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Evaluate the stimulated memory and learning activity of the ethanolic extract of grape seeds extract in albino mice

A search

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اشهد بأن هذا البحث الموسوم **(الاستخدامات الطبية والعلاجية لنبات**

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Abstract:

Grape (*Vitis vinifera*) member of family *vitaceae*, is one of the most commonly consumed fruits in the world both as fresh fruit (table grape) and processed fruit (grape juice, molasses, and raisins & others). The seeds are rich in polyphenols and phenolic acids and their consumption is safe and is recognized to exert several and meaningful health benefits. The aim of the present study was to evaluate the memory and learning processes activity of the ethanolic extract of grape seed by using morris water maze in experiment mice. The activity of grape seed extract on spatial memory using Morris water maze model (MWM) in mice. The present study revealed that the administration of alcoholic extract of *Vitis vinifera* (50 mg/kg, IP) showed significant reduction in the escape latency in MWM specially in the 4th & 5th day of experiment as compared with the control group.

Conclusion: grape seed extract may act as a memory enhancer formulation and may also be useful as a supportive adjuvant in the treatment of impaired memory functions.

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1-Introduction:

Learning and memory are closely associated at both cell and behavioral levels (Lee,2008). Memory is caused by changes in synaptic conductivity from one neuron to another one, leading to emergence of new or facilitating pathways to control messages in the neural circuit of the brain (Berman & Dudai,2001). The hippocampus and the cerebral cortex are the key structures of memory formation. Because the hippocampus is especially indispensable in the integration of spatial information, a decline in learning ability may be induced by the deterioration of hippocampal function.

Memory and learning are the most important functional levels of central nervous system (CNS). The CNS helps to encode, store, retain, and recall information in the brain. Ageing and stressors are the most important causes of disturbed memory and poor learning. Cholinergic drugs have positive effects on memory and anti-cholinergics, antipsychotics, and anesthetics have negative effects on memory (Francis *et al.*,1999).

Human beings have long discovered the values of medicinal plants and used them to treat any pains and diseases. The documents in medicine and pharmacy written thousands of years ago contain valuable experiences and information about medicinal plants and phytotherapy (Nikfarjam *et al.*,2016). Medicinal plants are particularly important in different communities' health care systems, because they could be effective for prevention and treatment of different disorders and diseases such as pediatric diseases, neurological dysfunctions, digestive disorders, hormonal imbalances etc (Bahmani *et al.*,2015). Also the role of the medicinal plants in learning and memory has recently attracted the attention of many researchers. So In this study , we are aimed to estimate the beneficial effect of the grape seeds ethanolic extract in the improvement memory skills in the experimental albino mice.

Learning and memory are closely associated at both cell and behavioral levels (Lee,2008) Memory is caused by changes in synaptic conductivity from one neuron to another one, leading to emergence of new or facilitating pathways to control messages in the neural circuit of the brain (Berman & Dudai,2001) Memory and learning are the most important functional levels of central nervous system (CNS). The CNS helps to encode, store, retain, and recall information in the brain. Ageing and stressors are the most important causes of disturbed memory and poor learning. Cholinergic drugs have positive effects on memory and anti-cholinergics, antipsychotics, and anesthetics have negative effects on memory (Sharifzadeh et al.,2005) Memory and learning are considered as the most important functional levels of central nervous system (CNS) which helps to encode, store, retain, and recall information in the brain. Memory is a cognitive process that can be studied throughout life span. Cognitive skills are used to be able to adapt to an ever changing environment. For thousand years spatial memory has contributed to our knowledge and exploration of available resources in our surroundings (Cimadevilla et al.,1999)The acquisition and retention of a spatial navigation task is examined using a Morris Water Maze (Kumar et al.,2006). The hippocampal formation plays an important role in memory and learning. The Morris Water Maze (MWM) is a test of spatial learning for rodents that relies on distal cues to navigate from start locations around the perimeter of an open swimming arena to locate a submerged escape platform. Spatial learning is assessed across repeated trials and reference memory is determined by preference for the platform area when the platform is absent (Vorhees & Williams,2006) The hippocampus and the cerebral cortex are the key structures of memory formation. Because the hippocampus is

especially indispensable in the integration of spatial information, a decline in learning ability may be induced by the deterioration of hippocampal function.

2-1- Botanical source:

Scientific name: *Vitis vinifera*, Family: Vitaceae, Common name: grape vine. *Vitis vinifera* is a high climbing vine, with stems up to 35m long in the wild. Tendrils growing

opposite leaves. Leaves palmately lobed, hairy/ bristly on underside. Flowers form in dense panicles that develop into bunches of berries-„grapes“. Stem bark tends to peel. Grape Seed Extract(GSE) is derived from the seeds of *Vitis vinifera*. Red grape seeds are generally obtained as a by-product of wine production. The typical commercial opportunity of extracting grape seed constituents has been for chemicals known as polyphenols having antioxidant activity in vitro.³ It is sold commercially in the form of nutritional supplements. As a nutritional supplement the extract is available in liquid, capsule or tablet form.

Grape Seed is a great source of polyphenols - flavonoids, Essential Fatty Acid - linoleic acid, vitamin E, and oligomeric proanthocyanidin(OPC), Gallic Acid.

The highest concentration of proanthocyanidins is found in the skin or membrane of the grape seed^{6,7}. Total proanthocyanidin content consumed in 100 g of dry grape seed is approximately 3,500 mg. Proanthocyanidins are one type of naturally occurring plant compounds called bioflavonoids. The most active proanthocyanidins are those bound to other proanthocyanidins: mixtures of proanthocyanidin dimers, trimers, tetramers, and larger molecules such as PCO. These great components make grape seed extract an asset in the treatment of many minor to severe health conditions. It has also been used in

the production of massage oils and balms, hair and hygienic products, face and body moisturizers, shampoos as well as in sunblocks and sunburn ointments. A polyphenol contained in grape seeds is resveratrol, which is under study for its possible effect on cancer cell growth, proliferation or apoptosis, among other potential chemopreventive mechanisms

2-2-Historical information :

From time immemorial grapes have been used both for medicinal and nourishment purposes, chiefly in Greece and in Italy. Grapes (*Vitis vinifera*) have been heralded for their medicinal and nutritional value for thousands of years: Egyptians ate grapes at least 6,000 years ago, and several ancient Greek philosophers praised the healing power of grapes, usually in the form of wine. The role that the grape has in the food culture of the Mediterranean countries is comparable only to that played by tea in among the peoples of Asia, indeed. An impressive body of the current scientific literature supports the health benefits claimed by the medical tradition. Several epidemiological studies have associated the consumption of grapes, wine, and grape juice with a wide variety of health-promoting effects, particularly the reduced risk of cancer and cardiovascular diseases (Pezzuto,2008).

2-3.Grape Seeds:

Grape (*Vitis vinifera*) member of family *vitaceae*, is one of the widely cultivated and most important fruit crops in the world (Satisha *et al.* 2008).Grape seed extract is a natural extract from the seeds of *Vitis vinifera*. A multitude of Flavonoids are contained in grape seed extract the most abundant of these are the Proanthocyanidins , which naturally occur in green tea ,chocolate ,coffee, cacao, red wine ,and many fruits. These. Flavonoids possess antioxidant properties,free

radical scavenging and chelating abilities ⁽¹¹³⁾ .Flavonoids have been reported to exert anti –inflammatory actions and to modulate immune function by reducing the permeability and fragility of capillaries they also have a protective effect against vascular disorders. By acting as free- radical scavengers proanthocyanidins inhibit lipid peroxidation a free –radical chain reaction that can produce cytotoxicity disrupt lipid –containing membranes and initiate low-density lipoprotein oxidation by exerting a sparing effect on other antioxidants such as vitamins E and C ⁽¹¹⁴⁾ .

Grape seed extract is derived from the small seeds used in Europe grape seed extract is rich in flavonides. The most valuable flavon seed extract are procyanidolic oligomers (also known as proanthocyanidins called OPCs are found to be 20-50 times as powerful as the antioxidant vitamin E taking several types of antioxidants tends to be more effective because the water-soluble (vitamin C) and fat-soluble (vitamin E) antioxidants. Grape seed has the ability to act as a point of contact between these two type of antioxidant improving the interaction between them ⁽¹⁰⁹⁾.

2-5.Pharmacological actions

As we age destructive free radicals accumulate and our bodies prevent antioxidants. This increases our risk of health problems grape seed extract in many European countries uses for the prevention and treatment of many health problems including cardiovascular disease ,varicose veins ,and other disease because it is used pharmaceutically. In the United States it is considered to supplement and may be purchased without prescription. Grape seed extract extraordinary safe and beneficial food supplement specifically grape seed extract may help to ⁽¹¹⁵⁾. antioxidant protection,prevent diabetes conditions,reduce cancer risk , and slow progression of macular degeneration and cataracts ⁽¹¹⁶⁾.

2-5-1-Antioxidant effects.

Grape seed extract has antioxidant and free radical scavenging activity (Jayaprakasha *et al.*, 2003; Caillet *et al.*, 2006). The sparing/recycling effect of procyanidins from *V. vinifera* seeds on alphatocopherol was established in phosphatidylcholine liposomes and red blood cells (Facino *et al.*, 1998). Procyanidines, in addition to scavenging free radicals, strongly and non-competitively inhibit xanthine oxidase activity, the enzyme which triggers the oxy-radical cascade (Facino *et al.*, 1994). In one study, polyunsaturated fatty acid peroxidation was inhibited by low concentrations of grape seed proanthocyanidins (2 mg/l) (Bouhamidi *et al.*, 1998). Other studies have confirmed that grape seed proanthocyanidin extract (GSPE) (50 mg/l) provided protection against free radicals in *in vitro* free radical scavenging assay and this effect was better than vitamins C and E (Bagchi *et al.*, 2000). Moreover, GSPE (100 mg/ kg), compared to other antioxidants, provided significant protection against 12-O-tetradecanoylphorbol-13- acetate (TPA)-induced oxidative damage (Bagchi *et al.*, 1998).

2-5-2-Antidiabetic effects.

GSE has been reported to be effective in treating diabetic nephropathy, though little is known about the functional protein changes. After GSE therapy in diabetic rats, only nine kidney proteins were found to return to normal levels. It was shown that these proteins are involved in oxidative stress, glycosylation damage, and amino acid metabolism (Li *et al.*, 2008). GSE (250 mg/kg body weight/d) also ameliorated glycation-associated cardiac damage in diabetic rats (Cheng *et al.*, 2007).

2-5-3-Allergies, Hay Fever :

Grape seed extract is one of the botanicals that can reduce allergies. It inhibits the production of inflammatory compounds that cause allergic reactions, particularly things like hay fever. It does this without causing the unwanted side effects that accompany antihistamines

2-5-4-Cardioprotective effects.

Oral consumption of standardized grape extract (100 and 200 mg/kg) provided significant cardioprotection by improving post-ischemic ventricular recovery and reducing the amount of myocardial infarction in rats (**Cui et al., 2002**). In an *ex vivo* experiment using rat aortic rings, ExGrape seeds (7 µg/ml) induced 77% endothelium-dependent relaxation, whereas ExGrape total and grape seed extract (30 µg/ml) induced 84 and 72%, respectively (Auger et al., 2004). Dietary grape seed tannins Procyanidin supplementation in rat and rabbit reduced ischemia/reperfusion damage in the heart and this was associated with an increase in plasma antioxidant activity (**Berti et al., 2003**). Also, it was able to prevent a peroxynitrite attack to vascular cells by layering on the surface of coronary endothelial cells, and enhancing endothelial NO-synthase-mediated relaxation in human internal mammary aortic rings (**Aldini et al., 2003**).

2-5-6-Edema :

The most positive scientific evidence according to the University of Maryland Medical Center shows that it may help with edema and chronic venous insufficiency. One study of breast cancer patients showed that taking 600 mg a day helped to reduce edema, that resulted from breast cancer surgery. It has also reduced swelling due to sports injuries in human studies

2-5-7-Antimicrobial and antiviral effects.

Antimicrobial activity has been reported in several components of grapes including gallic acid (Panizzi et al., 2002), hydroxycinnamic acids (Wen et al., 2003), flavanols (Rauha et al., 2000), flavonols (Mori et al., 1987), trans-resveratrol (Docherty et al., 2001), and tannins (Jayaprakasha et al., 2003). Moreover, antilisterial activity has been reported for grape seed extract (1%) (Ahn et al., 2004). The seed and skin of Ribier grapes extracts decreased L.

monocytogenes numbers from 10⁶–10⁷ CFU/ml to no detectable colonies within 10 min (Rhodes *et al.*, 2006).

2.5.8-other advantages

It is bioavailable and immediately absorbed from the stomach into the blood stream. It is distributed to virtually every organ and tissue ,and remains in the body for up 72 hours .Not only does it neutralize free radicals themselves ,but it also a powerful conserves and regenerates vitamins C and vitamin E is a powerful free radical scavenger ,but it is quickly used up PCO and vitamin C work synergistically to regenerate vitamin E.PCO is one of the few antioxidants that crosses the blood /brain barrier to protect neural tissue.PCO extracts have been proven to be completely safe ⁽¹¹³⁾.

2-6-Drug Interaction.

Proanthocyanidin from grape seeds 12.5 and 25 mg/l *in vitro* and 10 mg/kg *in vivo* enhanced the doxorubicin-induced antitumor effect and reversed drug resistance by increasing intracellular doxorubicin, Ca²⁺, and Mg²⁺ concentrations, and reducing pH and mitochondrial membrane potential. In this study, experimental transplantation Sarcoma 180 (S180) and Hepatoma 22 (H22) was done in mice (Zhang *et al.*, 2005). Also, grape juice impaired CYP2C9 activity *in vitro* (Greenblatt *et al.*, 2006). It was shown that grape seed extract has a synergic effect with amphotericin B against fungal infection in mice (Han, 2007).

2-7-.Bioavailability

Proanthocyanidins is water –soluble and extremely well-absorbed within 60 minutes of consumption, it is absorbed and distributed throughout the body. It has a long "half life" of seven hours ,meaning that after seven hours ,one –half of the original dose is still found to be functionally available within the body.Unlike most antioxidants, pco can cross the blood –brain barrier and

thus protect the brain from the effects of free radical damage associated with aging ⁽¹¹⁴⁾.

2-8-Side effect

An adverse reaction with grape seed extract, usage is considered relatively rare and is usually considered to have a low toxicity. PCO from grape seeds has been found to be non toxic even at extraordinary high dose In one year long study dogs were given a daily dose equivalent to a 150-pound human taking 19,800 mg daily ,with no adverse effects reported.

Laboratory tests have also found pco to be non carcinogenic non teratogenic (dose not cause birth defects) and non mutagenic (dose not cause cellular mutations). Millions of people have used grape seed extract (since 1970 in Europe)without any side effects whatsoever. However, nausea, allergic reactions in the form of a temporary skin rash have occurred in sensitive individuals.

3-Materials & methods

3-1-Plant material and preparation of extracts

Fresh seeds of *grape* were obtained from the local market in Al-Diwanyia city. The seeds were washed and dried under shade for one week, grounded and 200g of seed plant material were extracted with ethanol alcohol (95% v/v) in a soxhlet apparatus by continuous heat extraction. The extract was concentrated in a rotary flash evaporator at a temperature not exceeding 50°C. The alcohol extract was prepared in distilled water containing 2% v/v Tween 80 (as a suspending agent) for experimental purpose.

3-2-Animals:

Swiss albino mice weighing 20-25 g of either sex were used for the study. The animals were procured and housed in the animal house in college of veterinary medicine / Al-Qadissya university , maintained under standard hygienic conditions, at $20 \pm 2^{\circ}\text{C}$, humidity ($60 \pm 10\%$) with 12 hour day and night cycle, with food and water *ad libitum*.

3-3- Morris water maze test :

Mice were grouped as 5 animals each in 2 different groups as follows:

First Group : animals served as negative group control and received vehicle only (distilled water injected intraperitoneally) . second Group : animals received alcoholic extract of BM 50 mg/kg given intraperitoneally for three days . The apparatus used is a circular water tank (100 cm in diameter) filled to a depth of 15 cm with water (25°C). Four points equally distributed along the perimeter of the tank

served as starting locations. The tank was divided arbitrarily into four equal quadrants and a small platform (5 cm width) was located in the center of one of the quadrants. The platform remained in the same position during the training days. The mice were released into the water and allowed 90 s to find the platform. inter-trial interval for 5 days until the performance was stable and the latency to find the platform was low (<10 sec). The test formulations were administered 30 min prior to the first trial daily. Time to find the hidden platform is considered as escape latency. The platform in the water maze was kept at the same position throughout the test to assess the effect of **GSE** on spatial reference memory

3-4-Statistical analysis

All the values were statistically analyzed by one-way analysis of variance (ANOVA) followed by least significant differences (LSD). Comparison between control and plant extract treated group were considered to be significant. All values are expressed as mean \pm SEM.

Results :

4-1-Extraction ratio :

The percentage yield of the ethanolic extract of seeds of that are used in the present study was 28% from the crude material , the yield was dark brown in color with sticky consistency figure (1)

Figure (1) grape seed extract sample

4-2-Morris water maze result :

The time that needed by mice to reach the hidden platform in the water maze is illustrated in Figure (2). There was a significant differences between the group of mice that administered grape seed ethanolic extract (50 mg/kg intraperitoneally) compared with vehicle-treated animals on Days four and five from the beginning of experiment . while Data for Days 1, 2 and 3 did not show a significant difference in the time required for reach to the hidden platform which located in the centre of the tank. The mice treated with grape seed ethanolic extract (50 mg/ kg) showed a significant decrease in escape latency as compared with the control group (Figure 2). As well as The alcoholic extract of grape seed showed a decrease but there was not statistically significant when compared with control in the first three days from beginning of experiment .

Table (1) : effect of the grape seeds ethanolic extract on the spatial memory in albino mice

Groups of experiment Days	Control group	Treated group with grape seed extract
First day	74.2 ± 1.32	72.6 ± 2.28
Second day	71.5 ± 1.98	67.2 ± 4.2
Third day	64.2 ± 1.32	60.36 ± 3.1
Fourth day	60.1 ± 2.4	51.45 ± 1.68
Fifth day	54.2 ± 1.11	42.12 ± 0.94
Average	64.84 ± 3.66	58.74 ± 5.45

- Value represent mean \pm standard error for mean for 5 mice
- LSD value = 4.86

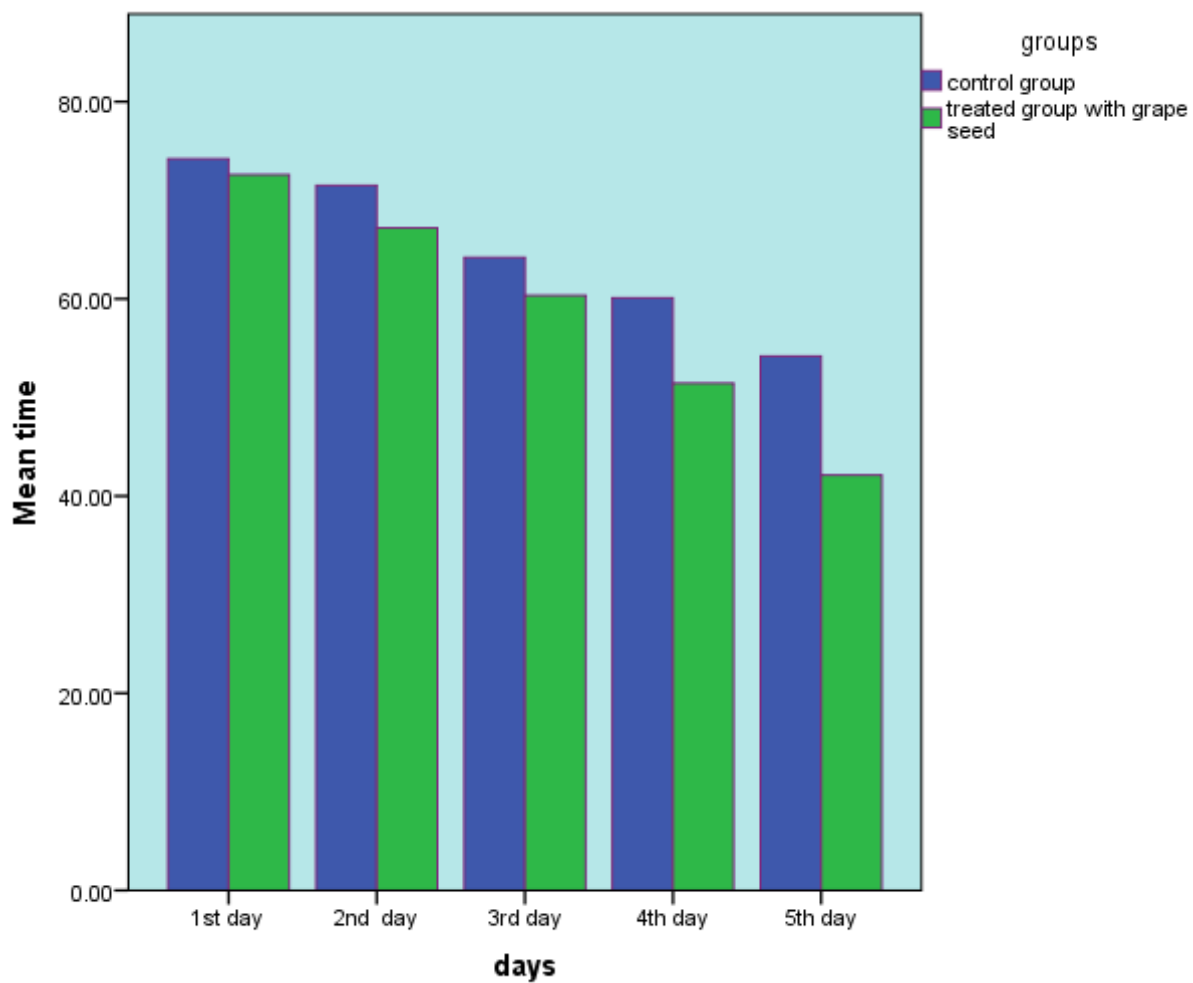


Figure (2) : effect of the grape seed ethanolic extract on the spatial memory in albino mice .

Discussion:

Memory and learning are considered as the most important functional levels of central nervous system (CNS) which helps to encode, store, retain, and recall information in the brain.(Nikfarjam *et al.*, 2016) Ageing and stressors are the most important causes of disturbed memory and poor learning. Cholinergic drugs have positive effects on memory and anti-cholinergics, antipsychotics, and anesthetics have negative effects on memory (Francis *et al.*,1999). Since the role of medicinal plants in learning and memory has attracted the attention of many researchers. Therefore, the aim of the present study to investigate the beneficial effect of the alcoholic extract of grape seed for support memory efficiency in the experimental mice. Grape seed oil is rich in phenolic compounds, fatty acids, and vitamins, with economic importance to pharmaceutical, cosmetic, and food industry. Its use as an edible oil has also been suggested, especially due to its pleasant sensory characteristics. Grape seed oil has beneficial properties for health that are mainly detected by in vitro studies, such as anti-inflammatory, cardioprotective, antimicrobial, and anticancer properties, and may interact with cellular and molecular pathways. The water maze task was introduced by Morris (1981) and colleagues as a spatial localization or navigation task. The task has been used extensively to study the neurobiological mechanisms that underlie spatial learning and memory, age-associated changes in spatial navigation and the ability of nootropic agents to influence specific cognitive

processes(KulKarni,1999) .The Morris water maze (MWM) is one of the most common tasks used to assess spatial learning and memory ability in rodents. The Morris water maze (MWM) is believed to be able to effectively distinguish spatial memory from sensational , motivational and retrieval processes of brain , and often used to test the capabilities of spatial memory , which is considered closely associated with septohippocampal cholinergic activity. (McNamara and Skelton,1993) ethanolic extract of grape seed significantly decreased the escape latency as compared with control group mice. The mice treated with grape seed ethanolic extract (50 mg/ kg) showed a significant decrease in escape latency time as compared with the control group in the fourth and fifth days of the beginning of the experiment. As well as The alcoholic extract of grape seed showed a decrease but there was not statistically significant when compared with control in the first three days from beginning of experiment . Our results also agree with most of the previous studies reporting improving effects of grape parts (seeds , oils or others) in animal models of learning and memory () earlier studies suggest that moderate consumption of red wine may reduce incidence of AD and attenuate AD-type cognitive deterioration and amyloid neuropathology (Dorozynski, 1997).Marambaud et al.,(2005) certain studies have suggested that some polyphenol compounds in the seeds could play role in reduce brain amyloid neuropathology and improve cognitive function by promoting non-myloidogenic secretase activity

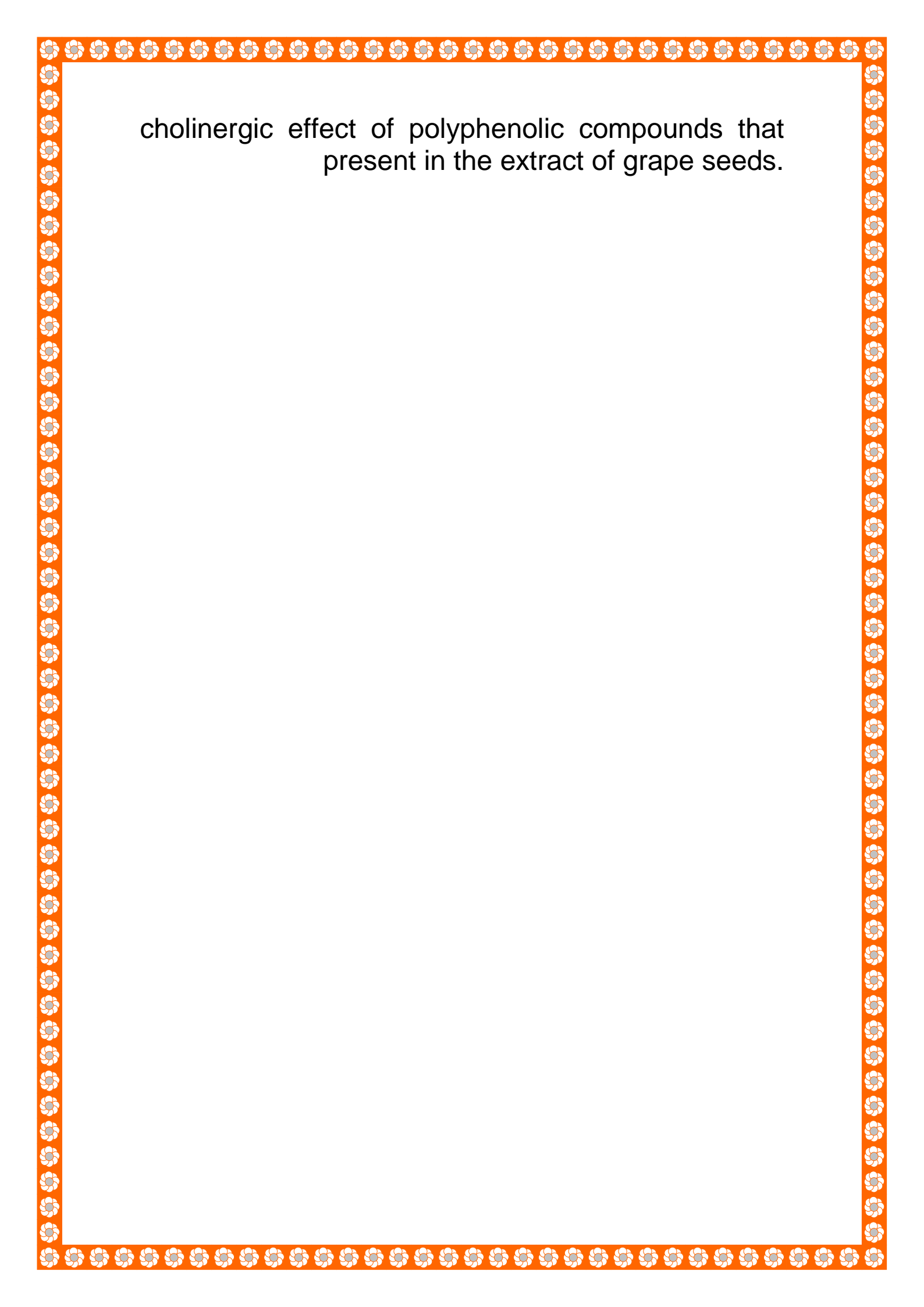
(Rezai-Zadeh et al.,2005) some clinical data have shown that the compounds procyanidin oligomers which present in the grape seeds are 20 time more potent than vit.C and 50 time more potent than vit.E as antioxidant and can play role in the protection of the brain from the effects of stress condition which the animals can be exposure to it through swimming .also reported that resveratrol a natural polyphenol compound that mainly present in the grape seeds , have ability to reduce $A\beta$ - peptides by promoting intracellular $A\beta$ peptides degradation in vitro.

A nother study also suggested that a few select grape derived polyphenolics compounds could play important effect in the reduce aggregation of synthetic $A\beta$ peptides in vitro (Porat *et al.*,2006) .

Wang et al.,(2008) used a naturally derived grape seeds polyphenolic extract and demonstrate its in vitro efficacy to attenuate AD-type $A\beta$ peptides neuropathology in TG2576 AD mouse model.

Grape seeds extract has many possible mechanisms for neuroimprovement action . Its an effective free radical scavenger that reduces lipid peroxidation.

Grape seeds extract provides superior antioxidant efficacy as compared with vitamins C & E .The observed improvement activity of ethanolic extract in water maze performance in mice followed grape administration may be due to antioxidant and

A decorative border composed of a repeating pattern of small, stylized flowers in orange and white, framing the entire page.

cholinergic effect of polyphenolic compounds that
present in the extract of grape seeds.

Conclusions & recommendation :

Conclusions:

- 1- The seeds of the grape plant has good effects in enhancing spatial memory and learning ability in experimental albino mice.
- 2- The Morris water maze (MWM) is one of the most common tasks used to assess spatial learning and memory ability in rodents.

Recommendations:

- 1- It is important to attempt to isolate and purificate the different active ingredients in grape seeds extracts which consider active area for further research on the memory & learning improvement
- 2- Use the other methods for evaluation the learning activity of plant and needed to further studies to identify the exact mechanism of action in this aspect.

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318..

الخلاصة :

يعد نبات العنب فردا من العائلة المعروفة علميا باسم *vitaceae* وهو واحد من اكثر الفواكه استهلاكا في العالم على شكل طازج والفاكهة المعاملة (عصير العنب ، الدبس ، الزبيب وغيرها) وتعد بذور العنب غنية بالمركبات متعددة الفينول والحوامض الفينولية واستهلاكه يعد امنا ومميز في اعطاء العديد من الفوائد الصحية . وكان الهدف من هذه الدراسة هو لغرض تقييم الفعالية المنشطة للذاكرة والتعلم للمستخلص الكحولي لبذور العنب المحلي في الفئران المختبرية وقيمت هذه الفعالية باستخدام اختبار مورس لمتاهة الماء MWM في الفئران. كشفت الدراسة الحالية ان اعطاء المستخلص الكحولي لبذور العنب وبتركيز ٥٠ ملغرام/كغم بالحقن داخل البريتون اظهر انخفاضا ملحوظا في سرعة الهروب الاختفاء في الاختبار المذكور مقارنة بمجموعة السيطرة السالبة وخصوصا في اليومين الرابع والخامس من التجربة ونستنتج من الدراسة الى ان استخدام مستخلص بذور العنب يعمل على تحسين الذاكرة ويمكن ان يكون مفيدا بوصفه عامل مساعد داعم في معالجة ضعف الذاكرة .

وزارة التعليم العالي والبحث العلمي

جامعة القادسية

كلية الطب البيطري

تقييم الفعالية المنشطة للذاكرة والتعلم لمستخلص بذور العنب في الفئران المختبرية

بحث مقدم إلى مجلس كلية الطب البيطري كجزء من متطلبات
الحصول على درجة البكالوريوس في الطب والجراحة البيطرية

تقدم به الطالبتين

اسراء ميري طينة

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علي محمد غازي المحنة

أذار ٢٠١٧

جمادى الآخرة ١٤٣٧