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In-silico and in-vivo evaluation of comparative enhanced neurogenic performance by energy drinks

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***Abstract*---**Objective: In the present society, the energy drinks (EDs) are used by general public and mainly by the sports persons. Though the caffeine content of EDs is creating health consequences on excess consumption, the present study targets their health benefits on central nervous system (CNS) focusing antidepressant and cognitive

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potentiality. The most typically used EDs have been selected for the study such as Red Bull, Monster and Enerzal for the present research. Methodology: The study started with in-silico studies to get information about the neurological receptor binding of the major and common chemical components of the EDs. The antidepressant study of energy drinks was carried out following FST (Forced Swim Test) and TST (Tail suspension test) methods. Their cognition effect was assessed by using Y-maze apparatus. Further, their mechanism of action was evaluated by estimating their effect on brain dopamine and serotonin level. Results: In-silico study revealed the enhanced agonistic binding of the major common components of the EDs to D2 and serotonin receptors. Further their significant ($p<0.001$) antidepressant property was estimated both in tail suspension and forced swim tests along with significant cognitive property. The mechanism behind these effects were confirmed by their potentiation in the brain dopamine and serotonin concentration significantly ($p<0.001$) in mice. Conclusion: The present study may be beneficial to utilise the EDs in a better prospective for the management of CNS depression and improving the cognition, where Red bull was considered to be the superior one to others after their further confirmatory studies in clinical trials.

Keywords---antidepressant, cognition, dopamine, serotonin, in-silico.

Introduction

The primary purpose of energy drinks (EDs) and sports drinks is to enhance the body energy during sports, exercises, and other athletic activities (Raizel et al., 2019; Sankararaman et al., 2018). The literature shows their therapeutic potential and enhanced performance on caffeine content intake (Hoffman JR, 2010). Some investigations have framed with caffeinated EDs to show the effects. Though**,** there are many other health benefits of EDs about which people are still unaware. On the other hand, EDs are alcohol free and mainly with herbal components (Collier et al., 2016; Inceday et al., 2019). EDs are mostly composed of vitamins, ginkgo biloba, caffeine, taurine, ginseng, glucuronolactone, guarana, and yerba mate which are present in different proportions in different EDs (Inceday et al., 2019). As such EDs are mainly a good combination of energy boosters and stimulants (Gilbert, 1984; Nehlig et al., 1992). The caffeine content of the EDs makes them psychoactive agents (Nehlig et al., 1992; Schneider and Benjamin, 2011) which is mainly known to activate the serotonin and noradrenaline neurones (Masengo et al., 2020; Chatterjee and Abraham 2019).

On the other hand, the excess consumption of EDs is producing health untoward effects. But EDs are also associated with some less known health benefits like to improve mood, etc. making them excellent supplements for body fitness physically and psychologically (Haskell et al., 2005; Smith, 2002). The most consumed three EDs are found to be Red Bull, Monster, and Enerzal as per the information from the retailers of local markets and from the athletes of nearby stadiums at Greater Noida, India. The athletes remain in stress during the

tournaments which should be reduced along with the enhancement of their cognition ability to perform better in their events. But there is not yet any research on the potentiality of the EDs in the management of depression and improvement of cognition. This investigation is mainly focused to these two major aspects of the consumption of EDs on animal models. Dopamine and serotonin have already been proven to be low in depression and cognition is influenced by serotonin brain concentration (Mokler et al., 2007). On the basis of the therapeutic importance of caffeine and taurine on dopamine and serotonin-mediated neurotransmission (Liguori and Robinson, 2001; Kuriyama and Hashimoto, 1998; Curran and Marczinski, 2017), the research was initiated with the in-silico investigations and further it has been included brain biochemical estimates and to learn more about how EDs work in the treatment of depression and improving cognition.

Materials and Methods

Collection of the Eds

The most prevalently consumed EDs were found to be Red bull, Monster and Enerzal which were considered for the research and availed from the local medical retail stores at Greater Noida.

In-silico study of the energy drinks on Central Nervous System
Target preparation

Based on the evident data**,** all the 6 crystal structures Human dopamine D2 receptor and 4 crystal structures of human serotonin receptor was downloaded from the Protein Data Bank (Berman et al., 2002). Based on resolution and sequence coverage we have selected one structure (PDB id: 7jvr) for Human dopamine D2 receptor (Zhuang et al., 2021) and another structure (PDB id: 6Vrh) for Human serotonin receptor (Coleman et al., 2020). The crystal structures were also freed from water molecules, ions, and covalent ligands by using the Dockprep procedure implemented in the UCSF (University of California, San Francisco) Chimera program (Pettersen et al., 2004). The key amino acids present in the active site of the dopamine D2 receptor were previously reported in the literature as LEU84, VAL91, LEU94, CYS107, PHE110, VAL111, VAL115, CYS118, THR119, CYS182, ILE183, ILE184, VAL190, SER197, TRP386, PHE389, PHE390, HIS393, TRP407, PHE411, TYR408, THR412, TYR429 (Coleman et al., 2016). And the key amino acids present in the active site of the serotonin receptor were taken from the literature as LEU90, ARG104, LEU292, ASP328, VAL374, GLU494, PHE556, LEU557, SER559, PRO561, TRP573, ILE576, LEU577 (Zhuang et al., 2021).

Ligand preparation

All the 3D structures of benzoic acid, caffeine, citric acid, cyanocobalamin, glucose, inositol, levocarnitine, l-tartrate, maltodextrin, niacin, niacinamide, panaxginseng, pyridoxine hydrochloride, riboflavin, sorbic acid, sucralose, sucrose, taurine, trisodium citrate were downloaded from the Pubchem Database (Kim et al., 2016). These structures were checked for any errors. Then, by using Open Babel software (O'Boyle et al., 2011), hydrogen was added, and the

structures were converted into PDBQT [Protein Data Bank, Partial Charge (Q), and Atom Type (T)] format.

Active sites and grid generation

Active sites were identified from the literature and were also checked by computational tools such as CASTp (Computed Atlas of Surface Topography of proteins) (Tian et al., 2018) and AADS (Automated Active site detection, docking and Scoring) (Singh et al., 2011). The optimal size of the Grid box was calculated by eBoxSize Script developed by (Feinstein and Brylinski 2015). For Human dopamine D2 receptor, the grid box was centered in X= 102.143228, Y= 128.429297, Z = 25.517069 and for serotonin receptor the grid box was centered in 128.068492**,** 124.603102 and 128.615864; respectively.

Molecular docking

Molecular docking and calculations were carried out using Auto Dock Vina (Trott and Olson 2010). The best-docked pose was selected based on its binding energy score and significant interactions in the active sites.

Experimental animals

The research was conducted using (126) Swiss albino mice of 25030 gm body weight and of either sex. The animal facility of Noida Institute of Engineering and Technology (Pharmacy Institute), Greater Noida, India was the source from where the animals were collected. They were kept in proper sized animal cages at standard environmental condition like temperature of $(27.00\pm1.00)^0$C and 55 – 65% humidity. The animals were sufficiently availed with pellet feed and water libitum. The animals were subjected to the laboratory environment for seven days to be well adapted before starting the experiment. To fulfil the ethical requirements**,** the experimental protocol (IAEC/NIET/2020/01/10) was sanctioned by the Institutional Animals Ethics Committee (CPCSEA Registration No. 1845/Re/S/16/CPCSEA).

In-vivo evaluation of the effect of EDs on central nervous system
Antidepressant Activity
Tail suspension test (TST)

Thirty Swiss albino mice were allocated into a control group (6 mice feed with saline), a standard group (6 mice feed with imipramine, 10 mg/kg) and a test group of 18 mice which was equally sub-grouped as I, II and III administered with Red bull, 8 ml/kg, Monster, 8 ml/kg and Enerzal, 8ml/kg; respectively (each subgroup with six mice). Mice were subjected to hang by their tails at 75 cm as performed by (Kadali et al., 2014). The immobility duration was noted for 6 min at 30 min, 60 min and 90 min after the drug ingestion.

Forced swim test (FST)

The animated as six in each group were allocated in the similar fashion as above. The experiment was performed as described by (Kadali et al, 2014) in their

research as 24 hrs of pretesting forced swimming session and recording of the duration of motionless floating of mice at 0, 30, 60 and 90 min of EDs consumption.

Effect of EDs on cognition
Y-maze test

For this test**,** thirty-six mice were allocated equally as negative control, positive control, standard, and test I, II and III groups who were administered with normal saline, scopolamine (1 mg/kg), piracetam (400 mg/kg) with scopolamine, Red bull (8ml/kg) with scopolamine, Monater (8ml/kg) with scopolamine and Enerzal (8ml/kg) with scopolamine; respectively. The test was performed following the methodology described by (Aziz et al, 2016) where the mice were observed for the number of entries for 3 min at 0, 30, and 60 min on EDs consumption after a week training period, to test their memory.

Effect of EDs on dopamine and serotonin level

Two sets of (30 each) mice were treated with the EDs and standard drug (Imipramine) and induced with depression by FST in the similar manner and were subjected to estimate their effect on brain dopamine and serotonin level following the method adopted by Das et al, 2008[31]. The mice brain was carefully removed out on anaesthesia of isoflurane and weighted and homogenized in hydrochloric acid**,** butanol and hydrochloric acid**;** respectively for dopamine and serotonin. Further it was centrifuged for 10 min. The supernatant was treated with hexane and hydrochloric acid for dopamine estimation, whereas zinc sulphate and sodium hydroxide for serotonin estimation and again centrifuged. The dopamine estimation targeted brain samples were further treated with hydrochloric acid and sodium citrate buffer followed by iodine solution and then with sodium sulphite and acetic acid. The obtained final brain samples were subjected to spectrofluorometer for obtaining the excitation- emission spectra at 330-75 nm and 290-550 nm for the determination of brain dopamine and serotonin levels respectively (Das et al., 2008; Kumar et al., 2020; Manikkoth et al., 2016)

Statistical analysis

The observed values in the present research were interpreted following one-way ANOVA (analysis of variance) and the outcomes are expressed as mean ± SEM (standard error mean). The observations with $p<0.001$ are considered as of significance effectiveness.

Result

In-silico study of the energy drinks on Central Nervous System

The most suitable orientation and interactions (hydrogen bonds and hydrophobic interactions) of each lead at the protein's active site were found to range from -11.05 kcal/mol to -4.3 kcal/mol. The Docking results has been shown in Table 1. Out of all the molecules, caffeine, cyanocobalamin, panax ginseng, riboflavin and sucralose had shown the best interaction with receptor with proper interaction

with the same residues mentioned in the literature as active sites. The Receptor Ligand Interaction diagram given in Figure 1-6.

Table 1
Binding Energy (Kcal/Mol) Results of Molecular Docking

Ligand	Dopamine D2 receptor	Human serotonin Receptor
Benzoic acid	-5.33	-4.95
Caffine	-5.56	-.35
Citric Acid	-4.83	-7.39
Cyanocobalamin	-6.43	-8.55
Glucose	-4.75	-6.38
Inositol	-4.4	-7.55
Levocarnitine	-4.3	-4.67
L-tartrate	-3.83	-5.05
Maltodextrin	-2.07	-7.81
Niacin	-4.97	-4.72
Niacinamide	-5.03	-4.83
Panax Ginseng	-12.63	-8.84
Pyridoxine hydrochloride	-5.26	-5.29
Riboflavin	-11.05	-8.59
Sorbic acid	-5	-4.54
Sucralose	-6.98	-8.22
Sucrose	-6.02	-7.51
Taurine	-3.35	-4.31
Trisodium citrate	-4.41	-5.29

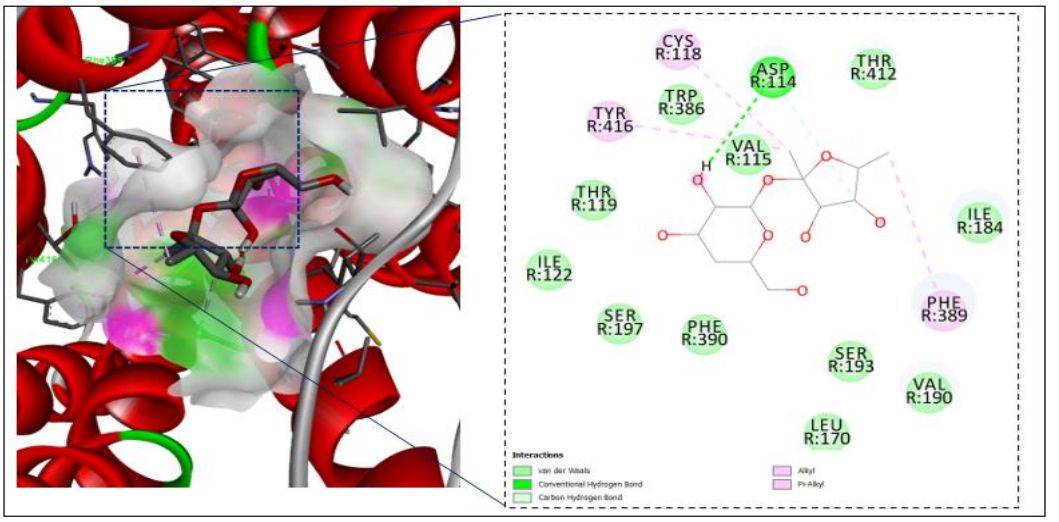

Figure 1. Dopamine D2 receptor - sucralose Complex depicted in Molecular surface representation at active sites, with 2D Depiction

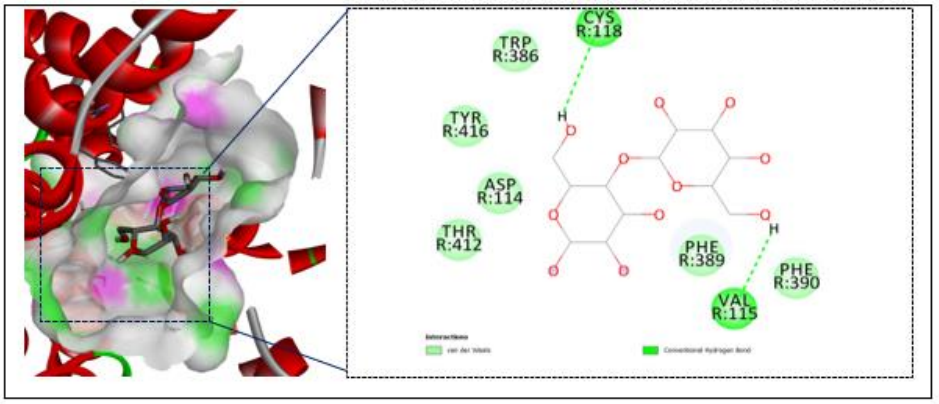

Figure 2. Dopamine D2 receptor - riboflavin complex depicted in molecular surface representation at active sites, with 2D Depiction

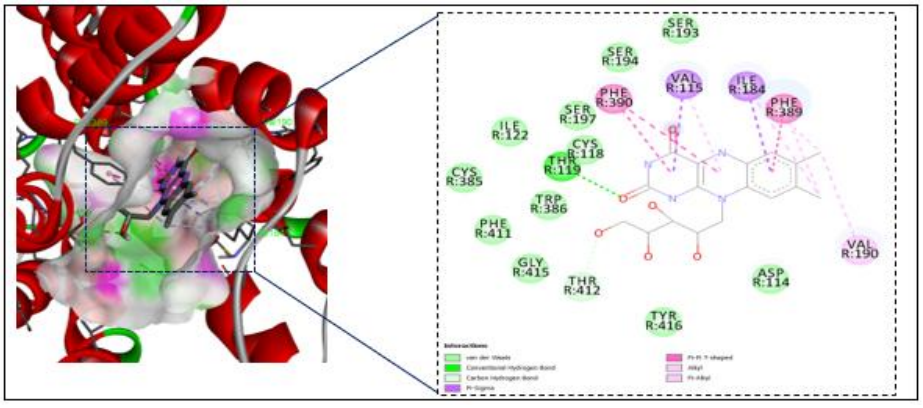

Figure 3. Dopamine D2 receptor - cyanocobalamin complex depicted in molecular surface representation at active sites, with 2D Depiction

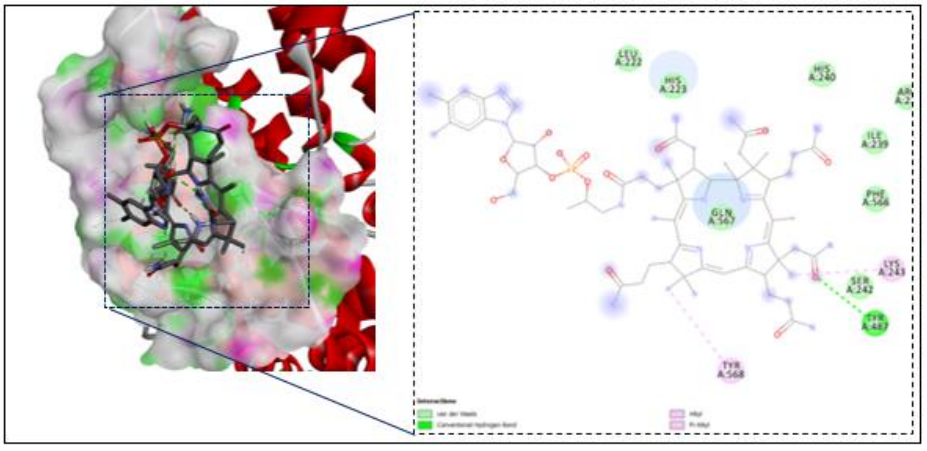

Figure 4. Human serotonin Receptor - Panax ginseng complex depicted in molecular surface representation at active sites, with 2D Depiction

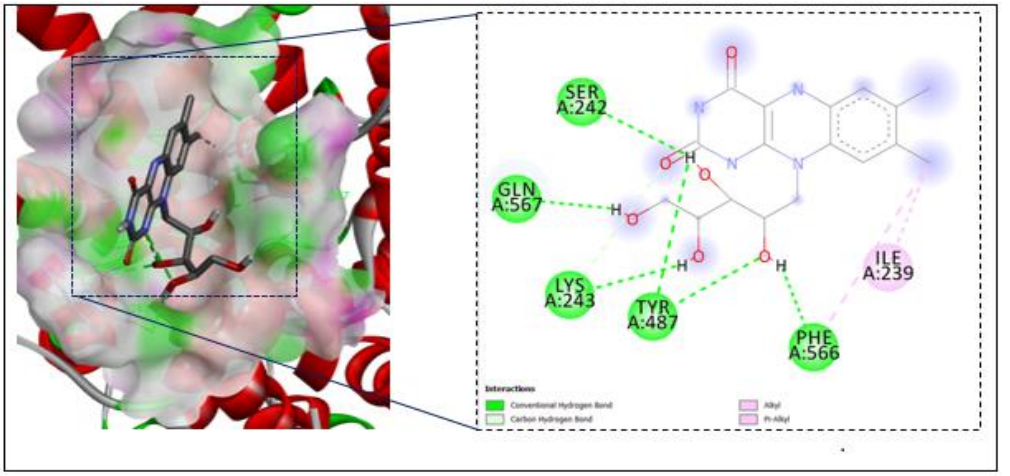

Figure 5. Human serotonin receptor - riboflavin complex depicted in molecular surface representation at active sites, with 2D Depiction

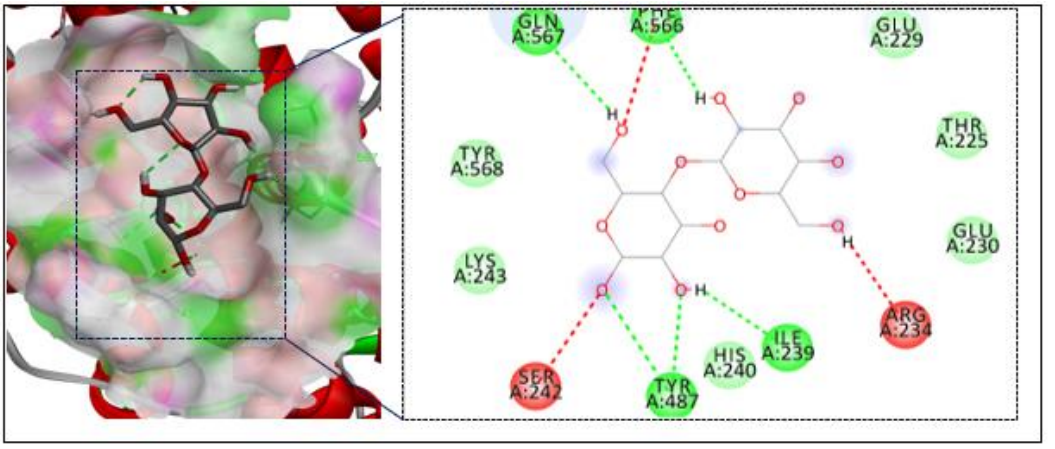

Figure 6. Dopamine D2 receptor - caffeine complex depicted with molecular surface representation at active.

Effect of EDs on TST

During TST testing, the EDs (Red Bull, Monster, and Enerzal) were observed to lower the immobility time period in mice in a significant way ($p<0.001$) (Table 2). Red bull exhibited profound reduction in the observed parameter starting from 30 min (149.3 ± 1.838), 60 min (145.7 ±1.571) and 90 min (142.3 ± 1.820) as compared to the normal saline treated group of mice, reaching a significant level for 60 min and 90 min; respectively ($p<0.001$). Whereas Monster and Enerzal were found to exhibit lesser reduction in immobility period as 30 min (142.5 ± 1.478 and 157 ± 2.338; respectively), 60 min (139.2 ± 1.851 and 155.3 ± 3.051; respectively) and 90 min (137.3 ± 1.430 and 151.2 ± 0.946, respectively) where the significance appeared for only 90 min ($p<0.001$ for both).

Table 2
Antidepressant activity of EDs by tail suspension test (TST)

Name of group	Treatment	Immobility time (sec.) 30 min.	60 min.	90 min.
Control	Normal saline	243.2 ± 1.302	246.3 ± 1.256	249.5 ± 0.922
Standard	Imipramine	123.8 ± 0.946	135.8 ± 1.014	126.3 ± 1.256
Test II	Red Bull	149.3 ± 1.838	145.7 ±1.571*	142.3 ± 1.820*
Test II	Monster	142.5 ± 1.478	139.2 ± 1.851	137.3 ± 1.430*
Test III	Enerzal	157.0 ± 2.338	155.3 ± 3.051	151.2 ± 0.946*

The values ~~are~~ were represented as mean ± S.E.M. (n=6). The values were compared with the control group. Significant variation against control *p<0.001 was estimated by Dunnett's test and considered as extremely significant. The results in EDs treated groups ~~are~~ were well comparable to that of the standard group.

Effect of EDs on FST

In FST test, the immobility duration was observed to be lowered by the mice consumed with the EDs in a significant manner (p<0.001) as shown in Table 3. The mice treated with Red bull were found to show reduction in immobility time at different time intervals of 0 min (147.7 ± 0.882), 30 min (148.5 ± 0.846), 60 min (147.5 ± 1.408) and 90 min (145.21 ± 1.237) in comparison to the saline treated group of mice. Similarly, Monster and Enerzal lowered the immobility duration as at 0 min (152.3 ± 0.988 and 160.5 ± 1.176; respectively), 30 min (158 ± 1.125 and 166.3 ± 1.585; respectively), 60 min (157.34 ± 1.155 and165.3 ± 1.706; respectively) and 90 min (155.27 ± 1.125 and 163.7 ± 1.520; respectively). On comparing with the control group, Red bull treated animals after 60 and 90 min, immobility durations were observed to be significant (p<0.001), whereas Monster and Enerzal showed their significant (p<0.001) result only after 90 min.

Table 3
Antidepressant activity of EDs by forced swim test (FST)

Name of group	Treatment	Immobility time (sec.) 0 min.	30 min.	60 min.	90 min.
Control	Normal saline	255.67±2.564	256.8 ± 0.873	259.5 ± 0.922	263.8 ± 0.946
Standard	Imipramine	148.52±1.245	122.34 ± 1.653	132.3 ± 3.232	139.8 ± 2.272*
Test I	Red Bull	147.7 ± 0.882	148.5 ± 0.846	147.5 ± 1.408*	145.21 ± 1.237*
Test II	Monster	152.3 ± 0.988	158 ± 1.125	157.34 ± 1.155	155.27 ± 1.125*
Test III	Enerzal	160.5 ± 1.176	166.3 ± 1.585	165.3 ± 1.706	163.7 ± 1.520*

The values are represented as mean ± S.E.M. (n=6). The values were compared with the control group. Significant variation against control *p<0.001 was

estimated by Dunnett's test and considered as extremely significant. The results in EDs treated groups are well comparable to that of the standard group.

Effect of EDs on Y maze

In case of the cognitive activity screening, EDs treated mice performed in an interestingly improved spontaneous alternation behaviour as compared to the positive control group of mice only treated with scopolamine. All three energy drinks were found to have reduced percentage of alteration (56.50 ± 1.628, 53.33 ± 0.494 and 51.67 ± 1.520 respectively), whereas the mice with scopolamine exhibited increased percentage alternation in comparison to the negative control mice (63.50 ± 0.885). Here also, the best cognitive effect was revealed with the mice administered with Red bull**.** The Red bull was shown to have a better and significant ($p<0.001$) effect on cognition than the other two, although not as much as the conventionally used agent piracetam (Figure 7).

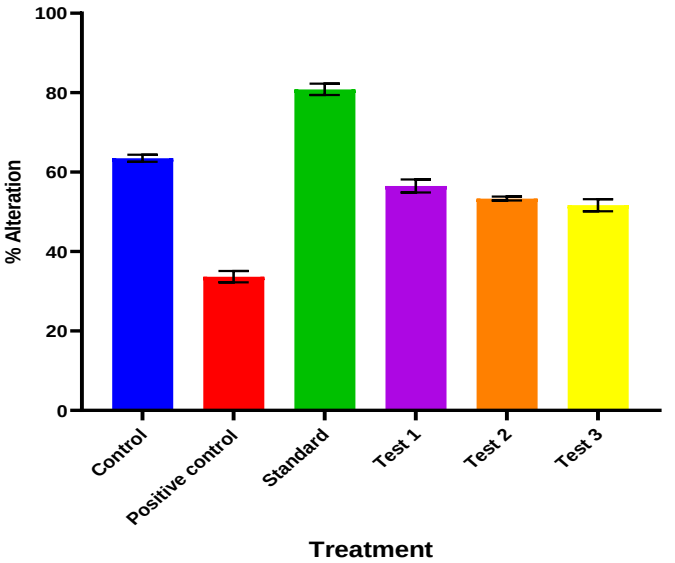

Figure 7. Effect of the EDs on cognition in brain of mice

The values are represented as mean ± S.E.M. (n=6). The values were compared with the control group. Significant variation against control *$p<0.001$ was estimated by Dunnett's test and considered as extremely significant. The results in EDs treated groups are well comparable to that of the standard group.

Effect of EDs on dopamine and serotonin level

From the brail biochemical level evaluation, it was observed that the animals of control group with depression have reduced dopamine (4.667 ± 0.33) and serotonin level (84.83 ± 0.83) in brain below the normal levels (24 µg/gm and 108 µg/gm of brain tissue**;** respectively) (Leonard and Kafoe 1976). Additionally, EDs were found to increase both ~~the~~ levels significantly ($p<0.001$). It was also revealed that Red bull consumed animal brains contained with highest brain level of

dopamine (21.33 ± 0.615) and serotonin (100.8 ± 1.759) as compared to the control group animals. Whereas Monster and Enerzal enhanced lesser amount of brain dopamine and serotonin (Figure 8 and 9).

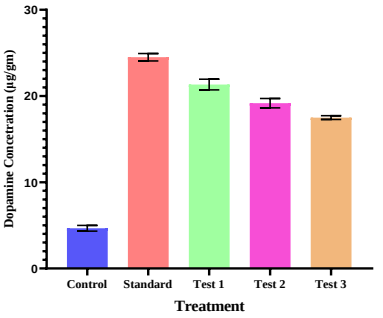

Figure 8. Estimation of brain dopamine concentration

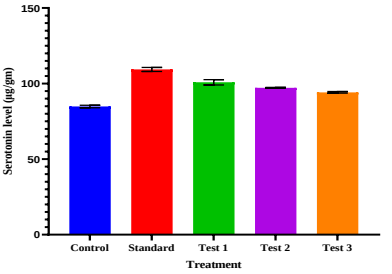

Figure 9. Estimation of brain serotonin concentration

The values are represented as mean ± S.E.M. (n=6). The values were compared with the control group. Significant variation against control *p<0.001 was estimated by Dunnett's test and considered as extremely significant. The results in EDs treated groups are well comparable to that of the standard group.

Discussion

The present study as initiated in the intention to explore the impact of EDs on Central Nervous System due to the rise in the consumption of EDs not only by the sports person but also the general youth. In order to verify the antidepressant effect of EDs, different animal models for depression were adopted like TST and FST. In this study, all three selected EDs were observed to reduce the immobility period of mice in both the models. After 60 min Red bull exhibited prominent reduced immobility duration, whereas rest two EDs exhibited after 90 min of EDs administration. From literature it is evident that there is significant role of dopamine and serotonin in the antidepressant property of imipramine (Wesołowska and Kowalska, 2008) which indicated the obtained antidepressant effect of EDs is due to the enhancement of brain dopamine level. This is an indicator pointing Red bull as more predominant CNS protective than that of Monster and Enerzal which may be due to the difference in the amount and types of constituents. Literature shows the important role of D2 receptor binding and agonistic effect in antidepressant and cognition effects (Persad, 2011).

It is also evident from previous studies that cognition impairment mainly in neurological degeneration in schizophrenia is due to impairment of activation of serotonin receptor and D2 receptors. Additionally, it has also been proven that the increased release of dopamine is one of the responsible mechanisms behind the management of depression (Mahmood, 2016; Ahmed et al., 2018; Saleem et al., 2017). In this analysis initially the molecular docking analysis was inducted and then compared with the in vivo results to interpret the mechanism of action behind the observed antidepressant effect of the EDs. The results of in-silico evaluation of the major components of EDs like riboflavin, cyanocobalamin, caffeine, panax ginseng exhibited their enhanced binding tendency to the responsible D2 receptor of dopamine and serotonin along with their enhanced synthesis. As observed**,** EDs provides antidepressant effect along with the enhanced cognition in mice. It was again supported by the extended research on the brain bioamines which showed their potentiality to increase in brain concentration of dopamine and serotonin.

Literature shows that the increased dopamine level potentiates motivation and EDs are used by the sports persons gets motivated (Papp et al., 2017). It was again evident that the main constituents present in the selected most abundantly consumed EDs Enerzal, Monster and Red bull are benzoic acid, caffeine, citric acid, cyanocobalamin, glucose, inositol, levocarnitine, l-tartrate, maltodextrin, niacin, niacinamide, panax ginseng, pyridoxine hydrochloride, riboflavin, sorbic acid, sucralose, sucrose, taurine, trisodium citrate. In addition, the results of brain dopamine and serotonin level are equally important and support their mechanism as the serotonergic pathway is considered to be one of the most important mechanisms for antidepressant property. The increased serotonin level supports the memory enhancement potentiality of the selected EDs. It also supports the evaluated protective potentiality of the selected EDs for central nervous system which is by elevated brain serotonin and dopamine levels along with the agonistic effect of major components (sucralose, caffeine, riboflavin, cyanocobalamin and Panax ginseng) of EDs to D2 and serotonin receptors.

Fortunately, the overall study revealed the positive aspect of EDs as observed from different animal models along with in-silico study though previous studies highlighted the negative effects and health problems associated with the consumption of energy drinks (Alasqah et al., 2021) and considered the consumption of energy drinks as an unhealthy dietary habit (Alsunni, 2015). In different animal models the antidepressant activity of EDs was evidenced. Another aspect of the study is that in the investigation the doses of the EDs are constant and these are showing positive effects. If the dose of EDs would be increased, it will lead to detrimental effects by further elevating the dopamine and serotonin level. The quantity to be consumed is to be controlled to get the health benefits of EDs.

Conclusion

In the present study ~~of~~ on the most consumed EDs by the youth and the athletes are explored for antidepressant and cognitive potentiality as a benefit to the sports person to achieve their goal. The targeted activities are proved by following in-silico and different in-vivo study designs on experimental animals. The

observed enhanced dopamine and serotonin level along with the receptor binding tendency of the major components of EDs have confirmed their neuroprotective potentiality. This positive evidence seems that the major common constituents of EDs play an important role in the explained effect. However, investigation into the metabolism of EDs and the effects their biproduct are recommended for future study. Sometimes the youth and during any sports events the participants remain in depression and the EDs as observed can be helpful to manage the depression along with boost their performance by enhancing their cognition. The study also supports the motivation of sports persons due the intake of sports drinks. The dose of EDs should be in a physiologically compatible amount. Further studies are needed to explore the perfect and limited quantities of these EDs to be consumed by the youth and athletes for improving the performance and lesser untoward effect.

Acknowledgement

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Conflict of interest

The authors declare no competing interests.

Authors' declaration statements

The authors of the manuscript declare that the authorship and contribution of this article is a teamwork by names, listed by us here. We also declare that we contributed significantly towards that research study. Conception, design and analysis and interpretation of data by Sanjita Das and Irfan Khan. In-silico study was conducted and interpreted by Abhijit Debnath. Drafting of the article and revising it critically for important intellectual content are carried out by Sanjita Das, Kumari Renu Singh and Shruti Dhasmana.

Ethics approval

The animal experimentation of the present study with protocol number IAEC/NIET/2020/01/10 was approved by the Institutional Animals Ethics Committee of Noida Institute of Engineering and Technology (Pharmacy Institute) (CPCSEA Registration No. 1845/Re/S/16/CPCSEA).

Availability of data and material

All data and materials of the scientific evaluation of enhanced neurogenic performance of EDs have been reported in this article.

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