, while PGI_2 induces the increase of cAMP, which inhibits platelet activation. The homeostasis of cAMP is regulated by both adenylate cyclase, which may be stimulated or inhibited by various compounds, including TXA_2, and phosphodiesterase.

Montoya et al. (2014) describe a series of *in vitro* and *in vivo* analyses of phosphodiesterase activity performed to determine the effect of coffee and its individual constituents on the level of cAMP in blood platelets. The *in vivo* studies included ten healthy subjects who consumed two different types of coffee: a commercial blend of 100% Arabica coffee, and a low-caffeine coffee consisting of a 3:1 mixture of decaffeinated Arabica Brazil and non-decaffeinated Arabica coffee. The subjects consumed the regular coffee at a rate of 750 ml/day for two weeks. The findings indicate that coffee consumption significantly inhibited phosphodiesterase (PDE) activity, and this inhibition was not dependent on the caffeine content. The *in vitro* study found that selected coffee constituents, e.g. caffeine, theophylline, paraxanthine and caffeine metabolites (0.1–5 mM), inhibited PDE activity in blood platelets *in vitro*. The authors suggest that moderate consumption of coffee may modulate blood platelet aggregation, at least in part by changing PDE activity and cAMP homeostasis.

Other *in vivo* experiments by Lev et al. (2007) examined the effect of caffeine on platelet inhibition by clopidogrel in healthy subjects and patients with coronary artery disease; clopidogrel inhibits the blood platelet P2Y12 receptor, leading to increased intracellular levels of cAMP. Blood platelet activation was measured using various markers: blood platelet aggregation (stimulated by ADP or collagen), P-selectin and GPIIb/IIIa receptor expression and vasodilator-stimulated phosphorylation (VASP) using flow cytometry. Acute administration of caffeine (one 300 mg pill, equivalent to a medium-sized coffee drink) after clopidogrel loading (75 mg daily) was found to be associated with enhanced blood platelet inhibition two to 4 h after clopidogrel intake. The authors suggest that the mechanism probably involves a synergistic increase in cAMP concentrations.

An *in vitro* study by Lee et al. (2014) also demonstrated that caffeic acid (10, 30 and 50 μM) increases cAMP, and subsequently phosphorylates both the inositol 1,4,5-trisphosphate receptor and vasodilator-stimulated phosphoprotein by A kinase activation. This inhibits the mobilization of Ca^{2+} and thromboxane A_2 synthesis in platelets activated by collagen, *via* the inhibition of cyclooxygenase activity.

It is important to note that metabolites of caffeine may also change blood platelet activation. A recent *in vitro* study by Baeza et al. (2017) suggests that the colonic metabolites dihydrocaffeic acid and dihydroferulic acid (at concentrations: 0.01–100 μg/ml) are more effective inhibitors of blood platelet activation than their phenolic precursors. Kamae et al. (2017) indicate that hydroxyhydroquinone, which can reach concentrations of 10 μM or more in coffee beans during roasting, significantly increases intracellular Ca^{2+} level in rat thymic lymphocytes. This process is associated with an increase in the permeability of membranes to divalent cations.

A few papers describe the effect of coffee and its bioactive substances on other elements of hemostasis, including coagulation process and fibrinolysis. Bak et al. (1990A and B) examined the effect of coffee or caffeine consumption on various coagulation factors, including coagulation factor VII activity and fibrinogen in 107 young, healthy adults. The participants were divided into three groups: one drinking filtered coffee, another drinking boiled coffee and a third drinking no coffee. In addition, 69 subjects received four to six tablets containing 75 mg caffeine. Blood samples were obtained at baseline and after nine weeks of intervention. It was found that coffee consumption and caffeine did not influence the factors involved in the clotting system. In this experiment, the level and activity of fibrinogen, protein C, protein S or clotting factor VII were measured.

However, Tsioufis et al. (2006) report that coffee inhibits fibrinolysis, most probably by increasing the concentration of plasminogen activator inhibitor 1 (PAI-1), a very important regulatory element of this process. In addition, Al Samarrae and Truswell (1977) report that whole blood fibrinolysis time was shortened 90 min after consuming coffee, Becker et al. (1981) found coffee to be potentially capable of activating coagulation factor XII in human plasma, Naito et al. (2011) found hot water coffee extracts to possess anti-thrombin activity, while Turnbull et al. (2017) report no clear relationship between coffee consumption and endothelial functions.

Elevated concentrations of homocysteine in human plasma are known to be associated with various diseases, including cardiovascular diseases. In addition, plasma homocysteine concentration is influenced by diet, including coffee consumption: for example, drinking coffee even in moderation has been shown to cause an increase in homocysteine levels. Drinking more than eight cups of coffee a day has been associated with an approximately 28% increase in total homocysteine levels in women and a 19% increase in men. Gokcen and Sanlier (2017) report that coffee has harmful actions: the bioactive compounds present in coffee (such as diterpenoid alcohols) not only increase serum homocysteine levels, but also cholesterol level. In addition, Olthof et al. (2001) suggest that the chlorogenic acid present in coffee increases total homocysteine level in plasma.

Miranda et al. (2017) demonstrated an association between the consumption of coffee and its polyphenols with cardiovascular risk factors, including high levels of homocysteine. A total of 557 individuals participated in the study. Daily coffee intake was categorized into three categories according to the standard cup size used in the study (50 ml): < 1 cup/day, 1–3 cups/day, and > 3 cups/day. It was found that consumption of more than three cups of filtered coffee per day lowered hyperhomocysteinemia, and moderate consumption of filtered coffee and its polyphenols (separate from the coffee) were also inversely associated with hyperhomocysteinemia. The authors suggest that caffeic acid not only inhibits hyperhomocysteinemia, but also decreases the production of free radicals; however, the mechanisms involved in the effect of coffee consumption on the concentration of homocysteine remain unknown.

Oxidative stress is believed to be involved in the modulation of hemostasis, and in the pathogenesis of cardiovascular diseases. Recently, Shaposhimkov et al. (2018) report coffee consumption to have no significant effect on various markers of oxidative stress including isoprostane level, a biomarker of lipid peroxidation, in healthy people aged between 35 and 65 years. More details about oxidative stress and coffee are given by Martini et al. (2016) and Giglio et al. (2010).

6.2. Energy drinks

Energy drink consumption may also influence hemostasis. Molnar and Somberg (2015) used a standard methodology to study the effect of three commonly consumed energy drinks (250 ml Red Bull, 57 ml 5-h Energy and 355 ml NOS energy drink) on an important element of this process: endothelial function. The effects of the energy drinks were evaluated in six subjects, and the effect of coffee on endothelial function was evaluated in 16 subjects. It was found that the energy drinks improved endothelial function to a significantly greater degree than coffee, but that the caffeine was probably not responsible. Higgins (2013) note the consumption of another energy drink, Monster Energy, also influenced endothelial function. Furthermore, a study of 50 healthy volunteers by Worthley et al. (2010) found that the consumption of 250 ml of a sugar-free energy drink not only decreases endothelial function, expressed as reactive hyperemia index, but also increases blood platelet aggregation following stimulation with 1 μM ADP.

An *in vivo* study by Pommerening et al. (2015) found that a sugar-free energy drink containing 140 mg of caffeine and other bioactive compounds such as taurine, *Panax ginseng* extract, guarana extract, inositol, glucuronolactone and L-carnitine induced increased blood platelet activation and platelet aggregation, stimulated by arachidonic acid. However, kaolin and rapid thrombelastography analysis did not suggest that the drink had any influence on the coagulation process.

Khayyat et al. (2014) report that energy drinks influence the hematological parameters and the ultrastructure of blood cells of male Wistar albino rats. The animals were treated orally with three popular energy drinks (Red Bull, Power Horse and Code Red) for four weeks. The authors observed significant reductions in erythrocyte count, blood platelet count, neutrophil count, hemoglobin concentration and hematocrit value in rats treated with Red Bull and Power Horse. Insignificant changes were observed in animals treated with Code Red. On the other hand, all tested rats demonstrated ultrastructural alterations to peripheral blood cells, including those associated with the cytoplasm and nucleus. These results indicate that Red Bull had the greatest effects on the hematopoietic system, followed by Power Horse, with Code Red being the least effective. This variation in the actions of the tested energy drinks may be due to their different compositions. The authors suggest that energy drinks have detrimental effects on the hematopoietic system. In addition, a study of diabetic rats administered an energy drink (Bullet®), alone or mixed with alcohol, observed a decrease in various hematological parameters, including hemoglobin concentration and total white blood cell count; however, the differences were not statistically significant (Ugwuja et al., 2014).

6.3. Taurine

Taurine is a nonproteinogenic acid added to energy drinks. It is also found in blood platelets, where it serves to down-regulate blood platelet aggregation by dampening the calcium influx evoked by activators (McCarty, 2004). Taurine supplementation has been shown to decrease the sensitivity of blood platelets to activators (*ex vivo*) when administered in amounts as little as 400 mg daily, but supplementation of about 150 mg daily may normalize blood platelet functions in vegetarians (McCarty, 2004).

Spohr et al. (2005) studied the effect of taurine supplementation on blood platelet aggregation in high-risk subjects with a positive family

history of type 2 diabetes mellitus. Twenty healthy men received 1.5 g taurine daily for eight weeks. Blood platelet aggregation was stimulated by ADP; however, taurine was not observed to have any effect on the process. In contrast, Ahmedian et al. (2017) found taurine administration to have anti-inflammatory and anti-atherogenic effects prior to and following incremental exercise in heart failure patients. The patients received oral supplementation of 500 mg taurine three times a day for two weeks. The authors measured the level of various atherogenic and inflammatory parameters including triglyceride level, blood platelet count and C-reactive protein level.

An *ex vivo* study found that 500 μM taurine inhibits blood platelet hyperactivity, more specifically the aggregation and reduction of P-selectin expression induced by ADP, collagen and arachidonic acid (Santakumr et al., 2012). Santakumar et al. (2013) also report that taurine and caffeine display synergistic activity on blood platelet aggregation and hemostatic function *in vitro* measured by coagulation profile test. Blood from twelve healthy volunteers was incubated with 500 μM taurine and 700 μM caffeine, either individually or in combination. It was found that taurine and caffeine inhibit blood platelet aggregation stimulated by collagen and ADP greater when administered together than individually. Moreover, prothrombin time increased following combined taurine and caffeine treatment and treatment with taurine alone, but decreased following treatment with caffeine alone. The authors suggest that taurine and caffeine act synergistically to attenuate the rate of clot formation by retarding the deposition of fibrin on established thrombi or by preventing the formation of new thrombi.

Hayes et al. (1989) and Miglis et al. (2002) note that taurine not only modulates platelet aggregation, but also the plasma coagulation system: e.g. 5 mM taurine inhibits platelet aggregation stimulated by ADP, and 25 mM taurine prolongs thrombin time by 9% *in vitro*. A Japanese study of 101 healthy volunteers also found taurine to have an antithrombotic effect, and that it enhances endogenous thrombolytic activity (Ijiri et al., 2013).

Freeman et al. (2001) studied the relationship between circulating and dietary taurine concentrations in 37 dogs of various breeds with dilated cardiomyopathy, including Cocker Spaniels, Golden Retrievers and Dalmatians. Although the circulating taurine concentration was found to be low in 20 of the 37 dogs, about 100 nmol/ml in plasma, dietary taurine concentration did not significantly differ between the taurine-deficient and non-deficient dogs; in addition, no correlation was found between dietary and circulating taurine concentrations. Torres et al. (2006) also note that taurine-deficient platelets do not seem to be hyper-reactive in dogs with mild taurine deficiency. More importantly, taurine has been found to induce thrombocytopenia in humans (Pasin et al., 2014).

6.4. L-carnitine

In humans, about 75% of carnitine (γ-trimethylamino-β-hydroxybutyric acid) is derived from the diet (Lohninger et al., 2005). Carnitine is also a popular supplement and component of various energy drinks. Some studies indicate that it may influence blood platelet functions: e.g. carnitine has been found to reduce superoxide anion generation and modulate arachidonic acid metabolism in platelets (Pignatelli et al., 2003). Carnitine may also act as an antioxidant in blood platelets *in vitro* (Saluk-Juszczak et al., 2010). However, Triggiani et al. (1999) report that it does not change platelet aggregation induced by thrombin.

6.5. Ginseng

Various beverages, including energy drinks, contain ginseng extracts, e.g. SoBe and Green Tea contain 50 mg of ginseng, while Original Rockstar contains 25 mg. The bioactive components in ginseng are ginsenosides (Vogler et al., 1999). Some studies describe changes in some elements of hemostasis following consumption of various ginseng preparations: ginseng has been found to alter the efficacy of anticoagulant therapy (Paoletti et al., 2011), induce vaginal bleeding (Hopkins et al., 1988) and increase blood clotting time (Janetzky and Morreale, 1997). Teng et al. (1989) suggest that it also has anti-platelet action, after observing that ginseng reduces biosynthesis of thromboxane in platelets *in vitro*.

As natural ginseng extracts and ginsenosides are relatively unstable and have low bioavailability (Tawab et al., 2003). Endale et al. (2012) examined their activity using ginsenopside-Rp1, a synthetic ginsenoside derivative, at four different concentrations: 2.5, 5, 10 and 20 μM (*in vitro*) and 15, 30, 50 and 100 mg/kg (*in vivo* and *ex vivo*). It was found that the compound reduces collagen-stimulated blood platelet activation through the modulation of early glycoprotein VI signaling events. *In vitro* administration was associated with VASP stimulation, p38-mitogen-activated protein kinase (MAPK) and ERK2 (extracellular signal-regulated kinase 2) inhibition, *in vivo* ginsenoside-Rp1 with reduced thrombus formation and *ex vivo* with blood platelet aggregation. However, ginsenopside-Rp1 did not change the bleeding time or the coagulation time. The same authors note that another stable chemical derivative of ginsenosides, ginsenoside-Rg3, also has anti-platelet activity *in vitro*. Administration elevated cAMP production and suppressed ERK2 phosphorylation.

Lee et al. (2010A and B) also observed that different ginsenosides isolated from processed ginseng have anti-aggregatory properties in samples treated with the platelet agonists: ADP, collagen and arachidonic acid. In addition, Jeong et al. (2017) report that *in vitro* administration of 50, 100 and 200 μg/ml ginsenoside-Rg3 not only reduces platelet aggregation stimulated by collagen, but also lowers $[Ca^{2+}]$ mobilization and ATP release; it also suppressed mitogen-activated protein kinase phosphorylation and inhibited the phosphatidylinositol 3-kinase/Akt pathway. It was also found that *in vivo* ginsenoside-Rg3 (50 mg/kg) application inhibits thrombus formation in mice. Other studies have shown that Siberian ginseng extract has an influence on selected elements of hemostasis in rats; for example, administration was associated with elevated antithrombin III concentration (Shakhmatov et al., 2011).

6.6. Ginkgo

Gingko preparations or gingko extracts are added to various products in amounts ranging from 40 to 240 mg a day (Abebe, 2002). They can also found in energy drinks in varying amounts: for example, Original Rockstar contains 150 mg of gingko extract. Ginkgo is a rich source of flavone glycosides and terpenoides (e.g. gingkolides A, B, C and bilobalide), which include the main bioactive compounds in ginkgo (Yoshikawa et al., 1999). However, natural ginseng extracts and ginsenosides have been shown to be relatively unstable. Sierpina et al. (2003) attribute the blood platelet-inhibiting qualities of ginkgo to the terpene ginkgolide B. In addition, several articles examining the effect of a combination of warfarin and/or aspirin and ginkgo indicate the presence of an association between ginkgo administration and hemorrhage (Vale, 1998; Diamond et al., 2000; Fong and Kinnear, 2003; Friedman et al, 2007). Moreover, other authors note that 75, 80 and 120 mg ginkgo extract supplementation induces bleeding (Gilbert, 1997; Bent et al., 2005; Jiang et al., 2005). Recently, Wang et al. (2015) report that various herbal medicines, including ginkgo extract may increase the risk of bleeding; however, a study of 12 healthy males by Kohler et al. (2004) notes that seven-day administration of ginkgo extract in combination with warfarin does not induce bleeding.

6.7. Guarana

Guarana is a popular herb native to the Amazon Basin. However, guarana itself is not added to soft drinks. Various preparations or extracts are added, mainly in Latin America, but also in the United States and other countries. Subbiah and Yunker (2008) observed that seeds of

this plant have anti-aggregatory effects.

7. Conclusions

Energy drinks are a common part of the diet, especially of young people. Recently, energy drinks, coffee and their bioactive compounds have been the subjects of various studies examining their role in the cardiovascular system (Riu et al., 2018); however, none of these cited examined the impact on the risk or etiology of cardiovascular diseases. The relevance of the short-term acute effects to the long latency of cardiovascular diseases should be examined in greater detail in further studies. The studies described in this review paper examine the roles played in hemostasis by energy drinks, coffee and their components, including caffeine, taurine and gingko extracts. Recent papers suggest that they have significant effects on the modulation of various elements of hemostasis (Table 1), and they have a range of endogenous targets in this process (Fig. 1).

It can be seen in Fig. 1 that some components of energy drinks are key ingredients in the modulation of hemostasis, especially blood platelet activation. It is important to note that the effects of coffee and energy drinks on blood platelet activation are dependent on a range of factors, including their bioactive components, blood platelet activators and sometimes the method used for monitoring blood platelet activation. For example, various studies, especially those based on *in vitro* approaches, indicate that caffeine may act as an inhibitor of platelet activation, although the role of caffeine in general is disputed. Table 2 describes the effect of selected energy drinks and coffee on animal and human blood platelets *in vivo*, while Fig. 2 presents the hypothetical anti-platelet properties of various components of energy drinks and coffee. The results (*in vivo* models), which are presented in Table 2 show that energy drinks have pro-aggregatory potential on platelets, which for example may be associated with an elevated risk of thrombosis. On the other hand, some studies indicate that coffee reduces blood platelet activation: this anti-aggregatory potential may be beneficial for prophylaxis of thrombosis. Energy drinks and coffee display a wide range of effects (Table 2), which may be associated with the dose of caffeine, its metabolites and other components of energy drinks; it is also difficult to explain this differential because many studies do not state the actual dose in a standard format, for example, as mg/kg/day.

Fig. 2 shows that the bioactive compounds present in energy drinks and coffee may modify the signal pathways in platelets in varied, and sometimes opposing ways. They may modify blood platelet reactivity by changing the activity of signaling enzymes, thus modifying the levels of cAMP and reactive oxygen species. Some experiments suggest that the components of energy drinks and coffee modulate other elements of hemostasis in various ways, thus inducing the coagulation process. In addition, the wide variety of effects and interactions is so complex that it is impossible to obtain a simple and coherent message about the mechanism of their actions in hemostasis.

However, due to the huge number of bioactive components present in energy drinks, further studies are required to determine whether synergistic actions may exist between the chemical components of energy drinks and coffee, and whether they may influence hemostasis. In addition, further experiments should indicate which component of energy drinks or coffee have the strongest effect on hemostasis.

Although both *in vitro* and *in vivo* studies have been performed examine the effect of energy drinks and coffee or their components on hemostasis in young people, only a few papers describe their action in older people. More studies examining the consumption of energy drinks and coffee and their effects on hemostasis and cardiovascular disorders including both younger and older people are required, particularly well-controlled and high-quality human clinical studies. A better understanding of the role of energy drinks and coffee in the modulation of hemostasis would be valuable for treating and preventing cardiovascular disorders induced by the bioactive ingredients of energy drinks.

Table 2
Effects of energy drinks and coffee on blood platelet parameters determined by various experiments (*in vivo*).

Consumption	Dose	Days	Subjects	Blood platelet parameters	References
in vivo experiments (humans)					
Sugar-free energy drink	250 ml sugar-free energy drink (containing caffeine (80 mg), taurine (1000 mg), glucuronolactone (600 mg)	–	50 volunteers (22 ± 2 years)	Increase in 1 μM ADP-induced platelet aggregation (negative effect – pro-aggregatory potential)	Worthley et al. (2010)
Sugar-free energy drink	470 ml of a sugar-free energy drink (containing caffeine (140 mg), taurine, *Panax ginseng* extract, L-carnitine, glucuronolactone, inositol, and guarana extract)	–	32 volunteers (18–40 years)	Increase in 0.5 mM arachidonic acid-induced platelet aggregation (negative effect – pro-aggregatory potential)	Pommerening et al. (2015)
Coffee	A cup of freshly prepared American coffee (200 ml)	–	10 volunteers (25–35 years)	Reduced 0.5 μM arachidonic acid/3 μg/ml collagen/2 μM ADP-induced platelet aggregation (positive effect – anti-aggregatory potential) Reduced 3 μg/ml collagen-induced thromboxane formation (positive effect – anti-aggregatory potential)	Natelle et al. (2008)
Coffee	Two different coffee: a commercial blend of 100% Arabica coffee and low-caffeine coffee (a 3:1 mixture of decaffeinated Arabica Brazil and non-decaffeinated Arabica coffee), 750 ml	Every day (in three equal portions: morning, noontime and afternoon) for 2–7 weeks	10 volunteers (20–44 years)	Inhibition of phosphodiesterase activity in platelets (positive effect – anti-aggregatory potential)	Montoya et al. (2014)
Chicory coffee	300 ml	Every day for 1 week	27 volunteers (23 ± 0.4 years)	Reduced 10 μM ADP-induced platelet aggregation (positive effect – anti-aggregatory potential)	Schumacher et al. (2011)
in vivo experiments (animals)					
Decaffeination of coffee samples	7.2 ml/kg/day	30 days	30 twelve-week old male Wistar rats with hyperlipidemia	No changes in platelet aggregation induced by 1 μM ADP (no effect)	Silverio et al. (2013)

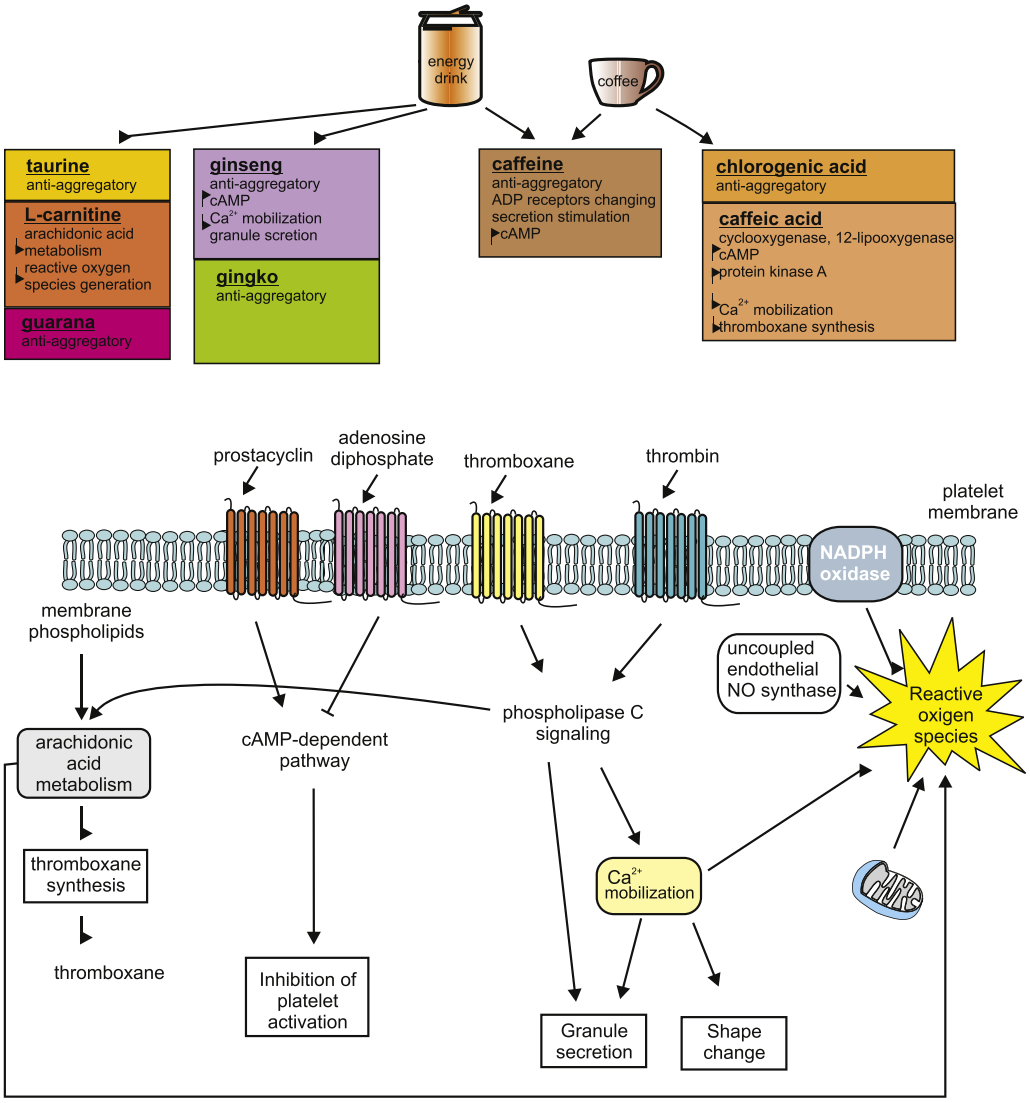

Fig. 2. Effect of different components of energy drinks and coffee on signal transduction in blood platelets. The following signaling pathways are associated with platelet activation: platelet aggregation, shape change, granule secretion, thromboxane synthesis, and reactive oxygen species generation. The molecular factors involved in anti-aggregation activity have not been marked on the diagram, because there no detailed data is available.

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