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PYCNOGENOL AND TALBINAH CAN AMELIORATE THE ANTIDEPRESSANT EFFECT OF DESVENLAFAXINE IN DEPRESSION-LIKE BEHAVIOR IN MICE

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ABSTRACT

This work was designed to investigate the possible antidepressant effects of pycnogenol and talbinah as monotherapy or in combination with desvenlafaxine (DV) in the socially isolated male mice for 4 weeks before the experiment to induce depression model. We used 70 mice divided into 7 groups (10 mice per each).Group I: Normal control group that receive only distilled water, Group II: the diseased control group, Group III: pycnogenol (PYC), Group IV: talbinah, Group V: DV (10 mg/kg, p.o.), Group VI: PYC + DV, Group VII: talbinah + DV. Forced swimming test (FST), tail suspension test (TST), and water finding test were carried out at the end of the 4 weeks of treatment. Social isolation induced depressive-like behaviors as observed by increased immobility time in the FST and TST. Also, it induced decreased learning performance as observed by increased water finding test. The administration of DV, talbinah and pycnogenol alone was able to reverse the increases in the immobility time and water finding test. The combination of pycnogenol / or talbinah and DV potentiated the observed effects of DV. These results suggest that augmentation therapy with the addition of a source of tryptophan as talbinah or an antioxidant drugs as PYC may be an important pharmacological approach for the treatment of depression.

KEYWORDS; talbinah, barley, pycnogenol, desvenlafaxine and depression.

1.1. INTRODUCTION

Major depressive disorder (MDD) is among the top three leading causes of disease burden worldwide (Katsunori Yamaura et al., 2012 and M.S. Bhatia et al., 2009). Depression suffers a huge treatment gap worldwide (Vaishnav Krishnan and Eric J. Nestler, 2011).

Desvenlafaxine (DV) is a serotonin and norepinephrine reuptake inhibitor (M.S. Bhatia et al., 2009). It was approved in 2008 by the US Food and Drug Administration for the treatment of MDD (Maria Teresa C Lourenco and Sidney H Kennedy, 2009). Limitations with the use of DV include its moderate efficacy in the treatment of MDD (Kamath J and Handratta V., 2008).

Studies have shown that one of the factors that influence mood and depression is food (Manal M Badrasawi et al., 2013).

Barley (Hordeum vulgare) is an annual cereal grain, rich in vitamins A, C, B1, B2, folic acid and B12; calcium; iron; potassium and chlorophyll (A.E. Bawazir, 2010 and Katsunori Yamaura et al., 2012). Unlike most plants, it provides all nine essential amino acids. It is one of the richest sources of antioxidants and contains the flavones C-glycoside, saponarin, and lutonarin. The study of M. Kamal E. Youssef et al. (2013) indicated that there were good balanced essential amino acids composition required for human nutrition.

There have been a number of unpublished, but reputable concerns on the antidepressive effects of the young green barley leaf in consumers in Japan (Katsunori Yamaura et al., 2012).

Talbina is an Arabic word means milk (M. Kamal E. Youssef et al., 2013). Among Arabs, talbinah food has been used to relieve depression. It is prepared by cooking ground roasted barley with milk for a few minutes. Aisha, the Prophet Mohammed's wife, used to recommend talbinah for the sick and for those who grieved over a dead person based on a recommendation by the Prophet Mohammed, peace be upon him (Hadith) (Manal M Badrasawi et al., 2013).

Other than the Hadith and the cultural use, there is little scientific evidence regarding the use of talbinah in reducing symptoms of depression.

On the other hand, pycnogenol (PYC) is a standardized plant extract obtained from the bark of the French

maritime pine Pinus pinaster which grows in the coastal southwest France (D'Andrea G, 2010 and Mei L et al., 2014). Major constituents of PYC are polyphenols, specifically, catechin, epicathechin and taxifolin (Kendra I. Siler-Marsiglio et al., 2004).

Pycnogenol is now utilized throughout the world as a nutritional supplement and as a phytochemical remedy for various diseases including several impaired psycho-physiological functions. The most obvious feature of pycnogenol is its strong antioxidant activity (D'Andrea G, 2010 and Mei L et al., 2014). PYC has been shown to prevent programmed neuronal cell death and glutamate-induced neurotoxicity (Kendra I. Siler-Marsiglio et al., 2004).

So, I supposed that the combination of talbinah or pycnogenol with DV may ameliorate their antidepressant effects. So, this tudy was conducted to assess the antidepressant effect of pycnogenol, talbinah and desvenlafaxine either as monotherapy or in combination in mice model.

1.2. MATERIALS AND METHODS

1.2.1. Animals

Male Swiss albino mice weighing 24-32 gram were purchased from the Modern Veterinary Office for Laboratory Animals (Cairo, Egypt). Mice were housed in polyethylene cages under hygienic laboratory conditions and normal dark/light cycle. Mice were acclimatized to the housing conditions for ten days before starting the experiment. Food and water were allowed ad libitum during the study period. The experiment was conducted according to the guidelines of the Animal Care and Use Committee at Suez Canal University.

1.2.2. Drugs and talbinah

Desvenlafaxine and Pycnogenol were purchased from Sigma Chemical (St. Louis, MO), and dissolved in distilled water (Mei L et al., 2014). Talbinah was prepared by adding whole barley flour to water (1:10 w/v) according to Zieliński H, et al. (2001), then the mix was heated at 80°C for five minutes with continuous stirring until reaching a porridge like texture.

1.2.3. Experimental groups

The current study was carried out on seventy healthy male albino mice allocated randomly into seven groups, ten mice per each. We used the social isolation model of depression for 4 weeks before the experiment. (Group I): normal mice (housed in group) that were treated with distilled water (vehicle), (Group II): socially isolated (diseased group), (Group III): socially isolated + pycnogenol (0.2 mg/mL p.o.) (Mei L et al., 2014), (Group IV): socially isolated + talbinah ((200 g. Barley/ kg /day grounded and cooked to prepare talbinah) (Awatef M. Ali and Fatma A. Hakami, 2012) was given orally by gavage tube, (Group V): socially isolated + DV (10 mg/kg, p.o.) (Silva MC et al., 2013), (Group VI): socially isolated + PYC + DV (10 mg/kg, p.o.), (Group VII): socially isolated + talbinah + DV (10 mg/kg, p.o.).

After 4 weeks, the animals were left overnight (food and water allowed) and the following parameters were comprised in the present investigations;

- Animal behavior

1. Mice of all groups observed daily for any behavioral changes and number of dead mice were recorded.
2. At the beginning of the experiment and weekly, body weights were detected.
3. The behavioral despair tests:

a. Forced swimming test (FST) as described by (Porsolt et al., 1978): Mice were dropped individually into the glass cylinder (height 45 cm, diameter 20 cm) filled with 20 cm of water maintained at 23-25 C". "Mice were left in the cylinder for 6 minutes". "After 2 seconds the total of immobility duration in mice were recorded by EthoVision XT8 machine". The mouse considered immobile if it is floating without struggling or moves slowly just to "keep its head above the water".

b. The tail suspension test (TST): according to the procedure of (Pandey et al., 2008) with slight modification. The animals were suspended individually using adhesive tapes from a horizontal rod 50cm above the flat surface of the tabletop. The point of attachment on the tail was 2cm from the tip. The duration of immobility during the six minutes observation period was recorded.

4. Water-finding test: was conducted to investigate latent learning performance of the animals (Mouri A, et al., 2007 and Boguslavsky GW, 1978) as an index of spatial learning. The experiment was performed according to (Mamiya et al., 1998). The apparatus used for this test consisted of an open field (30 cm × 30 cm × 30 cm high) with an alcove (10 cm × 10 cm × 10 cm) in the middle of one of the walls of the enclosure. A standard metallic drinking nozzle was set on the center of the alcove ceiling and had its end 5 and 7 cm above the floor in the training and test trials, respectively. The training and test trials were conducted on the last two days of experiment, respectively. In the training trial, animals were placed individually in one corner of the open field of the apparatus. The mice were allowed to explore the environment for 5 min. In the test trials, the animals were again placed individually into the apparatus and the latency for drinking water (drinking latency) was measured for each animal.

1.2.4. Statistical analysis

Data were tabulated and expressed as mean ± S.E.M. One-way analysis of variance (ANOVA) followed by Bonferroni's multiple comparisons test were employed

to analyze the data. Data analysis was performed employing the statistical package for social science, version 16 (SPSS Software, SPSS Inc., Chicago, USA). A P value less than 0.05 was considered significant.

2. RESULTS

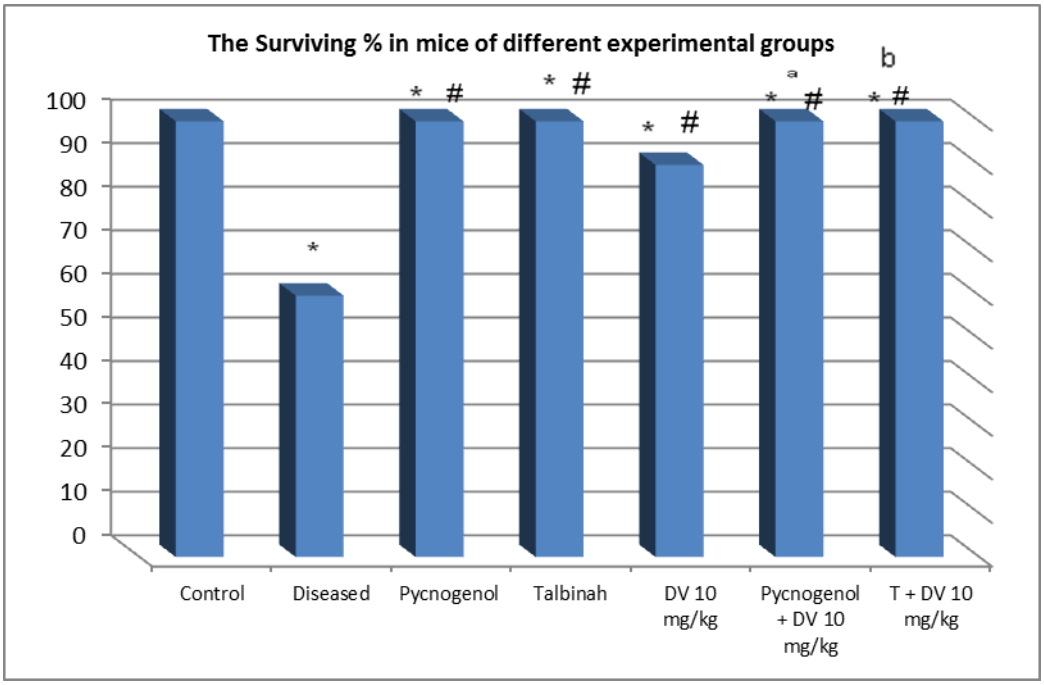

Figure 1. The percentage of survival of mice during the experimental period. All data are expressed as mean ± SE and were analyzed using one-way ANOVA and Bonferroni post-hoc test.
*Compared to control group at $p < 0.05$.
#Compared to diseased group at $p < 0.05$.
[a]Compared to monotherapy with pycnogenol at $p < 0.05$.
[b]Compared to monotherapy with talbinah at $p < 0.05$.

The surviving percentage for groups treated with pycnogenol, talbinah and desvenlafaxine either alone or in combination with DV were 100%. It was 60 % with DV in a dose of 10 mg/kg/day (Fig. 1).

Table 1; showed the weight of mice in different groups.

Week		Control	Diseased	Pycnogenol	Talbinah	DV 10 mg/kg	Pycn+ DV 10 mg/kg	T + DV 10 mg/kg
First	mean±S.E	30.9±1.4	31.5±1.5	31.7±1.2	31.4±1.6	30±1.7	31.2±1.5	31.5±1.6
Second	mean±S.E	31±1.3	31.9±1.2	31.8±1.5	31±1.5	29.5±1.3	31±1.4	31±1.5
Third	mean±S.E	31.4±1.5	32±1.1	31.9±1.3	30.7±1.2	29.2±1.5	30.8±1.5	30.7±1.3
Fourth	mean±S.E	31.6±1.6	31.9±1.4	31.7±1.5	30±1.5	28.5±1.2*	30±1.3	30.4±1.6

All data are expressed as mean ± SE and were analyzed using one-way ANOVA and Bonferroni post-hoc test.
*Compared to control group at $p < 0.05$.

The group treated by desvenlafaxine alone in a dose of 10 mg/kg/day showed significant decrease in weight than the control group as this antidepressant drug has the ability to decrease appetite as one of its side effects. But, when we used the combination therapy either with talbinah or pycnogenal, the mice showed less reduction in their body weight insignificantly (Table 1).

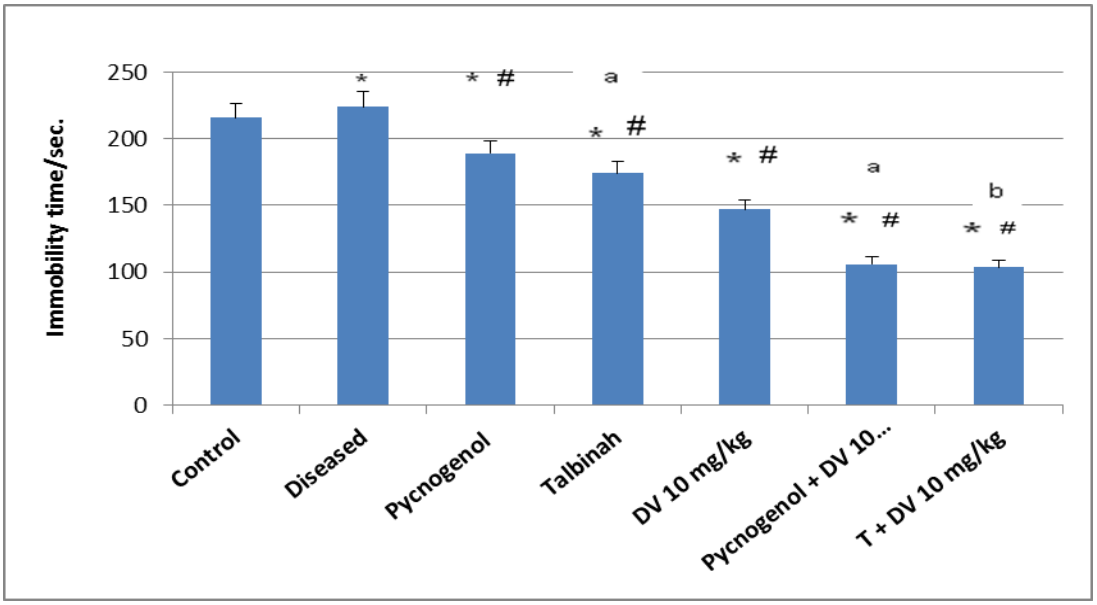

Figure 2. The mean of immobility time/second of mice in FST during the experimental period. All data are expressed as mean ± SE and were analyzed using one-way ANOVA and Bonferroni post-hoc test

*Compared to control group at $p < 0.05$.
[#]Compared to diseased group at $p < 0.05$.
[a]Compared to monotherapy with pycnogenol at $p < 0.05$.
[b]Compared to monotherapy with talbinah at $p < 0.05$.

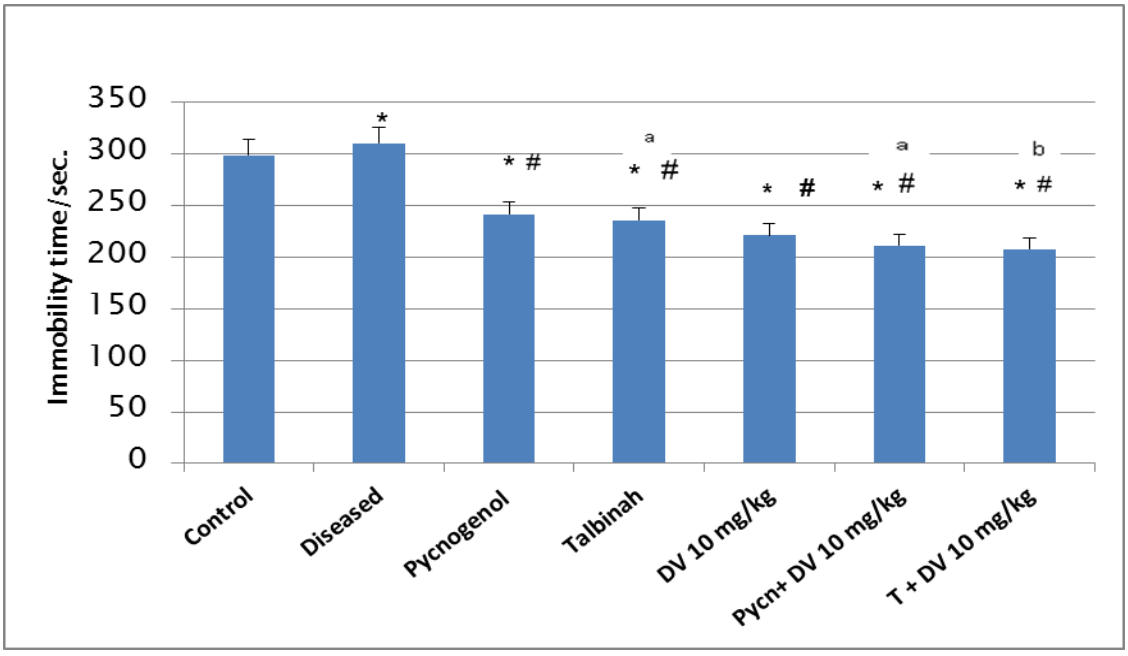

Figure 3. The mean of immobility time/second of mice in TST during the experimental period. All data are expressed as mean ± SE and were analyzed using one-way ANOVA and Bonferroni post-hoc test

*Compared to control group at $p < 0.05$.
[#]Compared to diseased group at $p < 0.05$.
[a]Compared to monotherapy with pycnogenol at $p < 0.05$.
[b]Compared to monotherapy with talbinah at $p < 0.05$.

Figure 2 and 3 showed that there was a significant treatment effect in the forced swimming test and the tail suspension test as the mean of immobility time in FST and TST was decreased significantly in all treated groups than the diseased group, indicating that desvenlavaxine (10 mg / kg), pycnogenol and talbinah were effective for producing an antidepressant-like effect in this behavioral model. Also, combination of desvenlavaxine with either pycnogenol or talbinah caused significant reduction in

immobility time than monotherpy with pycnogenol or talbinah respectively.

In FST, talbinah as monotherapy had significant better effect than monotherapy with pycnogenol as (means/second was 174.21versus 189.07). The effect of talbinah in combination with DV was significantly better than monotherapy (means/second was 103.72 versus 174.21 respectively).

While in TST, the effect of talbinah as monotherapy or in combination with DV was significantly better than pycnogenol either alone or in combination with DV (mean/second were 235.46 versus 241.55 and 207.76 versus 210.95 respectively).

So, we can conclude that combination of talbinah with desvenlavaxine had the best antidepressant effect of all drug regimens.

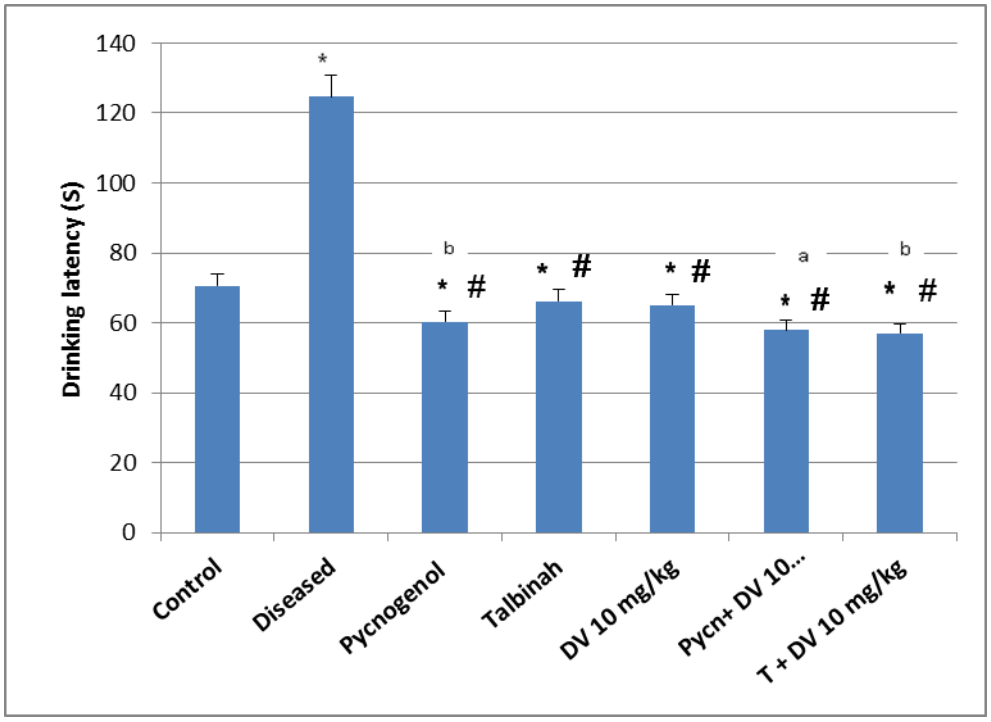

Figure 4. The mean of drinking latency in seconds of mice during the experimental period. All data are expressed as mean ± SE and were analyzed using one-way ANOVA and Bonferroni post-hoc test
*Compared to control group at $p < 0.05$.
#Compared to diseased group at $p < 0.05$.
[a]Compared to monotherapy with pycnogenol at $p < 0.05$.
[b]Compared to monotherapy with talbinah at $p < 0.05$.

In the training trial of the water-finding test, there was no significant difference in latency to drink water between the control group and the other experimental groups except the diseased untreated group where the drinking latency was significantly high than the other groups. This indicates that social isolation impairs latent learning performance in the water-finding test. In the test trials, baseline drinking latency of each animal group was decreased significantly in all treated groups in comparison to the diseased untreated group. Combination therapies decrease the drinking latency significantly than monotherapy either with pycnogenol or talbinah (58 versus 60.3 and 57 versus 66.2 respectively). The effect of combination therapy with talbina was better than with pycnogenol, but this was not statistically significant. These findings indicate that combination therapies improve latent learning performance.

2.1. DISCUSSION

In this study, I used the social isolation model for 4 weeks before the experiment to evaluate the antidepressant-like effect of pycnogenol, talbinah and desvenlafaxine either as monotherapy or in combination therapy in mice. The survival percentage was 100% in all treated groups except for the group treated with DV alone which is 60% which may be related to its side effects. Regarding the weight of mice, the group treated with DV alone in a dose of 10 mg/kg/day showed significant decrease in weight than the control group. This was similar to the results of M.S. Bhatia et al. (2009), in which he listed that data pooled from 7 clinical trials, showed that treatment with DV was associated with small mean decreases in weight in the short term (1 kg), which persisted up to 6 months with a small mean increase (<1 kg) and was comparable to placebo. This may be related to the adverse effects of DV as M.S. Bhatia et al. (2009), listed that the most frequently

reported adverse events other than nausea were: anorexia, dry mouth and constipation. All of these adverse effects can affect food intake and thus leads to decreased body weight. While groups treated with talbinah or pycnogenol as monotherapy didn't show any changes in body weight which is similar to the results of Mei L et al. (2014) in which they listed that body weights and food intake did not differ among the groups throughout the experimental period. But, when I used the combination therapy either with talbinah or pycnogenal, the mice showed less insignificant reduction in their body weight (Table 1). So, I can conclude that combination therapy can reduce the side effects of DV on survival and body weight.

The evaluation of therapeutic effects of different drugs was done through measurement of the forced swimming test, the tail suspension test and the water finding test. The FST and the TST is an animal model that is used as an experimental paradigm for the assessment of despair / depression-like behavior. While, the water finding test is used for the assessment of behavioral performance related to spatial learning. They are commonly used as screening tests for the antidepressant properties of drugs. Our results showed that talbinah, pycnogenol and desvenlafaxine administered orally significantly reduces immobility duration in the mouse FST and TST. Also, they reduce the drinking latencies in the mice water finding test. The antidepressant effect of talbinah is congruent with the results of M. Kamal E. Youssef et al. (2013) which revealed that tryptophan was increased after making talbina, and there was a relationship between tryptophan and the biosynthesis of serotonin which control our moods, or relieves some of our sorrow, as the prophet Mohammed peace be upon him said. Where, the antidepressant effect of pycnogenol may be related to its antioxidant effects as indicated in the study of Stough et al. (2012) where they listed that antioxidant supplementation results in improved cognition and behaviour in aged animals and concurrent decreases in oxidative insult to neural structures and there is evidence that pycnogenol prolongs the lifetime of the ascorbate antioxidant and stimulates the synthesis of antioxidant enzymes inside arterial cells. Moreover, Kobayashi MS et al. (2000) reported that pycnogenol had neuroprotective properties in HT-4 neuronal cells subjected to glutamate induced cytotoxicity (one of the principle sources of ROS in the brain). Also, Mei L et al. (2014) reported that it takes four weeks for the oxidative stress to be significantly lowered by PYC.

This study found that combination therapies with either talbinah or pycnogenol are better than monotherapies. Combination therapy with talbinah has a better effect than with pycnogenol as it reduces the immobility time in FST and TST and it reduces the drinking latency more than with pycnogenol, but this is not statistically significant. Thus, this study suggests that talbinah has a favorable antidepressant-like profile than pycnogenol and that combination therapy of talbinah with desvenlafaxine has the best antidepressant effect. But, I cannot explain this result. So, I suggest further studies on the mechanism of action of talbinah and PYC.

2.2. CONCLUSION

Pycnogenol, talbinah and desvenlafaxine had an antidepressant effect. Our results suggest that augmentation therapy with the addition of a source of tryptophan as talbinah or an antioxidant drugs as PYC to desvenlafaxine may be an important pharmacological approach for the treatment of depression. This study suggests that talbinah has a favorable antidepressant-like profile than pycnogenol and that combination therapy of talbinah with desvenlafaxine has the best antidepressant effect.

2.3. REFERENCES

1. A.E. Bawazir (2010). Investigations on the Chronic Effect of Talbina (Barley Water) on Hormone (Cortisol and Testosterone), Reproductive System and Some Neurotransmitter Contents in Different Brain Areas of Male Albino Rats. American-Eurasian Journal of Scientific Research; 5(2): 134-142.
2. Awatef M. Ali and Fatma A. Hakami (2012). Comparative studies on the effect of Prozac drug and Barely grains on the skeletal muscles of mice: behavioral and histological studies. Journal of Applied Pharmaceutical Science; 02(03): 45-51.
3. Boguslavsky GW (1978). A vigilance model for latent learning. Pavlovian Journal of Biological Science; 13: 236–40.
4. Con K Stough, Matthew P Pase, Vanessa Cropley, Stephen Myers, Karen Nolidin, Rebecca King, et al. (2012). A randomized controlled trial investigating the effect of Pycnogenol and BacopaCDRI08 herbal medicines on cognitive, cardiovascular, and biochemical functioning in cognitively healthy elderly people: the Australian Research Council Longevity Intervention (ARCLI) study protocol. Nutrition Journal; 11: 11.
5. D'Andrea G. (2010). Pycnogenol: a blend of procyanidins with multifaceted therapeutic applications? Fitoterapia. Oct; 81(7): 724-36.
6. Kamath J and Handratta V. (2008). Desvenlafaxine succinate for major depressive disorder: a critical review of the evidence. Expert Rev Neurother. Dec; 8(12): 1787-97.
7. Katsunori Yamaura, Noriyuki Nakayama, Maki Shimada, Yuanyuan Bi, Hideki Fukata and Koichi Ueno (2012). Antidepressant-like effects of young green barley leaf (Hordeum vulgare L.) in the mouse forced swimming test. Pharmacognosy Res. Jan-Mar; 4(1): 22–26.
8. Kendra I. Siler-Marsiglio, Gerry Shaw, and Marieta B. Heaton (2004). Pycnogenol and Vitamin E Inhibit Ethanol-Induced Apoptosis in Rat Cerebellar Granule Cells. J Neurobiol; 59: 261–271.
9. Kobayashi MS, Han D, and Packer L (2000). Antioxidants and herbal extracts protect HT-4

neuronal cells against glutamate-induced cytotoxicity. Free Radical Research; 32(2): 115-124.
10. M. Kamal E. Youssef, Fawzy Abd El-Kader El-Fishawy, El-Sayed Abd El-Naby Ramadan, and Asmaa Mohamed Abd El-Rahman (2013). Nutritional Assessment of Barley, Talbina and Their Germinated Products. Frontiers in Science; 3(2): 56-65.
11. M.S. Bhatia, G. Rajender, S. Srivastav, P. Kumar, and D. Choudhary (2009). Drug Review: Desvenlafaxine: A New Serotonin. Norepinephrine Reuptake Inhibitor. Delhi Psychiatry Journal; 12:(2).
12. Mamiya T, Noda Y, Nishi M, Takeshima H, Nabeshima T (1998). Enhancement of spatial attention in nociceptin/orphanin FQ receptor-knockout. Brain Research; 783: 236–40.
13. Manal M Badrasawi, Suzana Shahar, Zahara Abd Manaf, and Hasnah Haron (2013). Effect of Talbinah food consumption on depressive symptoms among elderly individuals in long term care facilities, randomized clinical trial. Clin Interv Aging.; 8: 279–285.
14. Maria Teresa C Lourenco and Sidney H Kennedy (2009). Desvenlafaxine in the treatment of major depressive disorder. Neuropsychiatr Dis Treat. 5: 127–136.
15. Mei L, Mochizuki M, and Hasegawa N (2014). Pycnogenol ameliorates depression-like behavior in repeated corticosterone-induced depression mice model. Biomed Res Int.; 942927.
16. Mouri A, Noda Y, Noda A, Nakamura T, Tokura T, and Yura Y (2007). Involvement of a dysfunctional dopamine-D1/N-methyl-d-aspartate-NR1 and Ca 2+/calmodulin dependent protein kinase II pathway in the impairment of latent learning in a model of schizophrenia induced by phencyclidine. Molecular Pharmacology; 71: 1598–609.
17. Pandey DK, Rajkumar R, Mahesh R, and Radha R (2008). Depressant-like effects of parthenolide in a rodent behavioural antidepressant test battery. Journal of pharmacy and pharmacology; 60: 1634-1650.
18. Porsolt R. D., Bertin A. and Jalfre M. (1978). "Behavioural despair" in rats and mice: strain differences and the effects of imipramine. Eur J Pharmacol; 51: 291-4.
19. Vaishnav Krishnan and Eric J. Nestler (2011). Animal Models of Depression: Molecular Perspectives. Curr Top Behav Neurosci.; 7: 121–147.
20. Zieliński H, Kozłowskaa H and Lewczuk B (2001). Bioactive compounds in the cereal grains before and after hydrothermal processing. Innovative Food Sci. and Emerging Technol. 2: 159-169.