

A New Horizon into the Central Effect of Quercetin on Human Vigilance in Normal Healthy Volunteers

Ali Kadhim Al-Buhadilly

Department of Pharmacology, Toxicology, and Medicine, College of Medicine, Al-Mustansiriya University, Baghdad, Iraq

Abstract

Background: Quercetin is one of the dietary flavonoids found in citrus fruits and leafy vegetables as well as seeds and green tea. Its name comes from Quercetum and belongs to flavonol class which is not synthesized in the human body. Many studies revealed a significant effect of quercetin in advancing psychomotor/cognitive performances and reversing the neurotoxin-induced neuronal damage. Therefore, the present study aimed to illustrate the central effect of quercetin on human vigilance and in normal healthy volunteers. **Subjects and Methods:** A total of fifty healthy volunteers with a mean age of 23 years were enrolled in this experimental study; they were divided into two groups: Group I: twenty healthy volunteers treated with placebo (500 mg/day starch capsule) for 2 weeks and Group II: thirty healthy volunteers treated with quercetin 500 mg/day for 2 weeks. Each volunteer in each group was subjected to vigilance-psychomotor testing by Leeds psychomotor performance tester which measures Psychomotor-vigilance test (PVT) and Cortical arousal activity (CAA). **Results:** Quercetin produced a more significant effect on total reaction time, recognition reaction time, movement reaction time, fusion index, % fusion ($P < 0.01$), and flicker percentage ($P < 0.05$) compared to control, but quercetin produced an insignificant effect on CFF^d, critical flicker-fusion frequency, and flicker index. **Conclusion:** Quercetin improves psychomotor performance and CAA in normal healthy volunteers.

Keywords: Cortical arousal activity, critical flicker-fusion frequency, psychomotor performance, quercetin

INTRODUCTION

Quercetin is one of the dietary flavonoids found in citrus fruits and leafy vegetables as well as seeds and green tea. Its name comes from Quercetum and belongs to flavonol class which is not synthesized in the human body. Quercetin is a lipid-soluble bioflavonoid used as a nutritional supplement against different diseases and acts as anti-bacterial, immunomodulator, anti-hypertensive, anti-diabetic, and other metabolic disorders.^[1]

Moreover, quercetin exerts a neuroprotective effect through modulation of neuro-inflammatory injury and prevents age-linked neurodegeneration; thus, it plays an important role in the modulation of the progression of Parkinson's and Alzheimer's diseases.^[2]

Indeed, quercetin improves cerebral blood flow, stimulates angiogenesis, and acts as an activator for neurogenesis when used in the management of cerebral stroke. Many studies revealed a significant effect of quercetin in advancing psychomotor/cognitive performances and reversing the

neurotoxin-induced neuronal damage. Additionally, mice fed on flavonoid-rich diet are linked with good cognitive function.^[3,4]

In addition, quercetin has strong anti-oxidant effect that lessens the incidence and occurrence of free radical and oxidative-induced neuronal injury, so quercetin along with other anti-oxidant vitamins is used successfully in the amelioration of neurodegenerative diseases.^[5]

On the other hand, a study reported that most of the licensed psychotropic drugs prior to 2007 were synthetic although a new trend for neuroprotective drugs should involve natural agents in the amelioration of human cognitive function and attenuation of psychomotor retardation.^[6]

Address for correspondence: Dr. Ali Kadhim Al-Buhadilly, Department of Pharmacology, Toxicology, and Medicine, College of Medicine, Al-Mustansiriya University, P.O. Box. 14132, Baghdad, Iraq. E-mail: alikadm1977@yahoo.com

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Since there are only little studies regarding the effect of quercetin on the cognitive function of normal healthy human volunteers, this study is warranted to expose the central effect of quercetin. Therefore, the present study aimed to illustrate the central effect of quercetin on human vigilance and in normal healthy volunteers.

SUBJECTS AND METHODS

This study was conducted at the Department of Clinical Pharmacology and Therapeutics, College of Medicine, Al-Mustansiriyah University, in April 2016. This was a double-blind, randomized, placebo-controlled study involving fifty healthy volunteers recruited from medical students of College of Medicine. The enrolled volunteers gave informed verbal and written consent for their participation in this study. Protocol of this study was approved by the scientific committee on the College of Medicine, Al-Mustansiriyah University. Human care and research procedures were done according to the Declaration of Helsinki.^[7]

Study design

A total of fifty healthy volunteers with a mean age of 23 years (20 females + 30 males) were enrolled in this experimental study; they were divided into two groups as follows:

- Group I – Twenty healthy volunteers (11 males + 9 females) treated with placebo (500 mg/day starch capsule) for 2 weeks
- Group II – Thirty healthy volunteers (19 males + 11 females) treated with quercetin 500 mg/day (Lamberts tablet, USA) for 2 weeks.

Inclusion criteria

Healthy young volunteers without any obvious disease, not taking any medication at least within 1 week, nonalcoholic, or not taking a caffeinated beverage were included in the study.

Exclusion criteria

Any volunteer with eye disorders or on eyeglasses and those with psychiatric, neurological, and metabolic diseases were excluded from the study. In addition, a volunteer with simple tremor or obesity was also excluded from this study.

Each volunteer in each group was subjected to vigilance-psychomotor testing by Leeds psychomotor performance tester which measures the following:

Psychomotor-vigilance test

Psychomotor-vigilance test (PVT) involved three main components including total reaction time (TRT), recognition reaction time (RRT), and movement reaction time (MRT) all measured in milliseconds. TRT represents the total time needed by each volunteer from recognition of visual stimuli to the end of the motor action. RRT represents the time needed by a volunteer from recognition of visual stimuli to the beginning of the motor action. MRT represents the time needed by a volunteer from the end of recognition of visual stimuli to the end of the motor action.

Both TRT and RRT were displayed on the digital screen of Leeds psychomotor tester, while MRT value was obtained by subtraction of RRT from TRT.^[8]

Cortical arousal activity

Critical flicker-fusion frequency (CFFF) measures the cortical arousal activity (CAA) of each volunteer. The components of CFFF include critical fusion frequency and critical flicker frequency. Critical fusion frequency, also called ascending frequency (CFF^A), measures the time needed in seconds by a volunteer for awareness of flicker red illuminated light to be fused (awareness of flicker to be steady). Critical flicker frequency, also called descending frequency (CFF^d), measures the time needed in seconds by a volunteer for awareness of fusion red light to be flickered. Better value for CFF^A should be >30 Hz and better value for CFF^d should be <30 Hz.^[9,10]

Other parameters of CAA can be calculated from CFF^A and CFF^d as follows:

- Flicker index = $\frac{\max}{\max + \min}$ (minimum and maximum values in CFF^d)
- Fusion index = $\frac{\max}{\max + \min}$ (minimum and maximum values in CFF^A)
- %Flicker = $\frac{\max - \min}{\max + \min} \times 100$ (minimum and maximum values in CFF^d)
- %Fusion = $\frac{\max - \min}{\max + \min} \times 100$ (minimum and maximum values in CFF^A)
- CFFF = $\frac{\text{CFFd} + \text{CFFA}}{2}$

These neurocognitive tests were assessed at baseline (before taking quercetin or placebo) and then second measurements after 2 weeks were also taken to illustrate the effect of quercetin and placebo, all procedures were done at 8–10 am to exclude diurnal variations.

Statistical analysis

All data were presented as mean $\pm$ standard deviation, and paired and unpaired Student's *t*-test was used to measure the significance of differences regarding $P < 0.05$ as significant.

RESULTS

Demographic characteristics of this study are illustrated in Table 1.

Consort flow diagram of the present study revealed that four volunteers were excluded from this study, while the fifty volunteers continued the course of the study without any withdrawal rate [Figure 1].

Regarding the effect of placebo and quercetin on the psychomotor variables, quercetin produced significant

reduction in TRT, MRT, RRT, flicker index, and % fusion with $P < 0.01$, whereas the placebo effect only reduced MRT from 195.94 ± 12.64 to 185.00 ± 12.55 ms ($P < 0.01$), less significant effect of quercetin on CFF^A and CFF^d ($P < 0.05$), and without significant effect on other psychomotor variables ($P > 0.05$) [Table 2].

Table 1: Demographic characteristics of the enrolled volunteers

Characteristics	n (%), mean $\pm$ SD
Number of volunteers	50
Control group	20 (40)
Treated group	30 (60)
Gender	
Male	30 (60)
Female	20 (40)
Age (years)	23.4 $\pm$ 1.6
Duration of experiment (days)	14
Drugs used	
Placebo	500 mg (starch capsule)
Quercetin	500 mg quercetin tablet

SD: Standard deviation

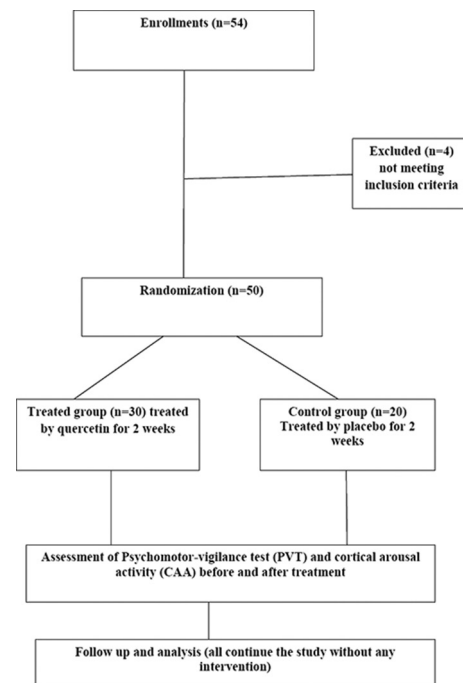


Figure 1: Consort flow diagram of the present study

Table 2: Effect of placebo and control on the psychomotor variables

Psychomotor variables	Placebo (n=20)		P	Quercetin (n=30)		P
	Before	After		Before	After	
TRT (ms)	662.86 $\pm$ 55.90	654.96 $\pm$ 54.83	0.65	669.97 $\pm$ 56.45	569.56 $\pm$ 43.64	0.0001*
RRT (ms)	467.22 $\pm$ 22.82	469.62 $\pm$ 22.84	0.74	459.59 $\pm$ 23.84	401.49 $\pm$ 18.56	0.0001*
MRT (ms)	195.94 $\pm$ 12.64	185.00 $\pm$ 12.55	0.009*	210.38 $\pm$ 10.85	168.07 $\pm$ 8.94	0.0001*
CFF ^A (Hz)	31.66 $\pm$ 9.43	31.85 $\pm$ 9.47	0.94	31.62 $\pm$ 9.57	35.99 $\pm$ 7.11	0.04†
CFF ^d (Hz)	29.76 $\pm$ 9.45	28.33 $\pm$ 9.53	0.63	29.69 $\pm$ 9.33	25.42 $\pm$ 6.56	0.04†
CFFF (Hz)	30.71 $\pm$ 8.22	30.09 $\pm$ 8.38	0.81	30.65 $\pm$ 7.85	30.63 $\pm$ 6.75	0.99
Flicker index	0.503 $\pm$ 0.021	0.503 $\pm$ 0.011	1.0	0.503 $\pm$ 0.011	0.402 $\pm$ 0.021	0.0001*
Fusion index	0.502 $\pm$ 0.02	0.501 $\pm$ 0.01	0.84	0.502 $\pm$ 0.01	0.505 $\pm$ 0.002	0.11
Percentage flicker	0.373 $\pm$ 0.055	0.371 $\pm$ 0.032	0.88	0.373 $\pm$ 0.052	0.301 $\pm$ 0.032	0.0001*
Percentage fusion	0.317 $\pm$ 0.066	0.318 $\pm$ 0.033	0.76	0.317 $\pm$ 0.062	0.403 $\pm$ 0.042	0.0001*

Data are expressed as mean $\pm$ SD, * $P < 0.01$, † $P < 0.05$. SD: Standard deviation, TRT: Total reaction time, RRT: Recognition reaction time, MRT: Movement reaction time, CFF^A: Critical fusion frequency (called ascending frequency), CFF^d: Critical flicker frequency (called descending frequency), CFFF: Critical flicker-fusion frequency

Table 3: Differential effects of quercetin on psychomotor variables compared to the control

Psychomotor variables	Placebo (n=20)	Quercetin (n=30)	t	95% CI	P
TRT (ms)	654.96 $\pm$ 54.83	569.56 $\pm$ 43.64	-6.115	113.48-57.31	<0.0001*
RRT (ms)	469.62 $\pm$ 22.84	401.49 $\pm$ 18.56	-6.115	-113.48-57.31	<0.0001*
MRT (ms)	185.00 $\pm$ 12.55	168.07 $\pm$ 8.94	-11.59	-79.94-56.31	<0.0001*
CFF ^A (Hz)	31.85 $\pm$ 9.47	35.99 $\pm$ 7.11	-5.57	-23.03-10.82	<0.0001*
CFF ^d (Hz)	28.33 $\pm$ 9.53	25.42 $\pm$ 6.56	1.76	-0.57-8.85	0.08
CFFF (Hz)	30.09 $\pm$ 8.38	30.63 $\pm$ 6.75	-1.28	-7.47-1.65	0.20
Flicker index	0.503 $\pm$ 0.011	0.402 $\pm$ 0.021	0.251	-3.77-4.85	0.80
Fusion index	0.501 $\pm$ 0.01	0.505 $\pm$ 0.002	-19.73	-0.111-0.09	<0.0001*
Percentage flicker	0.371 $\pm$ 0.032	0.301 $\pm$ 0.032	2.13	0.0002-0.007	0.03†
Percentage fusion	0.318 $\pm$ 0.033	0.403 $\pm$ 0.042	7.611	0.062-0.10	<0.0001*

Data are expressed as mean $\pm$ SD, * $P < 0.01$, † $P < 0.05$. SD: Standard deviation, CI: Confidence interval, TRT: Total reaction time, RRT: Recognition reaction time, MRT: Movement reaction time, CFF^A: Critical fusion frequency (called ascending frequency), CFF^d: Critical flicker frequency (called descending frequency), CFFF: Critical flicker-fusion frequency

Quercetin produced a more significant effect on TRT, RRT, MRT, fusion index, % fusion ($P < 0.01$), and %flicker index ($P < 0.05$) compared to control, but quercetin produced an insignificant effect on CFF^d, CFFF, and flicker index [Table 3].

On the other hand, there were insignificant gender differences in the central effect of quercetin ($P > 0.05$) [Figure 2].

DISCUSSION

PVT and CFFF parameters are reliable neurocognitive tests to estimate the vigilance and CAA, respectively.^[11] These tests are affected by different factors including age, health status, race, and age.^[12] These factors were excluded from this study since all the enrolled volunteers were healthy, younger, and of the same race.

The present study illustrated significant improvement effect of quercetin on most of the vigilance and CAA variables compared to the control, which was confirmed by Neha *et al.*'s study that demonstrated a significant effect of quercetin in advancing psychomotor performance due to the antistress effect of quercetin in the animal model study.^[13] In contrast, some positive stress (eu-stress) created a potential improvement of human vigilance and CAA.^[14]

Recently, Bahar *et al.*'s study showed that quercetin led to significant neurobehavioral effect via anti-oxidant activity and prevention of neuroinflammation induced by manganese, so it produced a potential neuroprotective effect through attenuation of oxidative stress.^[15] Therefore, most of the anti-oxidant herbal agents produce an acceleration of cognitive function and memory function as revealed by the study by Al-Kuraishy (2015) that disclosed the noteworthy effect of *Ginkgo biloba* and/or *Rhodiola rosea* on vigilance and working memory due to anti-oxidant effects.^[16] Oxidative stress markers were not evaluated in this study since all the enrolled volunteers were healthy and not smokers.

Quercetin in this experimental study produced differential effects on CAA variables as it accelerates CFF^A, but it created an insignificant effect on CFF^d and CFFF which means that there are different neuronal pathways involved in human

arousal capability.^[17] In addition, this differential effect of quercetin may be due to selective activation of brain regions as recently revealed by a study by Mehta *et al.* that divulged the selective effect of quercetin on hippocampus which *per se* attenuates locomotor deficit and behavioral dysfunction induced in mice.^[18] Moreover, Nassiri-Asl *et al.* demonstrated a dose-dependent effect of quercetin in quickening the psychomotor performances and acceleration of step-through latency of passive avoidance during experimental kindling in rats.^[19] Thus, the present study is in agreement with most of the recent studies that exemplified the nootropic effect of quercetin in the improvement of psychomotor vigilance task and human arousal facility.^[20,21]

The possible explanation of the central stimulant effect of quercetin may be through inhibition of acetylcholinesterase (AChE) that involved in the degradation of central acetylcholine as revealed by Sz wajgier's study which showed that flavonols of quercetin cause considerable inhibition of brain AChE.^[22] Indeed, phenolic constituents of quercetin lead to attenuation of cognitive dysfunction.^[23] Consequently, inhibition of AChE and anti-oxidant effect are the main pathways involved in the activation of human vigilance and arousal variables, but AChE was not measured in the present study.

On the other hand, placebo in the present study showed significant improvement effect on MRT as described by Kurdi and Muthukalai's study which illustrated that placebo may improve psychomotor performance and decrease preoperative anxiety.^[24] Besides, the placebo effect might affect both negative and positive directions during vigilance test, which may explain the specific expectation effect on human psychomotor performance.^[25] Certainly, Al-Greeb's study showed that neither nutraceuticals nor placebo produced a significant effect on psychomotor performance and the significant effect might be due to the nocebo effect.^[26] A study by Ashor (2012) confirmed the differential effect of placebo on human psychomotor performance; when placebo is known as a stimulant, it enhanced psychomotor performance and working memory; when placebo is unknown, it deteriorates only working memory; but when a placebo is known as inert, it produces an insignificant effect, thus placebo effect is related to the volunteer expectation.^[27]

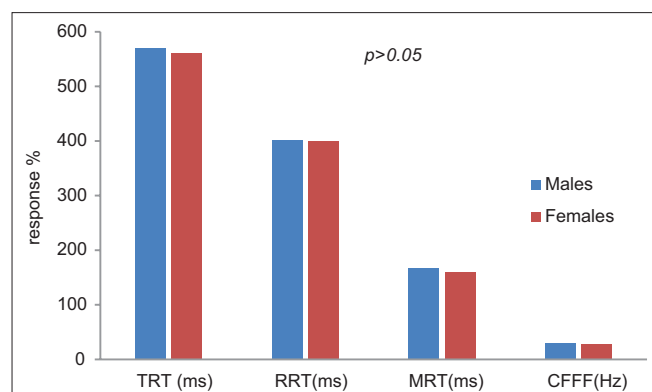


Figure 2: Insignificant gender differences in the central effect of quercetin

CONCLUSION

Quercetin improves psychomotor performance and CAA in normal healthy volunteers.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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