Available online on 15.07.2025 at http://jddtonline.info

Journal of Drug Delivery and Therapeutics

Open Access to Pharmaceutical and Medical Research

Open Access Full Text Article

Research Article

Therapeutic importance of hydrolic fraction of *Celtis integrifolia* roots for prevention of brain oxidative stress, increase of acetyl cholinesterase activity and tissues damage in monosodium glutamate-induced neurodegenerative-like diseases in mice

Bih Belta Lilian Fubi, Kada Sanda Antoine, Tangu Patience Neng, Mumbi Laurentine Ngenteh, Ndifor Rose Nchang, Nsah Bertrand Kiafonm, Oumar Mahamat

Department of Zoology, Faculty of Science, The University of Bamenda, Cameroon

Article Info:

Article History:

Received 10 April 2025
Reviewed 23 May 2025
Accepted 21 June 2025
Published 15 July 2025

Cite this article as:

Fubi BBL, Antoine KS, Neng TP, Ngenteh ML, Nchang NR, Kiafonm NB, Mahamat O, Therapeutic importance of hydrolic fraction of *Celtis integrifolia* roots for prevention of brain oxidative stress, increase of acetyl cholinesterase activity and tissues damage in monosodium glutamate-induced neurodegenerative-like diseases in mice, Journal of Drug Delivery and Therapeutics. 2025; 15(7):33-42 *DOI: http://dx.doi.org/10.22270/jddt.v15i7.7243*

*For Correspondence:

Oumar Mahamat, Department of Zoology, Faculty of Science, The University of Bamenda, Cameroon.

Abstract

Background: *Celtis integrifolia* is a common plant with its roots traditionally used to alleviate nervous problems. The current study aimed to assess the potential effects on cholinergic activity and oxidative status in the brain, as well as its impact in preventing neurological damage in neurodegenerative diseases.

Methodology: 35 mice were randomly distributed in seven groups (N=5). They were exposed to the monosodium glutamate (MSG) (2 g/kg/day) and given the hydrolic fraction at different doses for 21 days. The day after, CAT, SOD and GSH, NO and MDA concentrations in brain as well as the AchE activity were measured using colorimetric methods. The histoarchitectures of brain regions were also examined.

Results: Compared to non-treated mice exposed to MSG (Negative), the findings of this study revealed that plant extract significantly increased the antioxidant enzymes activity (CAT, SOD and GSH) and significantly decreased the NO and MDA concentrations in brain mice exposed to MSG. Furthermore, the extract significantly increased levels of AChE activity compared to the negative control. Moreover, hydrolic fraction of *C. integrifolia* significantly prevented necrosis in the Ca1 and Ca3 regions hippocampal, cortex, amygdala and gyrus as well as loss of hilum of dentate gyrus in mice exposed to MSG.

Conclusion: In conclusion, this study demonstrates that the hydrophilic fraction of Celtis integrifolia root has a neuroprotective effect in MSG-induced neurodegenerative-like diseases.

Keywords: *Celtis integrifolia*; antioxidant; Brain histoarchitecture.

BACKGROUND

Neurodegeneration is a complicated process that occurs when the functions of specific cells (nerve cells) in the brain subside; it is often connected to aging [1]. The pathological mechanism associated with neurodegenerative diseases depends on the biological factors associated resulting in nervous cell death [2]. These factors include proteins aggregation, inflammation, energy deficiency, oxidative stress and DNA damage. Globally, now it is recognized that oxidative stress causes changes in the biochemical and biomolecular parts of the body, leading to diseases [2-4]. However, it is important to note that small amounts of ROS and RNS are essential for signaling in the brain. They help with communication between cells and memory. However, too many of these reactive species can harm parts of cells, such as DNA, proteins, and fats [5,6]. This can cause stress and lead to nerve cells dying.

The current drugs against neurodegenerative diseases have side effects and are sometimes ineffective in preventing or stopping the progression of the illness [7]. The inadequate access to modern medicine and physicians, the high cost of actual therapies, and the side effects of modern drugs have prompted patients to search for alternative therapies. The use of plants particularly in low developing countries has gained interest as supported by their availability and less side effects [8]. *Celtis integrifolia* a plant belonging to the family Ulmaceace commonly found in Northern parts of Cameroon. A report by Muazu and Kaita [9] indicated that *C. integrifolia* is one of the components of a polyherbal formulation for the treatment of epilepsy and mental problems in Northern Nigeria. *C. integrifolia* is reported

to be used in preventing neurodegenerative diseases. The phytochemistry analysis of the plant also revealed the presence of saponins, flavonoids [10], which are components that have proven potential in treatments of these neurodegenerative diseases [11,12]. Therefore, the study of the protective potential of *C. integrifolia* in prevention of neurodegeneration may offer a great interest. In this study, the hydrolic fraction of *C. integrifolia* was evaluated whether it affects the cholinergic activity and oxidative status in brain and whether it prevents neurological damage in mice exposed to MSG.

MATERIALS AND METHODS

Plant Collection and Identification

A specimen of *Celtis integrifolia* was collected in Logone et Chari Division, Far North region of Cameroon. The plant material collected was identified by a botanist in the University of Maroua and confirmed in comparison with the voucher specimen of Letouzey 6513 of the National Herbarium, Yaounde-Cameroon (9032 SRF Cam). Roots of *C. integrifolia* were therefore collected, washed and dried at 50^0 C in thermostat oven (DHG-9101-1SA PEC). Dried root were crushed into powder. The fine powder was used for the extraction.

Preparation of Plant Extract

The hydrolic extract was obtained in sequential extraction as previously described [13] with slight modifications. The powdered plant materials (500 g) were subjected to exhaustive sequential solvent defection with varying polarities as follows, n-hexane, followed by acetone and lastly ethanol. Then the residue was macerated in 3 L of distilled water and procedure repeated thrice and evaporated at 40^0 C to obtain the hydrolic extract (16.11 g) given a yield of 6.7%.

Experimental Animals

Thirty-five (35) Swiss mice weighing 25±5 g age two months old were used in this experiment. These animals were bought from a breeder in Bamenda, Northwest Region, Cameroon. They were then acclimatized for two weeks in the animal house of Faculty of Science at the University of Bamenda. Mice were fed with a diet consisting of (50% corn_flour, 10% fish powder, 10% bone powder, 10% soya bean flour, 3% salt, 5% oil, and 2% water), given access to water ad libitum and maintained in a temperature and light-controlled room (25±2°C, natural day/night cycle). Animals were handled according to the guidelines of the Cameroon Bioethics Committee (reg. no. FWA -IRB00001954).

Animals Grouping and Treatment

Mice were distributed into seven groups (n=5): a normal control group (distilled water only 5 mg/L); negative control group was receiving MSG (2 g/kg/day). Three test groups were given the *C. integrifolia* hydrolic extract at 200, 400, 800 mg/kg followed by MSG. Two other groups were taken as positive control groups (1 group received the Vitamin C (300 mg/kg/day) + MSG and the second was given Donepezil (3 mg/kg) + MSG. Treatment was done orally (p.o) by gavage for 21 days.

Collection and Preparation of Biospecimens

After 21 days of treatment, on day 22 of the experiment, all mice were anesthetized (using sodium pentobarbital, 100 mg/kg b.w., i.p.) and quickly decapitated. The entire brain was harvested and weighed and some placed in 10% formalin for histological studies. While some of the brain tissue samples were homogenized with 0.1 M phosphate buffer (pH 7.4), centrifuged (3000 rpm for 15 minutes at 4°C), and the supernatant was collected and stored at -20°C for biochemical assay.

Evaluation of brain oxidative status

The evaluation of the enzymatic activities of superoxide dismutase (SOD) was done based on the ability of SOD to inhibit the reduction of nitroblue tetrazolium dye as described by [14] with little modifications. Moreover, catalase (CAT) activities was measured based on the breakdown rate of H_2O_2 according to the method of [15]. The determination of reduced glutathione (GSH) was assessed according to the method of [16]. Lipid peroxidation was assessed in terms of malondialdehyde (MDA) according the method mentioned by [17]. Moreover, nitric oxide (NO) level was measured in the brain homogenate through dye formation after adding the Griess reagent at 540 nm, as previously described [18].

Acetylcholinesterase activity in the brain

The level of acetyl cholinesterase was estimated by the method described by [16] with slight modifications. For the estimation of acetylcholinesterase, 20 µL of buffer Tris-HCl 0.1 M (pH 8.0) and 3mL Ellman reagent were introduced into all tubes (test and blank vials) and then 100µL homogenate followed by 100µL Tris buffer (HCl 50 mM; KCl 150 mM; pH 7.4) in the blank tube. Subsequently, 20 µL of 30 mM acetylthiocholine iodide was added to all the tubes. After a rapid homogenization of the mixture at room temperature, the absorbance was read at 412nm after 30s and 90s against the blank.

Histopathological analysis

Brain specimens were fixed in neutral buffered formalin (10%), dehydrated, embedded in paraffin wax and cut into sections (3-4 µm in thickness). Next, tissue sections were deparaffinized, and stained with hematoxylin and eosin and observed under a light microscope (OLYMPUS BX51) 100X magnification.

Statistical Analysis

All results were expressed as mean ± standard error mean (SEM) and analyzed using Graph Pad Prism version 8.01 software. Data analysis was performed using one-way analysis of variance (ANOVA) followed by Tukey post-test. A significant difference was considered at $p<0.05$.

RESULTS

Effect of *C. integrifolia* Extract on brain levels of malondialdehyde, catalase, superoxide dismutase and reduced glutathione in mice exposed to monosodium glutamate

Administration of monosodium glutamate significantly (*p<0.001*) caused an increase in the level of lipid peroxidation (or MDA) and decrease in level of SOD, GSH and CAT in brain homogenate compared to that in normal mice. The administration of the doses of hydrolic fraction of *C. integrigolia* (200, 400, and 800 mg/kg) increased significantly the brain catalase levels **(***p<0.01, p<0.01* and *p<0.001***)**, superoxide dismutase **(***p<0.01, p<0.001* and *p<0.001***)** and the reduced glutathione levels **(***p<0.01, p<0.01* and *p<0.001***)** of MSG-treated mice as compared to the negative group. It also decreased the level of lipid peroxidation **(***p<0.05, p<0.01* and *p<0.001***)** of MSG-treated mice as compared to the negative group (Table 1).

Table 1: Brain homogenate levels of catalase (CAT), superoxide dismutase (SOD), malondialdehyde (MDA) and reduced glutathione (GSH) after administration of *Celtis integrifolia* roots hydrolic extract in mice.

Test parameter	Controls			*Extract (mg/kg)*			*ANOVA sig. (F, p-value)*
	Normal	**Negative**	**Vit C**	**200**	**400**	**800**	
Catalase (U/g of tissue)	3.79±0.02***	1.07±0.04	2.26±0.03**	0.93±0.03*	1.12±0.002*	1.44±0.02***	*F (978) ; P<0.001*
SOD (%I)	36.4±0.62***	14.3±0.06	20.4±0.53***	14.9±0.05**	21.5±0.09**	28.5±0.26***	*F (275) ; P<0.001*
MDA (µmol/L)	0.24±0.01***	1.22±0.001	0.3±0.01***	1.01±0.01	0.76±0.01**	0.39±0.01[b]***	*F(1457); P<0.001*
GSH (µmol/L)	0.16±0.002***	0.07±0.001	0.1±0.001**	0.08±0.001**	0.08±0.003**	0.13±0.001***	*F (556) ; P<0.001*

*Values represent Mean ± SEM (n=5). *p<0.05; ** p < 0.01; ***p < 0.001 indicate the difference compared to the Negative control. Vit. C: Vitamin C. HCi: hydrolic fraction of Celtis integrifolia. Normal control: normal mice. Negative control: group of mice taking Monosodium glutamate only*

Effect of *C. integrifolia* root hydrolic extract on brain level of nitric oxide (NO) in mice exposed to monosodium glutamate

Brain nitric oxide (NO) level was significantly higher (*p<0.001*) in mice exposed MSG than in normal mice. Administration of extract at doses of 200, 400 and 800 mg/kg prior to the MSG exposure reduced significantly (*p<0.01; p<0.01; p<0.001*) the NO level compared to the negative group (Figure 1)

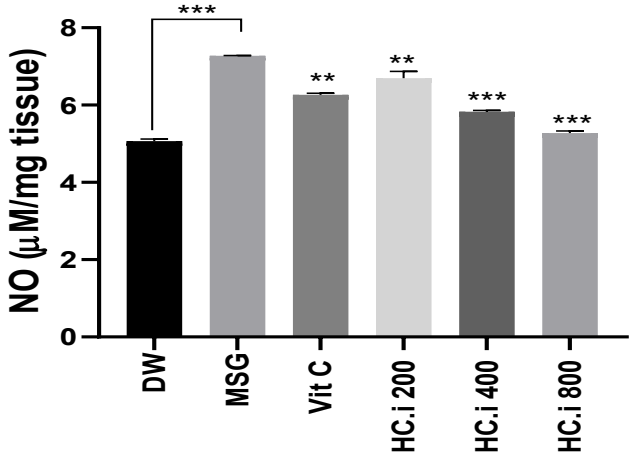

Figure 1: Serum level of nitric oxide following the administration of monosodium glutamate and *C. integrifolia* roots hydrolic extract. *Values represent Mean ± SEM (n=5). *p<0.05; ** p < 0.01; ***p < 0.001 indicate the difference compared to the Negative control. ns indicates not significant at p > 0.05 compared to the Negative control. Don: Donepezil. HCi: hydrolic fraction of Celtis integrifolia. Normal control: normal rats. Negative control: group of rats taken Monosodium glutamate only*

Effect of *C. integrifolia* Extract on brain acetylcholinesterase activity in mice exposed to monosodium glutamate

Exposure of mice to MSG caused a significant increase (*p < 0.01*) in brain acetylcholinesterase activity as compared to normal mice. Administration of the extract doses prior to exposure to MSG significantly (p < 0.01; p < 0.001; p < 0.001) decreased acetylcholinesterase activity in mice compared to the negative control (Figure 2).

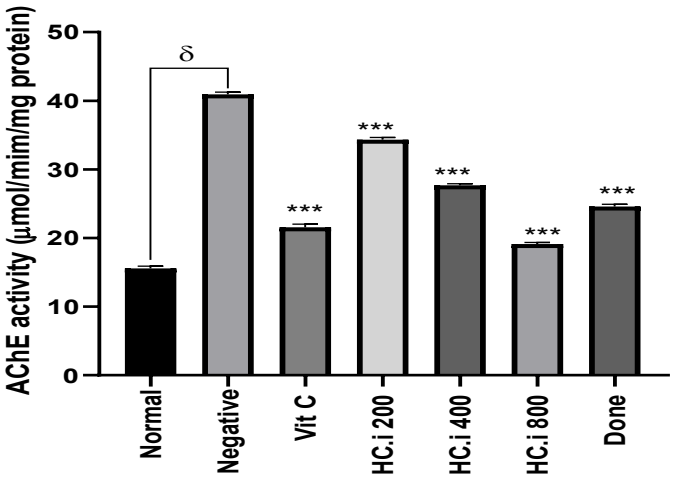

Figure 2: Serum level of brain Acetylcholinesterase activity following the administration of monosodium glutamate and *C. integrifolia* roots hydrolic extract. *Values represent Mean ± SEM (n=5). *p<0.05; ** p < 0.01; ***p < 0.001 indicate the difference compared to the Negative control. ns indicates not significant at p > 0.05 compared to the Negative control. Don: Donepezil. HCi: hydrolic fraction of Celtis integrifolia. Normal control: normal rats. Negative control: group of rats taken Monosodium glutamate only*

Effect of hydrolic extract of *C. integrifolia* root on the histoarchitecture of the cortex of mice exposed to monosodium glutamate

Plate 1 shows the effect of hydrolic extract of *Celtis integrifolia* on the histoarchitecture of cortical slices: group (Neg) revealed the presence of chromatilysis, pyknotic nucleus amid associated vacuolations or necrosis, and hyperchromatic neuron with overall decrease in neuronal density. Groups (*C.I* 200, 400, 800) showed restored neuronal density, numerous granular cells restored in a dose dependent manner.

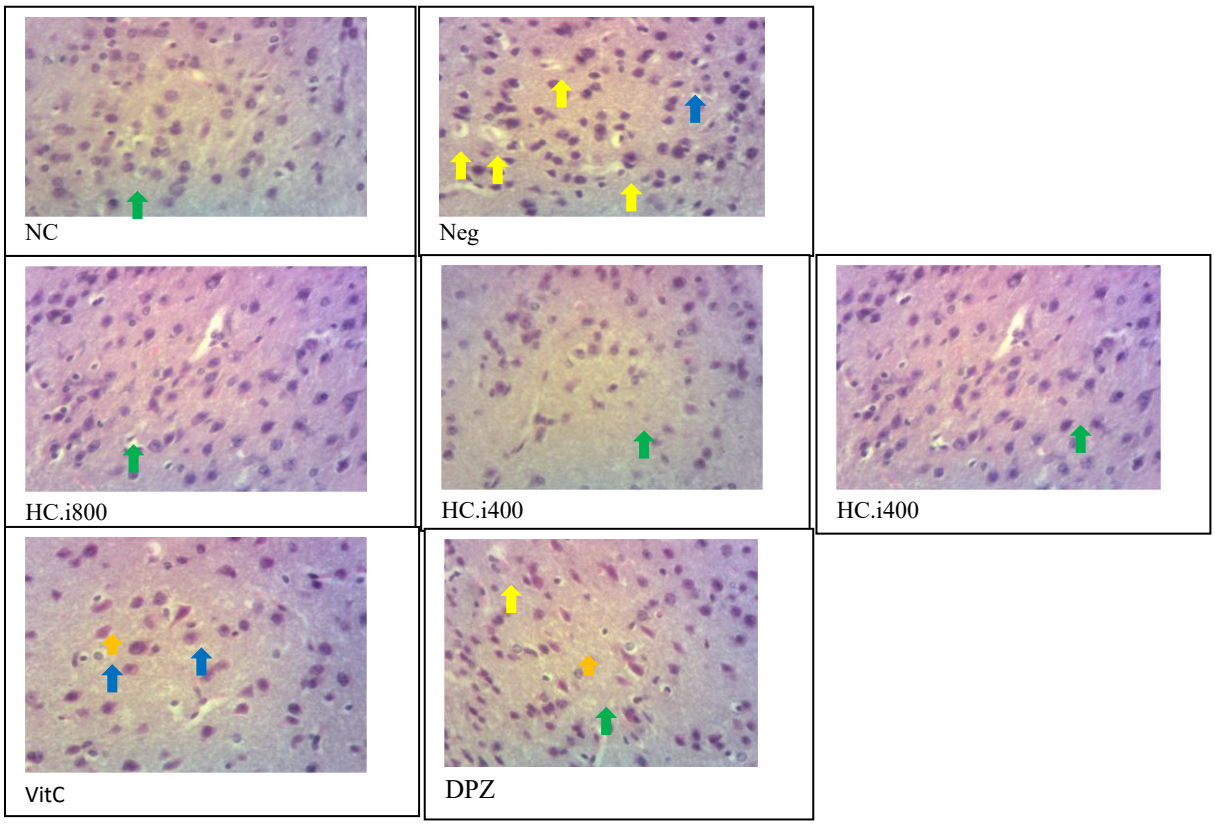

Plate 1: Effect of hydrolic extract of *Celtis integrifolia* on the histoarchitecture of cortical slices. *NC: normal, Neg: Negative (group exposed to MSG the monosoduim glutate), HC.I 200, 400 and 800: Groups taken exposed to MSG and receiving doses of extract, VitC: group exposed to MSG and receiving vitamine C, while DPZ: group exposed to MSG and receiving Donepezil. MSG: monosoduim glutate. The green arrow identifies normal neuronal cell, the blue arrow identifies chromatilysis, the yellow arrow identifies pyknotic nucleus amid associated vacuolations or necrosis, while the orange identifies hyperchromatic neuron. C.I (Celtis integrifolia); VitC (Vitamin C); DPZ) NC (Normal control).*

Effect of hydrolic extract of *C. integrifolia* root on the histarchitecture of CA1 region of hippocampus of mice exposed to monosodium glutamate

Plate 2 shows the effect of hydrolic extract of *C. integrifolia* on the histoarchitecture of CA1 region of the hippocampus: group (Neg) identifies damage area (abnormal cells indicating inflammation and tissue damage), eosinophilic necrosis with overall decrease in neuronal density. Groups (*C.I* 200, 400, 800) showed restored neuronal density, numerous granular cells restored in a dose dependent manner.

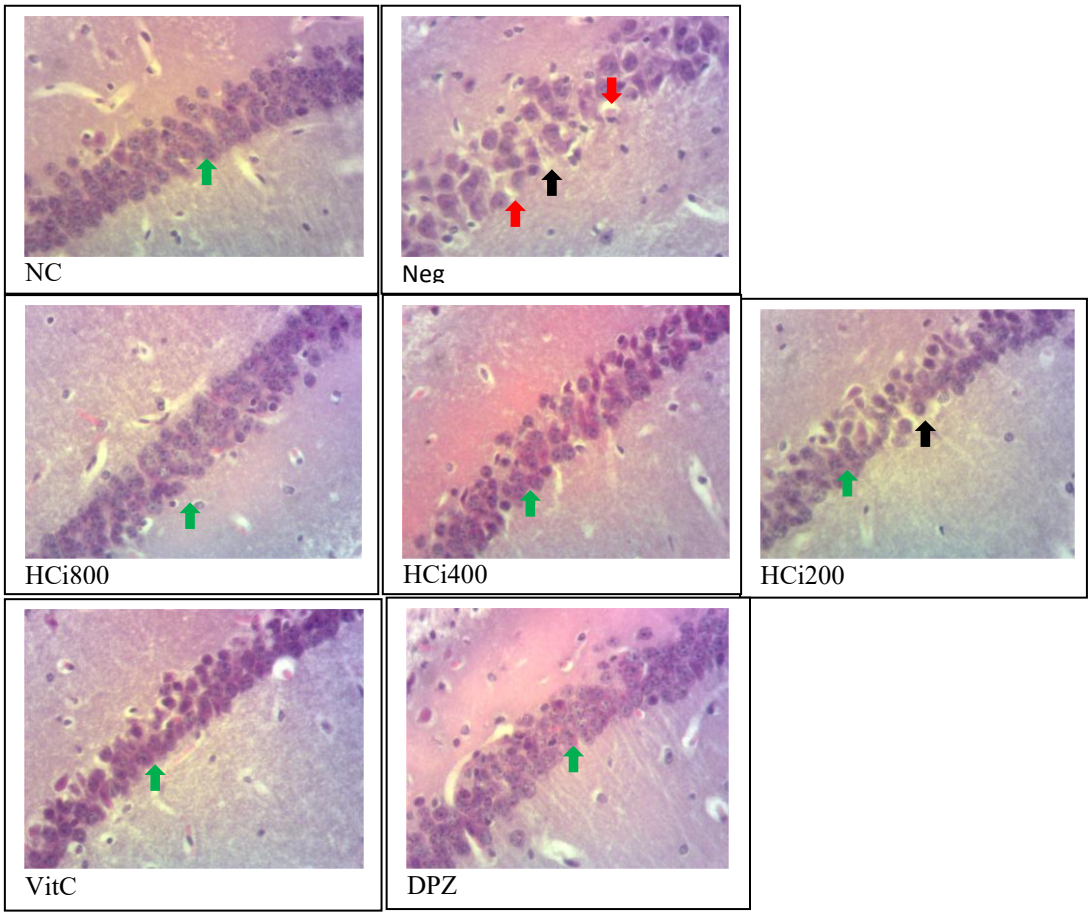

Plate 2. Effect of hydrolic extract of *Celtis integrifolia* on the histoarchitecture CA1 area of hippocampus. *NC: normal, Neg: Negative (group exposed to MSG the monosoduim glutate), HC.I 200, 400 and 800: Groups taken exposed to MSG and receiving doses of extract, VitC: group exposed to MSG and receiving vitamine C, while DPZ: group exposed to MSG and receiving Donepezil. MSG: monosoduim glutate. The red arrow identifies the damage area (abnormal cells indicating inflammation and tissue damage), the black arrow identifies eosinophilic necrosis, while the green arrow identifies relatively normal neuronal cell.*

Effect of hydrolic extract of *C. integrifolia* root on the histarchitecture of CA3 region of hippocampus of mice exposed to monosodium glutamate

Plate 3 shows the effect of hydrolic extract of *C. integrifolia* on the histoarchitecture of CA3 region of the hippocampus: group (Neg) identifies eosinophilic necrosis, abnormal cells with pyknotic nucleus, with chromatolysis and overall decrease in neuronal density. Groups (*C.I* 200, 400, 800) showed restored neuronal density, numerous granular cells were restored in a dose dependent manner.

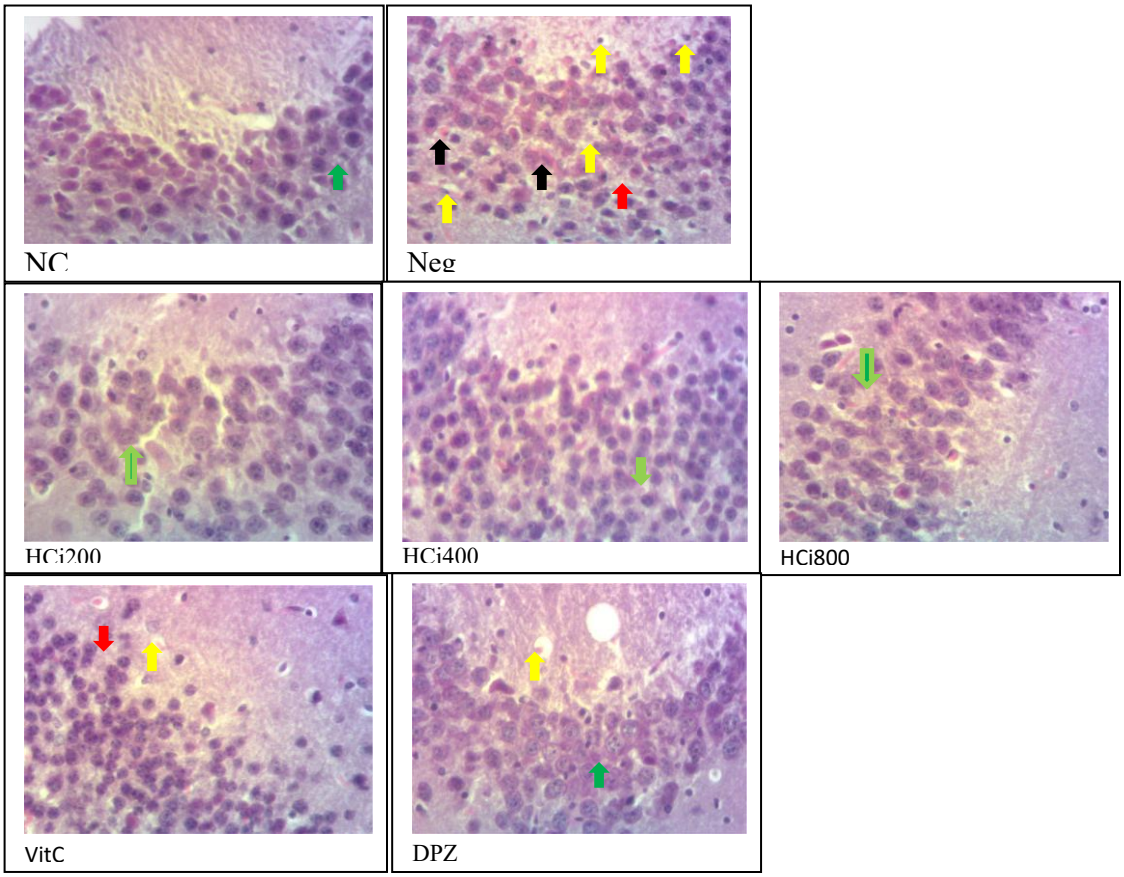

Plate 3: Effect of hydrolic extract of *Celtis integrifolia* on the histoarchitecture of CA3 area of hippocampus. *NC: normal, Neg: Negative (group exposed to MSG the monosoduim glutate), HC.I 200, 400 and 800: Groups taken exposed to MSG and receiving doses of extract, VitC: group exposed to MSG and receiving vitamine C, while DPZ: group exposed to MSG and receiving Donepezil. MSG: monosoduim glutate. CA:cornu ammonis. The black arrow identifies eosinophilic necrosis, abnormal cells with pyknotic nucleus, while the red arrow identifies chromatolysis, while the green arrow identifies relatively normal neurons.*

Effect of hydrolic extract of *C. integrifolia* root on the histarchitecture of dentate gyrus of mice exposed to monosodium glutamate

Plate 4 shows hydrolic extract of *C. integrifolia* on the histoarchitecture of gyrus: Group (Neg) showed loss of neuronal density, loss of hilum of the DG vacuolations, neuronal dispersal, neuronal atrophy, presence of necrosis. Groups (*C.I* 200, 400, 800) showed restored neuronal density, preserved DG hilum, numerous granular cells were restored in a dose dependent manner.

Effect of hydrolic extract of *C. integrifolia* root on the histarchitecture of amygdala of mice exposed to monosodium glutamate

Plate 5 shows the effect of hydrolic extract of *C. integrifolia* on the histoarchitecture of amygdala: group (Neg) identifies eosinophilic necrosis, abnormal cells with pyknotic nucleus, with chromatolysis and overall decrease in neuronal density. Groups (*C.I* 200, 400, 800) showed restored neuronal density, numerous granular cells restored in a dose dependent manner.

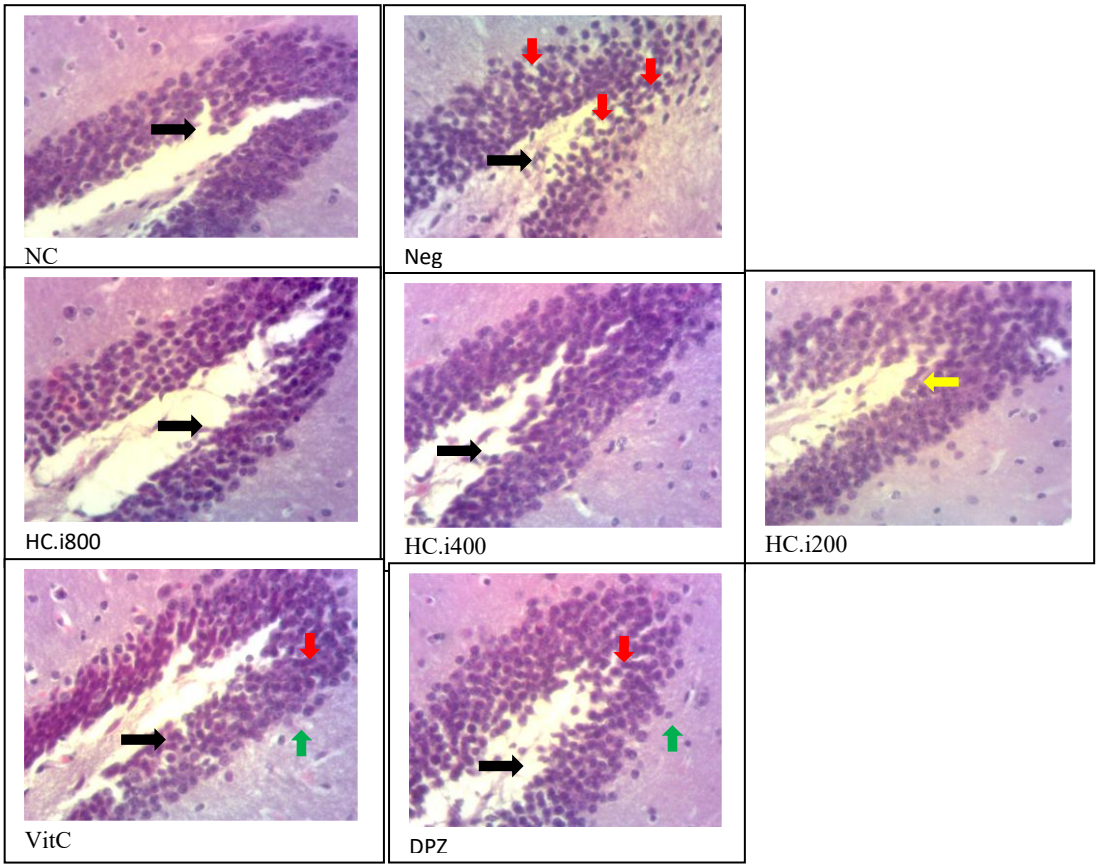

Plate 4: Effect of hydrolic extract of *Celtis integrifolia* on the histoarchitecture of gyrus. *NC: normal, Neg: Negative (group exposed to MSG the monosoduim glutate), HC.I 200, 400 and 800: Groups taken exposed to MSG and receiving doses of extract, VitC: group exposed to MSG and receiving vitamine C, while DPZ: group exposed to MSG and receiving Donepezil. MSG: monosoduim glutate.The red arrow identifies necrosis, the yellow arrow identifies pyknotic nucleus amid associated vacuolations, while the green arrow identifies relatively normal granular neurons with preserved density, the black arrow identifies hilum of the Dentate Gyrus.*

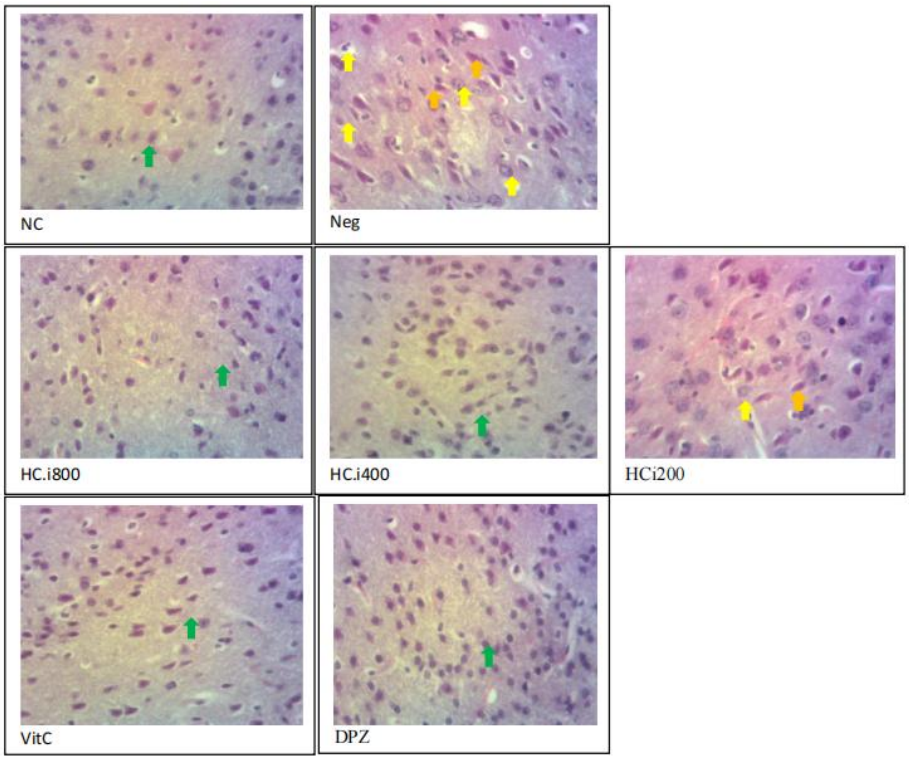

Plate 5: Effect of hydrolic extract of *Celtis integrifolia* on the histoarchitecture of a*mygdala. NC: normal, Neg: Negative (group exposed to MSG the monosoduim glutate), C.I 200, 400 and 800: Groups taken exposed to MSG and receiving doses of extract, VitC: group exposed to MSG and receiving vitamine C, while DPZ: group exposed to MSG and receiving Donepezil. MSG: monosoduim glutate. The green arrow identifies normal neuronal cell, the orange arrow identifies chromatilysis, while the yellow arrow identifies pyknotic nucleus amid associated vacuolations or necrosis.*

DISCUSSION

In experimental model, monosodium glutamate (MSG) causes oxidative stress and activation of inflammatory pathways [19]. In addition, it has been established that chronic administration of MSG results in an excessive accumulation of glutamate, which stimulates the hypothalamus, leading to impairment of the hypothalamic–pituitary–adrenal (HPA) axis. Hence, the underlying pathophysiology common to all forms of neurodegenerative disease seems to involve oxidative stress (OS) [3,4].

Findings from previous studies have established that MSG induces brain oxidative damage by the over-generation of reactive oxygen species (ROS) that is a possible cause of the excitotoxicity [20]. Oxidative injury is a key mechanism of oxidative stress is the consequence of uncontrolled production of ROS that results in antioxidant depletion and imbalance between pro-oxidant and antioxidant status [21]. The brain tissue vulnerable to free radical effect due to its high oxygen consumption rate, low levels of antioxidant enzymes and the high lipid content (polyunsaturated fatty acids) [22]. This results in neuronal injury and subsequent progress of neurodegenerative diseases [21]. Findings in this study revealed significant decrease in SOD, CAT activities in MSG group. In addition, MSG induced decrease in GSH with resulting increase in MDA levels. Also, MSG-induce lipid peroxidation cause decrease in GSH. As a radical scavenger, GSH maintains the membrane structure by removing the acyl peroxides that resulted from lipid peroxidation [23]. More so, GSH plays a vital role in antioxidant defense system by maintaining the redox homeostasis in neurons [24]. The oxidative damage in brain is generally altered histopathological features confirmed with the presence of necrosis and hyperchromatic neuron and an overall decrease in neuronal density in cortex, amygdala, gyrus. The hydrolic fraction *C. integrifolia* showed antioxidant activities with potent free radical scavenging capacity. This was proved by high levels of CAT, SOD, and GSH with concomitant decrease in MDA levels in mice exposed to MSG. This is in line with previous studies, indicating that flavonoids free radical scavenging property is attributed for the presence of hydroxyl and keto groups in its chemical structure [25]. Previous studies revealed that apigenin scavenges free radicals by donating its hydrogen atom and electron to the hydroxyl, peroxyl, peroxynitrite radicals to form stable flavonoid radicals [26]. Therefore, these results suggest that *C. integrifolia* protect against neurotoxicity by enhancing the cellular antioxidant system.

NO is an important inflammatory mediator, and its release is controlled by the level of NOS expression in activated macrophages [27]. Marked upregulation in iNOS gene expression has been reported to be strongly implicated in neurotoxicity [21]. Our study revealed high levels of NO in mice treated with MSG only. In contrast, administration of the plant extraction reduced NO concentration in brain mice exposed to MSG. this suggests that *C. intergrifolia* prevents neurons from cytotoxic levels of NO by decreasing iNOS activation.

Increased AChE activity cause the loss of cholinergic neurotransmissions leading to cognitive impairment [4]. Previous studies have establish that Inhibition of AChE decrease the hydrolysis of ACh in the brain and increase cholinergic neurotransmissions which might be helpful in targeting cognitive decline [25,26]. In the present study, administration of MSG to mice causes significant increase in AchE activity. This is because suppressed activity of AChE is associated with increased ACh concentration that results in over stimulation of cholinergic, muscarinic and nicotinic receptors [28]. Thus, over activation of these receptors results in excess neuronal excitation and paralysis of cholinergic transmission [25]. On the contrary, the administration with hydrolic extract of *C. integrifolia* reduced this effect by decreasing greatly the activity of this enzyme. Indicating that the ability of *C. integrifolia* to inhibit AchE activity thereby restoring cholinergic functions and allowing more retention of acetylcholine in the brain, which is essential for enhancing cognitive functions especially learning, and memory [4,29,30].

The results a low density of cells in mice given the MSG evidenced by the presence of necrotic cells observed in histopathology analysis of cerebral cortex CA1, CA3 regions of hippocampus and Gyrus indicate MSG causes the degeneration of different regions of brain. This effect of MSG is similar to that reported in various studies and this could account for high levels of ROS observed in these mice. Therefore, the administration of *C. integrifolia* prior to the MSG exposure showed that extract has prevented the damage of normal architecture of cortex, CA1, CA3, Gyrus pyramidal cell layer with a high cell density characteristic of nervous cells. These findings demonstrate that *C. integrifolia* root aqueous extract may prevent neurodegeneration.

CONCLUSIONS

In MSG-induced neurodegenerative like disease, the results revealed that the hydrolic fraction of *Celtis integrifolia* downregulated the brain AChE activity. Moreover, *C. integrifolia* extract reduced the brain level of NO, MDA, while increased the CAT, SOD and GSH levels. In addition, it prevented necrosis in different regions of brain. Therefore, *C. integrifolia* extract may alleviate the neurodegenerative like symptoms by preventing the brain oxidative stress, inflammation, high level of neurotransmitters, dysregulation of the HPA-axis and necrosis.

DECLARATIONS

Ethical clearance

Not applicable

Availability of data and material

The data generated or analyzed during this study are available under request to the corresponding author

Competing interests

Authors of this manuscript declare that they have no conflicts of interest

Funding

Not applicable

Abbreviations

CAT: Catalase

SOD: Superoxide dimutase

GSH: Reduced Glutathione

NO: Nitric oxide

MDA: Malondialdehyde

AChE: Acetylcholinesterase

REFERENCES

1. Gadhavea DG, Vrashabh V, Sugandhia, Saurav K, Sopan N, Nangared, Gaurav G, Sachin KS, Kamal D, Hyunah C, Philip M, Hansbrok, Keshav RP, Neurodegenerative disorders: Mechanisms of degeneration and therapeutic approaches with their clinical relevance, Ageing Research Reviews, 2024; 99: 102357 https://doi.org/10.1016/j.arr.2024.102357 PMid:38830548

2. Torrezan R, Malta A, de Souza Rodrigues WDN, Dos Santos AAA, Miranda RA, Moura EG, Monosodium l-glutamate-obesity onset is associated with disruption of central control of the hypothalamic-pituitary-adrenal axis and autonomic nervous system, J Neuroendocrinology, 2019; 31(6):e12717 https://doi.org/10.1111/jne.12717 PMid:30929305

3. Hebatallah HA, Amal F. Gharib, Mervat EA, Manar HA, Amr TS, Monosodium glutamate induces hypothalamic-pituitary-adrenal axis hyperactivation, glucocorticoid receptors down-regulation, and systemic inflammatory response in young male rats: Impact on miR-155 and miR-218. Open Chemistry, 2024; 22: 20240101 https://doi.org/10.1515/chem-2024-0101

4. Ajisebiola BS, Abdur-Rahman KM, Omotayo OO, Johnson OO, Akindele OA, Kaempferol alleviates neurodegenerative disorders induced by Naja nigricollis venom via mechanisms of antioxidants, anti-inflammatory, dopaminergic and neuronal functions, Phytomedicine Science, 2024; Plus 4:100584 https://doi.org/10.1016/j.phyplu.2024.100584

5. White S, Mauer R, Lange C, Klimecki O, Huijbers W, Wirth M, The effect of plasma cortisol on hippocampal atrophy and clinical progression in mild cognitive impairment, Alzheimers Dement (Amst), 2023; 15:e12463 https://doi.org/10.1002/dad2.12463 PMid:37583892 PMCid:PMC10423926

6. Sheng JA, Bales NJ, Myers SA, Bautista AI, Roueinfar M, Hale TM, The hypothalamic-pituitary-adrenal axis: development, programming actions of hormones, and maternal-fetal interactions. Front Behav Neurosci, 2021; 14:601939. https://doi.org/10.3389/fnbeh.2020.601939 PMid:33519393 PMCid:PMC7838595

7. Tamfu AN, Kucukaydin S, Yeskaliyeva B, Ozturk M, Dinica, RM, Non-Alkaloid Cholinesterase Inhibitory Compounds from Natural Sources, Molecules, 2021; 26 https://doi.org/10.3390/molecules26185582 PMid:34577053 PMCid:PMC8472022

8. Gamo FZ, Sefirin D, Charline FA , Adjoffoin CN and Dieudonne N, Neurological disorders: The use of traditional medicine in Cameroon, Traditional Medicine and Modern Medicine, 2024, vol 7 https://doi.org/10.1142/S2575900024300017

9. Mu'azu J, and Kaita AH, A review of traditional plants used in the treatment of epilepsy amongst the Hausa/Fulani tribes of northern Nigeria Afr. J. Trad. Med, 2008, 5: 387 - 390 https://doi.org/10.4314/ajtcam.v5i4.31294 PMid:20161961 PMCid:PMC2816574

10. Abba-Idris and Abba, Halima Mohammed (2021). Phytochemical Screening, Antimicrobial and Antioxidant Activities of Celtis integrifolia (Lam.) Leaves. International Journal of Scientific Research and Engineering Development- Volume 4

11. Maan G, Sikdar B, Kumar A, Shukla R, and Mishra A Role of flavonoids in neurodegenerative diseases: limitations and future perspectives, Current Topics in Medicinal Chemistry, 2020, 20 (13): 1169-1194 https://doi.org/10.2174/1568026620666200416085330 PMid:32297582

12. Ullah A, Munir S, Badshah SL Important flavonoids and their role as a therapeutic agent, Molecules, 2020, 25(22): 5243 https://doi.org/10.3390/molecules25225243 PMid:33187049 PMCid:PMC7697716

13. Suphunwadee S, Dumrongsak P, Pennapha S, Thanwarat W, Worasak K, Julintorn S, Chaidan I, Supawadee P& Piyarat S Calotropis gigantea stem bark extracts inhibit liver cancer induced by diethylnitrosamine, Scientific reports, 2022

14. Mishra HP, & Fridovich I, The role of superoxide anion in the autooxidation of epinephrine and a simple assay for superoxide dismutase, Journal of Biological Chemistry, 1972, (247); 3170-3175. https://doi.org/10.1016/S0021-9258(19)45228-9 PMid:4623845

15. Aebi HC, Wyss B, Scherz and Skvaril F, Heterogeneity of erythrocyte catalase II, Isolation and characterization of normal and variant erythrocyte catalase and their subunits, European Journal of Biochemistry, 1984, (48), 137-145 https://doi.org/10.1111/j.1432-1033.1974.tb03751.x PMid:4141308

16. Ellman GL, Courtney KD, Andres VJr, and Featherstone RM, A new and rapid colorimetric determination of acetylcholinesterase activity, Biochemical Pharmacology, 1961, (7); 88-95. https://doi.org/10.1016/0006-2952(61)90145-9 PMid:13726518

17. Wilbur KN, Bernheim F, and Shapiro OW, Determination of lipid peroxidation." Archives of Biochemistry and Biophysics, 1949, (24); 305-310

18. Green LC, Wagner DA, Glogowski J, Skipper PL, Wishnok JS, Tannenbaum SR, Analysis of nitrate, nitrite, and [15N] nitrate in biological fluids, Analytical biochemistry 1982, 126, 131-8 https://doi.org/10.1016/0003-2697(82)90118-X PMid:7181105

19. Aftab A, Neuroprotective Efficacy of Europinidin in StreptozotocinInduced Memory Impairment by Modulation of Oxidative Stress, Inflammatory Mediators, and Cholinesterase Activity in Rats, Hindawi Oxidative Medicine and Cellular Longevity, 2023, 11 pp. https://doi.org/10.1155/2023/5248127 PMid:36760351 PMCid:PMC9904885

20. Blaylock RL, The biochemical basis of neurodegenerative disease: The role of immunoexcitoxicity and ways to possibly attenuate it, Surg Neurol Int, 2023, 14:141 https://doi.org/10.25259/SNI_250_2023 PMid:37151454 PMCid:PMC10159298

21. Othman MS, Khaled AM, Al-Bagawi AH, Fareid MA, Ghany RA, Habotta OA, Moneim AEA, Hepatorenal protective efficacy of flavonoids from Ocimum basilicum extract in diabetic albino rats: A focus on hypoglycemic, antioxidant, anti-inflammatory and anti-apoptotic activities, Biomedicine & Pharmacotherapy, 2021 144, 112287 https://doi.org/10.1016/j.biopha.2021.112287 PMid:34649220

22. Mirzakhani N, Farshid AA, Tamaddonfard E, Tehrani A, Imani M, Comparison of the effects of hydro-alcoholic extract of Capparis spinosa fruit, quercetin and vitamin E on monosodium glutamate, 2020

23. Wang Q, Xia, M, Liu C, Guo H, Ye Q, Hu Y, Cyanidin-3-O-beta-glucoside inhibits iNOS and COX-2 expression by inducing liver X receptor alpha activation in THP-1 macrophages, Life Sci, 2018, 83:176-184 https://doi.org/10.1016/j.lfs.2008.05.017 PMid:18619979

24. Gautam V, Rawat K, Sandhu A, Kumari P, Singh N, Saha L, An insight into crosstalk among multiple signaling pathways

contributing to epileptogenesis, European journal of pharmacology, 2020, 910, 174469 https://doi.org/10.1016/j.ejphar.2021.174469 PMid:34478688

25. Albrakati AA, Monosodium glutamate Induces cortical oxidative, apoptotic, and inflammatory challenges in rats: The potential neuroprotective role of apigenin, Research square, 2022 https://doi.org/10.21203/rs.3.rs-1950266/v1

26. Abd Allah HN, Abdul-Hamid M, Mahmoud AM, Abdel-Reheim ES, Melissa o cinalis L. ameliorates oxidative stress, inflammation, and upregulates Nrf2/HO-1 signaling in the hippocampus of pilocarpine-induced rats, Environmental Science and Pollution Research, 2021, 1-13 https://doi.org/10.1007/s11356-021-15825-y PMid:34363578

27. Bickel M, The role of interleukin-8 in inflammation and mechanisms of regulation. Journal of periodontology, 1993, 64, 456-460

28. Chen D, Pan D, Tang S, Tan Z, Zhang Y, Fu Y, Lü G, Huang Q, Administration of chlorogenic acid alleviates spinal cord injury via TLR4/NF-κB and p38 signaling pathway anti-inflammatory activity Mol Med Rep, 2018, 17, 1340-1346 https://doi.org/10.3892/mmr.2017.7987

29. Nazir N, Nisar M, Zahoor M, Uddin F, Ullah S, Ullah R, Ansari SA, Mahmood HM, Bari A, Alobaid A, Phytochemical Analysis, In Vitro Anticholinesterase, Antioxidant Activity and In Vivo Nootropic Effect of Ferula ammoniacum (Dorema ammoniacum) D. Don. In Scopolamine-Induced Memory Impairment in Mice, Brain Sci. 2021, 11, 259 https://doi.org/10.3390/brainsci11020259 PMid:33669503 PMCid:PMC7922987

30. Balbine KK, Guillaume CW, Simon Desire GN, Linda DKJ, Léa Blondelle KD, Germain ST. Antioxidant and Anticholinesterase Properties of the Aqueous Extract of Balanites aegyptiaca L. Delile Fruit Pulp on Monosodium Glutamate-Induced Excitotoxicity in Swiss Mice. Evid Based Complement Alternat Med. 2022; 2022:7576132. https://doi.org/10.1155/2022/7576132 PMid:35449814 PMCid:PMC901751