Clinical Pathology of caffeinated and non-caffeinated energy drinks: Review

I. Gheith

Department of Medical Laboratories Technology, Faculty of Applied Medical Sciences, Taibah University, 344
e.m.gheith@hotmail.com

Abstract: This report reviews the most recent literature and results published about the different effects of different brands of power/energy drinks, their chemical composition, benefits and health hazards, clinicopathological and histopathological alterations upon habituation to consume them. To highlight the extent of the impact to limit the use in order to put national and international regulations for use and spread of such drinks, we thought to mention the most recent results following consuming these products on different health criteria, including, body weight, liver, heart & kidney functions; as well as histopathology. Moreover, the effects on blood glucose, as almost all of the energy drinks contain considerable concentrations of it in their composition whether labelled or not. All of the previous studies confirmed that each constituent (s) included in the energy drinks composition may adversely affect the subject health down to life-threatening end-point. Nevertheless, a positive effect may be gained if they are used in suitable labelled doses; the point that may do not be welcomed by marketing policy of the producing companies. The aim of work is to focus on the life-threatening aspects to encourage all medical and educational institutions to apply more workshops and labels explaining the truth about these products and construct an awareness program suitable for all personnel with different levels of education. The seriousness of these drinks on public health, regulators to monitor local markets, awareness campaigns through the media and various visual and audio by government, encouraged all scientific investigators and researchers to destine more experimental work to study the effects of energy drinks on all the body organs in details. More research and more need to show alternative natural products giving energy to consumers without any chemical constituents that may cause adverse effects on the subject health. Almost all people lack information about these products except that it supplies the body with energy and power. Not all the people are familiar to the research or can understand the conclusions raised by it. Adult family members must monitor the consumption of these drinks by their children and check all of the ingredients labelled on all the products available in the market to know exactly about the composition and to ask the specialist about the contents and their possible effects.
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1. Introduction

The topic of energy drinks is a matter of debate and, thus, true information about such drinks becomes a must. Energy or power drinks constitute a group of commercial products which contain a lot of ingredients that have the ability to generate energy; they are widely used, nowadays, all over the Arabic and International markets without any restrictions.

Recently, we have noted appearance and growing of “generator of energy” concept among young and old people during exercise, under what is called “energy drinks” that invaded Arabic and international markets, due to increment in the rate of its consumption. Scientific researchers noted that these drinks are attractive to the consumers at all different ages, especially during the driving for long distances and during studying by all students during exam times; students consume a lot of these drinks in the belief that it can reduce the need for sleep, increase thinking ability and prolong time of studying. Athletes believe that such drinks increase the body's energy which will be used during the exercise and supply them with extra power to can do extra sport and can built good musculature, and its ability to reduce fatigue while performing exercise.

All athletes turned to consumption of these products, rather than the past use of sport steroids injections, tonics, hormones especially growth hormones and proteins that may have side effects on the body, or may have been banned internationally or regulated illegal by the laws of most governments and athletes who may use these agents must be excluded or stopped.

Also, most of the working women turned to consumption of these energetic drinks as a power source to enable them to can manage their work and perform their duties at home in a good manner.

These drinks have invaded both of the local and global markets under different brand names but with almost the same ingredients in different

concentrations without any control from governments. Such drinks are not expensive, and thus accessible to everyone without any restrictions.

Moreover, most companies add alcohol as an ingredient to energy drinks. Many authors reported experimental data confirming that using caffeine plus alcohol may enhance wakefulness and alertness, diminish alcohol-associated exhaustion and thus keep the desire to continue consumption (McKetin et al., 2015).

Till now, a limited number of studies and literature targeted the effect of energy drink consumption either in animals or human on different body organs and their functions. The effect on different haemopoietic organs and parameters, in particular, and histopathological alterations still unclear. At least to our information, no final report about the safety of these drinks or their toxic/lethal doses, if any, has been published.

Generally, the main ingredients of energy drinks are caffeine, sugar, taurine and gluconolactone (van den Eynde et al., 2008). Accordingly, some countries and organizations regulated the consumption of these drinks. For examples, International Olympic Committee has banned the main ingredients in the energy drinks, caffeine because of its positive increasing endurance effect (Higgins et al., 2010). Denmark and Norway have banned Red Bull®. Ward (2008) mentioned that United Kingdom declared a warning against Red-Bull® to be used during pregnancy and childhood. US Food and Drug Administration (FDA) or the US Department of Agriculture do not list/approve products named power or energy drinks (Heneman and Zidenberg-Cherr 2011).

In both Arabic and International markets, a lot of brand names of energy drinks are being widely distributed and extensively purchased, including: Red-Bull®, Bison®, Power-Horse®, Bugzy®, Code-Red® and Boom-Boom®. The products may contain the same contents with a little bit changes in their concentrations or even without any changes except in the different attractive colors and shapes of cans that all the media use to encourage the consumer to purchase the products with target of high selling rates.

Some other points that may be stressed for promoting selling of such products are that a certain brand increases the efficiency of mental and physical performances, attention, stamina, and weight loss. Also, it may increase the sexual activity in male. However, some side effects may be associated as those of caffeine which include anxiety, and disturbance of GIT this can explain the less food intake in the diabetic group (Boyle and Castillo 2006).

Power/Energy drinks are attractive to young persons (Wallimann et al., 1992). The Bullet® (an energy drink) contains natural ingredients and, thus, is more attractive to man than woman as the musculature need and desire are higher in male.

More attention should be given to and be care must be taken for energy drinks when used; including monitoring all heath parameters during its consumption. Educational institutes and medical organizations with cooperation with governmental authorities must design a complete program for all involved personnel to be fully informed about all data about those products. Government, also, must regulate a perfect system to control the high speed of invading of these drinks into the market; with strict measures on their ingredients and legislating the permissible limit for each ingredient in each drink. A warning label for the best age and the possible side effects of these ingredients must be printed on each drink vessel.

More literature and studies about the effects of such drinks on the immunity and its response; brain tissue and function; nervous system; metabolism (glucose in particular); wound healing; haemipoietic organs and its ability; possibility of addiction; anesthesia and surgery; pregnancy, embryo and neonate; cardiovascular system and blood pressure; minerals (calcium deposition in particular); reproductive organs and fertility in male and female; and on genetics. More and more scientific papers on experimental animal and volunteers are seriously needed to determine the lethal dose and the tolerable levels as well as any neurologic consequences (Babu et al., (2011); Wolk et al., (2012)).

Despite that lack of information; however, a few reports, reviewed here; have indicated that consumption of energy drinks alone or in combination with alcohol undelay significant changes in many clinicochemical biomarkers. Therefore, Care must be taken while consuming any of these agents. Public health education is urgently needed to correct the wrong impression already formed by the unsuspecting consumers, especially among the youth**.**

2. Definition of energy drinks

Energy drinks have been defined in various terms all over the past years since their appearance in markets. Nevertheless, till now, no standard definition of an “energy drink” is documented in the scientific published literature. In the past, energy drinks are a group of beverages that has gained their fame since 1997 (Boyle and Castillo 2006).

Miller (2008) defined the energy drinks as those containing caffeine, taurine, vitamins, and usually sugar. The products are marketed on the basis of their capability of improving alertness or giving a transient energy push and, in the same time, are not resources

for rehydration or electrolyte compensation in relation to various athletic exercises.

In other words, Attila and Cakir (2011) defined energy drinks as beverages (for example Red Bull, Venom, ED, and Adrenaline Rush) that contain large doses of caffeine and other approved enhancers such as carbohydrates, taurine, glucuronolactone, niacin, inositol, and B-complex vitamins… *etc*.

Energy drinks are defined by Akande and Banjoko (2011) as non-alcoholic, lightly carbonated beverages which give energy to consumers and that contain lot of ingredients enhancing energy, as caffeine; they are manufactured as small, bullet-shaped cans in different shapes.

It is commonly understood that these drinks are non-alcoholic liquids containing caffeine (usually as a main ingredient), taurine, vitamins; and sometimes a combination of other different constituents, including guarana and ginseng among others, distributed and sold for its real benefits as a enhancers, for increasing physical and mental performances *via* increasing energy (Zucconi et al., 2013).

Power/Energy drinks were defined as non-alcoholic, mostly lightly carbonated beverages that are formulated to provide energy by incorporation of metabolism and energy promoting constituents. They are consumed on a large scale by young people, especially at times of studying, exercising sports and driving for long times to distant places (Khayyat et al., 2014).

3. Nomenclature of energy drinks

Every company decides a good catchy names for its energy drink name (s) carrying the potential of the power, energy, speed, sexuality… *etc*. Examples for such names are Bullet®, Power-Horse®, Monster®, Red-Bull®, No-Fear®, Spark, Full-Throttle®, Lost-Venom®, Rock-Star®, Impulse®, Double-Shot®, Rip-It®, Superman®, Tab-Energy®… *etc*.

4. Composition of energy drinks and proposed medical uses

Malinauskas et al., (2007) reported that almost all energy drinks contain, in addition to caffeine, small concentration of nature-derived enhancers (guarana, ephedrine, yerba mate), also as all drinks products must contain simple sugars (glucose, fructose), also contain protein precursors as amino acids (taurine, carnitine, creatine), herbs (different types of *Ginseng, Ginkgo biloba*), maltodextrin, inositol, glucuronolactone (a naturally occurring sugar metabolite) and members of vitamins-B complex family as B6 and B12. More or less statement has been mentioned by Seifert et al., (2011).

Every company selects a brand name with almost the same composition but with minute changes in the concentration of the contained ingredients. In addition, more recently, more than one researcher have documented that the most famous incorporated constituents in power drinks are sodium and its compounds, guarana, carbohydrates and taurine. However, it is difficult to determine the amounts contained in these products. Other different components that might be added to power products include B-vitamins, glucuronolactone *Ginseng*, *Gingko biloba*, antioxidants and trace elements (Higgins et al., 2010).

Most brands often contain caffeine, taurine, guarana, ginseng, B vitamins, *Ginko biloba*, L-carnitine, sugars, antioxidants, glucuronolactone, Yerba mate, Creatine, Acai Berry, Milk Thistle, L-theanine, Inositol and artificial sweeteners (Babu et al., (2008); Bigard (2010)).

A single can (100 ml) contains caffeine at concentration range of 72~150 mg. However, many bottles may contain 2~3 servings, causing the caffeine content to be raised as high as 294 mg per can. On the other hand, the caffeine concentration, per serving (236.56 ml) of brewed coffee, tea and cola lies in the range of 134~240 mg, 48~175 mg, and 22~46 mg, respectively, (Nawrot et al., 2003). Ingredients of different energy drinks and their medical actions, applications are summarized in the table designed below.

The ingredient	Medical use	References
Caffeine	Caffeine indirectly affects the activity of dopamine, a chemical neurotransmitter in the brain's pleasure center, by impeding its binding with its specific D-receptors [a]. It is one of the central stimulants belonging to methylated xanthine class *via* blocking A1 adenosine purinoceptors and phosphodiesterase (PDE) enzyme [b]. It can enhance performance by stimulation; have the ability to reduce physical fatigue; prevent sleep, and so increases wakefulness, better general body coordination [c].	[a] (Ferré 2010) [b] (Nehlig et al., 1992) [c] (Bishop 2010) [d] (Mathew 2011) [e] (Kugelman and Durand 2011) [f] (Qi and Li 2014) [g] (Schmidt et al., 2006) [h] (Schmidt et al., 2012) [i] (Gupta and Lipsitz 2007)

	It can be used in treatment of premature infant breathing disorders [d & e]. Considered as protective ingredient against Parkinson's disease [f]. Has the ability to improve body weight during the therapy process [g]. Reduces the incidence of cerebral palsy as well as reduce language and cognitive delay [h]. In orthostatic hypotension treatment [i].	
The ingredient	**Medical use**	**References**
Taurine	Natural Taurine is a ubiquitous β-amino sulfonic acid. In human, it is considered semi-essential since it can be synthesized endogenously, found in most mammalian tissues and in particularly high concentration in cardiac and skeletal muscles [a]. Taurine is considered as one of the abundant amino acids in the body. It is present in relatively high amounts in skeletal and cardiac muscle [b]. Exogenous taurine intake is rapidly absorbed from the gastrointestinal tract. Both ingested and endogenous taurine is transferred intracellularly across plasma membranes through specific taurine transporter (TAUT) [c]. Taurine may improve brain function and lower blood pressure, in certain conditions [d]. Also, it may improve ocular and biliary health and guard against congestive cardiac failure and strengthen cardiac contractility [e & f]. Interacting with neurotransmitters in the thalamus which enveloped sleep thalamus is involved in sleep/wake cycle pathways in the brain [g]. Some reports documented synthetic taurine in certain illnesses ranging from hypertension to strokes and seizures to cardiac disease [h]. Taurine enhances cardiovascular function; improves development and function of skeletal muscle, the retina, and CNS [i]. It is one of essential amino acids, for adipose tissue regulation and thus downgrading obesity; and for calcium homeostasis [j, k & l]. Also, acts as an antioxidant and thus guard against various toxicities (as those of lead and cadmium) [m]. Taurine supplementation was found to ameliorate oxidative stress caused by excessive exercise [n].	[a] (Malinauskas et al., 2006) [b] (Timbrell et al., 1995) [c] (Tappaz 2004) [d] (Pennay et al., 2011) [e] (Akinmolusun et al., 2012) [f] (Seifert et al., 2011) [g] (Malinauskas et al., 2006) [h] (Reissig et al., 2009) [i] (McCarty 1996) [j] (Dominy et al., 2004) [k] (Birdsall 1998) [l] (Ide et al., 2002) [m] (Gürer et al., 2001) [n] (Das et al., 2008) [o] (Zhang et al., 2004) [p] (Warskulat et al., 2004) [q] (Nakaya et al., 2000) [r] (Huxtable 1992) [s] (Mollon 1986) [t] (van den Eynde et al., 2008) [u] (Xu et al., 2008)

	Also, body weight has been decreased after taurine supplementation [o]. It is needed for normal muscle maintenance and function; and has also been proved to improve congestive heart failure *via* improving the force and outcome of cardiac muscle contractions [p]. It has a beneficial effect in persons with hypertension, diabetes and skeletal muscle disorders [q]. It also essential for the human retina. It plays an important role to maintain the structure and function of photoreceptors. Accordingly, it is essential during the period of organogenesis for the foetal development, especially of the eye; therefore, lower supplements of taurine may lead to defective vision may occur [r]. It is documented to have dominant roles for the foetal development of vision and hearing [s & t]. An echocardiographic study has assessed the influence of a drink containing taurine and caffeine in healthy subjects. An improvement of left ventricular contractility about forty minutes after taurine administration has been demonstrated [u].	

The ingredient	Medical use	References
Guarana	As a dietary supplement, guarana is an effective stimulant [a]. Seeds contain about double fold of caffeine concentration in coffee seeds (2–4.5% in guarana seeds *vis* 1–2% in coffee seeds) [b]. Used in carbonated or sweetened in soft drinks and energy boluses; and as ingredient in herbal teas or capsules. Generally, South America extracts most of its caffeine from such plant [c].	[a] (Johannes 2010) [b] (Bempong et al., 1993) [c] (Carlson and Thompson 1998)

The ingredient	Medical use	References
Ginseng	Ginseng may be found in small doses in energy drinks or herbal teas, such as ginseng coffee [a]. Ginsenosides from *Panax* species are under study for their potential application in medicine [b]. Traditional medicine various benefits to oral administration of American and Asian Ginseng (*P. ginseng*) roots, including aphrodisiac and/or stimulant effects [c & d]. Components of ginseng can elicit hypoglycemia in both normal and diabetic mice [e].	[a] (Kim 2007) [b] (Sievenpiper et al., 2014) [c] (Qi et al., 2011) [d] (Izzo and Ernst 2009) [e] (Tomoda et al., 1984)

The ingredient	Medical use	References
Ginkgo biloba	*Ginko* is marketed as food supplement on purpose of it may enhance cognitive function in people without determined cognitive problems. Studies are still needed to explain such effects on memory or attention in normal persons [a].	[a] (Laws et al., 2012) [b] (Birks and Grimley Evans 2009) [c] (Cooper et al., 2013) [d] (Xiong et al., 2014)

	A standardized extract from *Ginkgo biloba* leaf, called EGb 761, has been investigated as a possible treatment for dementia and Alzheimer's disease, with mixed results [b]. Some literature have concluded no good evidence supporting the use of *Ginkgo* in dementia, whereas others have concluded that the EGB761 extract may help [c]. No good evidence explains and supports utilization of *Ginkgo* for controlling hypertension [d], menopause-associated cognitive decline [e], tinnitus [f], post-stroke recovery [g], peripheral vascular disease [h], macular degeneration [i], or altitude sickness [j].	[e] (Clement et al., 2011) [f] (Hilton and Stuart 2004) [g] (Zeng et al., 2005) [h] (Nicolaï et al., 2009) [i] (Evans 1999) [j] (Gertsch et al., 2004)
The ingredient	**Medical use**	**References**
L-Carnitine	*l*-Carnitine is considered as an amino acid-like substance and aids with metabolism and provides energy. It increases metabolic rate and increases calorie levels elongating endurance time.	(Lohningen et al., 1987)
The ingredient	**Medical use**	**References**
Sugars	They are the body's main fuel but too much of it can get you hyperactive and energy drinks are loaded with them. However, sugars may affect metabolic homeostasis.	(Brenner and Swanik 2007)

The ingredient	**Medical use**	**References**
Antioxidants	Agents that can ameliorate the damaging effects of free radical species inside the body.	(Higgins et al., 2010)

The ingredient	**Medical use**	**References**
Inositol	It is a constituent of phosphatidylinositol, a phospholipid, which plays an essential role in growth, metabolism regulation and signal transduction. It is a normal component of human tissue and can be synthesized in some tissues. It is a normal part of food derived from plants in the form of phytate and from animals in the form of free and phosphorylated inositol and as inositol phospholipid. Adults may ingest 500~1000 mg of inositol per day. Such amount is relatively high compared to the 50 mg of inositol incorporated in a single serving of a typical energy drink. Potential benefits of inositol may include decreased cholesterol levels and thus a lowered risk of cardiovascular disease.	(Authority 2001)

The ingredient	**Medical use**	**References**
B-Vitamins	Include a wide variety of vitamins, such as folate, B12, and B6. B-vitamins deficiency may lead to some neurological and psychological functioning problems [a]. Members of Vitamin-B complex are co-factors/co-enzymes of many enzymes mediating the energy-producing processes [b].	[a] (Selhub et al., 2010) [b] (Ferreira et al., 2006)

The ingredient	**Medical use**	**References**
Other	Other additives may include Glucuronolactone, β-Phenylethylamine HCl, Evodiamine, Yohimbine that may exert neurotropic actions [a & b].	[a] (Chawla and Suleman 2013) [b] (Babu et al., 2008)

5. Potential effects of energy drinks on general health

5.1 Side effects

Various side effects were reported in relation with consumption of energy drinks, including death (Iyadurai and Chung 2007). In 2011, an Irish, 18 years old, athlete, named Ross Cooney turned dead because of playing a basketball game just after drinking 4 cans of the power drink Red-Bull®, (Alsunni 2011).

Health hazards associated with the uncontrolled consumption of power drinks are mainly attributed to their caffeine or caffeine-like ingredient- contents. Over dosage of caffeine might lead to extra systoles, palpitations, hypertension, anxiety, nausea, vomiting, hypocalcemia, metabolic acidosis, convulsions (WHO 2005), and, in scarce cases, death ((Kerrigan and Lindsey (2005); Starling (2011)). In addition, a higher risk of arterial hypertension (Brown et al., 2011) and insulin-nondependent diabetes mellitus (Seifert et al., 2011) are documented, because excessive consumption of caffeine declines insulin sensitivity (Lee et al., 2005). Excessive caffeine consumption during pregnancy increases the risk of late miscarriages, smaller-than-normal for gestational age babies and stillbirths (Greenwood et al., 2010).

5.2. Effects on body weight and obesity

Experimental findings demonstrating the effects of energy drinks on body weight indicate that there was a significant ($P < 0.05$) increase in the weights (g) of body and brain, and a significant ($P < 0.05$) decrease in relative brain weight (%) of the animals treated with energy drinks as compared to the control group and it was concluded that the long-term consumption of power drinks may, therefore, effect adversely on the weights of either body and/or brain weights of adult rats (Adjene et al., 2014).

It could be speculated that such effects could be attributed to the exciting effects of the caffeine incorporated in the energy drink as suggested by Howard and Marczinski (2010). The significant gain of weight reported by authors in that study could also be attributed to the higher rate of catabolism caused by the effects of higher availability of insulin induced by the sugar components of the power drinks; thereby causing elevated rates of lipid storage in the adipose tissues (Malik et al., 2006). This may support an already proposed hypothesis that an elevation in sugar consumption could be associated with higher risk of weight gain because of the inhibited satiety center and the insufficient compensatory decrease in energy intake (Bray (2007); Anton et al., (2010)). That result is also in agreement with the suggestion that excessive consumption of artificial sweetening agents, as the case of power drinks, might increase obesity and over-weights instead of decreasing them (Fowler et al., 2008).

Continuous consuming of Sugar-Sweetened Beverages (SSBs) has been associated with the higher occurrence rates obesity and type-II diabetes mellitus (Schulze et al., (2004); Malik and Hu (2012).

Previous studies have shown that the high sugar content of regular soft drinks could have an influence on energy balance and body weight, especially in childhood and adolescent periods (Libuda and Kersting 2009). High sweeteners content in the caffeinated power drinks as the case of other soft drinks is known to contribute to the incidence of obesity (Riddell and Keast 2007).

However, the above observations are not parallel with those of Ayuob and El Beshbeishy (2016) that there is no significant change in the body weight of rats that received energy drinks for four weeks. Also, with those of (Ebuehi et al., 2011) who got similar data.

Other reports stated that the addition of the energy drinks to diet diminished body weight gains of the treated animals (per energy unit in the diet) as compared to the group of animals fed unmodified diet. Experimental animals administered energy drinks were, in addition, characterized by lower amounts of peri-intestinal and intramuscular adipose tissues, however, significantly higher amounts of fat were deposited peri-cardially (Sadowska 2012).

5.3. Effects on different body organ functions and structures

5.3.1. Effect on heart muscle and enzymes

Cardiac muscle enzyme levels give indication about the health status of the heart, as AST, ALT, LDH. On experimentation or sample analysis, measured high values of such biomarkers may indicate that the agent under experimentation may cause injurious effects on the cardiac myocytes. Therefore, caution should be taken upon consuming any of energy drinks (Chimezie 2013).

Red Bull® administration to Wistar rats led to myocardial metabolic abnormalities. Recently, some researchers have noted that cardiac muscle and cardiac enzyme activities as (LDH, AST, and ALT) were influenced by consumption of Red bull® as an example for highly marketed power drinks. The authors concluded that that Red Bull® administration to rats induces significant changes in the cardiac myocytes metabolism, in both sedentary and trained animals, which is considered as life threating (Crisan et al., 2014).

Some studies reported increases in heart rates (Steinke et al., 2009); whereas some others showed decreases in heart rate or even no change at all (Seifert et al., 2011). This might be explained on the basis of the various ingredients contained in different brands of energy drinks and the various amounts of these ingredients consumed in each experiment as well

(Steinke et al., 2009). For example, taurine which is a common component of almost all energy drinks can reduce heart rate and thus it has even been used for treatment of palpitation (Seifert et al., 2011). Accordingly, any study involving a brand of energy drink containing higher amount of taurine might not produce the same effects as those containing taurine lesser amount.

A heart function study revealed that the activity of creatine-kinase was significantly inhibited in all energy drinking groups except those of Red-Bull® and Bugzy®, (Backer and Baeissa 2014).

The above reported results are not in harmony with the conclusion reported by (Machado et al., 2009), who mentioned that the consumption of 5.5 mg caffeine/kg body weight were with no significant effects on muscle cell integrity in football players. Menci et al., (2013) observed acute alterations on echo-cardiographic criteria evaluated by classical echo-doppler analysis and by speckle-tracking echo-cardiography after administration of a power drink in young normal persons. Consuming power drinks resulted in significant increases of right and left ventricular functions, proposing a possible enhancement of cardiac contractility force (positive inotropic effect).

Findings of another study included that power drinks consumption has elevated platelet aggregation and decreased endothelial function in normal persons. The two parameters under investigation were assessed an hour before and after administration of 0.25 L of a sugar-free-power-drink can. Moreover, myocardial infarction is strongly associated with both platelet and endothelial dysfunction (Worthley et al., 2010).

Concerning the effect of energy drinks on the arterial wall structure, Howard and Marczinski (2010) observed a transient stiffening of arterial walls as a sequel of consuming of power drinks containing caffeine as an ingredient.

Significant elevation of platelet aggregation, a decrease in reactive hyperemia index (RHI), an elevation in mean arterial pressure after power drink consumption were observed compared to control (P <.05); unlike heart rate that was unaffected. Endothelial integrity and function were evaluated *via* recording changes in peripheral arterial tonometry and expressing the reactive hyperemia index (RHI) (Worthley et al., 2010).

(Berger and Alford 2009) reported that excessive ingestion of caffeine and taurine combination–containing energy drinks caused cardiac ischaemia by induction of a coronary spasm. While Bichler et al., (2006) reported some changes in heart rate and blood pressure associated with chronic intake of energy drinks.

The cardiac abnormalities may also be partly attributed to disorders in lipid metabolism as evidenced by significant elevation of plasma triglycerides in rats administered energy drink plus alcohol. Dyslipidaemia was documented to be associated with cardiac abnormalities. Usman and Jawaid (2012) recorded a case of hypertension in a young boy who used to consume a power drink. However, the authors implied that it is yet to be ascertained whether the elevated triglyceride observed in their study is due to the effects of alcohol or energy drink or both.

Piirainen et al., (2011) explained the effect of energy drinks on the heart on the basis of that caffeine activates β-adrenoceptors on the cell membranes cardiac myocytes, and thus increases the amount of the second messenger, cyclic-AMP intracellularly (by inhibiting the enzyme that deactivates 3,5-cyclic-AMP), giving responses similar to those of adrenaline (which stimulates cell membrane-bound β1-adrenoceptors that activate 5-cyclic-AMP). Cyclic AMP acts as an intracellular "2nd messenger" that can activate a large number of protein kinase-A (PKA). This pathway mediates increasing the rate of glycolysis and increasing ATP molecules available for cardiac muscle activity (contraction and relaxation).

5.3.2. Effects on haemopoietic cells and haematological parameters

Research studies implied that energy drinks have serious impacts on haematopoietic system following their consumption (Ragsdale et al., (2010); Higgins et al., (2010); Worthley et al., (2010); Khayyat et al., (2014)). In 2014, a comparative investigation on the different effect of various brands of power drinks on hemopoietic system in rats was carried out; observation revealed a significant decrease ($P < 0.05$) in RBCs count, hemoglobin concentration, packed cell volume value, thrombocyte and neutrophil counts in animals treated with power drinks, including Red Bull® or Power Horse®. Insignificant alterations were recorded from rats treated with Code Red®. The microscopic alterations in both nucleus and cytoplasm of peripheral blood cells, have been observed in all treated rats under experimentation, however, they were more pronounced in animals treated with Red Bull® and Power Horse®. Alterations in the cardiovascular and haematopoietic system

The above findings may give indication that energy drinks may affect production by the bone marrow of RBCs with impaired structure with increased probability of their destruction in circulation (Karmakar et al., 2000). Decrement of Hb may be attributed to the impaired ability of bone marrow to synthesize and produce of haem (Abdel Aziz and Zabut 2011).

On the other hand, the recorded increase in lymphocytes and monocytes may indicate the stimulation of hemipoietic system for production by caffeine (El-Demerdash 2004).

Other researchers, including Ugwuja (2014) reported results that were not parallel with the above results, where no significant effects on packed cell volume and haemoglobin concentration after administration of either an energy drink or energy drink plus alcohol in comparison to the control.

5.3.3. Effect on glucose concentration and pancreas structure

Power Horse® intake as an example for energy drinks caused significant changes in the histological picture of the pancreatic tissue, including lesions in the islet of Langerhans and pancreatic acini as well. The authors suspected that all of those changes may hypothesize that energy drinks produce these changes via its caffeine content that may induce oxidative stress on the pancreatic tissue cells (Ayuob and El Beshbeishy 2016).

Serum data showed significant increases of glucose concentration in all energy drinking animal groups (Baeissa 2011).

Similarly, Sadowska (2012) and Crisan et al., (2014) recorded elevated blood sugar in rats, which were treated with power drinks for 2 and 6 weeks, respectively. The incorporated ingredients of a power drink (sugar, caffeine and others) may act synergistically to increase the postprandial blood sugar (Kolnes et al., 2010).

Additionally, it was stated that oral administration of some power drinks as Power Horse® and Red Bull® to laboratory animals might affect cholinergic neurotransmission and neurohumoral responses mediated by acetylcholine that increase blood glucose (Ebuehi et al., 2011). In addition, the combination of high sugar content or carbohydrate rich diets with niacin as in energy drinks might affect carbohydrate metabolism and lead to diabetes (Zhou et al., 2010).

Bleich et al., (2009) found that sugar-sweetened beverages (SSB) comprise a considerable source of total daily intake and is the largest source of beverage calories. SSB consumption is highest among subgroups also greatly predisposed to obesity and type 2 diabetes.

5.3.4. Effect on kidney function and structure

Creatinine, urea and uric acid values in serum are routinely investigated in research studies as both of they act as a mirror reflecting the health status of the kidney of subjects under investigation.

Khayyat et al., (2014) reported that the energy drinks induced elevations of renal biomarkers urea, uric acid and creatinine. The elevation in these parameters was time-dependent and more pronounced after administration of Power Horse®, then by Red-Bull® and then after Code-Red®.

Those results are in agreement with those of Ugwuja (2014) who reported that consumption of energy drink Bullet® alone or with alcohol resulted in elevated urea, uric acid and creatinine values in the sera of experimental rats. The author mentioned that both urea and creatinine are products of protein metabolism, which are accumulated in the blood when the kidneys are negatively affected.

In addition, Akande and Banjoko (2011) recorded an elevation in the urea concentration in rats treated with Power-Horse®. It was observed that urea level in the experimental groups treated with power drinks were significantly (P<0.05) elevated compared with those of control (10.10±0.15mmol/L vs.3.66±0.10 mmol/L). No significant difference (P>0.05) was detected in the concentrations of creatinine in the experimental groups compared with the control group (44.20±00 mmol/L vs. 44.20±02 mmol/L.

The results may be interpreted on the basis of that caffeine content in the energy drinks. This could be speculated from what was reported by many researchers who stated that caffeine can increase the serum urea and creatinine concentration (Tofovic et al., (2002);Tofovic et al., (2007), Abd El-Moneim et al., (2009).

Caffeine may do so through inhibition of A2A adenosine receptors, which accelerates the development of interstitial inflammation, augments proteinuria and alters renal physiology and histology.

These data were further supported in 2007 where consumption of caffeine-containing power/energy drinks exhibited more adverse effects on hepatocytes and nephrocytes and increased creatinine (Tofovic et al., 2007). Taurine, however, has controversial results on renal and liver functions as reported by (Childs and de Wit 2008); and thus further studies are still needed to solve that debate..

Regarding histopathological alterations of the kidney tissue, Shide and Chandrasekaran (2011) proposed that if kidney tissue is exposed to a high enough concentration of energy drink ingredients, it could possibly be disrupted. This is justifiable since the renal tubules are in contact with toxic chemicals during their excretion and elimination (Kukner et al., 2007). Distinct histopathological lesions have been observed upon power drink ingestion, including necrosis of renal tubules and degenerated glomeruli as well as inter-tubular hemorrhage and inflammatory leucocytic infiltrations. Moreover, mentioned that energy drinks showed disruptions of the actin cytoskeleton networks in kidney cells. On the other hand, the presence of membranous structure and

lipofuscin granules in the cytoplasm of some proximal tubular cells may reflect the probable injury caused by energy drinks. Similar alterations have been reported due to the use of many chemicals which had a direct nephrotoxic effects (Akande and Banjoko (2011); Sorour and Al-Rawi (2011).

Electron microscopic results revealed marked structural alterations in the nucleus and cytoplasmic organelles in the cells of both proximal and distal tubules as well as in the renal glomeruli. Those lesions were more obvious in tissues of rats treated with Power-Horse® drink. These adverse effects of the power/energy drinks on the kidney structure/function could be attributed to the variations in mixtures of their formulations (Khayyat et al., 2014).

The recorded necrotic degenerative changes in most renal structures may be attributed to depletion of adenosine tri-phosphate (ATP), which finally leads to necrosis of the renal cells (Shimizu et al., 1996). The inter-tubular hemorrhage and the inflammation areas which were recorded during this study could be mediated *via* the disturbances of micro-circulation that may occur because of the caffeine and/or caffeine-like contents of the power/energy drinks. Moreover, the increase in the number of lysosomes in epithelial cells of the proximal tubules, presence of inter-tubular inflammatory cells and cytoplasmic bulges in some distal cells could be related to the alteration of cytoskeleton structure in these cells (Caglar et al., 2003).

Parallel to and might be explanatory to the above mentioned findings, Tofovic et al., (2002) reported that caffeine produced severe tubule-interstitial damage including renal tubular atrophy, casts, tubular dilatation, interstitial inflammation and fibrosis, as well as increased glomerulosclerosis and adversely affects renal function in rats.

5.3.5. Potential side effects of energy drinks on bone mineralization

Caffeine-containing beverage consumption has been reported to be associated with reduced bone mass and predisposed to fracture in some, but not most, experimental trials. Physiological and controlled balance studies revealed a very small, yet significant, inhibitory effect for caffeine itself on intestinal calcium absorption, with almost no effect on the total urinary calcium excretion per day. Epidemiologic studies declaring a negative effect might be understood partly on the basis of the inverse relationship between consumption of milk and caffeine-containing drinks. It is well-established that low calcium intake is associated with skeletal fragility, and it is likely that high caffeine intake is often a co-factor of a lower calcium intake (Heaney 2002).

Serum Na and HCO_3^{2-} in the animals of treated groups were significantly increased ($P<0.05$) when compared with the control group (Akande and Banjoko 2011).

Only Bison among six energy drinks Red-Bull®, Power-Horse®, Bison®, Bugzy®, Boom-Boom® and Code-Red® revealed a significant increase in calcium concentration of treated rats (Baeissa 2011).

5.3.6. Effect on liver function and structure

Liver tissue damage causes leakage of the contained cellular enzymes to the blood and thus their increase in plasma or serum give indication about the hepatic injury after consumption of energy drinks that is confirmed by histopathology. Almost all authors are in agreement regarding the adverse effects of power/energy drinks on liver function and structure (Akande and Banjoko (2011); Baeissa (2011); Bukhar et al., (2012); Khayyat et al., (2015).

For instance, Khayyat et al., (2015) reported that power beverages caused elevations of hepatic biomarkers: AST, ALT and ALP after 2 or 4 weeks of continuous administration. Results proved that Power-Horse® was more pronounced regarding its effect on hepatic biomarkers, then RedBull® and then Code-Red® for a little extent. That variation in the effects of the studied power/energy drinks on hepatic function may be explained, by rule, by the different ingredients in their formulations.

Chimezie (2013) mentioned that caffeinated energy drinks consumption has damaging effects on the hepatocytes. However, such damage is reversible as observed in the results of the blood chemistry analysis and the histopathological study of the organs of animals in the recovery group.

Despite the alterations in blood chemistry and hepatic enzymes activities; on contrary, no obvious histopathological alterations in the cerebral and hepatic tissues were recorded after Ebuehi et al., (2011). Plasma albumin was decreased after energy drink consumption.

The cytoplasm of hepatic cells of rats given power drinks appeared vacuolated (vacuolar degeneration) with lipid droplets (fatty degeneration) (Khayyat et al., 2015). Histopathological examination revealed mild~moderate hepatotoxic effects after administration of Power-Horse®, Red-Bull® and Code-Red® administration. The observed ultrastructural lesions in the hepatic tissue were nearly similar; yet, the necrotic foci and the pyknotic nuclei were marked post-administration of Power-Horse® and Red-Bull® than those after Code-Red® (Khayyat et al., 2015).

Disruption of some mitochondriae may indicate impairment of their function (Balaban et al., 2005). Nuclei of hepatocytes showed irregular outlines and pyknosis with numerous mitotic figures. Those data

might be considered as toxicity signs. Mubarak (2012) referred such changes to the preservatives routinely added to power/energy drinks such as benzoate, and/or to the toxic action of the caffeine and/or caffeine-like-substances in the drink.

Alrasheedi and Abdel-Mageid (2007) reported that administration of power/energy drinks may cause death of hepatic cells (necrosis) and reduction in the number of nuclei leading finally to loss of some liver weight.

Histopathological studies by both light and electron microscopes revealed congestion and leukocytic through the hepatic parenchyma. This is, by rule, could be attributed to ingredients contained in the power/energy drinks as taurine and caffeine.

From another aspect of view, it is well-established that taurine combines with the bile acids and to form bile salts, components of bile, that is responsible for hydrolysis and digestion of lipids. In addition, it contributes in vital physiological functions as detoxifying, membrane stabilizing, osmo-regulatory processes and cellular calcium homeostasis (Huxtable 1992).

However, the above mentioned results are not in the same line with Ebuehi et al., (2011) who found that power beverages as Power-Horse® and Red-Bull® affected blood chemistry, hepatic enzyme activities; yet, did not significantly affect the histological structure of the cerebral, cardiac and hepatic tissues of the experimental animals.

From another aspect of view, on contrary, Ruhl and Everhart (2005) and Cadden et al., (2007) found that caffeine administration decreases serum ALT. Such decline in the value of such hepatic enzyme may be underlined by the herbal additives to the power/energy drinks such as *Kava-Kava* that causes hepatic failure according to Kraft et al., (2001). Moreover, a study published by Skinner et al., (2000) implied that *Ephedra* plant affects the hepatic function decreasing the activity of its enzymes. Yet, this may be in contrast with findings of other researchers including, Bukhar et al., (2012) and Khayyat et al., (2015) who recorded high significant elevation of liver enzymes in animals treated with energy drinks. Higher serum albumin was recorded from rats administered power drink-alcohol combinations. This phenomenon might be explained on the basis that the alcohol in the mixture may have exacerbated dehydration *via* excessive diuresis with consequent hemoconcentration and increase in serum proteins, including albumin. Thus it could be speculated that uncontrolled drinking of either a power drink alone and/or drink mixed with alcohol may worsen the dehydration associated with diabetes mellitus (Ugwuja 2014).

5.3.7. Effect of energy drinks on endurance

Continuous consumption of power/energy drinks/beverages can significantly improves physical and mental performances, driving ability upon tiring, and delays exhaustion and mental fatigue upon its consumption for long periods (Seifert et al., 2011).

Heckman et al., (2010) have suggested that the energy drink consumption may improve the mood, physical endurance, reduces mental fatigue and increases the reaction time.

Drinks containing caffeine may be an beneficial supplement for enhancing upper body strength and thus, could be utilized for competitive and recreational athletes who perform resistance training (Beck et al., 2006).

Some other studies, in addition, revealed modest improvements after consumption of power drink on physical endurance (Baum and Weiss 2001). However, on contrary some other studies showed no significant enhancing effects of endurance post-consumption of power/energy drinks (Carvajal-Sancho and Moncada-Jiménez 2005).

6. Conclusion

Although consumption of power/energy beverages may promote physical and mental performances, yet its excessive consumption may cause several adverse effects on body organs; and thus its use must be regulated.

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Corresponding Author:
Ibtsam M. Gheith,
Department of Medical Laboratories Technology,
Faculty of Applied Medical Sciences,
Taibah University,
344 Medinah, KSA.
E-mail address: e.m.gheith@hotmail.com

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