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Hypnotic Effect of Red Cabbage (*Brassica oleracea*) on Pentobarbital-Induced Sleep in Mice

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Abstract

Objective:

The present study was performed to investigate the effect of hydroalcoholic extract of red cabbage and its fractions on sleeping behavior in mice.

Materials and Methods:

The extract and its fractions were injected to mice and sleep duration as well as sleep latency were recorded. Furthermore, toxicity of the extract was determined both *in vivo* and *in vitro*.

Results:

The extract increased sleep duration at doses of 50–200mg/kg ($P < 0.001$). This observed hypnotic effect was comparable to that of diazepam (3mg/kg) ($P < 0.001$ in comparison with control group). Ethyl acetate, *n*-butanol, and aqueous fractions could increase sleep duration ($P < 0.001$). The sleep latency was decreased by the extract ($P < 0.001$) and only ethyl acetate fraction ($P < 0.001$). LD_{50} value for red cabbage extract was 2.4g/kg. There was no toxic effect on viability of cultured neuronal cells (PC12). Rotarod test results showed that there were no significant differences between the extract groups and the control group.

Conclusion:

The results suggest that red cabbage potentiates pentobarbital hypnosis without any toxic effect. The main component(s) responsible for this effect is most likely to be intermediate polar agent(s) such as flavonoids, which are found in ethyl acetate fraction of this plant.

KEYWORDS: *Diazepam*, *PC12*, *pentobarbital*, *red cabbage*, *sleep*

INTRODUCTION

Insomnia is defined as repeated difficulty in falling asleep, difficulty maintaining sleep, and/or experiencing low-quality sleep, which results in some form of daytime disturbance.[1] Low sleeping leads to mental problem and fatigue. According to recent reports, 45% people suffer from sleeping disorder; this

problem is higher in women than men.[2] There are some drugs such as benzodiazepines and antihistaminic agents that are used for inducing sleep.[2] γ -Aminobutyric acid receptor A ($GABA_A$) is an important target for sleep-inducing drugs.[3] However, they are not suitable for long-time administration because of their tolerance-related issues and dependence.[4] There is a need to find new hypnotic drugs with lower adverse effects. Natural products have always been good sources for developing new treatments for the management of several diseases.[5] Some of the herbs that are used in insomnia include *Humulus lupulus*, *Ziziphus jujuba* (sour date), *Valeriana officinalis, Passiflora incarnata* (passion flower), *Eschscholzia californica* (California poppy), *Piper methysticum*, and *Lactuca sativa*.[6,7,8,9] The red cabbage (*Brassica oleracea* var. capitata f. rubra) belongs to Brassicaceae family (order: Brassicales).[10] Red cabbage is a cheap source of anthocyanin pigment.[11] Red cabbage contains flavonoids, and recent studies have shown that flavonoids have good therapeutic effects.[10] The pharmacological effects of red cabbage include reducing oxidative stress, decreasing blood glucose,[12,13,14] possessing anticancer properties,[15,16,17] and reducing blood cholesterol.[18] In some traditional medicinal books, it is reported that red cabbage has sedative–hypnotic effect.[19] There is no pharmacological report about the hypnotic effect of red cabbage. Therefore, this study has been designed to evaluate the sleep-prolonging effect of red cabbage extract and its different fractions. Also, flumazenil was used to guess possible sleep mechanism.

Materials and Methods

Drugs and chemicals

Penicillin–streptomycin, pentobarbital sodium, and flumazenil were purchased from Sigma (St. Louis, MO, USA). Diazepam was purchased from Chemidarou Company (Tehran, Iran). Tween 80 was provided from Merck (Darmstadt, Germany). Dulbecco's modified Eagle's medium (DMEM) and fetal bovine serum (FBS) were purchased from Gibco Life Technologies (Grand Island, NY, USA). Flumazenil, pentobarbital, and diazepam were dissolved in saline to make 30, 2, and 3mg/mL solutions, respectively.

Plant Collection and Extraction

Plant material

The red cabbage was purchased from a local market in Dargaz and the voucher specimen (No. 21373) was deposited in Dargaz Payame Noor University herbarium. The aerial parts of red cabbage were dried in shadow, powdered, and subjected to extraction with 70% ethanol with a Soxhlet apparatus for 48h. Then, the hydroalcoholic extract (HAE) was dried in a water bath, and the yield (19% w/w) was dissolved in saline containing 1% (v/v) of Tween 80. For preparation of fractions, a part of HAE was suspended in distilled water and transferred to a separator funnel. With solvent–solvent extraction, it was fractionated using ethyl acetate or *n*-butanol. The ethyl acetate fraction (EAF) and *n*-butanol fraction (NBF) were separated to obtain water fraction (WF).[9] The resulting fractions were dried on a water bath, and working solutions were made up in saline and saline containing 1% Tween 80 for WF and EAF or NBF, respectively.[20] The yields obtained from the extract fractionation were 73.5% WF, 12.5% EAF, and 14% NBF.

Animals

Male albino mice weighting 20–30g were maintained at a controlled temperature (22°C ± 1°C) with a 12-h light/dark cycle and free access to water and food. The study was carried out in accordance with ethical guidelines of Mashhad University of Medical Sciences (IR.MUMS.REC.1392.206). The animals (n = 88) were randomly divided into different groups (the number of animal in each group was 8); group 1 received normal saline and served as a negative control for HAE. Animals of group 2 received 3mg/kg diazepam as positive control. Mice in groups 3–7 received extracts at doses 12.5, 25, 50, 100, and 200mg/kg, respectively. Animals in groups 8–10 received 50mg/kg WF, 50mg/kg EAF, and 50mg/kg NBF, respectively. Moreover, animals were treated with 2mg/kg flumazenil as a diazepam antagonist before receiving diazepam (group 11), HAE (group 12), or EAF (group 13).

Evaluation of pentobarbital-induced sleep

The hypnotic assessment method is based on prolongation of sleep induced by pentobarbital.[20] Briefly, a single dose of HAE (12.5–200mg/kg), fractions of HAE, diazepam (3mg/kg), or vehicles was injected (i.p.) to the mice. After 30min, pentobarbital (30mg/kg, i.p.) was administrated to induce sleep.[21] Flumazenil (2mg/kg) was administrated (i.p.) 30min before diazepam or HAE.[21] The animals were considered asleep if stayed immobile and lost their righting reflex when positioned on its back. The time interval between administration of pentobarbital and onset of sleep was considered as sleep latency.

Rotarod behavioral method

The rotarod test was used to measure motor resistance and coordination. The experimental procedure for learning and adaptation was conducted for 3 consecutive days. On the next day, mice were placed on a rotating rod that accelerated smoothly from 4 to 40rpm over a period of 5min. The length of time they could maintain their balance on the turntable against the movement's strength was recorded. Then, the extract (50mg/kg) or vehicle was injected, and after 30min, the animals were placed on rotarod again.[22] Each group included seven mice.

LD_{50} determination

Eight groups, each containing five mice, were used for determination of LD_{50} of HAE. Groups 1–7 were injected i.p. with 50, 100, 200, 400, 800, 1600, and 3200mg/kg, respectively, of HAE and group 8 received normal saline as vehicle. Mortality rate was observed and recorded for 24-h period. The highest dose that did not kill any mice and the lowest dose that led to death of one animal were recorded. The mean of these two doses was considered as the median lethal dose.[23]

Neurotoxicity assessment

The possible cytotoxicity of red cabbage was tested on rat pheochromocytoma-derived cells (PC12). The cells were cultured in 96-well plates for 24h in DMEM supplemented with 10% FBS, penicillin (100 units/mL), and streptomycin (100 µg/mL). Then, the culture medium was changed to fresh one containing vehicle dimethyl-sulfoxide (DMSO 1%) or HAE (50, 100, 150, 200, 400, and 800 µg/mL). The cells were incubated for 24h at 37°C in an atmosphere of 5% CO_2. Cell proliferation was evaluated using MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay as previously described.[9]

Statistics

All values are expressed as mean ± standard error of the mean (SEM). Statistical analysis was performed using one-way analysis of variance followed by Tamhane's T2 post hoc test. Differences were considered significant at $P < 0.05$.

Results

Effects of red cabbage on duration of sleep

As expected, the reference drug diazepam was able to increase duration of sleep. The HAE at doses of 50, 100, and 200mg/kg could significantly increase sleep duration. As expected, pretreatment of mice with flumazenil decreased the sleep-prolonging effect of diazepam. Similarly, the effect of HAE on sleep duration was significantly inhibited by flumazenil [Figure 1].

Effects of red cabbage on sleep latency

Diazepam (min, $P < 0.001$) and HAE at doses 50, 100, and 200mg/kg significantly ($P < 0.001$) reduced the latency in comparison to the saline [Figure 2]. Results showed that flumazenil (2mg/kg, i.p.) reversed the effects of diazepam and 50mg/kg of HAE. Therefore, in flumazenil-treated mice, there was an increased latency to sleep in pentobarbital-induced hypnotic test.

Effects of fractions on duration of sleep

As shown in Figure 3, all of fractions increased sleep duration, but the effect of EAF was more than that of

NBF and WF (EAF: $P < 0.001$; WF: $P < 0.001$; NBF: $P < 0.001$). In addition, flumazenil reversed the effects of EAF.

Effects of fractions on sleep latency

As shown in Figure 4, only EAF decreased sleep latency significantly. In addition, flumazenil reversed the effects of EAF.

Toxicity assessments

The highest dose, which did not kill any mice, and the lowest dose, which led to death of mouse, were 1.6 and 3.2g/kg, respectively. The mean of these two doses (2.4g/kg) was considered as LD_{50}.

Result of MTT showed that none of the HAE concentrations (200, 400, 800, and 1600 μg/mL) decreased the proliferation of PC12 cells. Similarly, the HAE fractions exhibited no cytotoxicity [Figure 5].

Effect of red cabbage on motor coordination

Considering the results from the rotarod test, there were no significant differences between the groups when the animals were examined 30min after injection of the extract. The results showed that injection of diazepam (3mg/kg) significantly shortened the length of time ($P < 0.001$) that the mice maintained their balance on rotarod apparatus compared to the control and extract groups [Table 1].

Discussion

According to the ancient Ayurveda literature, red cabbage has anticonvulsive, sedative, and hypnotic effects;[24] also, it is used in aromatherapy for relieving stress and insomnia.[24] In this study, we evaluated the hypnotic effect of HAE of red cabbage and its fractions in mice. To study the comprehensive effect of red cabbage, the following issues were investigated in mice: sleep latency, sleep duration, loss of motor coordination, and neurotoxicity, and its fraction effects on sleep latency and duration. In this study, the hypnotic evaluation method was based on potentiation of sleep induced by pentobarbital. This method is used for investigating sedative–hypnotic agents.[9,21,25] In the previous reports and as expected, diazepam significantly enhanced the sleeping time induced by pentobarbital, indicating that our experimental method was well optimized.[26] The effect of HAE of red cabbage on sleep duration was not dose dependent in the range of given doses, and the maximum effect was observed with a dose of 50mg/kg. The higher doses (100 and 200mg/kg) led to lesser sleep in comparison with 50mg/kg. It may be related to the fact that the solution that is concentrated at higher doses leads to pain and causes lower sleep in comparison to the lower dose. We observed that when high dose was injected to mice, it led to righting syndrome. The hypnotic effect was comparable to that of diazepam, but HAE did not affect the animals' performance on the rotarod test; it seems that its effects on sleeping time and sleep latency are not due to affecting motor movement while diazepam decreased motor movement. To obtain a better insight into the nature of compounds responsible for the sleep-prolonging effect of this plant, three fractions were prepared from HAE of red cabbage. The WF contained polar compounds such as tannins, glycosides, and some alkaloids. The EAF included intermediate polarity such as flavonoids. The NBF contained low polar agents including alkanes, sterols, and terpenoids.[27,28,29] Our data showed that among these three fractions, EAF prolonged the duration of sleep and could decrease the sleep latency more than other fractions. Therefore, it can be concluded that the active constituents responsible for sleep-prolonging effects of red cabbage are intermediate polar agents in EAF. Several neurotransmitters have been shown to be involved in the regulation of sleep behavior. GABA is released from neurons that are located in the anterior hypothalamus and inhibits wake-promoting areas of the hypothalamus and brainstem.[30,31] Barbiturates such as pentobarbital tend to bind to GABA receptor ionophore complex to facilitate GABA action. Diazepam, a benzodiazepine agonist, is used in the management of sleep disorders such as insomnia; this compound has a binding site on $GABA_A$ ionophore complex.[3,32] It decreases activity, moderates excitement, and calms the recipient. Substances such as diazepam reduce the onset and increase duration of barbiturate-induced sleep and reduce exploratory activity, possessing potentials as sedative.[33] Our findings showed pretreatment with flumazenil inhibits sleep-prolonging effect of diazepam. Also, we found

that in the presence of flumazenil, red cabbage is unable to increase the duration of sleep or decrease sleep latency time. This observation may be related to the effect of extract on GABA receptors and possible involvement of GABAergic transmission. Previously, it has been reported that flavonoids as natural active compounds tend to bind to benzodiazepine $GABA_A$ receptors, and they act pharmacologically as partial agonists. Some semisynthetic flavonoid derivatives are much more potent than diazepam *in vivo*.[34,35,36] Baicalin, a flavonoid extracted from *Scutellaria lateriflora* (Lamiaceae), exerts anxiolytic activity that is antagonized by a $GABA_A$-specific antagonist.[37] It has also been suggested that chrysin, another natural flavonoid from *Passiflora caerulea* (Passifloraceae), exerts anxiolytic effects without any sedative and muscle relaxation activities. Recent studies have shown the presence of flavonoids in red cabbage. Therefore, it is rational to assume that the sleep-prolonging action of red cabbage is mediated, at least in part, by potentiating GABAergic system by flavonoids. Although we did not investigate the exact compound responsible for the sleep-prolonging effect of extract, further studies should be performed to test and to isolate active compounds from red cabbage. The rotarod test is a widely used method to evaluate the motor coordination or muscle relaxant effect in rodents. It is well established that some benzodiazepines such as diazepam cause muscle weakness,[38] decrease of ambulatory activity, and sedation, consequently impairing the performance of rodents in the rotarod.[39,40] As expected, we also found that diazepam caused muscle relaxation in the animals, causing a decrement of the falling time in rotarod but extract did not have muscle relaxation effect. Also, evaluation of the toxicity of red cabbage showed that LD_{50} value for HAE is 2.4g/kg. This value was markedly higher than that of hypnotic doses of extract (50–200mg/kg). Similarly, HAE and its fractions did not diminish the viability of neuronal cells even at high concentrations. Therefore, it seems that the sleep-prolonging effect of red cabbage is not accompanied by a neurotoxic action.

Conclusion

This study showed that red cabbage potentiates the pentobarbital-induced sleeping behaviors in mice. The sleep-prolonging effect was comparable to that induced by diazepam and accompanied with no neuron toxicity. The main components responsible for the effects are most likely of polar agents found in EAF. Isolation of the active compound(s) may yield novel sleep-prolonging agents.

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Conflicts of interest

None.

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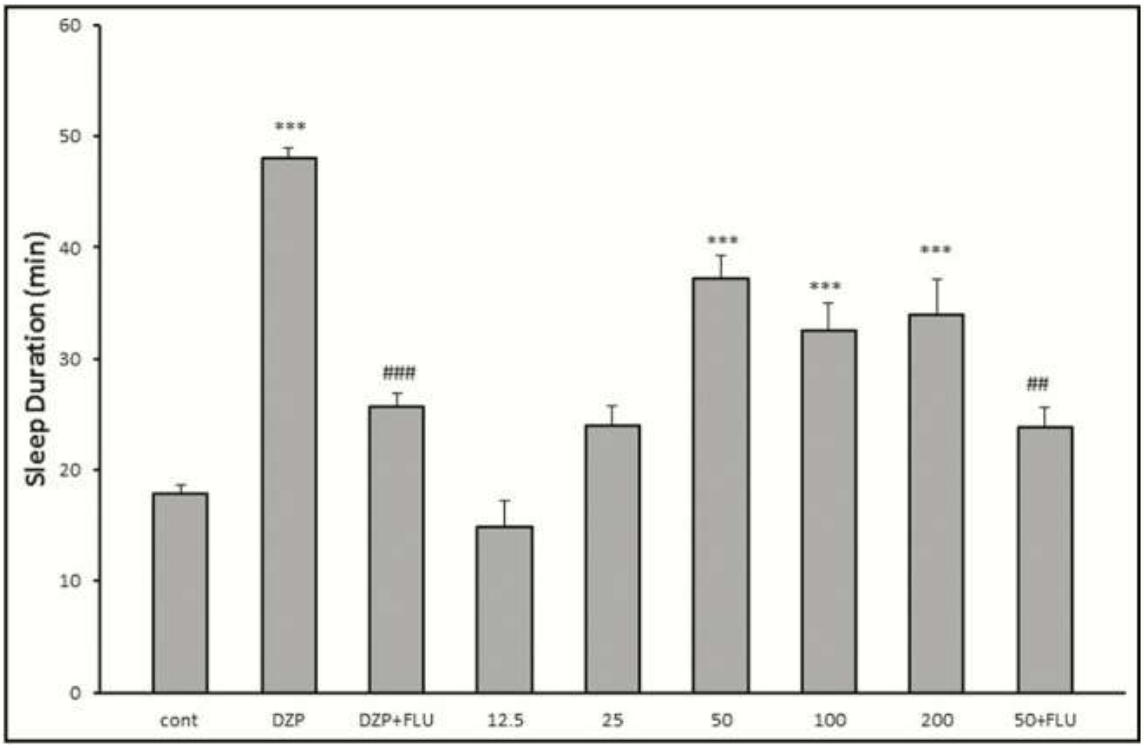
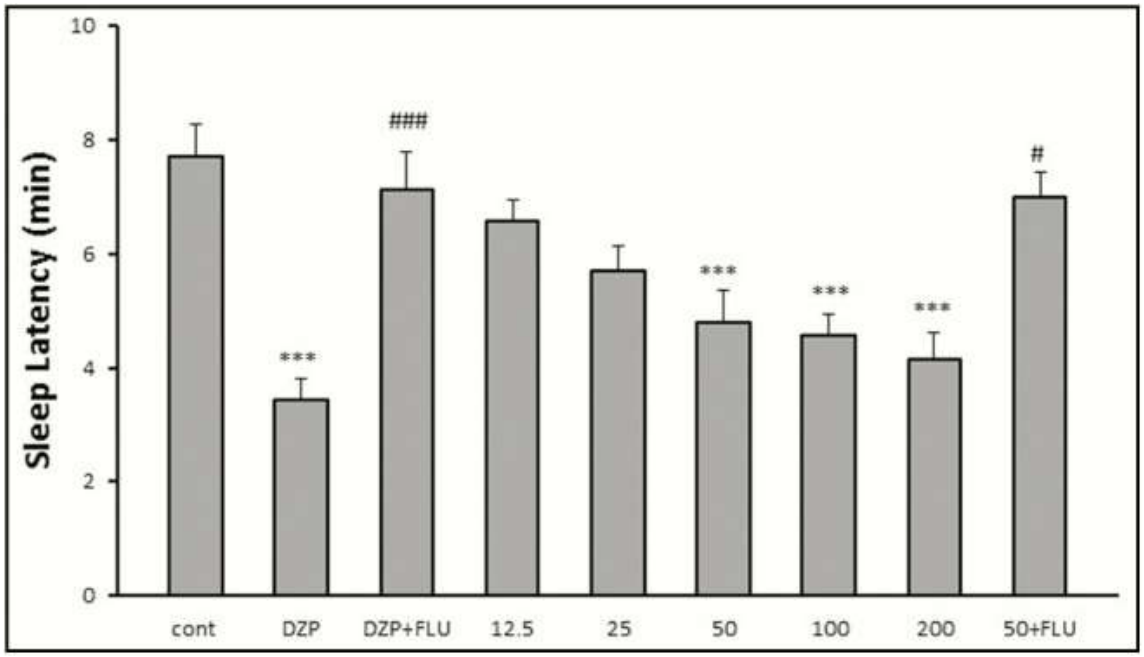
Figures and Tables

Figure 1



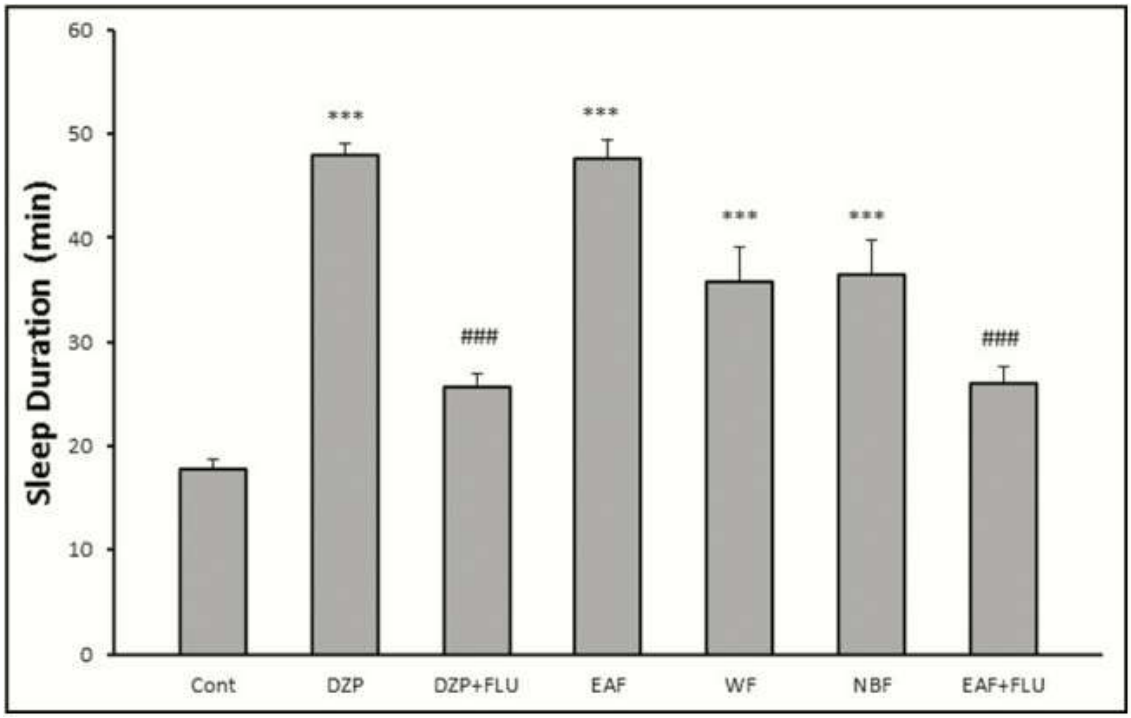
Effects of red cabbage HAE on sleeping time in pentobarbital-induced hypnotic test. Data are mean ± SEM of eight animals in each group. FNx18$P < 0.001$ significantly different from the control group. $^{\#\#}P < 0.01$, $^{\#\#\#}P < 0.001$ significantly different from the same group plus flumazenil (2mg/kg). DZP: diazepam; Flu: flumazenil

Figure 2



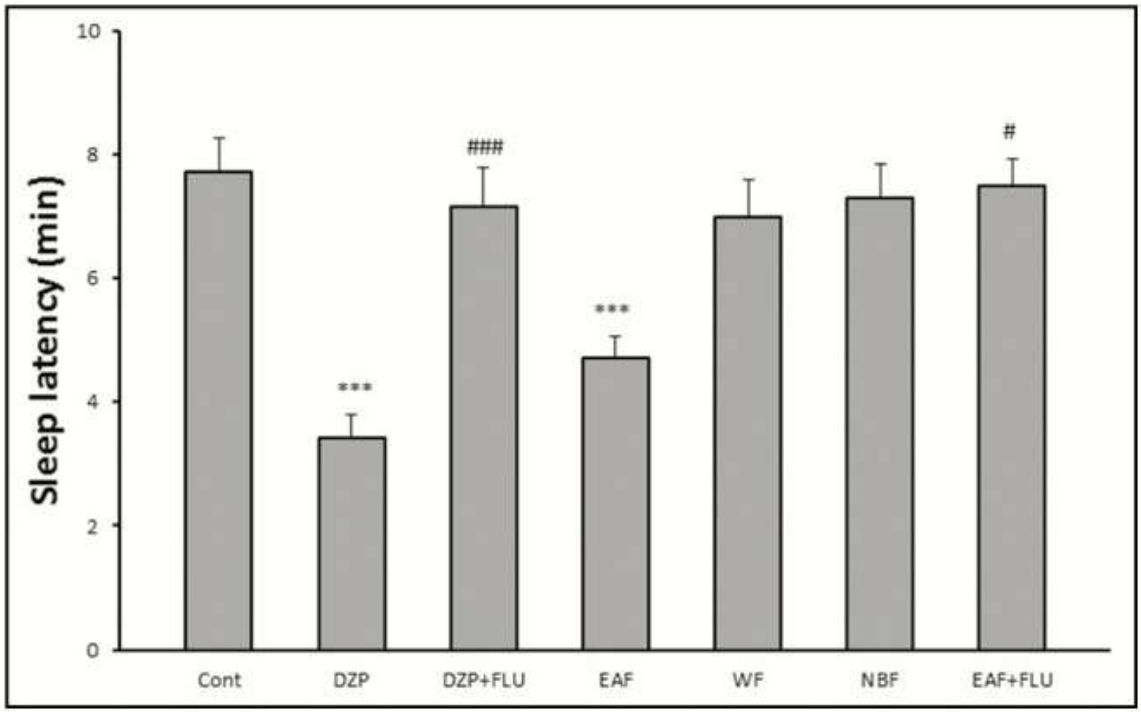
Effects of red cabbage hydro-alcoholic extract on sleeping latency in pentobarbital-induced hypnotic test. Data are mean ± SEM of eight animals in each group. FNx18$P < 0.001$ significantly different from the control group. $^{\#}P < 0.05$, $^{\#\#\#}P < 0.001$ significantly different from the same group plus flumazenil (2mg/kg). DZP: diazepam; FLU: flumazenil

Figure 3



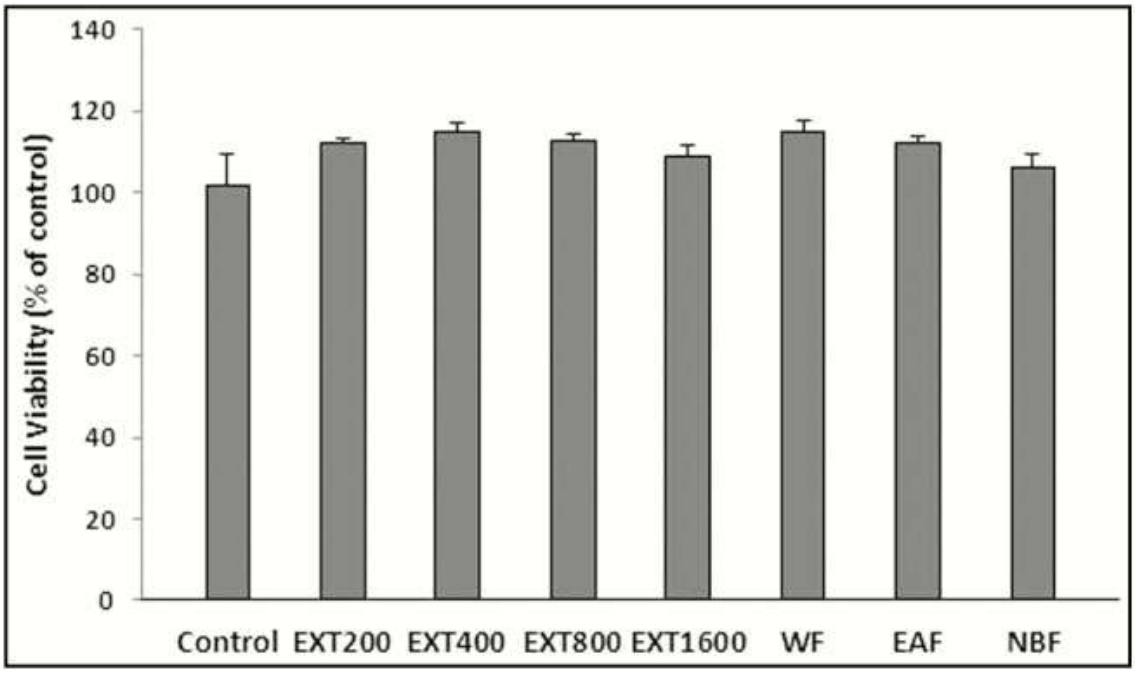
Effects of HAE fractions of red cabbage on sleeping time in pentobarbital-induced hypnotic test. Data are mean ± SEM of eight animals in each group. FNx18$P < 0.001$ significantly different from the control group. $^{###}P < 0.001$ significantly different from the same group plus flumazenil (2mg/kg)

Figure 4



Effects of HAE fractions of red cabbage on sleeping latency in pentobarbital-induced hypnotic test. FNx18$P < 0.001$ significantly different from the control group. $^{\#}P < 0.05$, $^{\#\#\#}P < 0.001$ significantly different from the same group plus flumazenil (2mg/kg)

Figure 5



Effect of HAE and its fractions of red cabbage on PC12 cell viability. Cell viability was quantitated by MTT assay. Results are mean ± SEM

Table 1

Effects of HAE of red cabbage on motor performance in rats. Data are expressed as mean ± SEM of seven animals in each group

	Saline	Diazepam	HAE (50 mg/kg)
Time (second)	237.5	30***	262.23

***$P < 0.001$ vs. the control and the extract groups