Introduction

Aescin or β-escin is the main and active constituent of horse chestnut seed (Aesculus hippocastanum) used for treatment of inflammatory edema, venous insufficiency and ischemic ulcers. Aescin has many actions due to induction of endothelial nitric oxide and prostaglandin F2-α production moreover; aescin antagonizes the effect of histamine and 5HT at receptor levels. The present study was to evaluate the neurobehavioral effects of aescin on normal healthy volunteers. A total number of 65 healthy participants with mean age of 21±1.1 years were recruited to study the effects of aescin on the neurobehavioral effects of normal healthy volunteers compared to placebo. The neurobehavioral effects were assessed by psychomotor performances and sensorimotor reaction, cortical arousal and central integrity processes and assessment of memory capacity. Placebo produced insignificant amelioration of TRT and RRT p>0.05, whereas; aescin produced a significant neuroprotective effect via inhibition of TNF-α mediated inflammation and NFkB activations induce production of amyloid protein precursor, excitatory amino acid and pro-inflammatory cytokines that cause severe excitotoxicity and neuronal damage. Additionally, TNF-α is mainly produced from astrocytes and microglialcytes during brain insults causes significant direct brain damage or indirectly through the activation of other areas.
NFkB; thus, aescin is regarded as a potent neuroprotective agent through inhibition of both NFkB and TNF-α.  

Furthermore, aescin stimulate release of ACTH and corticosterone that may modulate brain neurotransmitters. 

Moreover, selvakumar et al., study illustrated that administration of aescin in mouse model Parkinson led to a significant amelioration in the movement and behavioral signs due to anti-inflammatory and anti-oxidant effects. 

Because of little is known about the central effect of aescin in human thus; the aim of the present study was to evaluate the neurobehavioral effects of aescin on normal healthy volunteers.

**MATERIALS AND METHODS**

This study was done and completed in Department of Clinical Pharmacology and Therapeutic, College of Medicine, Al-Mustansiriya University in Baghdad-Iraq from March to April 2017. All of enrolled volunteers were interviewed and gave them a brief explanation about this experimental study and for the health status since all volunteers should be healthy and free from any illness even mild fatigue. An exclusion criterion includes metabolic, neurological, psychiatric and somatic disorders. Moreover, a history of drug intake was taken thoroughly and all participants were recommended not drink any beverage, stimulant agents and caffeinated drinks for at least three days prior of commencing the study. 

All participants in this study gave an informed permission to their contribution in the study. The research principles were approved and endorsed by a specialized scientific jury and medical committee in Department of Clinical Pharmacology and Therapeutic, College of Medicine, Al-Mustansiriya University.

**Study design**

This study was randomized, double-blind, placebo-controlled study, according to the Declaration of Helsinki. A total number of 65 healthy participants (30 males+35 females) with mean age of 21+1.1 years were recruited from students of third stage medical college they were divided into two groups: 

Group I: 30 volunteers (14 males+16 females) received placebo (starch capsule 500mg/day)

Group II: 35 volunteers (16 males+19 females) received aescin tablet 20mg/day (Reparil, MADAUS GmbH 51101 koln, FRG).

The volunteers in each group were subjected to the neurocognitive stimuli before (baseline) and after receiving the placebo or aescin daily for five consecutive days to illustrate the differences between placebo and aescin on the neurobehavioral response on normal healthy volunteers. All drugs were purchased from private pharmacy and given as free of charge to all volunteers.

**Assessment of psychomotor performances and sensorimotor reaction**

The psychomotor performance of the participants was evaluated by the Leeds battery psychomotor tester (Zac-Gmb.O-8346-Simbach/Inn) which calculates of the total reaction time (TRT), movement reaction time (MRT) and recognition reaction time (RRT). The subject should sit in a comfortable position and asked to place the index finger on the neutral central button and should press urgently the site of red light appearance as soon as possible, the mean of five consecutive readings was recorded on specific digital screen in a millisecond. TRT represents the time from the onset of the stimulus to the end of the reaction time, RRT represents the time that needed for recognition of the stimulus while; MRT represents the time from onset of motor action to the end of the reaction time. TRT and RRT were recorded during the stimulus reaction, whereas MRT was calculated from subtraction of RRT from TRT (a marker of sensorimotor reaction). 

**Assessment of cortical arousal and central integrity processes**

Critical flicker-fusion frequency threshold (CFFFT) is an indicator of cortical arousal activity is composed of two components, critical flicker frequency and critical fusion frequency that are measured in Hz. Assessment of CFFFT components was done by the Leeds battery psychomotor tester when it switched to CFF record, the participant should be in a comfortable position and concentrated on four illuminated red light diodes that are located on a panel about one meter distance that allows binocular discrimination. When the test was started up, the researcher asks the participant about the type of the frequency, when it changes from steady to flicker the participant should press a specific button this represent critical flicker frequency or descending frequency (CFFD), and when it changes from flicker to steady state this represent critical fusion frequency or ascending frequency (CFFA). This test repeated four times and then takes the mean. Normally CFFD is ranged from 1-30 Hz and CFFA is ranged from 30-60 Hz. Thus; when CFFD decrease, CFFA and CFFFT increase this indicating an excellent central integrity and cortical arousal abilities. 

Then from these records we can measure the following:

- **Fusion index= max/min(maximum and minimum values of CFFA)**
- **Fusion percent= max-min/max+min(maximum and minimum values of CFFA)**
- **Flicker index = max/min(maximum and minimum values of CFFD)**
- **Flicker percent = max-min/max+min(maximum and minimum values of CFFD)**

\[
CFFFT = CFFD + CFFA/2
\]
Assessment of memory capacity

The memory capacity was assessed by two methods:

- **Visual working memory capacity**

  The capacity of visual working memory was assessed by N-back test, briefly this test was done on the laptop screen; the eight squares at different locations were accessed on the laptop screen at a rate of 3 seconds. In 1-back test, the participant seeks the square in one reverse trial, in 2-back test, the participant seek the square in two reverse trials and in 3-back test the participant seek the square in three reverse trials. At the end of the test, the participant should press the letter A on laptop keyboard, then the number of correcting responses representing the visual working memory that be measured as accuracy percentage.\(^1\^\)\(^2\)

- **Short term memory test**

  This test was done online, it consists of six trials. In each trial the participant should graph the number of letters that was remembered as a percentage. In the first trial, there are two letters, when the participant remembered two letters, then the percentage is 100% if remembered one letter then the percentage is 50%. In the second trial there are four letters, in the third trial, there are six letters and so on (https://faculty.washington.edu/chudler/stm0.html), table 1.

  All neurocognitive tests were done daily at morning 9 am for five consecutive days to avoid the diurnal variations.

**Statistical analysis**

Data of the present study were analyzed using SPSS version 21 (IBM SPSS Statistic for Windows, Version 21,2015 Armonk, NY, IBM Corp) and presented as mean± SD, paired, unpaired student t test were used to evaluate the significance of difference in terms of 95% confidence interval and t value regarding \( P \) value less than 0.05 as significant. The chi-square test was used to determine the differences between percent changes % of placebo and aescin.

**RESULTS**

The characteristics of the present study illustrated that all of enrolled volunteers were younger with age mean 21±1.1 years. A total number of 65 healthy volunteers were enrolled in the present study with 30:35 male- female ratios. 46.15% of the volunteers were treated with placebo, while 53.85% of them treated with aescin, for five consecutive days; there was no any withdrawal rate. Additionally, 92.3% and 7.69% of enrolled volunteers were right hand dominant and left hand dominant respectively, table 2.

Placebo produced insignificant amelioration of TRT and RRT \( p > 0.05 \), but it has shown mild significant effect on MRT since; placebo decreased MRT from 227.45±11.54 (ms) to 233.51±11.33 (ms) \( p = 0.03 \). Aescin produced a significant effect in the amelioration of psychomotor performances and sensorimotor reaction since; aescin reduced TRT, RRT and MRT more significantly \( p < 0.001 \) table 3.

Regarding the differential effect of placebo and aescin on the cortical arousal and central integrity processes, placebo illustrated insignificant effect \( p > 0.05 \) whereas; aescin showed mild significant effect on critical fusion frequency (CFF\(^3\)) \( p < 0.05 \) and highly significant effect on the other parameters \( p < 0.01 \) except for critical-fusion frequency threshold when aescin illustrated insignificant effect \( p > 0.05 \) table 4.

**Table 1: Short term memory test**

| Trial number | Number of letters | Correct letters | Number of remembered letters | Percentage |
|--------------|-------------------|-----------------|------------------------------|------------|
| 1            | 2                 | UM              |                              |            |
| 2            | 4                 | TZLD            |                              |            |
| 3            | 6                 | KXCEJO          |                              |            |
| 4            | 8                 | AVCYISEH        |                              |            |
| 5            | 10                | LBFQRPMAUX      |                              |            |
| 6            | 12                | ZQECTBUMONRV    |                              |            |

**Table 2: Demographic characteristics of the present study**

| The characteristics | Mean ±SD, number, % |
|---------------------|---------------------|
| Age (years)         | 21±1.1              |
| Number              | 65                  |
| Male: Female ratio  | 30:35               |
| Study type          | Double-blind, placebo controlled study |
| Duration of the study (days) | 5 |
| Drugs used          | Periapone, Placebo |
| Placebo             | 30(46.15)           |
| Aescin              | 35(53.85)           |
| Dominant hand       | Right               |
|                      | Left                |
| Right               | 60(92.3)            |
| Left                | 5(7.69)             |

Concerning the memory capacity that was measured by n-back working memory accuracy and short term memory, placebo produced insignificant improvement on the working and short term memories \( p > 0.05 \). On the other
hand, aescin illustrated significant acceleration of II-back WMA, III-back WMA and Second trial short term memory (STM) \( p<0.01 \) and insignificant effect on other parameters \( p>0.05 \) table 5.

Moreover, the differences between before and after exposure to the placebo or aescin was measured by percent change differences. The difference between the placebo and aescin was insignificant in the most parameters of psychomotor performances, sensorimotor reaction, cortical arousal, central integrity processes and memory capacity \( p>0.05 \), but aescin effects were more pronounced on TRT, RRT, fusion percent and flicker percent \( p<0.01 \) compared to the percent change of placebo table 5.

Furthermore, the present study showed insignificant effect of gender on the psychomotor performances, sensorimotor reaction, cortical arousal, central integrity processes and memory capacity in view of the fact that male: female ratio was 30:35, table 6.

### Table 3: Differential effects of placebo and Aescin on the psychomotor performances and sensorimotor reaction

| Variables     | Placebo (n=30) |   | Aescin (n=35) |   |
|---------------|---------------|---|---------------|---|
|               | Before        | After | Before        | After |
| TRT (ms)      | 671.38±22.78 | 673.49±22.12 | 0.7          | 677.82±23.79 | 528.26±20.59 ¶ | 0.0001 ** |
| RRT(ms)       | 443.93±18.77 | 439.98±18.23 | 0.3          | 467.79±19.41 | 341.52±17.73 ¶ | 0.0001 ** |
| MRT(ms)       | 227.45±11.54 | 233.51±11.33 | 0.03*        | 210.03±10.19 | 186.74±9.75 ¶ | 0.0001 ** |

Data are presented as mean ±SD, *\( p<0.05 \), **\( p<0.01 \), ¶\( p<0.01 \)(post-treatment of aescin versus post-treatment of placebo) TRT: total reaction time, RRT: recognition reaction time, MRT: movement reaction time

### Table 4: Comparing the effects of placebo and aescin on the cortical arousal and central integrity processes

| Variables     | Placebo (n=30) |   | Aescin (n=35) |   |
|---------------|---------------|---|---------------|---|
|               | Before        | After | Before        | After |
| CFF\(^a\) (Hz) | 31.42±3.75    | 31.33±3.11 | 0.9          | 31.62±3.54 | 33.71±4.99 * | 0.04* |
| CFF\(^b\) (Hz) | 28.56±2.77    | 28.85±2.97 | 0.4          | 28.94±2.84 | 26.22±1.99 | 0.0001 ** |
| CFFFT(Hz)     | 29.99±2.81    | 30.09±2.72 | 0.14         | 30.28±2.66 | 29.66±1.81 ¶ | 0.25 |
| Fusion index  | 0.601±0.002   | 0.601±0.003 | 0.9          | 0.601±0.0002 | 0.608±0.0003 ¶ | 0.0001 ** |
| Fusion percent | 0.315±0.057 | 0.315±0.057 | 1.0          | 0.316±0.068 | 0.211±0.011 ¶ | 0.0001 ** |
| Flicker index | 0.603±0.00040 | 0.603±0.00041 | 1.0 | 0.603±0.00040 | 0.607±0.0003 ¶ | 0.0001 ** |
| Flicker percent | 0.371±0.044 | 0.371±0.043 | 1.0          | 0.371±0.045 | 0.228±0.011 ¶ | 0.0001 ** |

Data are presented as mean ±SD, *\( p<0.05 \), **\( p<0.01 \), ¶\( p<0.01 \)(post-treatment of aescin versus post-treatment of placebo) CFFA: critical fusion frequency (ascending), CFFD: critical flicker frequency (descending), CFFFT: critical-fusion-frequency threshold

### Table 5: Effects of placebo and aescin on the memory capacity regarding working memory accuracy and short term memory

| Variables     | Placebo (n=30) |   | Aescin (n=35) |   |
|---------------|---------------|---|---------------|---|
|               | Before        | After | Before        | After |
| I-back WMA (%) | 94.88±8.93   | 95.34±9.11 | 0.85         | 95.73±9.82 | 99.98±9.84 | 0.07 |
| II-back WMA (%) | 82.83±8.94   | 84.73±8.93 | 0.41         | 84.89±9.87 | 92.93±10.11 ¶ | 0.001 ** |
| III-back WMA (%) | 75.66±6.98   | 77.22±6.83 | 0.38         | 75.33±6.81 | 79.99±7.91 | 0.01* |
| First trial STM (%) | 99.87±1.13    | 99.90±1.10 | 0.10        | 99.88±1.14 | 99.98±0.16 | 0.60 |
| Second trial STM (%) | 87.45±9.99    | 87.88±9.79 | 0.86        | 86.85±9.55 | 94.72±9.11 ¶ | 0.008 ** |
| Third trial STM (%) | 80.55±8.82    | 81.83±8.59 | 0.57        | 80.75±8.93 | 84.62±7.94 | 0.05 |
| Fourth trial STM (%) | 73.66±8.83    | 72.93±8.66 | 0.74        | 73.55±8.62 | 75.81±8.99 | 0.28 |
| Fifth trial STM (%) | 67.72±6.22    | 67.33±6.39 | 0.81        | 67.99±6.71 | 69.98±6.91 | 0.22 |
| Sixth trial STM (%) | 45.23±5.85    | 45.78±5.11 | 0.69        | 45.11±5.81 | 45.97±5.94 | 0.54 |

Data are presented as mean ±SD, *\( p<0.05 \), **\( p<0.01 \), ¶\( p<0.01 \)(post-treatment of aescin versus post-treatment of placebo) WMA: working memory accuracy, STM: short term memory
Results of therapy showed that the central arousal function and memory capacity significantly improved step by step, that showed three consecutive days of therapy with aescin and MRT significantly as supported by Zhang et al. therapy compared to the placebo effect on normal healthy volunteers, since, aescin improve and accelerate TRT, RRT, and MRT significantly as supported by Zhang et al., study that showed three consecutive days of therapy with aescin significantly improved step-down avoidance and Morris tests that reflect the cognitive and psychomotor performance functions.

| Variables          | Placebo (n=30) | Aescin (n=35) | Difference | 95% CI          | χ²   | P      |
|--------------------|---------------|---------------|------------|-----------------|------|--------|
| TRT (ms)           | 0.314↑        | 22.06↓        | 21.746     | 4.73-38.94      | 7.11 | 0.007**|
| RRT (ms)           | 0.889↓        | 26.99↓        | 26.101     | 7.79-43.75      | 8.525| 0.003**|
| MRT (ms)           | 2.66↑         | 11.088↓       | 8.428      | 7.29-23.87      | 1.691| 0.19   |
| I-back WMA (%)     | 0.484↑        | 4.43↑         | 3.946      | 8.7-16.82       | 0.975| 0.32   |
| II-back WMA (%)    | 2.29↑         | 9.47↑         | 7.18       | 7.95-22.11      | 1.419| 0.23   |
| III-back WMA (%)   | 2.06↑         | 6.18↑         | 4.12       | 10.05-17.90     | 0.659| 0.41   |
| First trial STM (%)| 0.03↑         | 0.100↑        | 0.07       | 11.52-10.16     | 0.012| 0.91   |
| Second trial STM (%)| 0.49↑       | 9.06↑         | 8.57       | 5.33-23.21      | 2.412| 0.12   |
| Third trial STM (%)| 1.58↑         | 4.79↑         | 3.21       | 10.32-16.34     | 0.512| 0.47   |
| Fourth trial STM (%)| 0.99↑        | 3.07↑         | 2.08       | 10.66-14.29     | 0.333| 0.56   |
| Fifth trial STM (%)| 0.57↑         | 2.92↑         | 2.35       | 10.04-14.45     | 0.488| 0.48   |
| Sixth trial STM (%)| 1.21↑         | 1.90↑         | 0.69       | 12.00-12.23     | 0.049| 0.82   |
| CFF^A (Hz)         | 0.28↑         | 6.60↑         | 6.32       | 6.75-20.117     | 1.791| 0.18   |
| CFF^B (Hz)         | 1.01↑         | 9.39↑         | 8.38       | 5.96-23.15      | 2.141| 0.14   |
| CFF^F (Hz)         | 0.33↑         | 2.04↑         | 1.71       | 10.32-13.28     | 0.377| 0.53   |
| Fusion index       | 0.000001↑     | 1.16↑         | 1.159      | 10.46-12.12     | 0.345| 0.55   |
| Fusion percent     | 0.000001↓     | 33.22↓        | 33.21      | 14.31-51.12     | 11.950| 0.0005**|
| Flicker index      | 0.000001↑     | 0.66↑         | 0.65       | 10.92-11.23     | 0.196| 0.65   |
| Flicker percent    | 0.000001↓     | 38.54↓        | 38.53      | 18.87-56.45     | 14.36| 0.0002**|

Data are expressed as percent change %, X^²: chi-square, **p<0.01, TRT: total reaction time, RRT: recognition reaction time, MRT: movement reaction time, CFF^A: critical fusion frequency (ascending), CFF^B: critical flicker frequency (descending), CFF^F: critical-fusion frequency threshold, WMA: working memory accuracy, STM: short-term memory.

| Variables          | Male (n=30) | Female (n=35) | t       | 95% CI              | P      |
|--------------------|------------|--------------|---------|---------------------|--------|
| TRT (ms)           | 661.48±21.75 | 663.86±21.22 | 0.44    | -8.292-13.052      | 0.65   |
| RRT (ms)           | 463.93±19.27 | 459.98±18.98 | -0.83   | -13.453-5.535      | 0.40   |
| CFF^A (Hz)         | 31.17±3.66  | 31.76±3.85   | 0.63    | -1.281-2.461       | 0.53   |
| CFF^B (Hz)         | 28.22±2.64  | 27.56±2.94   | -0.94   | -2.055-0.735       | 0.34   |
| CFF^F (Hz)         | 29.47±2.21  | 28.88±2.95   | -0.90   | -1.900-0.7203      | 0.37   |
| I-back WMA (%)     | 93.34±9.84  | 94.66±9.43   | 0.55    | -3.463-6.1035      | 0.53   |
| II-back WMA (%)    | 80.45±7.55  | 82.74±7.44   | 1.22    | -1.434-6.0144      | 0.22   |
| III-back WMA (%)   | 76.48±6.23  | 76.34±6.11   | -0.091  | -3.205-2.9255      | 0.92   |
| Mean STM (%)       | 66.88±11.92 | 67.43±11.23  | 0.19    | -5.194-6.294       | 0.84   |

DISCUSSION

The present study demonstrated a significant effect of aescin on the psychomotor performances and sensorimotor reaction after five consecutive days of therapy compared to the placebo effect on normal healthy volunteers. Since, aescin improve and accelerate TRT, RRT, and MRT significantly as supported by Zhang et al., study that showed three consecutive days of therapy with aescin significantly improved step-down avoidance and Morris tests that reflect the cognitive and psychomotor performance functions.

Placebo in the current study produced mild significant improvement effect on MRT with no advance in the TRT and RRT since; the placebo may illustrate positive or negative effect that was expectancy-dependent in addition De la Fuente-Fernandez study confirmed that placebo effect on the cognitive function and psychomotor performance was mediated by augmentation the release of endogenous dopamine in the ventral and dorsal striatum.

Moreover, the present study confirmed the positive effect of aescin therapy on the cortical arousal function and central integrity process through optimistic modulation of critical fusion frequency and critical flicker frequency
without significant effect on CFFFT compared to the placebo effect which produced insignificant effect, these findings sustained by many studies that disclosed a short term effect of aescin causes significant central nervous stimulation and improve the vigilance-weak fullness state due to augmentation of brain function and metabolism since; aescin yields vitamin B12, B6, riboflavin and thiamine that are regarded as cognitive enhancer.5,12,13.

Furthermore, aescin improves working memory significantly with mild significant effect on the short term memory that was observed on second trial short-term memory due to neuroprotection and activation of acetylcholineestrase activity.15.

Aescin is regarded as a neuroprotective agent that enhance brain neurobehavioral response due to effective anti-inflammatory effect via inhibition of TNF-α since; Qiu and Yue study reported that curcumin can improve memory and learning functions via down-regulation of neuronal TNF-α.20

In view of the fact that, aescin contains saponin triterpenes as active constituents; these may play an important role in advancing and upgrading the neuronal functions as illustrated by Guo et al., study that demonstrated the protective effective of triterpenoid saponins through reduction of neuroinflammation and modulation of cholinergic activity via activation of choline acetyltransferase and amelioration of oxidative stress.18. But unfortunately aescin active constituents were not measured in the present study.

Moreover, aescin is regarded as potent anti-oxidant that reduced free radical-induced neurobehavioral impairments as revealed by Wanker et al., study that showed reactive free radical can provoke lipid peroxidation at cerebellar purkinje cells causing motor in-coordination and motor deficit.19. But in our study oxidative stress marker was not estimated.

Additionally, prostaglandin F2-α that is stimulated by aescin play an important task in maintaining of neuronal function since; prostaglandin F2-α is responsible for formation of central myelin of brain white matter20; the main function of neuronal myelin is increasing the impulse speed and neuronal propagations21 these findings have corresponded with result of present study since aescin augments the motor function and central integrity process.

All these findings support the neurobehavioral effect of aescin in augmentation of memory and vigilance functions. Besides, gender difference in effect of aescin on the neurobehavioral effect was not observed in our study may be due to small sample size also, other factors may affect the outcome of neurocognitive tests like race, age and circadian rhythm22 but Beijamni et al., study confirmed the gender differences during psychomotor vigilance test.23.

Finally, dominant hand of enrolled volunteers was not regarded as dependent factor of the present study since; 92.3% of enrolled volunteers are right-hand dominant as supported by Kagerer study that showed insignificant differences between dominant and non-dominant hand during visuomotor perturbation.24.

CONCLUSION
Short term therapy with aescin improves the neurobehavioral effects of healthy volunteers.

Suggestions for Future Research
1. Study the dose-dependent effect of aescin on the neurobehavioral effect on normal healthy volunteers
2. Assessment of the effect of aescin on nitric oxide (NO) levels during psychomotor performances
3. Estimation of lipid peroxidation and anti-oxidant capacity following aescin therapy in patients with neurodegenerative diseases likes Parkinson and Alzheimer dementia.

Limitations of the Study
1. In spite of this study is regarded as novel study some limitations were observed these are
2. Serum levels of different biomarkers were not estimated likes NO, ACTH, cortisol and TNF-α
3. Similarity of education levels since all of enrolled participants were students of medical college which may affect the cognitive function and memory capacity.

REFERENCES
1. AL-KURAIISHY, Hayder M.; AL-GAREEB, Ali I. Central beneficial effects of trimetazidine on psychomotor performance in normal healthy volunteers. Advanced Biomedical Research, 2017, 6.
2. AL-KURAIISHY, Hayder M.; AL-GAREEB, Ali I. Eustress and malondialdehyde (MDA): Role of Panax ginseng: Randomized placebo controlled study. Iranian journal of psychiatry, 2017; 12.3: 194.
3. AL-KURAIISHY, Hayder, ALGAREEB, Ali I. The Effects of Vinpocetine on the Psychomotor Performances: Randomized clinical trial, single blind random clinical study. Al-Nahrain Journal of Science, 2012;15.3: 129-133..
4. AL-KURAIISHY, Hayder M.; AL-GAREEB, Ali I. Advanced central effects of yohimbine on the cognitive function, psychomotor performance task and working memory: A randomized controlled clinical trial study. Journal of Pharmaceutical Research International, 2015; 328-335..
5. Gupta SC, Tyagi AK, Deshmukh-Taskar P, Hinojosa M, Prasad S, Aggarwal BB. Downregulation of tumor necrosis factor and other proinflammatory biomarkers by polyphenols. Arch Biochem Biophys. 2014; 1;559:91-9.
6. Martinez-Miguel P, Medrano-Andrés D, Grier-Merino M, Ortiz A, Rodríguez-Puyol M, Rodríguez-Puyol D et al. Tweak up-regulates endothelin-1 system in mouse and human endothelial cells. Cardiovasc Res. 2017; 113(2):207-221.
7. Harikumar KB, Sung B, Pandey MK, Guha S, Krishnan S, Aggarwal BB. Escin, a pentacyclic triterpene,
chemosenstizites human tumor cells through inhibition of nuclearfactor-kappaB signaling pathway. Mol Pharmacol. 2010; 77(5):818-27.

8. Hiai S, Yokoyama H, Oura H. Effect of escin on adrenocorticotropic and corticosterone levels in rat plasma. Chem Pharm Bull (Tokyo). 1981; 29(2):490-4.

9. Selvakumar GP, Janakiraman U, Essa MM, Justin Themozhi A, Manivasagam T. Escin attenuates behavioral impairments, oxidative stress and inflammation in a chronic MPTP/probenecid mouse model of Parkinson’s disease. Brain Res. 2014; 1585:23-36.

10. Hayder M Al-Kuraishy, Ali I Al-Gareeb. Eustress and Malondialdehyde (MDA): Role of Panax Ginseng: Randomized, Placebo Controlled Study. Iran J Psychiatry 2017; 12:3: 194-200

11. Al-Kuraishy H.M. Al-Gareeb A.I. Co-administration effects of α-lipoic acid and nucleo CMP on arousal and sensory cortical activity. J Young Pharm, 2016; 8(1): 12-17

12. Al-Kuraishy H.M. Central additive effect of Ginkgo biloba and Rhodiola rosea on psychomotor vigilance task and short-term working memory accuracy. J Intercult Ethnopharmacol. 2015; 5(1):7-13.

13. Zhang L, Fu F, Zhang X, Zhu M, Wang T, Fan H. Escin attenuates cognitive deficits and hippocampal injury after transient global cerebral ischemia in mice via regulating certain inflammatory genes. Neurochem Int. 2010; 57(2):119-27.

14. Draganich C, Erdal K. Placebo sleep affects cognitive functioning. J Exp Psychol Learn Mem Cogn. 2014; 40(3):857-64.

15. AL-KURAISHY, Hayder M., et al. Role of vinpocetine in ischemic stroke and poststroke outcomes: A critical review. Brain Circulation, 2020;6:1: 1.

16. De la Fuente-Fernández R. The placebo-reward hypothesis: dopamine and the placebo effect. Parkinsonism Relat Disord.2009;15 Suppl 3:S72-4.

17. Rafiq SI, Jan K, Singh S, Saxena DC. Physicochemical, pasting, rheological, thermal and morphological properties of horse chestnut starch. J Food Sci Technol.2015;52(9):5651-60.

18. Margină D, Olaru OT, Ilie M, Grădinaru D, Guţu C, Voicu S, et al. Assessment of the potential health benefits of certain total extracts from Vitis vinifera, Aesculus hippocastanum and Curcuma longa. Exp Ther Med.2015;10(5):1681-1688.

19. Qi Z, Yue S. Curcumin improves learning and memory function through decreasing hippocampal TNF-α and iNOS levels after subarachnoid hemorrhage in rats. Xi Bao Yu Fen Zi Mian Yi Xue Za Zhi. 2016; 32(3):343-6.

20. Guo C, Shen J, Meng Z, Yang X, Li F. Neuroprotective effects of polygalac acid on scopolamine-induced memory deficits in mice. Phytomedicine. 2016; 23(2):149-55

21. M AL-KURAISHY, Hayder; I AL-GAREEB, Ali. Citicoline Improves Human Vigilance and Visual Working Memory: The Role of Neuronal Activation and Oxidative Stress. Basic and Clinical Neuroscience, 2020;11:4: 423-432.

22. Yoshikawa K, Takei S, Hasegawa-Ishi S, Chiba Y, Furukawa A, Kawamura N, et al. Preferential localization of prostamide/prostaglandin F synthase in myelin sheaths of the central nervous system. Brain Res. 2011; 1367:22-32.

23. AL-KURAISHY, Hayder M. Desmopressin Acetate Effects on Human Vigilance Task and Psychomotor Performances in Normal Healthy Volunteers: Randomized Single Blind Clinical Trail. IRAQI JOURNALOF COMMUNITY MEDICINE, 2012;25.3: 191-195.

24. Santhi N, Lazar AS, McCabe PJ, Lo JC, Groeger JA, Dijk DJ. Sex differences in the circadian regulation of sleep and waking cognition in humans. Proc Natl Acad Sci U S A. 2016;113(19):E2730-9.

25. Beijamini F, Silva AG, Peixoto CA, Louzada FM. Influence of gender on psychomotor vigilance task performance by adolescents. Braz J Med Biol Res. 2008;41(8):734-8.

26. Kagerer FA. Nondominant-to-dominant hand interference in bimanual movements is facilitated by gradual visuomotor perturbation. Neuroscience. 2016; 318:94-103.

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