Journal of Advances in Medical and Pharmaceutical Sciences

14(1): 1-7, 2017; Article no.JAMPS.34323
ISSN: 2394-1111

Effect of Curcumin on Blood Glucose Level and Some Neurobehavioral Responses in Alloxan-induced Diabetic Swiss Albino Mice

U. A. Garkuwa[1*], A. W. Alhassan[2] and Y. Tanko[2]

[1]Department of Physiology, Faculty of Basic Health Sciences, Bauchi State University, Gadau, Nigeria.
[2]Department of Human Physiology, Faculty of Medicine, Ahmadu Bello University, Zaria, Nigeria.

Authors' contributions

This work was carried out in collaboration between all authors. Author UAG designed the study, performed the statistical analysis, wrote the protocol and wrote the first draft of the manuscript. Authors AWA and YT managed the analyses of the study. Author YT managed the literature searches. All authors read and approved the final manuscript.

Article Information

DOI: 10.9734/JAMPS/2017/34323
Editor(s):
(1) Atef Mahmoud Mahmoud Attia, Biochemistry Department, Biophysical laboratory, Division of Genetic Engineering and Biotechnology, National Research Centre, Dokki, Cairo, Egypt.
Reviewers:
(1) Bhaskar Sharma, Suresh Gyan Vihar University, Rajasthan, India.
(2) Dhastagir Sheriff, Benghazi University, Libya.
(3) Abdullahi M. Nuhu, Cst. Kaduna Polytechnic, Kaduna, Nigeria.
Complete Peer review History: http://www.sciencedomain.org/review-history/19765

Original Research Article

Received 24th May 2017
Accepted 24th June 2017
Published 29th June 2017

ABSTRACT

The aim of this study was to evaluate the effect of curcumin on blood glucose level and neurobehavioral response in Alloxan-induced diabetic Swiss Albino mice. The animals were divided into five (5) groups of four each (n=4). Group I served as control and received distilled water, group II, III, IV and V were diabetic and received olive oil 1 ml/kg, glibenclamide 1 mg/kg, curcumin 50 mg/kg and curcumin 100 mg/kg respectively. Diabetes was induced using Alloxan (150 mg/kg). All administrations were done for duration of 21 days. Blood glucose level was determined using glucose oxidase principle and cognitive impairment was determined using novel object recognition task (NORT). The result obtained from this study showed that curcumin at both doses (50 mg/kg and 100 mg/kg) significantly ($p < 0.05$) reduced the fasting blood glucose level and recorded an improvement in memory, recognitive and discriminatory indices when compared with the diabetic

**Corresponding author: E-mail: garkus_ua@yahoo.com;*

control group. This study demonstrated that curcumin significantly ($p < 0.05$) attenuated diabetes-induced cognitive impairment in the NORT. The findings of this study suggest that curcumin may ameliorate diabetes-induced cognitive impairment in Swiss albino mice.

Keywords: Curcumin; cognitive impairment; mice; diabetes.

1. INTRODUCTION

Chronic high blood glucose levels have been shown to have negative effects on cognitive functions and brain structure [1]. Hyperglycemia is a characteristic in both T1DM and T2DM. Numerous studies have demonstrated a close relationship between glucose intolerance and cognitive decrements and dementia [2]. It has been shown that people with poor glycemic control, with glycosylated hemoglobin (HbA1c) higher than 7.0%, have a 4-fold higher risk of developing cognitive impairment [3]. Similarly, an inverse association of HbA1c and cognitive function such as working memory, learning, and executive functioning has been observed in T2DM patients [1,4].

It has been shown that cognitive deficit caused by hyperglycemia in diabetic rat is associated with an increase in ROS levels and reduction of antioxidant levels [5,6]. In addition, increased ROS generation has been shown to activate various cellular signaling pathways, such as the polyol pathway, protein kinase C activation and increase of glucose shunting via the hexosamine pathway, all of which are related to neuronal injury and cerebral damage [7].

Turmeric (*Curcuma longa*) is an intriguing ingredient with a rich history as a dietary spice and herbal supplement in ancient China and India. This distinctive yellow- colored spice, derived from the rhizome of the plant (*C. longa*), is a member of Zingiberaceae family and is widely cultivated in India and Southeast Asia. The use of turmeric in Asia dates back more than 2000 years where it was used in cooking, medicine, cosmetics and fabric dyes [8]. In traditional medicine turmeric is used to enhance the immune system and as a cure for different respiratory diseases such as asthma and for allergy [9]. Turmeric has also been traditionally used for the treatment of diabetes, cough, sinusitis, flu, rheumatism and liver disorders. Meanwhile, traditional Chinese medicine practitioners regularly use turmeric for treating abdominal pain associated diseases [10]. It has widely been accepted since ancient times that this polyphenol compound possesses anti-inflammatory properties [10]. Advancements in modern medicine have revealed many unknown medicinal properties of turmeric which include anti-oxidant, anti-mutagenic, anti-cancer, anti-microbial and anti-cardiovascular activities [9]. Studies have also strongly indicated that curcumin, the active compound in turmeric, is the key ingredient responsible for the major therapeutic activities of turmeric [10]. The aim of the study was to determine the effect of curcumin on blood glucose level and some neurobehavioral responses in alloxan-induced diabetic Swiss albino mice.

2. MATERIALS AND METHODS

2.1 Chemicals and Drugs

All chemicals and drugs were of analytical grade. Curcumin was purchased from Arkure Health Center (Haryana, India). Alloxan was purchased from (Sigma chemical Company St. Louis U.S.A.). A digital glucometer (Accu-Chek Advantage, Roche Diagnostic, Germany) was used for the determination of the blood glucose levels of the animals.

2.2 Experimental Animals

A total of twenty (20) Swiss Albino Mice of both sexes weighing (20 – 30) grams were used for the study. The animals were housed in plastic cages under standard laboratory conditions with free access to food and water. Animals were allowed for two weeks to acclimatization to the laboratory environment before the commencement of the experiments.

2.3 Induction of Diabetes

The animals were fasted for 12-16 h with free access to water prior to the induction of diabetes. It was induced by single intraperitoneal injection of Alloxan monohydrate (Sigma St. Louis, U.S.A.) at a dose of 150 mg/kg b w dissolved in 0.9% cold normal saline [11]. The mice were kept for the next 24 h on 5% glucose solution bottles in their cages to prevent hypoglycemic [12]. The blood samples were obtained from the tail. A digital glucometer was used to measure the

blood glucose levels using glucose oxidase principle [13]. Hyperglycemia was defined by fasting blood glucose level > 200 mg/dl [14].

2.4 Experimental Design

The animals were randomly divided into five (5) groups of four (4) mice each. Curcumin and glibenclamide were dissolved in olive oil and distilled water respectively. Administrations were done orally for duration of 21 days as follows

Group I: Normoglycemic, received distilled water

Group II: Diabetic, received olive oil 1 ml/kg

Group III: Diabetic, received glibenclamide (glib) 1 mg/kg

Group IV: Diabetic, received curcumin (cur) 50 mg/kg

Group V: Diabetic, received curcumin (cur) 100 mg/kg

2.5 Estimation of Blood Glucose

The blood samples were obtained from the animal tail vein. A glucometer was used to measure the blood glucose levels using glucose oxidase principle [15] using the digital glucometer (Accu-Check Advantage, Roche Diagnostic, Germany), and results were obtained as mg/dL [16].

2.6 Novel Object Recognition Task

This task comprised a sample phase and a test phase separated by a 24 hours delay. In the sample phase, the mice were presented with two same objects. These objects will be placed in the corners of an arena 15 cm from each adjacent wall. Each rat will be placed in the center of the arena and allowed to explore the objects for 5 min, between the sample and test phases, all of the objects were cleaned with alcohol to remove olfactory cues. In the test phase, one of the objects was changed, and the mice were allowed to explore the objects for 5 min. The time spent exploring the two objects that had changed was compared with the time spent exploring the other object using the following equations [17-20].

Difference = Tn – Tf (Tn = time spent exploring the novel object, Tf = time spent exploring the familiar object).

$$\text{Discriminative Index (DI)} = \frac{\text{Tn}-\text{Tf}}{\text{Tn}+\text{Tf}}$$

$$\text{Recognitive Index (RI)} = \frac{\text{Tn}}{\text{Tn}+\text{Tf}} \times 100$$

2.7 Statistical Analysis

Data obtained were expressed as mean ± SEM. The data were statistically analyzed using ANOVA followed by Tukey's post hoc analysis to compare the level of significance using Statistical Package for Social Sciences (SPSS) version 22. The value of $p < 0.05$ was taken as significant.

3. RESULTS AND DISCUSSION

Table 1 showed the results of the effects of Curcumin (50 mg/kg and 100 mg/kg) on blood glucose level of alloxan-induced diabetic Swiss albino mice. The Curcumin treated groups showed significant ($p < 0.05$) decrease in the fasting blood glucose levels after 21 days of administration, when compared to diabetic control group (group II) treated with olive oil with values of 108.25 ± 16.01 mg/dl and 114.75 ± 5.56 mg/dl (with percentage glycemic change of 59.73% and 61.00%) for 50 mg/kg and 100 mg/kg compared to 221.50 ± 6.12 mg/dl (8.00%) respectively.

Table 1. Effect of curcumin on fasting blood glucose levels of Alloxan-induced diabetic Swiss albino mice

Groups	Day 0 (mg/dl)	Day 21 (mg/dl)	PGC (%)
Normal control	96.25 ± 6.79	94.00 ± 6.12[a]	2.34
Diabetic control	240.75 ± 5.85	221.5 ± 14.03[b]	8.00
Glib 1 mg/kg	272.75 ± 14.53	126.5 ± 11.32[ab]	53.62
Cur 50 mg/kg	267.50 ± 11.53	108.25 ± 16.01[ab]	59.73
Cur 100 mg/kg	294.25 ± 31.15	114.75 ± 5.56[ab]	61.00

Values having superscript letter are statistically significant ($p < 0.05$); a = compared with diabetic control, b = compared to day 0; Glib = glibenclamide, cur = curcumin and PGC = percentage glycemic change

The result obtained in this study showed that curcumin at both doses significantly ($p < 0.05$) decreased the fasting blood glucose level when compared to the diabetic control group on day 21. The decrease in the fasting blood glucose level observed in the present study suggest that daily administration of curcumin has significantly decreased the blood glucose level as compared to diabetic control. This implies that curcumin has strong antihyperglycemic effect. The results also indicated that the two doses of curcumin and standard anti-diabetic drug, glibenclamide, showed a significant decreased in the blood glucose levels after 21 days treatment. Hence suggesting that curcumin might have led to the recovery of the pancreatic beta cells and or increase peripheral insulin utilization by increasing tissue sensitivity to insulin. However the two doses of curcumin given have higher percentage glycemic change (PGC) compared to the standard anti-diabetic drug as showed in Table 1. Furthermore, when compared with the treatment groups and normoglycemic control group, showed a significant increase. The result of the present study agrees with the findings of Sharma et al. [21] who also demonstrated that curcumin alleviates fluoride induced hyperglycemia in rats.

Table 2. Show the results of the effects of curcumin (50 mg/kg and 100 mg/kg) on short term memory of alloxan-induced diabetic Swiss albino mice. The curcumin treated groups showed significant ($p < 0.05$) increase in the time spent exploring the novel object after 21 days of administration, when compared to the pre-treatment (day 0) with values of 11.66 ± 9.39 seconds and 14.85 ± 6.46 seconds compared to the -11.20 ± 0.55s and -10.90 ± 6.46 seconds respectively.

The short term memory version was assessed using the NORT. It is the difference between the time spent exploring novel object and time spent exploring the familiar object. From the results obtained in this study, there is no significant ($p < 0.05$) difference between the curcumin treated groups and the diabetic control group after treatment. This may be because the mice were able to adapt to the condition and surrounding environment. Also, the result from the curcumin treated groups indicates clearly that hyperglycemia is associated with short term memory impairment and that the curcumin at both doses significantly ($p < 0.05$) improved the short term memory of the mice considering the pre-treatment (day 0) and post-treatment (day 21) respectively. This may be associated with the antihyperglycemic effect of curcumin and its antioxidant properties [22]. Hyperglycemia and reactive oxygen species are the leading causes of dementia and cognitive deficits. Hyperglycemia is one of the leading cause of neurotoxicity and cognitive impairment through increase generation of ROS, activation of polyol pathway and advanced glycation end products and glucose shunting into hexosamine pathway which lead to end organ damage and neuronal death [4,23]. This finding agree with the report of Jithendra and Talasila, [24] who reported improvement in short term memory of curcumin treated experimental animals in statin induced short term memory loss in rats.

Table 3 Showed the results of the effects of curcumin (50 mg/kg and 100 mg/kg) on discrimination index level of alloxan-induced diabetic Swiss albino mice. The curcumin treated groups showed significant ($p < 0.05$) increase in discrimination after 21 days of administration, when compared to the pre-treatment (day 0) with values of 0.39 ± 0.04 and 0.24 ± 0.21 seconds compared to the -0.44 ± 0.03 and -0.27 ± 0.11 seconds respectively.

Table 2. Effect of curcumin on the difference using NORT in Alloxan-induced Diabetic Swiss albino mice

Groups	Day 0 (sec)	Day 21 (sec)
Normoglycemic control	24.00 ± 10.41	16.45 ± 1.86
Diabetic control	-5.00 ± 4.77	0.85 ± 4.88
Glib 1 mg/kg	-8.03 ± 0.49	8.80 ± 3.31[a]
Cur 50 mg/kg	-11.20 ± 0.55	11.66 ± 9.39[a]
Cur 100 mg/kg	-10.90 ± 6.40	14.85 ± 6.46[a]

Values having superscript letter a are statistically significant ($p < 0.05$) compared with day 0.
Glib = glibenclamide, cur = curcumin

Table 3. Effect of curcumin on discriminatory index of Alloxan-induced Swiss albino mice

Groups	Day 0 (sec)	Day 21 (sec)
Normoglycemic control	0.28 ± 0.11	0.34 ± 0.05
Diabetic control	-0.15 ± 0.14	0.04 ± 0.19
Glib 1 mg/kg	-0.17 ± 0.01	0.28 ± 0.12[a]
Cur 50 mg/kg	-0.44 ± 0.03	0.24 ± 0.21[a]
Cur 100 mg/kg	-0.27 ± 0.11	0.39 ± 0.04[a]

Values having superscript letter a are statistically significant (p < 0.05) compared with day 0. Glib = glibenclamide, cur = curcumin

The discriminatory index was assessed using the NORT. The findings of this study does not show any significant change (p < 0.05) when compared to the diabetic control group. Although the difference in the discrimination ability of the experimental animals between pre-treatment (day 0) and post-treatment (day 21) in the diabetic control group is not significant, the animals show some degree of improvement which may be associated with some degree of learning or the effect of olive oil. Also, from the result observed in the curcumin treated group, it is evident that hyperglycemia is associated with impairment of discrimination ability in the experimental animals which was significantly (p < 0.05) improved by the daily administration of curcumin as seen in the groups treated with different doses of curcumin. There was no statistically significant (p < 0.05) difference between the curcumin treated groups and the standard anti-diabetic drug treated groups.

Fig. 1. Showed the results of the effects of curcumin (50 mg/kg and 100 mg/kg) on recognition index of alloxan-induced diabetic Swiss albino mice. The curcumin treated groups showed significant (p < 0.05) increase in the recognition after 21 days of administration (post-treatment), when compared to the pre-treatment (day 0) with values of 63.71 ± 2.95 and 58.17 ± 2.55 seconds compared to the 36.04 ± 8.19 and 38.20 ± 4.73 seconds respectively.

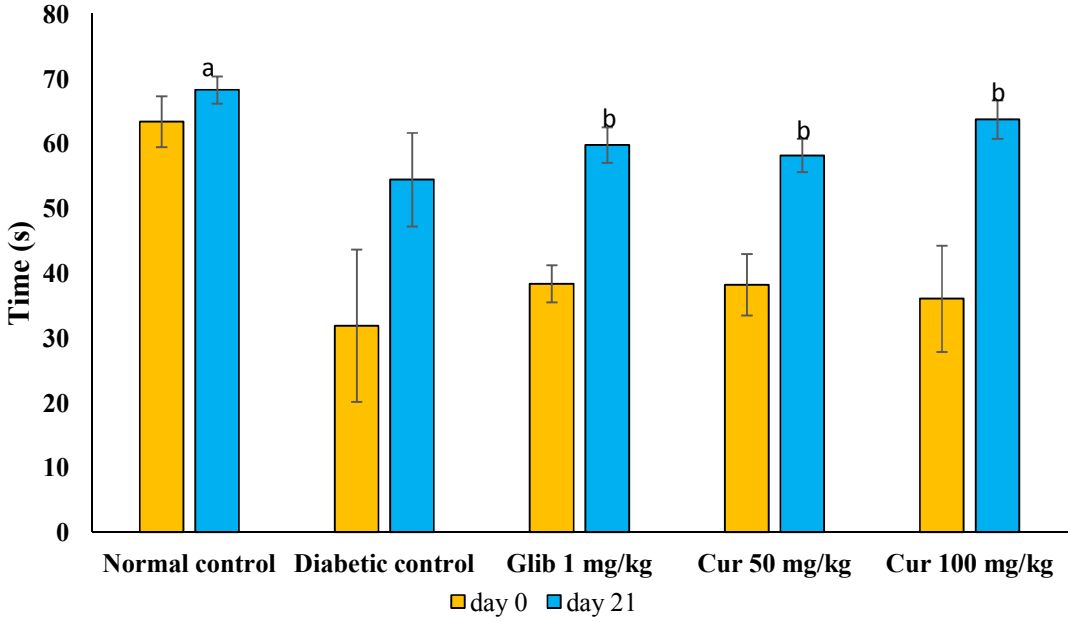

Fig. 1. Effect of curcumin on recognitive index using NORT in alloxan-induced diabetic Swiss albino mice

Values with error bars having different superscripts are significantly (p < 0.05) different; a and b = compared to diabetic control and day 0 respectively. Glib = glibenclamide, cur = curcumin

The findings for recognitive index of this study does not show any significant ($p < 0.05$) change when compared to the diabetic control group. Although the difference in the recognition ability of the experimental animals on day 0 and 21 in the control group is not significant, the animals show some degree of improvement which may be associated with some degree of learning or the effect of olive oil on retention. Also, from the result observed in the same group, it is evident that hyperglycemia impair retention ability in the experimental animals which was significantly ($p < 0.05$) improved by the daily administration of curcumin as seen in the groups treated with two doses of curcumin (50 and 100 mg/kg) on day 0 and 21 respectively. This improvement may be associated with the antihyperglycemic together with the effect of curcumin on inflammation as reported by Al Rubaei et al. [25]. Inflammation has been implicated in the pathogenesis and progression of cognitive impairment (CI) through the numerous proinflammatory markers and cytokines, such as C-reactive protein (CRP), tumor necrosis factor-α (TNF-), interleukin- (IL-) 1β, and IL-6, which have been shown to be upregulated in both T1DM and T2DM [26].

4. CONCLUSION

In conclusion, oral administration of curcumin has significant antihyperglycemic activity and improves social memory on diabetic Swiss albino mice and this positive effect is comparable to or even stronger than that of standard anti-diabetic drug (glibenclamide). This may justify the use of supplements in the management of memory loss in diabetes and the use of curry powder which is rich in curcumin might be considered.

CONSENT

It is not applicable.

ETHICAL APPROVAL

All authors hereby declare that all experiments have been examined and approved by Ahmadu Bello University committee on animal use and care (ABUCAUC). All authors hereby declare that “principles of laboratory animal care” (NHI publication No. 85-23, revised 1985) were followed.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

REFERENCES

1. Gold SM, Dziobek I, Sweat V. Hippocampal damage and memory impairments as possible early brain complications of type 2 diabetes. Diabetologia. 2007;50(4):711–719.
2. Yaffe K, Blackwell T, Whitmer RA, Krueger K, Barrett-Connor E. Glycosylated hemoglobin level and development of mild cognitive impairment or dementia in older women. Journal of Nutrition, Health and Aging. 2006;10(4):292–295.
3. Reaven GM, Thompson LW, Nahum D, Haskins E. Relationship between hyperglycemia and cognitive function in older NIDDM patients. Diabetes Care. 1990;13(1): 16–21.
4. Comin D, Gazarini L, Zanoni JN, Milani H, de Oliveira RMW. Vitamin E improves learning performance and changes the expression of nitric oxide-producing neurons in the brains of diabetic rats. Behavioural Brain Research. 2010;210(1):38–45.
5. Fukui K, Omoi NO, Hayasaka T. Cognitive impairment of rats caused by oxidative stress and aging, and its prevention by vitamin E. Annals of the New York Academy of Sciences. 2002;959:275–284.
6. Brownlee M. The pathobiology of diabetic complications: A unifying mechanism. Diabetes. 2005;54(6):1615–1625.
7. Auer RN. Hypoglycemic brain damage. Metabolic Brain Disease. 2004;19(3-4):169–175.
8. Lee WH, LooC Y, Bebawy M, Luk F, Mason RS, Rohanizadeh R. Curcumin and its Derivatives: Their application in neuropharmacology and neuroscience in the 21st century. Current Neuropharmacology. 2013;11(4):338–378.
9. Araujo MCP, Antunes LMG, Takahashi CS. Protective effect of thiourea, a hydroxy/ radical scavenger on curcumin-induced chromosomal aberrations in an *in vitro* mammalian cell system. Teratogenic Carcinoma Mutation. 2001;21:175–180.
10. Gupta SC, Patchva S, Koh W, Aggarwal BB. Discovery of curcumin a component of golden spice and its miraculous biological activities. Clinical Experiment Pharmacology and Physiology. 2012;39: 283–299.
11. Katsumata K, Katsumata K, Jr. Katsumata Y. Protective effect of diltiazem hydrochloride on the occurrence of alloxan or STZ-induced diabetes in rats. Hormonal Metabolism Research. 1999;24:508-510.

12. Dhandapani S, Subramanian VR, Rajagopal S, Namasivayam N. Hypolipidemic effect of *Cuminum cyminum* L. on alloxan-induced diabetic rats. Pharmacology Research.2002;46:251-255.
13. Beach EF, Turner JJ. An enzymatic methods for glucose determination in body fluids. Clinical. Chemistry. 1958;4:462-465.
14. Matteucci E, Giampietto O. Proposal open for discussion: Defining agreed diagnostic procedures in experimental diabetes research. Journal of Ethnopharmacology. 2008;115:163-172.
15. Beach EF, Turner JJ. An enzymatic methods for glucose determination in body fluids. Clinical Chemistry. 1958;4:462-465.
16. Rheney CC, Kirk KK. Perfomance of three blood glucose meters. Annals of Pharmacotherapy. 2000;34(3):317-321.
17. Barker GRI, Bird F, Alexander V, Warburton EC. Recognition memory for objects, place, and temporal order: A disconnection analysis of the role of the medial prefrontal cortex and perirhinal cortex. Journal of Neuroscience. 2007; 27(11):2948–2957.
18. Baxter MG. I've seen it all before: Explaining age-related impairments in object recognition. Theoretical Comment on Burke SN, Wallace JL, Nematollahi S, Uprety AR, Barnes CA. Behavioral Neuroscience. 2010;124:706–709.
19. Gaskin S, Tardif M, Cole E, Piterkin P, Kayello L, Mumby DG. Object familiarization and novel-object preference in rats. Behavioral Procedures. 2010;83: 61–71.
20. Antunes M, Biala G. The novel object recognition memory: Neurobiology, test procedure, and its modifications. Cognitive Process. 2012;13(2):93–110.
21. Sharma C, Pooja S, Piyu S, Jaiswal N, Bhatnagar M. Curcumin attenuates neurotoxicity induced by fluoride: An in vivo evidence. Pharmacognosy Evidence. 2014;10(37):61-65.
22. Tokaç M, Taner G, Aydın S, Ozkardeş AB, Dündar HZ, Taşlıpınar, MY, Arıkök AT, Kılıç M, Başaran AA, Basaran N. Protective effects of curcumin against oxidative stress parameters and DNA damage in the livers and kidneys of rats with biliary obstruction. Food Chemical Toxicology. 2013;61:28-35.
23. Valente T, Gella A, Fernàndez-Busquets X, Unzeta M, Durany N. Immunohistochemical analysis of human brain suggests pathological synergism of Alzheimer's disease and diabetes mellitus. Neurobiology of Disease. 2010;37(1):67–76.
24. Jithendra C, Talasila EGK. Effect of curcumin on statin induced short term memory loss. Journal of Pioneering Medical Sciences. 2012;2(2):53-57.
25. Al-Rubaei ZM, Mohammad TU, Ali LK. Effects of local curcumin on oxidative stress and total antioxidant capacity *in vivo* study. Pakistan Journal of Biological Sciences. 2014;17(12):1237-41.
26. Seto SW, Kwan YW, Ngai SM. Modulatory effect of interleukin-1β on rat isolated basilar artery contraction. European Journal of Pharmacology. 2006;531(1–3): 238–245.

Peer-review history:
The peer review history for this paper can be accessed here:
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