



Manuscript IDZUMJ-2506-4012

DOI:10.21608/zumj.2025.395110.4012

REVIEW ARTICLE

Naringenin Ameliorates Energy Drinks-Induced Structural Alterations of The Hippocampus in Rats: A Narrative Review

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Submit Date 29-06-2025

Revise Date 18-09-2025

Accept Date 20-09-2025

ABSTRACT

Background: Since Red Bull's 1997 debut, energy drinks have become more popular. High levels of caffeine and other stimulants included in these drinks can have a negative impact on the central nervous system, especially the hippocampus (HC), a vital brain region involved in learning, memory formation, and cognitive function. This narrative review examines the structural and functional alterations induced by energy drinks in the hippocampus and evaluates the neuroprotective potential of naringenin, a naturally occurring flavonoid, in ameliorating these adverse effects. A comprehensive review of literature was conducted focusing on energy drink-induced neurotoxicity, hippocampal vulnerability to environmental stressors, and the neuroprotective mechanisms of naringenin. The review examined studies on caffeine's neurological effects, hippocampal neurogenesis, oxidative stress mechanisms, and naringenin's pharmacological properties. Energy drinks containing high caffeine concentrations (>500 mg) cause neurological complications, including seizures, anxiety, and cognitive impairment through overstimulation of the adrenergic system and disruption of adenosine receptors. The hippocampus, being highly sensitive to environmental stressors due to its high metabolic rate and low antioxidant defenses, undergoes structural alterations, including reduced volume, impaired neurogenesis, and oxidative damage. Naringenin demonstrates significant neuroprotective effects through multiple mechanisms, including free radical scavenging, anti-inflammatory activity, restoration of mitochondrial function, and enhancement of endogenous antioxidant capacity. **Conclusion:** Energy drinks use neurotoxic processes and oxidative stress to seriously jeopardize the structure and function of the hippocampus. Naringenin's strong antioxidants and neuroprotective qualities make it a promising therapeutic agent for preventing and treating hippocampus damage brought on by energy drinks.

Keywords

Naringenin, Energy drinks, Hippocampus, Neurotoxicity.



INTRODUCTION

Energy drinks (EDs) are carbonated drinks that don't include alcohol. These come in little cans that resemble bullets. They are produced using a combination of methylxanthines, vitamin B complex, and unusual botanical ingredients to provide the customer with an energy boost [1].

Caffeinated energy drinks have been linked to negative cognitive consequences, including headaches, anxiety, tension, and exhaustion, according to numerous writers. Additional negative effects, such as sadness, insomnia, and irritability, were reported by others [2, 3].

The hippocampus, a component of the limbic system, is crucial for learning, emotions, and the consolidation of recent short-term memory into long-term memory. The limbic system, which links emotions and visceral states to thought and behavior, is made up of interrelated cortical and subcortical structures [4].

The majority of people who take energy drinks want to enhance their memory and other higher cognitive abilities. Nevertheless, there is currently no evidence linking the effects of energy beverages like Red Bull on hippocampus structure and memory [5].

Citrus flavonoid naringenin has drawn interest due to its neuroprotective qualities. It demonstrates a number of defense mechanisms against inflammation, oxidative damage, and apoptosis. Naringenin's protective effects against various neurotoxic chemicals have been shown in a number of investigations, which gives optimism for its application against organophosphorus neurotoxicity. Naringenin, for example, has demonstrated efficacy in lowering oxidative stress and

decreasing inflammation in models of neurotoxicity caused by other substances [6].

This narrative review evaluates the anatomical and functional changes that energy drinks cause in the hippocampus and also assesses the neuroprotective potential of naringenin, a naturally occurring flavonoid, in reducing these negative effects.

Energy Drinks: Adverse Effects

Energy drinks are a type of liquid product that usually contains caffeine, either with or without additional dietary supplements. In 1949, the first energy drink was introduced in the United States under the name "Dr. Enuf." They were first introduced in Europe in 1987, and once Red Bull was introduced in 1997, the market spread around the globe and gained immense popularity. Since then, the market for energy drinks has expanded significantly, and other brands have been introduced globally. In 2013, more than 5.8 billion liters of energy drinks were consumed annually in almost 160 countries. The retail energy drink market in the United States grew 56% between 2002 and 2006, with an anticipated total value of 12.5 billion USD in 2012 [7].

Recently, manufacturers have turned their attention from athletes to young people as their target market. In locations where teens and young people congregate, energy drinks are heavily advertised. Boys make up two-thirds of the market for energy drinks, and two-thirds of users are between the ages of 13 and 35. About 30% of young people regularly consume energy drinks, making them the second most popular dietary supplement among them in the United States. Energy drinks appear to be just as popular in the Kingdom of Saudi Arabia as they are elsewhere in the world. Approximately 50% of the Saudi

University students who took part in the survey acknowledged using energy on a regular basis [8].

Energy drinks are made with a blend of stimulants and energy boosters to provide the consumer with a "boost." Caffeine is the main ingredient in the majority of energy drinks. They typically include 80–150 mg of caffeine per 8 ounces, which is the same amount as two 12-ounce cans of caffeinated soda or five ounces of coffee. While some companies provide artificially sweetened variants, the majority of brands on the market include significant quantities of glucose. Taurine, methylxanthines, vitamin B, ginseng, guarana, yerba mate, acai, maltodextrin, inositol, carnitine, creatine, glucuronolactone, and ginkgo biloba are additional frequently utilized ingredients [9].

Potential adverse effects of energy drinks in relation to their ingredients

Cardiovascular effect

Numerous studies have demonstrated that consuming energy drinks causes an increase in arterial blood pressure and heart rate. These results were ascribed to the ergogenic effects of the energy drink's caffeine content. Furthermore, excessive consumption of energy drinks has been linked to serious cardiac symptoms like ventricular arrhythmias, ST segment elevation, and QT prolongation. Additionally, two healthy boys, ages 14 and 16, have been reported to develop atrial fibrillation following the consumption of high-energy drinks. Energy drink usage has recently been linked to myocardial infarction in boys aged 17 and 19 who are in good health. The results showing that energy drink consumption decreases endothelial function and increases platelet activity through arachidonic acid-induced platelet aggregation in healthy young adults corroborate this finding [10].

Gastrointestinal and metabolic effects

Energy drinks typically have high sugar contents, ranging from 21 to 34 grams per ounce. High fructose corn syrup, sucrose,

or glucose make up the majority of the sugar content. Consequently, consuming large amounts of energy drinks may raise the risk of type 2 diabetes and obesity. Furthermore, energy drinks' high sugar content may lower gut bacterial activity, diversity, and gene expression, raising the risk of obesity and the metabolic syndrome. Acute caffeine use reduces insulin sensitivity, which may account for the spike in blood sugar levels observed in certain studies following energy drink consumption. According to Beaudoin et al., caffeine consumption decreases insulin sensitivity in a dose-dependent way, increasing insulin by 5.8% for every mg/kg of caffeine consumed [11, 12].

Renal effects

It has been demonstrated that the caffeine in energy drinks increases diuresis. Because of the risk of dehydration, energy drinks should be avoided when exercising for extended periods of time in a hot climate. According to studies, a 1.5% level of dehydration after extended exercise may raise heart rate, body temperature, and perceived effort rate [13].

Additionally, caffeine encourages natriuresis, or the loss of salt in the urine, which affects plasma volume and significantly changes cardiovascular function during exercise. Furthermore, a sodium imbalance brought on by extended activity in a hot climate may lessen the legs' isometric force. According to Greene et al., a 40-year-old man experienced acute renal injury following two to three weeks of daily energy drink consumption. After quitting energy drinks, the blood creatinine rose five times from baseline and stabilized two days later [14].

Dental effects

Energy drinks and dental degradation are strongly correlated, according to a Swedish study. Marshall et al. also showed that American children exhibited a similar observation. The usage of energy drinks was linked to a roughly 2.4-fold increase in tooth deterioration. The low pH and high

sugar content of energy drinks have been blamed for this. Furthermore, Pinto et al. discovered that energy drink consumption may cause cervical dentin hypersensitivity by eliminating the teeth's smear layer [15].

Effects on the Neurological System

Manic psychosis, cerebral vasculopathy, and seizures are among the central nervous system side effects that can result from consuming energy drinks that contain caffeine and other chemicals. According to studies, these components overstimulate the adrenergic system, which results in metabolic acidosis, leukocytosis, hyperglycemia, and hypokalemia. Even at modest concentrations, caffeine exhibits psychostimulant effects [16].

By blocking adenosine A2A receptors and boosting transmission through dopamine

D2 receptors, caffeine improves dopamine-related behavior. Lorist and Tops highlighted the brain's alpha wavelength (alpha power) using an echoencephalograph (EEG). They discovered that caffeine use raised left frontal activation relative to right, indicating that dopamine function and exhaustion may be related, with caffeine alleviating fatigue. Less than 500 mg doses cause less sleep, less weariness, and enhanced alertness as well as faster speech and brain processes. Higher dosages can result in tremors, anxiety, sleeplessness, restlessness, and seizures that don't go away when antiepileptic medications are used (Figure 1) [17, 18].

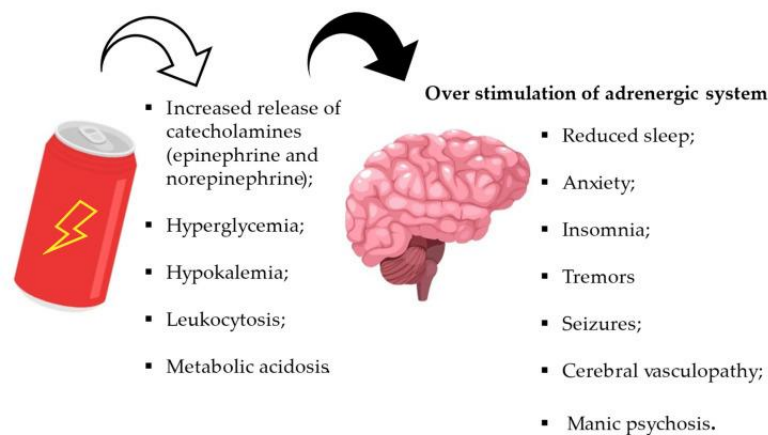


Figure 1. Pathological effects of energy drinks on cerebral tissues [16].

The potential for seizures has been linked to the consumption of extremely high (pharmacological) quantities of coffee. Caffeine administered intraperitoneally causes electroencephalogram-related convulsions in animal models. Seizures have been seen in humans following drug preparation intake or overdose. Both individuals with known epilepsy and those without a history of the condition have experienced seizures in response to energy drink use. The high caffeine content of energy drinks might be the cause of this [16].

Caffeine functions as an adenosine receptor antagonist with comparable affinity for A1 and A2A receptors at typical, average human dosages. Caffeine has a dominant effect on A1 receptors when given acutely (because ambient adenosine activates them). A1 receptor tolerance results from long-term caffeine consumption. Then, caffeine mostly affects A2A receptors while having minimal effects on A1 receptors. In reaction to increasing neuronal excitement, the endogenous ligands of the cannabinoid receptors, known as endocannabinoids, are

synthesized as needed. They activate the presynaptic CB1 receptor, lower the amounts of cyclic AMP (cAMP) produced, and limit the release of neurotransmitters. By inhibiting acetylcholine in the hippocampus and prefrontal cortex, controlling the opening of potassium channels mediated by A1 receptors, and speeding up the firing rate of A2A receptors in the striatum dendritic spines of neurons, caffeine enhances the release of neurotransmitters. Through cell activation and adenylate cyclase pathway stimulation, this inhibits glutamatergic thalamocortical neurons. Adenosine's stimulatory effects on cAMP are diminished by caffeine, which also inhibits A2A receptors [16].

By decreasing striatal neuron activity and disinhibiting thalamo-cortical projection neurons, caffeine can lessen the inhibition on striatal dopamine transmission. A2A receptor activation results in the synthesis of cAMP, whereas D2 receptor activation decreases cAMP production and results in an inverse control of cAMP-dependent protein kinase (PKA) activity. Caffeine gradually sensitizes cannabinoid CB1 receptors, which regulate GABAergic inhibitory postsynaptic currents (IPSCs), by imitating the impact of dopamine on striatopallidal neurons [19].

Glutamate release, mGlu5 metabotropic receptor activation, and endocannabinoid release are all enhanced when caffeine blockades A2A receptors, which decreases cAMP-PKA pathway activation. Caffeine's psychoactive effects have been related to its blockage of adenosine A2A receptors in the striatum. Additionally, there is proof that a particular genetic variation of the adenosine A2A receptor affects people's habitual intake of caffeine [20].

Richard and Smith looked at the research on energy drinks' long-term consequences on mental health. They came to the conclusion that whereas energy drinks seem to have good short-term impacts on mood, long-term use is linked to stress, anxiety, and depression. Taurine is a chemical that attaches itself to GABA receptors and penetrates the blood-brain barrier. It has the ability to replicate the actions of glycine and GABA, producing an anticonvulsant effect that stabilizes membranes both within and outside of cells [21].

Neurotoxicity and the Hippocampus

The limbic system includes the hippocampus (HC), which is crucial for short- and long-term memory formation, information consolidation, and spatial navigation. The dentate gyrus and cornu ammonis (CA) are two of the cortical tissues that make up the hippocampus formation (Fig. 2). The entorhinal cortex connects to the dentate gyrus, which serves as the main input into the hippocampus development. During postnatal life, the dentate gyrus's subgranular zone (SGZ), a subregion of the hippocampus situated at the base of the granule cell layer (GCL), unusually continues to produce new neurons. We refer to this process as "adult neurogenesis." Certain types of learning and memory depend on adult neurogenesis in the dentate gyrus, which is influenced by pathological circumstances. Morphological deformity and malfunction of the dentate gyrus are linked to certain neurological and mental conditions. Notably, mature rodents, primates, and humans all have high levels of hippocampus neurogenesis [22].

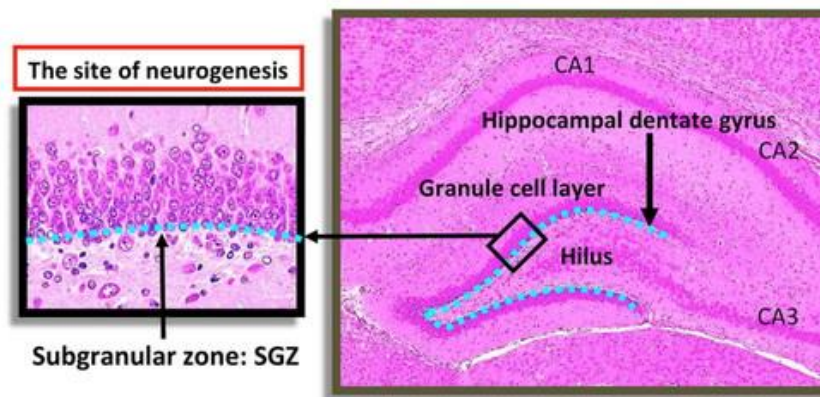


Figure 2. Neurogenesis in the dentate gyrus of the rat hippocampus [22].

Importance of the HC in cognition, memory, and learning

With its intricate internal circuitry, the HC, a crucial brain structure in the medial temporal lobe, promotes learning, memory formation, and cognitive processes. It is crucial for committing new knowledge and experiences to memory. As we learn new information, abilities, or spatial layouts, the HC interprets and combines these inputs into a symbolic representation through synaptic long-term potentiation (LTP). This process makes it possible for neurons to fire in unison, strengthening their bonds and promoting the development of memories. The HC integrates multimodal signals from the entorhinal cortex and amygdala to support declarative and episodic memories, which are essential to the conscious recall of experiences. Both short-term and long-term consolidations are supported by the coherent memory representations created by this integration [23].

With place cells firing in particular areas, the HC also supports navigation and spatial memory. This neural map facilitates the recall of ambient landmarks and item configurations. Notably, animals' ability to learn spatially is hampered by hippocampus lesions. In order to facilitate flexible thinking, reasoning, and decision-making, HC also mediates the relational coupling of distinct objects, occasions, or ideas. Connections between discontinuous events

are captured by its relational coding. Additionally, HC affects language, working memory, attention, executive functioning, and social cognition through its extensive cortical and subcortical connections. The HC plays an essential role in cognitive function, as evidenced by the wide-ranging cognitive deficits that arise from damage to it [24].

Sensitivity of the HC to external environments

Numerous studies conducted on both humans and animals have demonstrated that HC changes morphologically, functionally, and molecularly in response to a variety of environmental exposures throughout the course of a lifetime. Environmental stressors such as prolonged stress, noise, sleep disturbance, and microgravity alter the structure and volume of the hippocampus. After these exposures, studies show decreased dentate gyrus, CA thickness, and gray matter atrophy. Depending on the surroundings, HC functions with neurogenic, synaptic, and neuroendocrine plasticity. Stress, sensory input, and enriched settings all influence adult hippocampus neurogenesis, synaptic effectiveness through LTP or depression, and glucocorticoid (GC) signaling [25].

Environmental stressors alter the expression of genes in HC that govern its shape and structure at the molecular level. Changes in transcription patterns are seen in genes related to stress pathways, neurotrophin signaling, neurite outgrowth,

and synaptic remodeling. These effects are mediated by epigenetic changes. In reaction to outside stimuli, the HC demonstrates dynamic structural, functional, and molecular flexibility. To completely understand hippocampus-environment interactions and key times of vulnerability across various exposures and developmental stages, more research is necessary [26].

Environmental stressors and the HC

According to research, the HC is extremely malleable and sensitive, changing both structurally and functionally in response to external stimuli. According to neuroanatomy, stresses including long-term stress, noise, lack of sleep, and microgravity cause the hippocampus to shrink and subfields like the dentate gyrus and CA to atrophy, as shown by magnetic resonance imaging (MRI). These morphological changes are probably caused by elevated GC levels through (HPA) activation [27].

In terms of function, stresses change the expression of GC receptors, disrupt synaptic plasticity and LTP, and modify hippocampus neurogenesis in the dentate gyrus. Molecularly, pathways related to synaptic remodeling, neuronal outgrowth, neurotrophins, and the stress response itself exhibit variable gene expression brought on by stress. These alterations in gene regulation are mediated by epigenetic modifications. In conclusion, the HC shows significant adaptability in response to environmental stressors by altering its volume, cellular makeup, chemical mediators, and synaptic connections. Targeting therapies for stress-related diseases and comprehending cognitive resilience depend on elucidating the chronology of hippocampus sensitivity over life stages [28].

Observations in rodent studies

Rodent experiments in space or ground-based microgravity analogs have shown similar deficiencies in mapping and spatial recall. According to these results,

hippocampus function and related cognitive functions may be directly impacted by the microgravity environment [29].

Anatomical and physiological changes in the HC: Changes in the HC brought on by microgravity are probably linked to the cognitive impairments shown in rats and astronauts. Neuronal signaling pathways, neurogenesis, synaptic plasticity, and neuronal structure may all be affected [30].

Function of the HC in spatial cognition and contextual memory: The HC is essential for the integration of spatial and contextual information, as well as for the development of contextual memory. Impairments in several cognitive domains may result from microgravity-induced disruptions in hippocampus function [31].

Affective disorders and mood dysregulation: In addition to cognitive deficiencies, changes in hippocampus function have been connected to mood dysregulation and affective disorders. Astronauts may experience emotional and psychological difficulties both during and after extended space travel as a result of this. These results highlight how crucial it is to comprehend how microgravity affects the HC and related cognitive processes. In addition to creating countermeasures and interventions to lessen the detrimental effects of microgravity on the brain and cognitive function, addressing these concerns is essential for guaranteeing the health and performance of astronauts during prolonged space missions [26].

Oxidative stress

Radiation and poisons are two examples of environmental exposures that can raise the generation of reactive oxygen species (ROS) and harm hippocampus cells oxidatively. The HC's proper function may be hampered by oxidative stress, which can cause DNA damage, lipid peroxidation, and neuronal death. Because of its rapid metabolic rate and very weak antioxidant defenses, the HC is especially susceptible to oxidative damage. The negative effects of oxidative stress on the HC brought on by

specific environmental exposures may be lessened by interventions using antioxidant therapies and substances with free radical scavenging capabilities. For neuronal integrity, synaptic plasticity, and cognitive function to be maintained—especially in demanding environments—the HC must maintain a balance between oxidants and antioxidants. To protect the HC and cognitive functions during spaceflight and other harsh environments, it may be helpful to comprehend the mechanisms of oxidative stress and create targeted antioxidant therapy [32].

Neurogenesis in the Hippocampus

Several developmental phases, including stem cell self-renewal, facilitating

precursor cell division to produce newborn granule cells, and the subsequent differentiation and migration of new granule cells to the proper location within the GCL, comprise adult neurogenesis in mammals (Figs. 3 and 4). In the dentate gyrus's SGZ, stem cells (type-1) divide slowly to become intermediate progenitor cells, which are a subset of transient amplifying cells. In the hippocampus dentate gyrus, undifferentiated intermediate progenitor cells (type-2a and type-2b) proliferate quickly to become neuronally committed intermediate progenitor cells (type-3), which respond to stimuli that affect neuronal formation [33].

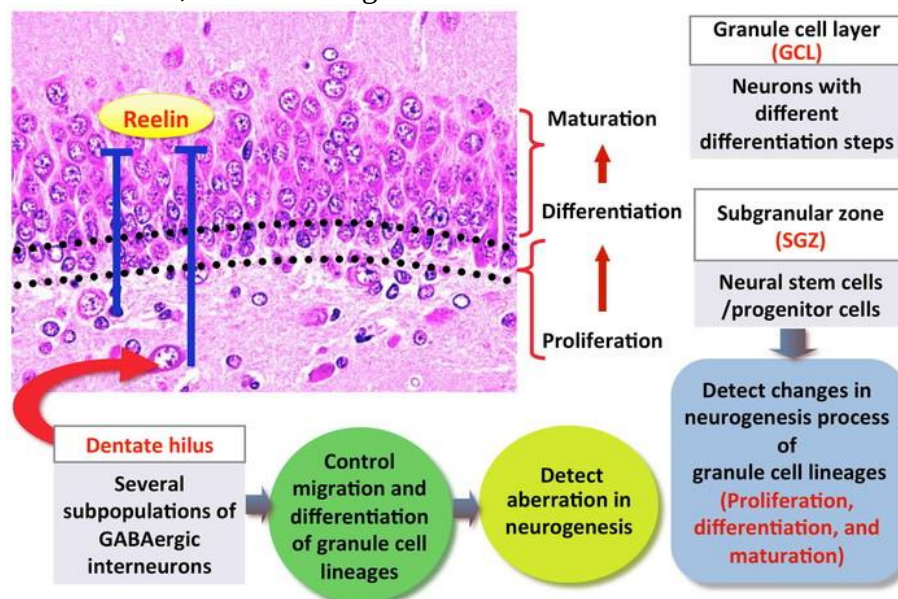


Figure 3. Schematic presentation of adult neurogenesis in the hippocampal dentate gyrus [22].

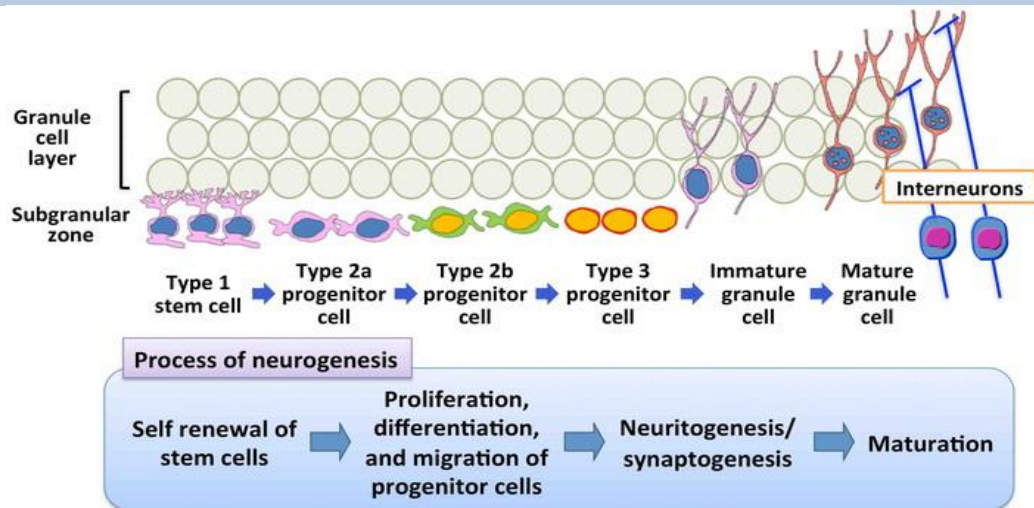


Figure 4. Generation of granule cell lineages in the hippocampal dentate gyrus [22].

Postmitotic immature neurons are produced by type-3 intermediate progenitor cells, and those neurons that make it through the regulatory phase integrate as granule cells into the GCL. Changes in the complete processes of the granule cell lineages can be identified by tracking cellular subpopulations in the SGZ and GCL, as well as cell proliferation activity and apoptosis in the SGZ (Fig. 5). For this purpose, immunohistochemical analysis could be a powerful tool for detection of target cells using primary antibodies against proliferating cell nuclear antigen (PCNA), a cell proliferation marker, brain lipid binding protein (BLBP), expressed in radial glia as type-1 cells in the brain,

paired box 6 (Pax6), expressed in type-1 stem cells and type-2a progenitor cells, SRY (sex determining region Y)-box 2 (Sox2), expressed in type-1 stem cells and type-2a and type-2b progenitor cells, T box brain 2 (Tbr2), expressed in type-2b progenitor cells, dihydropyrimidinase-like 3 (Dpysl3), also known as Tuc4, an early postmitotic cell marker of immature granule cells, NeuroD1 (Nd1), expressed in type-3 progenitor cells and immature granule cells, and doublecortin (Dcx), expressed in type-3 progenitor cells and immature granule cells, as well as measurement of apoptosis utilizing terminal deoxynucleotidyl transferase-mediated dUTP-biotin nick end-labeling assay [22].

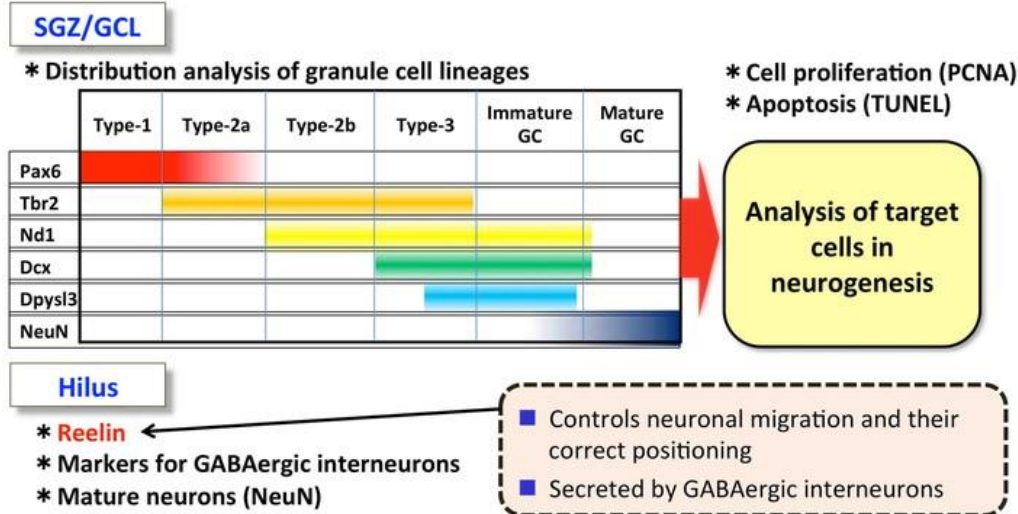


Figure 5. identification of abnormalities in rodents' hippocampus neurogenesis.

Cellular markers like paired box 6 (Pax6), T box brain 2 (Tbr2), NeuroD1 (Nd1),

doublecortin (Dcx), dihydropyrimidinase-like 3 (Dpysl3), and neuron-specific nuclear protein (NeuN) in the subgranular zone (SGZ) and granule cell layer (GCL) can be used to immunohistochemically analyze the distribution of granule cell lineages. It is also possible to quantify cell growth and apoptosis in the SGZ. Immunohistochemical analysis of the dentate gyrus's hilus can reveal the distribution of neuronal inputs from outside the SGZ, including GABAergic interneurons and reelin-producing cells [22].

The increase in GABAergic interneurons that produce reelin in the dentate hilus (Fig. 6) indicates that acrylamide inhibits rat offspring's hippocampus neurogenesis, according to research of maternal exposure to the chemical using rats. Using a similar developmental exposure model, they then investigated the cellular target of acrylamide on hippocampal neurogenesis and its reversibility following maternal exposure. They discovered reversible affection of neurogenesis that targets the proliferation of type-3 progenitor cells, resulting in a decrease of immature granule cells (Fig. 6) [34].

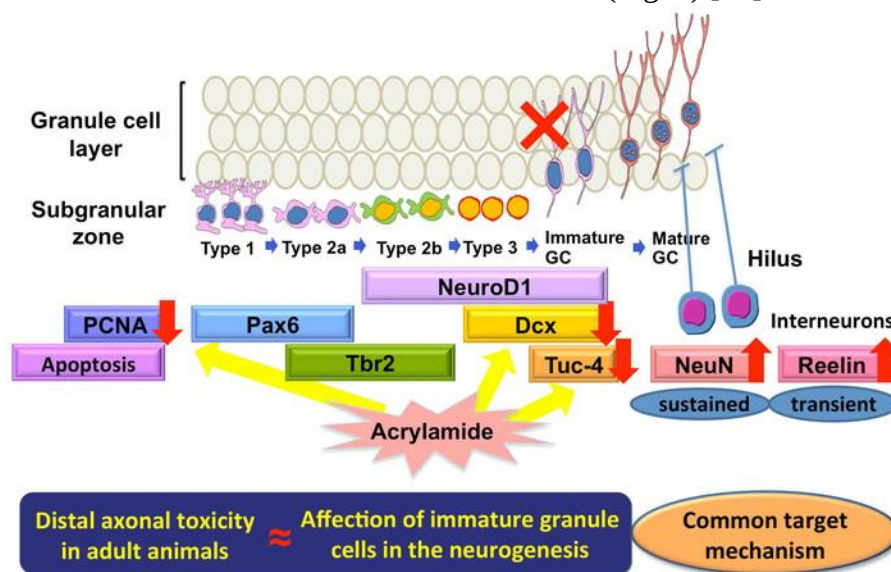


Figure 6. Developmental neurotoxic target of acrylamide in the process of hippocampal neurogenesis in rats [22].

It is known that juvenile granule cells in the SGZ already feature recurrent basal dendrites and dendritic growth cones, indicating an entry into the synaptogenesis process. It was proposed that acrylamide directly damages young granule cells by influencing the newly forming nerve terminals because it targets nerve terminals by impairing neurotransmission through a variety of nerve terminal activities. Crucially, we also discovered that acrylamide inhibited the growth of progenitor cells without also promoting their demise. Acrylamide may instead

target earlier type-3 progenitor cells to restrict their proliferation, resulting in a decrease in immature granule cells, since immature granule cells are no longer able to proliferate [35].

Following embryonic exposure, axon terminal toxicant was observed to exhibit a similar target cell population at the late-stage differentiation in hippocampus neurogenesis. Inducing distal axonopathy in dams and reducing immature granule cells in the SGZ of offspring were the findings of a developmental exposure study to glycidol (Fig. 7). The International

Agency for Research on Cancer (IARC) has categorized glycidol as a group 2A carcinogen, meaning it is "probably carcinogenic to humans." Due to the potential for glycidol to be released by the hydrolysis of glycidol fatty acid esters in the gastrointestinal system, glycidol exposure through food has recently raised concerns around the world. Infant formulae and other refined dietary oils and fats include glycidol fatty acid esters,

particularly in high amounts in diacylglycerol oil [36].

A 13-week repeated oral dose toxicity study in rats and mice revealed neurotoxicity with cerebellar necrosis. The findings of the developmental exposure research of glycidol indicate that, like acrylamide, glycidol suppresses late-stage hippocampus neurogenesis by targeting the newly forming nerve terminals of immature granule cells (Fig. 7) [22].

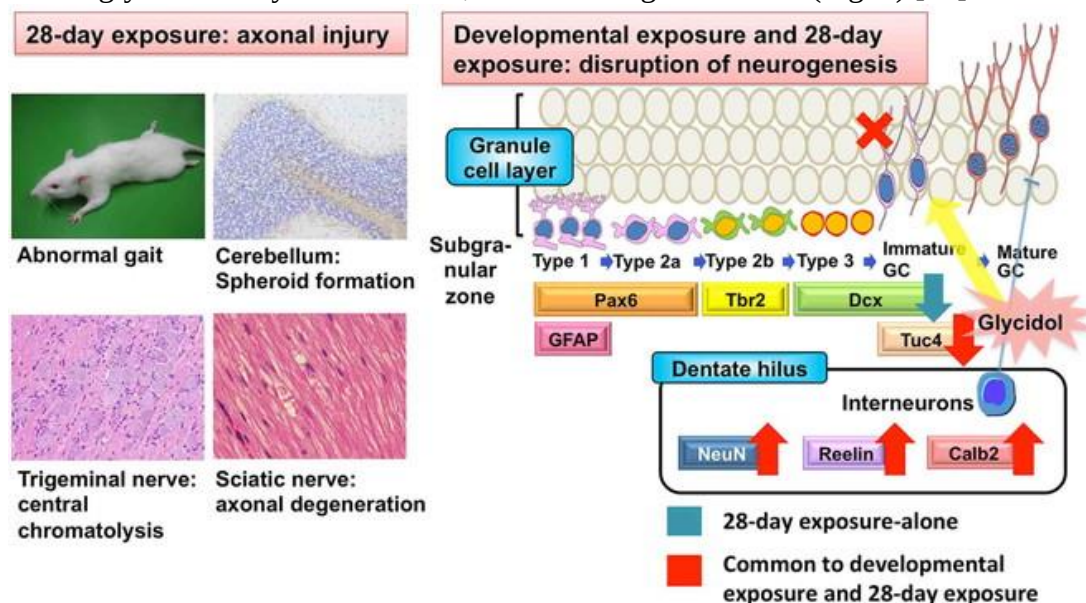


Figure 7. Comparison of the effect on hippocampal neurogenesis between developmental exposure study and 28-day exposure study of glycidol in rats [22].

Detection of developmental neurotoxicity (DNT) in a Framework of 28-day Regular Toxicity Study

It seems sense to include the toxicity of the neurogenesis process in a framework of routine toxicity studies, like a 28-day repeated oral dose toxicity study, as postnatal adult neurogenesis persists into the adult stage. They used glycidol as an axon terminal toxicant and MMI as an ATA in a repeated oral dose toxicity trial to examine the effects on neurogenesis in order to shed light on this potential [37].

From gestational day (GD) 10 to weaning on day 21 postpartum (developmental hypothyroidism), pregnant rats were treated to MMI in the MMI research (38). By establishing a comparable exposure period

from postnatal day (PND) 46 to PND 77 (adult-stage hypothyroidism), adult male rats were also exposed to MMI. Consequently, during developmental hypothyroidism, a temporary decrease in Dcx⁺ late-stage progenitor cells and a persistent decrease in Pax6⁺ stem or early progenitor cells were noted (Fig. 1S). The adult stage of hypothyroidism had no effect on these cells. However, following both embryonic and adult-stage hypothyroidism with MMI, the dentate hilus showed an increase in Calb2⁺ interneurons and a decrease in Pvalb⁺ GABAergic interneurons (Fig. 1S). The findings suggest that the unifying characteristic of both embryonic and adult-stage hypothyroidism is variations in GABAergic

interneuron subpopulations. Given their function in neurogenesis, variations in GABAergic interneuron subpopulations could offer a sensitive method for identifying abnormal neurogenesis even after exposure at the adult stage. Additionally, they propose that the examination of interneuron subpopulations could serve as a means of identifying minor alterations in neurogenesis, especially for routine toxicity studies like the 28-day repeated-oral dose-toxicity test [38].

Glycidol was administered by gavage to male young adult rats for 28 days (adult-stage exposure research) and to pregnant rats from GD 6 until weaning on day 21 postpartum (developmental exposure study). Offspring in the developmental exposure research increased juvenile reelin⁺ or Calb2⁺ GABAergic interneurons and NeuN⁺ mature neurons in the dentate hilus upon weaning, while decreasing Dpysl3⁺ immature granule cells in the SGZ [37].

Hilar alterations persisted until the adult stage, when the SGZ modification vanished but reelin⁺ interneurons and NeuN⁺ mature neurons increased. Animals in the adult-stage exposure research showed abnormalities in neurogenesis at the late-stage differentiation, as shown by increases in reelin⁺ and Calb2⁺ GABAergic interneurons and NeuN⁺ mature neurons in the dentate hilus and decreases in both Dcx⁺ and Dpysl 3⁺ cells in the SGZ. These findings imply that glycidol inhibits late-stage hippocampus neurogenesis in both developmental and adult-stage exposure studies by targeting the newly generated nerve terminals of immature granule cells [22].

Naringenin:

Chemistry of Naringenin and Its Sources

One of the most important naturally occurring flavonoids (I) is naringenin. The three rings (A, B, and C) make up the fundamental structure of flavonoids (I). The chemical name of naringenin (II) is 2,3-dihydro-5,7-dihydroxy-2-(4-

hydroxyphenyl) 4-H-1-benzopyran-4-one, and its molecular formula is C₁₅H₁₂O₅. It has a melting point of 251 °C and a molecular weight of 272.26 g•mol⁻¹. This molecule dissolves in organic solvents like alcohol but is insoluble in water. Naringenin is found in aglycone form or its glycosidic form, naringenin-7-O-glucoside. Naringin (naringenin-7-rhamnoglucoside) and narirutin (naringenin-7-O-rutinoside) are other glycosidic forms of naringenin (Figure 2S). Depending on their sugar moiety, naringenin glycosides bind to the flavonoid via a glycosidic bond at C7. When particular enzymes break these glycosides, naringenin (aglycone) is produced [39, 40].

The fundamental structure of naringenin, a flavonoid, is biosynthesized through the metabolic pathways of acylpolymalonate and shikimic acid. Phenylpropane, a derivative of cinnamic acid that is generated from shikimic acid, is a beginning molecule. Three acetate residues are added, and then the ring is closed. The flavone structures, which may be hydroxylated and reduced at various locations, are intermediate to the chalcone structure. (Figure 3S) [41].

The arrangement of similar functional groups in naringenin's structure determines its spectrum of pharmacological characteristics. High reactivity against reactive oxygen species (ROS) and reactive nitrogen species is exhibited by the hydroxyl groups (OH). After giving electrons to free radicals, the 5,7-m-dihydroxy arrangement in ring (A) stabilizes the structure. The chelation of substances like heavy metals is facilitated by the interaction of 5-OH and 4-oxo substituents [42].

Citrus fruits include the (2S)- and (2R)-enantiomer versions of naringenin, which have a single chiral center at carbon 2 (C2). Over pH 9–11, it has been shown to be resistant to enantiomerization. For more than 20 years, enantiomer separation has been investigated, mostly using high-

performance liquid chromatography (HPLC) on chiral stationary phases generated from polysaccharides. The broad range in naringenin's reported bioactivity has been explained by evidence pointing to stereospecific pharmacokinetic and pharmacodynamic characteristics [43].

The most prevalent flavonoids in plants include flavanols, flavones, flavanones, isoflavones, and anthocyanidins. They are also powerful free radical scavengers. Both naringenin and naringin are strong antioxidants and are promising flavonoids; however, naringin is less effective due to the steric hindrance of the scavenging group caused by the sugar moiety. Compared to the aglycone form, the naringenin-7-glucoside form appears to be less bioavailable. A wide range of fruits, vegetables, and nuts, including grapefruit, bergamot, sour orange, tart cherries, tomatoes, cocoa, Greek oregano, water mint, drynaria, beans, and drinks like coffee, tea, and red wine, as well as medicinal herbs, have been found to contain naringenin and its glycoside [44, 45].

Naringenin and Neurotoxicity

The neurotransmitter glutamate, metals (iron, sodium tungstate, aluminum), and hypoxia are among the neurotoxicant agents that can cause extensive neurobehavioral alterations and brain and spinal damage. By causing an excessive production of ROS, hypobaric hypoxia contributes to neuronal death and behavioral impairment. The apoptotic pathway and the increase of hypoxia-inducible factor 1 α (HIF 1 α) and its primary target protein, vascular endothelial growth factor (VEGF), are both caused by hypoxia. After neurotoxicity, there is an increase in free radicals and a decrease in antioxidants, which is then connected to the onset of NDs [46].

Naringenin is a desirable option for the treatment of neurotoxicity because of its anti-inflammatory and free radical scavenging qualities. Naringenin

pretreatment reduced behavioral impairment in mice exposed to hypoxia. Additionally, by inhibiting caspase-3 and ubiquitin and downregulating HIF1 α and VEGF, naringenin reduced hypoxia-induced oxidative stress and apoptosis. Additionally, as ubiquitin E3 ligases or accumulated proteins in NDs, naringenin increased the amounts of parkin and chip. Additionally, naringenin decreased oxidative stress (by reducing ROS), repressed apoptosis (by suppressing Bax and caspase-3 and upregulating Bcl-2), and enhanced the survival of mouse neuroblastoma cells after carbaryl-induced toxicity. Additionally, it reversed the carbaryl-induced decrease in mitochondrial membrane potential [47].

Furthermore, by reducing the production of ROS, increasing endogenous antioxidant capacity (GSH, CAT, SOD), upregulating AChE activity, and increasing ectonucleotidase enzymes (like adenosine triphosphate diphosphohydrolase and 50-nucleotide enzyme), which control extracellular ATP and adenosine concentrations in the synaptic cleft, naringenin demonstrated neuroprotective effects against iron-induced neurotoxicity and anxiety-like behavioral deficit. Naringenin reduced neurotoxicity by considerably restoring the reduced amount of mitochondrial complex I–V enzyme activity and mitochondrial membrane potential [48].

Co-administration of iron and naringenin may have eliminated oxidative insult indicators such as MDA, NO, ROS production, and protein carbonyl content in a related investigation. In the cerebral cortex of rats exposed to iron, naringenin also markedly increased enzymatic and non-enzymatic antioxidant activities, along with an increase in AChE and Na⁺/K⁺ ATPase activity. Furthermore, naringenin and iron co-treatment reduced apoptotic damage, which was supported by a reduction in DNA fragmentation brought on by endogenous endonucleases.

Furthermore, iron-induced morphological alterations (necrotic cells with a pyknotic nucleus and vacuolated gaps) were lessened by naringenin [49].

In a rat model of sodium tungstate-induced neurological changes, Sachdeva and colleagues found that co-administration of naringenin and N-acetylcysteine (NAC) for three months dramatically recovered biogenic amines (dopamine, 5-HT, and NE). By raising GSH and inhibiting TBARS in the brain, co-administration of naringenin and NAC also decreased oxidative stress in their study [50].

Naringenin's neuroprotective properties against glutamate and associated downstream molecular processes were investigated. By decreasing caspase 3 and calpain1 (Ca²⁺-dependent protease), also referred to as the caspase-independent pathway, naringenin may have prevented excitotoxicity and eliminated apoptosis. In primary culture of mouse hippocampus neurons treated with naringenin, phosphorylated Akt and ERK were markedly increased, favoring neuronal survival and demonstrating a critical function in apoptotic regulation [51].

According to a different molecular perspective, the remyelination process depends critically on brain fatty acid-binding protein 7 (FABP7). By improving neurophysiological factors (increased total antioxidant capacity, Ca ATPase, and FABP7) and suppressing oxidative stress by blocking total oxidant capacity, total nitrite oxide, and cytochrome P450 activation, naringenin demonstrated neuroprotective activity against oseltamivir-induced neurotoxicity [52].

The use of naringenin to treat neurodegenerative disorders (NDs) has shown promise. The molecular processes behind naringenin's neuroprotective impact in the fight against NDs are shown in Figure 4S [40].

CONCLUSION:

Through a variety of pathophysiological processes, this narrative review shows that

energy drinks seriously jeopardize the integrity and function of the hippocampus. Energy drinks' high caffeine and other stimulants promote oxidative stress, interfere with neurogenesis, and change the structure of the hippocampus, especially the dentate gyrus and CA regions that are important for memory formation and cognitive function. Naringin supplementation may be a useful therapeutic and preventive measure for people who are susceptible to energy drink-induced neurotoxicity, according to the research that has been presented. To determine the best dose schedules, bioavailability factors, and long-term safety profiles for clinical use, more investigation is necessary. Since energy drink consumption is rising worldwide, especially among teenagers and young people, it is critical for public health to comprehend these neurotoxic effects and create protective measures. This review emphasizes how crucial it is to control energy drink intake and investigate natural neuroprotective substances like naringin as possible treatment options.

No potential conflict of interest was reported by the authors.

REFERENCES

1. Abdel-Kareem R, Hulail ME, Mohamed GA, Qenawy NM. Structural and biochemical changes induced by energy drinks in the pancreas of adult male albino rats: ameliorative effect of green tea. *Egypt J Histol* 2023;46(3):1236–51.
2. Guilbeau JR. Health risks of energy drinks: what nurses and consumers need to know. *J Nurs Fam Womens Health* 2012;16(5):423–8.
3. Buck R, Dixon J, Matjasich L, Petersen R. Energy drink consumption among adolescents and young adults: health effects and implications for practice. Westminster College, Salt Lake City 2013.
4. Kamar SA, Malak HWA, Saad SA. Effect of caffeinated energy drinks on the structure of hippocampal cornu ammonis 1 and dentate gyrus of adult male albino rats. *Anat Cell Biol* 2020;53(3):330–41.
5. Malinauskas BM, Aeby VG, Overton RF, Carpenter-Aeby T, Barber-Heidal K. A survey of

- energy drink consumption patterns among college students. *Nutr J* 2007;6:35.
6. Saati AA. Naringenin's neuroprotective effect on diazino-induced cerebellar damage in male albino rats, with modulation of acetylcholinesterase. *J Basic Sci* 2025;15(3):242.
7. Bailey RL, Saldanha LG, Gahche JJ, Dwyer JT. Estimating caffeine intake from energy drinks and dietary supplements in the United States. *Nutr Rev* 2014;72(suppl 1):9–13.
8. Alsunni AA, Badar A. Energy drinks consumption pattern, perceived benefits and associated adverse effects amongst students of University of Dammam, Saudi Arabia. *J Ayub Med Coll Abbottabad* 2011;23(3):3–9.
9. Alsunni AA. Are energy drinks physiological? *Pak J Physiol* 2011;7(1):44–9.
10. Pommerening MJ, Cardenas JC, Radwan ZA, Wade CE, Holcomb JB, Cotton BA. Hypercoagulability after energy drink consumption. *J Surg Res* 2015;199(2):635–40.
11. Jovel CE, Mejia FS. Caffeine and headache: specific remarks. *J Neurol* 2017;32(6):394–8.
12. Beaudoin MS, Allen B, Mazzetti G, Sullivan PJ, Graham TE. Caffeine ingestion impairs insulin sensitivity in a dose-dependent manner in both men and women. *Appl Physiol Nutr Metab* 2013;38(2):140–7.
13. Alsunni AA. Energy drink consumption: beneficial and adverse health effects. *Int J Health Sci* 2015;9(4):468–74.
14. Greene E, Oman K, Lefler M. Energy drink–induced acute kidney injury. *Ann Pharmacother* 2014;48(10):1366–70.
15. Pinto SC, Bandeca MC, Silva CN, Cavassim R, Borges AH, Sampaio JE. Erosive potential of energy drinks on the dentine surface. *BMC Res Notes* 2013;6:67.
16. Costantino A, Maiese A, Lazzari J, Casula C, Turillazzi E, Frati P, et al. The dark side of energy drinks: a comprehensive review of their impact on the human body. *Nutrients* 2023;15(18):1–23.
17. Morgan JC, Sethi KD. Drug-induced tremors. *Lancet Neurol* 2005;4(12):866–76.
18. Lorist MM, Tops M. Caffeine, fatigue, and cognition. *Brain Cogn* 2003;53(1):82–94.
19. Rossi S, De Chiara V, Musella A, Mataluni G, Sacchetti L, Siracusano A, et al. Effects of caffeine on striatal neurotransmission: focus on cannabinoid CB1 receptors. *Neuropharmacology* 2010;54(4):525–31.
20. Persad LAB. Energy drinks and the neurophysiological impact of caffeine. *Front Neurosci* 2011;5:116.
21. Richards G, Smith AP. A review of energy drinks and mental health, with a focus on stress, anxiety, and depression. *J Caffeine Res* 2016;6(2):49–63.
22. Shibutani M. Hippocampal neurogenesis as a critical target of neurotoxicants contained in foods. *Food Saf* 2015;3(1):1–15.
23. Nomoto M, Murayama E, Ohno S, Okubo-Suzuki R, Muramatsu S-i, Inokuchi K. Hippocampus as a sorter and reverberatory integrator of sensory inputs. *Nat Commun* 2022;13(1):7413.
24. Clemente L, Gasparre D, Alfeo F, Battista F, Abbatantuono C, Curci A, et al. Theory of mind and executive functions in individuals with mild cognitive impairment or healthy aging. *Front Psychol* 2023;13(10):1356.
25. Lee MT, Peng W-H, Kan H-W, Wu C-C, Wang D-W, Ho YC. Neurobiology of depression: chronic stress alters the glutamatergic system in the brain—focusing on AMPA receptor. *Biomedicine* 2022;10(5):1005.
26. Albadawi EA. Structural and functional changes in the hippocampus induced by environmental exposures. *Neurobiol J* 2025;30(1):5–19.
27. Rezaei S, Seyedmirzaei H, Gharepapagh E, Mohagheghfard F, Hasankhani Z, Karbasi M, et al. Effect of spaceflight experience on human brain structure, microstructure, and function: systematic review of neuroimaging studies. *Neurosci Biobehav Rev* 2024;18(5):1256–79.
28. Sanacora G, Yan Z, Popoli M. The stressed synapse 2.0: pathophysiological mechanisms in stress-related neuropsychiatric disorders. *Nat Rev Neurosci* 2022;23(2):86–103.
29. Rocha M, Wang D, Avila-Quintero V, Bloch MH, Kaffman A. Deficits in hippocampal-dependent memory across different rodent models of early life stress: systematic review and meta-analysis. *Transl Psychiatry* 2021;11(1):231.
30. Krukowski K, Grue K, Becker M, Elizarraras E, Frias ES, Halvorsen A, et al. The impact of deep space radiation on cognitive performance: from biological sex to biomarkers to countermeasures. *Sci Adv* 2021;7(42):eabg6702.
31. Julian JB, Doeller CF. Remapping and realignment in the human hippocampal formation predict context-dependent spatial behavior. *Nat Neurosci* 2021;24(6):863–72.
32. El-Missiry MA, Shabana S, Ghazala S, Othman AI, Amer ME. Melatonin exerts a neuroprotective effect against γ -radiation-induced brain injury in the rat through the modulation of neurotransmitters, inflammatory cytokines, oxidative stress, and apoptosis. *Environ Sci Pollut Res Int* 2021;28(24):31108–21.
33. Steiner B, Klempin F, Wang L, Kott M, Kettenmann H, Kempermann G. Type-2 cells as link between glial and neuronal lineage in adult hippocampal neurogenesis. *Glia* 2006;54(8):805–13.
34. Ogawa B, Wang L, Ohishi T, Taniai E, Akane H, Suzuki K, et al. Reversible aberration of neurogenesis targeting late-stage progenitor cells in

- the hippocampal dentate gyrus of rat offspring after maternal exposure to acrylamide. *Toxicol Sci* 2012;86(5):779–90.
35. LoPachin RM, Barber DS, Gavin T. Molecular mechanisms of the conjugated α , β -unsaturated carbonyl derivatives: relevance to neurotoxicity and neurodegenerative diseases. *Toxicol Sci* 2008;104(2):235–49.
 36. Bakhiya N, Abraham K, Gürtler R, Appel KE, Lampen A. Toxicological assessment of 3-chloropropane-1,2-diol and glycidol fatty acid esters in food. *Mol Nutr Food Res* 2011;55(4):509–21.
 37. Akane H, Shiraki A, Imatanaka N, Akahori Y, Itahashi M, Abe H, et al. Glycidol induces axonopathy and aberrations of hippocampal neurogenesis affecting late-stage differentiation by exposure to rats in a framework of 28-day toxicity study. *Toxicol Pathol* 2014;224(3):424–32.
 38. Shiraki A, Akane H, Ohishi T, Wang L, Morita R, Suzuki K, et al. Similar distribution changes of GABAergic interneuron subpopulations in contrast to the different impact on neurogenesis between developmental and adult-stage hypothyroidism in the hippocampal dentate gyrus in rats. *Toxicol Sci* 2012;86(10):1559–69.
 39. Jiménez-Moreno N, Cimminelli MJ, Volpe F, Ansó R, Esparza I, Mármol I, et al. Phenolic composition of artichoke waste and its antioxidant capacity on differentiated Caco-2 cells. *Antioxidants* 2019;11(8):1723.
 40. Nouri Z, Fakhri S, El-Senduny FF, Sanadgol N, Abd-ElGhani GE, Farzaei MH, et al. On the neuroprotective effects of naringenin: pharmacological targets, signaling pathways, molecular mechanisms, and clinical perspective. *Biomolecules* 2019;9(11):690.
 41. Patel K, Singh GK, Patel DK. A review on pharmacological and analytical aspects of naringenin. *Chin J Integr Med* 2018;24(7):551–60.
 42. Heim KE, Tagliaferro AR, Bobilya DJ. Flavonoid antioxidants: chemistry, metabolism and structure–activity relationships. *J Nutr Biochem* 2002;13(10):572–84.
 43. Gaggeri R, Rossi D, Collina S, Mannucci B, Baieri M, Juza M. Quick development of an analytical enantioselective high performance liquid chromatography separation and preparative scale-up for the flavonoid naringenin. *J Chromatogr A* 2011;1218(32):5414–22.
 44. Vallverdu-Queralt A, Odriozola-Serrano I, Oms-Oliu G, Lamuela-Raventós RM, Elez-Martinez P, Martin-Belloso O. Changes in the polyphenol profile of tomato juices processed by pulsed electric fields. *J Agric Food Chem* 2012;60(38):9667–72.
 45. Sung Y-Y, Kim D-S, Yang W-K, Nho KJ, Seo HS, Kim YS, et al. Inhibitory effects of *Drynaria fortunei* extract on house dust mite antigen-induced atopic dermatitis in NC/Nga mice. *J Ethnopharmacol* 2012;144(1):94–100.
 46. Cheraghi G, Hajiabedi E, Niaghi B, Nazari F, Naserzadeh P, Hosseini MJ. High doses of sodium tungstate can promote mitochondrial dysfunction and oxidative stress in isolated mitochondria. *J Biochem Mol Toxicol* 2019;33(4):e22266.
 47. Muthaiah VPK, Venkitasamy L, Michael FM, Chandrasekar K, Venkatachalam S. Neuroprotective role of naringenin on carbaryl induced neurotoxicity in mouse neuroblastoma cells. *J Pharmacol Pharmacother* 2013;4(3):192–8.
 48. Chtourou Y, Fetoui H, Gdoura R. Protective effects of naringenin on iron-overload-induced cerebral cortex neurotoxicity correlated with oxidative stress. *Biol Trace Elem Res* 2014;158(3):376–83.
 49. Chtourou Y, Slima AB, Gdoura R, Fetoui H. Naringenin mitigates iron-induced anxiety-like behavioral impairment, mitochondrial dysfunctions, ectonucleotidases and acetylcholinesterase alteration activities in rat hippocampus. *Neurochem Res* 2015;40(8):1563–75.
 50. Sachdeva S, Pant SC, Kushwaha P, Bhargava R, Flora SJ. Sodium tungstate induced neurological alterations in rat brain regions and their response to antioxidants. *Food Chem Toxicol* 2015;82:64–71.
 51. Fakhri S, Dargahi L, Abbaszadeh F, Jorjani M. Effects of astaxanthin on sensory-motor function in a compression model of spinal cord injury: involvement of ERK and AKT signalling pathway. *Eur J Pharmacol* 2019;23(4):750–64.
 52. Hegazy HG, Ali EH, Sabry HA. The neuroprotective action of naringenin on oseltamivir (Tamiflu) treated male rats. *J Basic Appl Zool* 2016;77:83–90.

Supplementary material

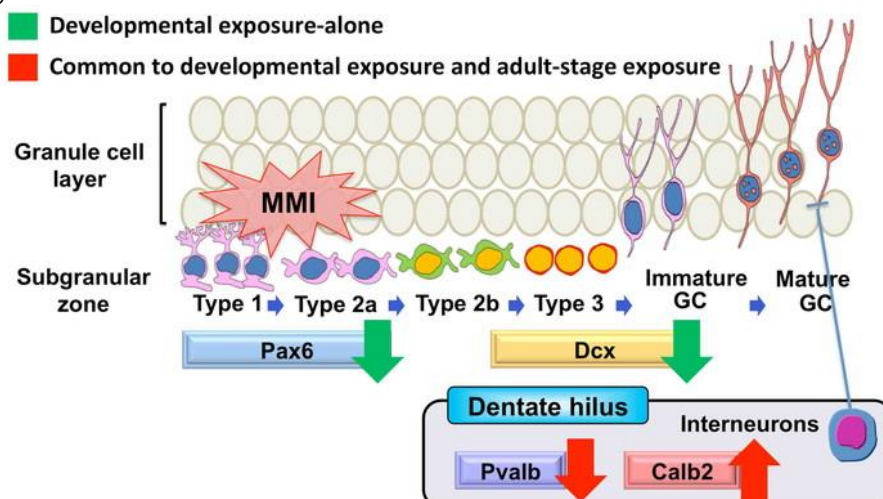


Figure 1S. Comparison of the effect on hippocampal neurogenesis between developmental exposure study and adult-stage exposure study of methimazole (MMI) in rats [22].

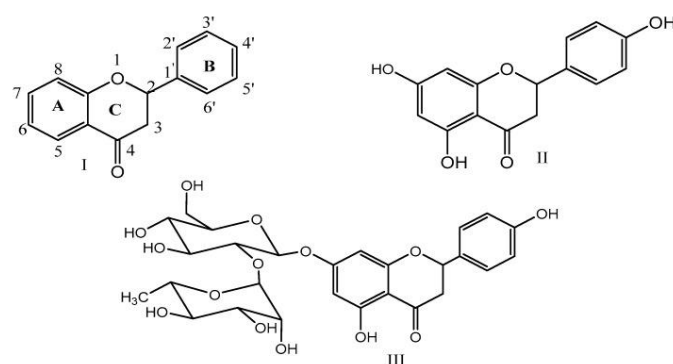


Figure 2S. Structures of flavonoids (I); naringenin (II); and naringin (III) [40].

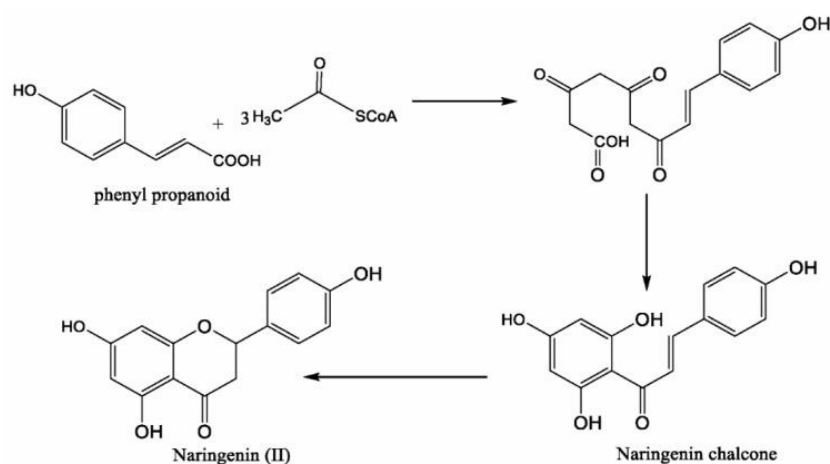


Figure 3S. Biosynthesis of naringenin [40].

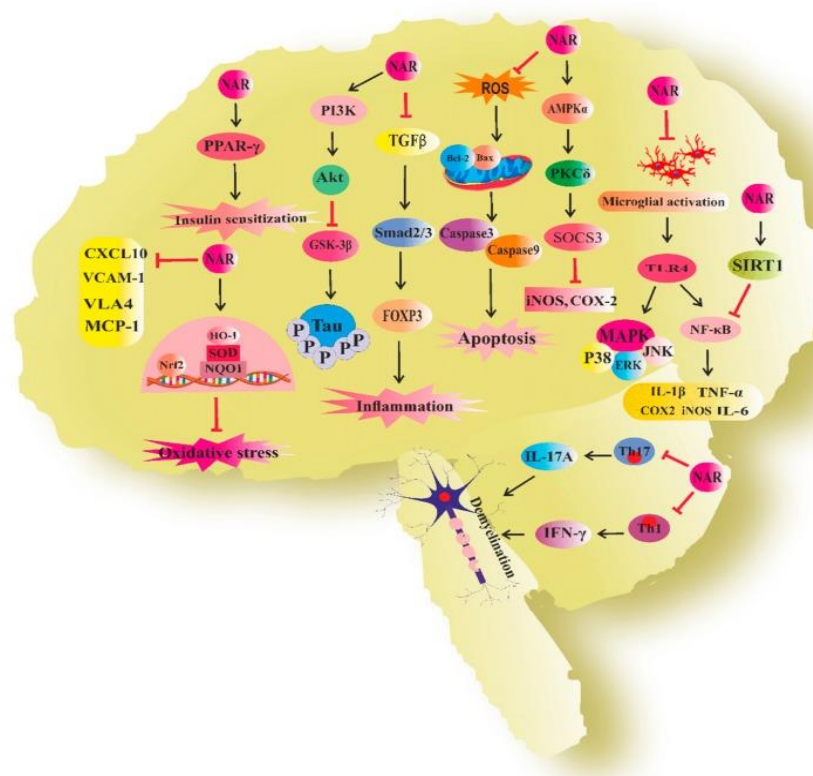


Figure 4S. Naringenin's neuroprotective actions. Naringenin, NAR; VLA4, very late antigen 4; VCAM-1, vascular cell adhesion molecule-1; MCP-1, monocyte chemoattractant protein-1; Nrf2, nuclear factor E2-related factor 2; HO-1, hemoxygenase-1; SOD, superoxide dismutase; PPAR- γ , peroxisome proliferator-activated receptor gamma; CXCL10, C-X-C motif chemokine ligand 10; GSK3- β , glycogen synthase kinase3- β ; PI3K/AKT, phosphoinositide 3-kinase/AKT; NQO-1, NAD(P)H quinone dehydrogenase1; Foxp3, forkhead box P3;

Treg, regulatory T cell; Th1, T helper1; iNOS, inducible nitric oxide synthase; TGF- β , transforming growth factor- β ; COX-2, cyclooxygenase-2; SOCS-3, suppressor of cytokine signaling 3; AMPK α , (AMP)-activated protein kinase α ; PKC δ , protein kinase C δ ; JNK, c-Jun N terminal kinase; ERK, extracellular-signal-regulated kinase; MAPK, mitogen-activated protein kinase; TNF- α , tumor necrosis factor α ; INF- γ , interferon γ ; IL-1 β , interleukin 1 β ; NF- κ B, nuclear factor- κ B; TLR4, toll-like receptor 4; ROS, reactive oxygen species [40].

Citation

Mohammed, H., Mohamed, E., Ibrahim, A., Agaga, R. Naringenin Ameliorates Energy Drinks-Induced Structural Alterations of The Hippocampus in Rats: A Narrative Review. *Zagazig University Medical Journal*, 2025; (5432-5449): -. doi: 10.21608/zumj.2025.395110.4012