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Original Article

Toxicity effects of energy drinks in combination with alcohol on the cerebellar cortex of adult Wistar rats

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ABSTRACT

Background and aim: Alcohol in combination with energy drink becomes a popular combined drink among young and old people, for different reasons. This study aimed at investigating the acute toxicity associated with energy drinks in combination with alcohol on the cerebellum of adult Wistar rats.

Methodology: A total of 40 Male weight 121-134g and were divided into four groups, Red bull + Alcohol, Herbal Energy Drink+ Alcohol and Alcohol + Red bull + Herbal Energy Drink, as experimental groups and control group, and each group comprises of 7 rats each. Group Red bull + Alcohol (2.4ml), Herbal Energy Drink+ Alcohol (2.4ml) and Alcohol + Red bull + Herbal Energy Drink received (3.6ml), while control group received distilled water for a period of 28 days. After administration, they were euthanized using cervical dislocation, and the brains were collected and fixed in 10% neutral buffered formalin for analysis.

Results: The results showed significant increase ($p<0.05$), in body weight of the treated groups Red bull + Alcohol (87.66±2.04), Herbal Energy Drink + Alcohol (107.97±1.19) and Red bull + Herbal Energy Drink + Alcohol (93.77±1.22), compared to the control. Superoxide Dismutase (SOD), reduced glutathione (GSH) decreases statistically ($p<0.05$), in energy drinks in combination with alcohol compared to control while Malondialdehyde (MDA) increased statistically ($p<0.05$). Histopathological analysis showed that energy drinks in combination with alcohol induced neuroinflammation.

Conclusion: Our results suggested that energy drinks consumption with alcohol causes an inflammatory response and oxidative stress lending to neuronal death cell.

Keywords:
Energy Drink; Herbal Drink; Alcohol; Oxidative stress; Cerebellum

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INTRODUCTION

In recent years, the consumption of energy drinks has become increasingly prevalent among individuals seeking a quick boost in energy and alertness (Costantino *et al*., 2023; Arbo *et al*., 2018). Certain beverages have been reported to contains high concentrations of caffeine, taurine, and carbohydrates (sucrose and glucose) with B-complex vitamins, and concerns has been raised regarding their potential adverse effects on health, particularly on neurological function (Alfonso *et al*., 2016). Costantino *et al*., (2023), reported that Food and Drug Administration (FDA) defines energy drinks (EDs) as "a class of products in liquid form that contains large amounts of caffeine, added sugars, other additives, and legal stimulants such as guarana, taurine, and L-carnitine.

Several authors have reported different reasons for the consumption of either energy drinks or alcohol. Consumers are said, to consumed these products as enhancers of mental acuity and physical performance (Seifert, *et al*., 2011; Heckman *et al*., 2010). Whereas the Folklore reported that caffeine has long been used as a stimulant to keep the individual wakefulness, and the monks used it for their nightly prayers (Chris *et al*., 2012). Young people, and students used caffeinated drinks for enhance memory and concentration or to counteract sleepiness (Chris *et al*., 2012; O'Brien *et al*., 2008). Whether or not consumption of energy drinks constitutes a health risk have been a contention over the years (Costantino *et al*., 2023; Alfonso *et al*., 2016; Chris *et al*., 2012). Energy drinks beside containing caffeine, also has other ingredients, most which are plant extracts such as guarana, yerba mate, simple sugars (glucose, fructose), glucuronolactone (a naturally occurring glucose metabolite), amino acids (e.g taurine, carnitine, creatine), herbs (e.g ginkgo biloba, ginseng) and vitamins (Costantino *et al*., 2023; Ferreira & McKenna, 2017; Schimpl *et al*., 2013). The effects of these ingredients are incompletely

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understood (O'Brien *et al*., 2008). Alcoholism is rated as global public health emergency challenge with the World Health Organization estimating the prevalence of 4% and is reported to associated with c. 3 million deaths annually (WHO, 2018). The combination of energy drinks with alcohol is also alarmingly on the increase (Marczinski, 2011). Studies suggest that caffeine (present in energy drinks) may increase alcohol toxicity (Reissig *et al*., 2009). Even though this has been disputed by laboratory study done by Marczinski *et al*. (2006), the larger body of knowledge and research has shown that caffeine combination with alcohol may lead to deleterious consequences (Iyadurai and Chung, 2007; Clauson *et al*., 2008; Thombs *et al*., 2010; Woolsey *et al*., 2010; Brache and Stockwell, 2011; Arria and O' Brien, 2011) Although research work on the effects of energy drinks on different organs of the body exists and may will be on-going, little is known on the effect of energy drinks on the brain. The brain is a very sensitive organ in the body. Its' complexity is due to an enormous neuronal network. As a result of its sensitivity, it may be damaged either physiologically or morphologically if exposed to noxious agents who may not affect other organs of the body. It is then of utmost importance to investigate the effect of energy drinks on the brain. This research work will be centered on the possible morphological and induced oxidative stress on the brain as a result of consumption of energy drinks, with particular interest on the cerebellum. The cerebellum is present in the posterior cranial fossa of the skull. Its importance to the body is great and such functions as fine tuning of the quality of movement (Jueptner *et al*., 1995), coordination of skilled voluntary movement (Miall *et al*., 1987), skill acquisition (Williangham, 1998) and optimization of the output of the motor system (Ito, 1984) are just a few examples. The prototype energy drink of choice for this study is Red Bull™ (Brenda *et al*., 2007). Red Bull™ was first introduced into the Austrian market in 1987 (Reissig *et al.*, 2009). It has however fast gained acceptance in other countries of the world. In 2011, a total of 4.631 billion cans were sold in over 161 countries and generated about 4.25 billion Euros in revenue. The company is said to operate in about 164 countries and employs, 8,000 people. Over the years, the Red Bull™ energy drink has become the world's most consumed energy drink with 5.2 billion cans sold in 2012, according to the company's website (www.redbull.com). In this study, we demonstrate that energy drinks in combination with alcohol induces oxidative stress and histomorphological changes in cerebellar cortical cells leading neuroinflammation.

MATERIALS AND METHODS

Sources of Energy Drinks and Alcohol

Lord Whisky of 45 40% was purchased from open market at Mushin area of Lagos State. Vodka energy drinks of 40% with expiry date of 15th December, 2024 were purchased from Yem-Yem superstores within the premises of the College of Medicine University of Lagos, Idi-Araba. Herbal energy drink was purchased from certified vendor at Lagos, with expiry date of 6th January 2025.

Experimental Design and Animals

The experiment was performed in the Anatomy Department animal house, Faculty Basic Medical Sciences of the College of Medicine of University of Lagos, Idi-Araba. A total number of 40 male Wistar rats weight 121-134g was obtained from animal house, College of Medicine of the University of Lagos, Lagos, and taken to Anatomy Department animal house. They were acclimatized for a period of three weeks, with standard conditions of temperature (25±2^{0}C), and light (12h light/ 12h dark). They were fed twice daily with standard pellet diet bought from Okoko and feeds PLC Agege, Nigeria. All experimental protocol and handing were done in accordance with Nigeria Ethical code of animal research as approved by Health Research Ethics Committee of University of Lagos, with approval Number: NHREC/19/08/2019B. The animals were dosed as follow; Control group was administered with distilled water (2ml), group RDB+ ALC received 2.4ml of Red bull + Alcohol, group HED + ALC received 2.4ml of Herbal Energy Drink+ Alcohol while group RDB + HED + ALC received 3.6 ml of Alcohol + Red bull + Herbal Energy Drink.

The administration was by oral route twice daily and for a period four weeks, while animals feed and water were allowed *ad libitum*.

Animals grouping and duration of administration of Alcohol + Red bull + Herbal Energy Drink.

Group	Dosage/kg body weight/ Group (n=10)	Treatment duration (weeks)
1	2ml Distilled water	1-3
2	2.4ml of Red bull + Alcohol	1-3
3	2.4ml of Herbal Energy Drink+ Alcohol	1-3
4	3.6 ml of Alcohol + Red bull + Herbal Energy Drink	1-3

Animal Sacrificing and Tissue Processing Procedure

After administration, animals were sacrificed by cervical dislocation. The animals decapitated and incision was made through the skin and base of the skull was cracked to reflect the cranium. The brain carefully lifted and removed and brain cerebellum was carefully removed from other aspect of the brain and was then placed on filter paper and weighed. Cerebellum of the rats were cut into small pieces. According to the standard protocol, and small pieces of the brain cerebellum were fixed in neutral buffered formalin (10%) and embedded in paraffin wax. And the other in 0.25m sucrose solution for homogenization and preserved at ice temperature for biochemical analysis and hormonal assay. Five-micrometer slices of neutral formalin-fixed and paraffin-embedded tissues of the cerebellum were routinely cut by a microtome. All small pieces of the brain cerebellum were dehydrated through ascending grades of ethanol by immersion. Dehydrated tissues of the cerebellum were further cleared in two changes of xylene for 30 minutes each. The cleared tissues were

infiltrated in three changes of molten paraffin wax at 56^{0}C. Tissues were then embedded in paraffin wax using stainless steel embedding moulds smeared with glycerine so that Paraffin blocked tissues can be separated from the mould after embedding. Paraffin blocked tissues are trimmed and mounted on wooden blocks for sectioning on a rotary microtome. Sections of 5 µm were obtained on a rotary microtome. The sections are spread in warm bath, and collected on clean glass slides smeared with egg albumen. Thereafter, the slides are stained with hematoxylin and eosin (Bancroft & Gamble, 2002). For routine histopathology diagnosis, stained slides were examined under Digital Compound Microscope (OMAX 40-2000X 3MP Digital Compound Microscope, USA).

Statistical analysis

Results are expressed as the mean ± SD. The data were analyzed via Student's t-test or ANOVA. A $p< 0.05$ was considered statistically significant.

RESULTS

The effects of Alcohol and energy drinks administration on the body and the brain weight of the male Wistar rats.

Administration of energy drink in combination with alcohol increase in body weight of male Wistar rats. A statistically significant increase in body weight of male Wistar rats was observed in the groups administered with energy drink in combination with alcohol when compared with control. The brain weight shows no statistically significant different in each group as compared to control (Table 1).

Activities of oxidative stress marker following Alcohol and energy drinks administration alcohol and energy drinks induced oxidative stress in rat cerebellar cortex

In table 2. The level of oxidative stress marker of cerebellar cortex decreases statistically in energy drink in combination with alcohol compared to control while lipid peroxidation levels increase significantly compared to control (**Table 2**).

Alcohol in combination with energy drinks induced cortical changes and astroglia activation in the cerebellar cortex

To investigate neurotoxicity of alcohol in combination with energy drink on neuroinflammation, the present study showed morphological changes showing intact meninges, with severe, focal mixed inflammatory infiltrates (Figure 1)

Table 1: The effects of Alcohol and energy drinks administration on the body and the brain weight of the male Wistar rats.

Group	Mean Initial weight (g)	Mean Final weight (g)	Mean weight difference	Brain Weight
CONTROL	151.7 ± 8.41	218.6 ± 1.4	66.91 ± 8.53	1.60 ± 0.34
RDB+ ALC	134.4 ± 1.12	215.0 ± 2.02	93.8 ± 2.83*	1.50 ± 0.07
HED + ALC	134.4 ± 1.12	242.4 ± 1.91	107.97 ± 1.19*	1.70 ± 0.21
RDB + HED + ALC	121.2 ± 1.98	215.0 ± 2.02	93.77 ± 1.22*	1.70 ± 0.18

N=10, *p<0.05 represents statistically significant level. ALC +RDB + HED = Alcohol + Red bull + Herbal Energy Drink; RDB+ ALC = Red bull + Alcohol; HED + ALC = Herbal Energy Drink+ Alcohol

Table 2: Activities of brain antioxidants following Alcohol and energy drinks administration

Group	GSH (Unit/mg Protein)	SOD (Unit/mg Protein)	CAT (Unit/mg Protein)	MDA (Unit/mg)
Control	3.32±0.02	11.05±3.23	52.17±0.18	0.270±0.98
RDB+ ALC	2.00±0.07*	5.63±5.05*	41.15±0.91	0.287±1.98*
HED + ALC	1.70±0.07*	6.38±1.85*	47.28±0.19	0.301±0.62*
RDB + HED + ALC	1.70±0.04*	3.33±5.27*	42.72±0.77	0.320±0.65*

Data are expressed as mean, N=10, *p < 0.05 represent statistically significant level; RDB+ ALC = Red bull + Alcohol; HED + ALC = Herbal Energy Drink+ Alcohol and ALC +RDB + HED = Alcohol + Red bull + Herbal Energy Drink

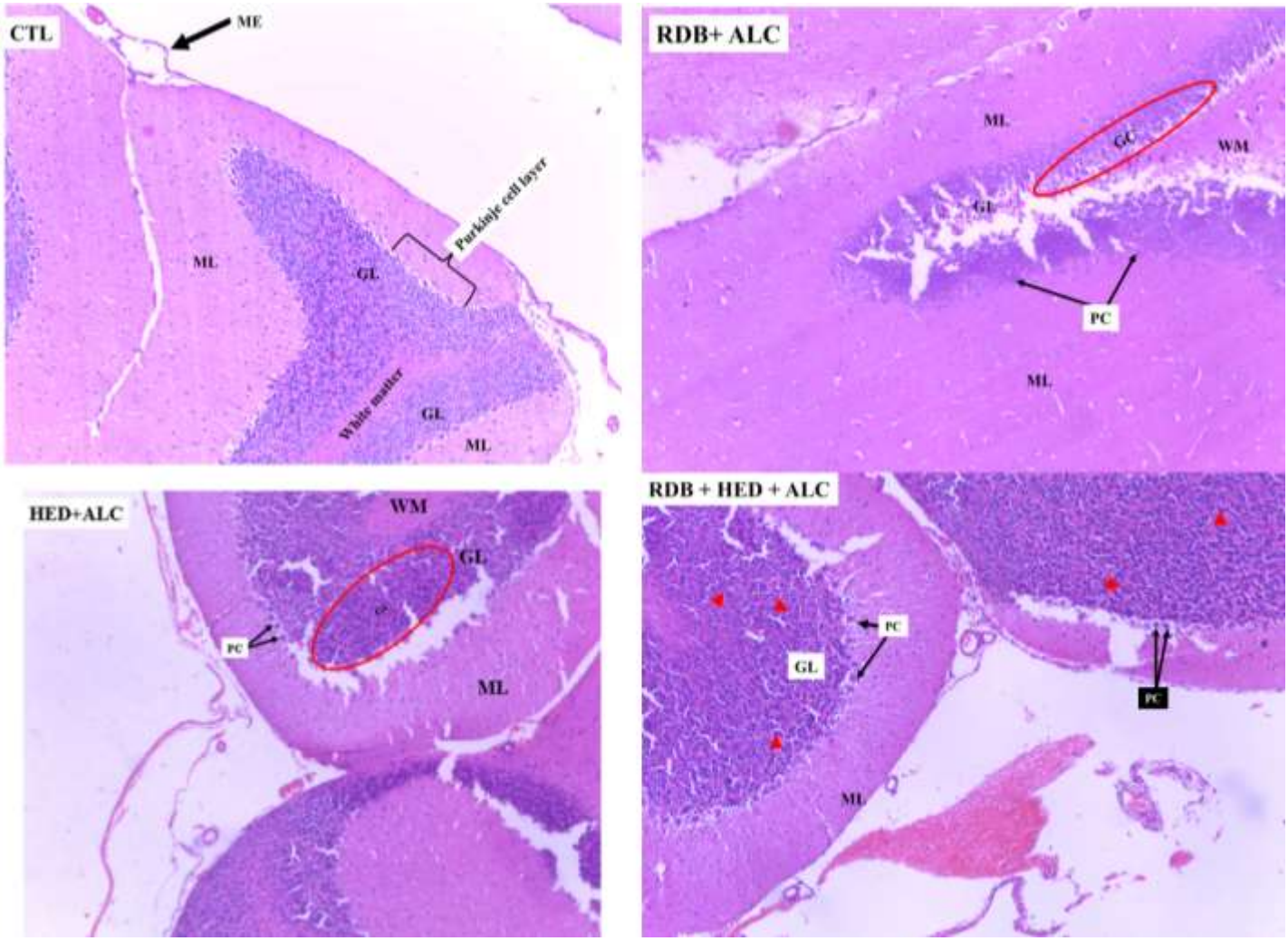

Fig. 1: Alcohol and energy drinks induced neurotoxicity in rat cerebellar cortex. CTL control rat showing normal morphology and cyto-architectural layers of cerebellar cortex. RDB+ ALC showing shrunken granule cells and deeply stained nuclei (circle red) disarranged and deposition of Purkinje cells (PC). HED + ALC showing moderate gliosis (GC) with shrunken with pale stains Purkinje cells (PC). ALC +RDB + HED showing intact meninges, with severe, focal mixed inflammatory infiltrates and marked gliosis characterize by shrunken with pale stains Purkinje cells (PC) and halo of empty spaces around the Purkinje cells (black arrows), granule cells densely shrunken in size with deeply stained nuclei (black arrows head). H&E 100×. RDB+ ALC = Red bull + Alcohol; HED + ALC = Herbal Energy Drink+ Alcohol and ALC +RDB + HED = Alcohol + Red bull + Herbal Energy Drink; ML = Molecular Layer; GL = Granular Layer

DISCUSSION

Consumption of energy drinks (EDs) is constantly increasing among young people, and students and the populace at large, due to peculiar interest including enhancing memory and concentration or to counteract sleepiness. Studies has reported that energy drinks have potential adverse effects as result of the presence of caffeine, and consumption of a large doses of caffeine (3 mg/kg) can lead to health problems characterized by impaired glucose tolerance, gastrointestinal irritation, anxiety, irritability and nausea, and tachycardia (Salih *et al*., 2018; Heckman et al. 2010; O'Brien *et al*., 2008). Alcohol have been reported possess neurotoxic properties by cause thiamine deficiency thereby disrupting thiamine transport via an active sodium independent transporter and may requires both energy and a normal pH level (Nutt *et al*., 2021; Reidling & Said, 2005; Gastaldi *et al*., 1989; Thomson *et al*., 1970). Evidence have also shown that thiamine deficiency can result in nerve damage, leading to alcoholic neuropathy (Nutt *et al*., 2021; Behse & Buchthal, 1977). Pro-inflammatory responses have been reported to increases, as result of alcohol consumption and its metabolism in bacteria. And the cumulative increases circulation of pro-inflammatory cytokines can cross the blood brain barrier and cause inflammation in the brain (Nutt *et al*., 2021; Crews *et al*., 2015; He & Crews, 2008). While caffeine and alcohol have been reported as the two oldest commonly consumed psychoactive compounds, and caffeinated drinks have been mixed with alcohol for many years (Joris *et al*., 2012). Alcohol and energy drinks in combination have been reported to associated with neurotoxicity (Arbo *et al*., 2018).

The finding in this present study showed that oxidative stress marker of cerebellar cortex decreases significantly when energy drink administered in combination with alcohol and lipid

peroxidation levels increase significantly when compared to control. This is consistent with studies of Alfonso *et al*., (2016); Hilbert *et al*., (2013). Alfonso *et al*., (2016) reported that many researchers have suggested that chronic use of these psychoactive substances (EDs) in combination with alcohol can trigger oxidative and inflammatory response. They further reported that alcohol in combination with ED showed a significant increase in the formation of free radicals and lipid peroxidation, compared with the control group, while Hilbert *et al*., (2013) in their study indicate that alcohol induced inflammatory response, together with the ED, could be responsible for the NO production since NO is an important source of ROS, which contribute to oxidative stress and death in neurons.

Body weight of rats significantly increase in EDs in combination with alcohol, in this present study while weight of brain cerebellum slightly decreases in alcohol + red bull + herbal energy drink group compared with the control. Our present finding is in lined with Zahr *et al*., 2010, who work revealed that chronic alcohol consumption can lead to loss of cerebellar volume, this further increases with age. Similarly, Nutt *et al*., (2021), reported that high level of alcohol consumption can affect brain volume and white matter. Chronic alcohol consumption can therefore cause the de-regulation of microglial activation. This in turn can lead to degeneration of brain tissue and is likely associated with brain volume loss (Topiwala *et al*., 2021). These studies validate our present result of alcohol in combination with EDs but differ because present study was the combined of alcohol and EDs while their work was on alcohol alone. There was increase in the brain weight in red bull + Alcohol and herbal energy drink+ alcohol in this present study. Our study suggests that increase in red bull + Alcohol and herbal energy drink+ alcohol in this present study may have result from inflammatory responses of its combination with E.Ds.

The present study has showed that alcohol and energy drinks in combination induces histomorphological changes of the cerebellar cortex characterized with intact meninges, severe, focal mixed inflammatory infiltrates and marked gliosis, as well as vascular congestion. This is in agreement with study of Nutt *et al*., 2021, who work reported that chronic alcohol consumption is thought to contribute directly to neurotoxicity via thiamine deficiency, metabolite toxicity and neuroinflammation, leading to others developmental diseases and the acceleration of neurodegeneration in general. it is often established fact that pro-inflammatory responses contribute immensely in progression of neuroinflammation and neurodegeneration at large. Salih *et al*., 2018, reported that energy drinks have potential adverse effects which attributed to the presence of caffeine. And a large dose of caffeine (3 mg/kg) may lead to health problems such as impaired glucose tolerance, gastrointestinal irritation, anxiety, irritability and nausea, and tachycardia (Salih *et al*., 2018; Rogers *et al*., 2003). Their study further reported that energy drink causes neuronal degeneration and aggregation of focal plaque in the brain. This is consistent with our present study, infiltration and vascular congestion were evidence of neuroinflammation in sequence to pro-inflammatory responses against neurotoxicity. Morphological changes of the cerebellar cortical cells and astrocytic proliferation were markedly seen in alcohol + red bull + herbal energy drink group, presence severe cortical degeneration when compared to red bull + alcohol and herbal energy drink+ alcohol while herbal energy drink+ alcohol presence moderate cortical degeneration compared to red bull + alcohol and red bull + alcohol group was found with mild disarranged cortical cells compared with the control. Neuroinflammation was found across the treated group when compared with the control. These diversity in cortical degeneration found in our presence study may have been a combined effect of alcohol. Similarly, Alford *et al*., (2012) reported energy drink in combination with alcohol has multifaceted impairment including motor activities and cognitive impairment. And cognitive impairment has been reported to be associated with progressive brain damage (Nutt *et al*., 2021; Eriksson, 2001). This consistent with our preset study which showed progressive neuroinflammatory response validating cerebellar cortical damage. Energy drinks in combination with alcohol induced neurotoxicity leading to cerebellar cortical cells proliferation, thereby causing neuronal death and severe brain damage. It is therefore necessary to educate the populace on the detrimental risk of energy drink in combination with alcohol. There should be control government agencies to implement regulations of energy drink in combination with alcohol.

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