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Assessment of the influence of cilostazol on learning-memory and motor co-ordination by rodent models

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ABSTRACT

Dementia is a set of symptoms that include worsening of the routine of cognitive tasks, learning, reproducibility, and gait disturbances beyond typical aging. Activated c AMP can produce anti-apoptosis activity, neuroprotective activity, motor improvement, and cognitive enhancement activity. Cilostazol can increase c AMP levels, so this study aimed to evaluate the influence of cilostazol on learning-memory and motor coordination by rodent models. The rats were divided into 5 and 6 groups with 6 rats in each to test the hypothesis respectively. Before MES seizure induction the rats were trained for conditioned avoidance response for 14 days and the best one was selected for assessment. The performance of intervention treated groups to determine the memory retention effect was measured by applying a fixed number of shocks. The intervention treated groups were tested for motor coordination performance by rotarod test (4-45 RPM accelerating speed for 5 min) after 30 and 60 min. The latency time of each rat falls off from the rod for the first time was noted. The results were presented as Mean ± SD, tested by ordinary two way ANOVA followed by Tukey's multiple comparisons test. Cilostazol 100 mg/kg p.o demonstrated a significant memory enhancement activity in the conditioned avoidance response technique. Cilostazol 20mg/kg i.p alone and along with diazepam 2 mg/kg demonstrated a significant motor coordination performance in both sessions. The present study concludes that cilostazol has improved the learning & memory and motor coordination performances.

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INTRODUCTION

According to the world health organisation, dementia is a set of symptoms that include deterioration of the performance of cognitive tasks, learning, and reproducibility beyond the predictable from typical ageing. This is frequently associated with the worsening of emotional control, inspiration, creativeness, social performance, wondering, struggle in walking. The primary form of dementia is Alzheimer's disease in 60 to 70% of patients where the progressive loss of memory and loss abilities on language can be appreciated (WHO, 2020). There

are several forms of dementia which include frontotemporal, vascular, stroke, Lewy body, syphilitic, senility, mixed dementias (Al, 2018). The global prevalence of dementia is nearly 50 million, with increasing 10 million every year and may reach 82 million in 2030 and 152 million 2050 (WHO, 2020). Every 3 seconds there is an occurrence of a new case, which may increase the economic burden up to 2 Trillion USD by 2050 for the medical needs of the patients (Rao *et al.*, 2020). Dementia may be reversible and irreversible types according to their nature. Regain of memory can be observed in revisable dementia after the leading cause vanished. Irreversible dementia needs medical care where there is no treatment to cure, but galantamine, donepezil, rivastigmine (anticholinergic agents) and memantine (NMDA glutamate receptor blockers) are available (WHO, 2017; Shaji *et al.*, 2018). Apart from pharmacological approach reminiscence therapy, cognitive stimulation therapy may also improve the quality of life (Shaji *et al.*, 2018). The above facts may lead to a new search for an effective therapeutic agent. Dementia may be associated with a low physical performance which may include gait disorder, irregular automatic actions, seizures, metabolic disorders, skin diseases, visual abnormalities, anaemia (Draper and Withall, 2016). In elderly patients, there are precise shreds of evidence to establish co-occurrence of sluggish walking and diminished cognition performance (Wennberg *et al.*, 2017). The gait of an individual can be performed by the neuromusculoskeletal system, which can be impaired in neurological diseases (e.g. Alzheimer's disease, Parkinson's disease) (Ferrucci *et al.*, 2016). Activated cyclic adenosine monophosphate (cAMP) can produce anti-apoptosis activity, neuroprotective activity, motor improvement, and cognitive enhancement activity.

Phosphodiesterase (PDE) inhibitors raise intracellular cAMP levels and promote its mediated activities by inhibiting the breakdown of cAMP into its metabolites. PDE 3 inhibition by cilostazol may increase cAMP levels and approved as an antiplatelet agent (Chattipakorn *et al.*, 2014). There is no adequate research on the cilostazol role in cognition and motor co-ordination. So the present study aimed to assess the influence of cilostazol on learning-memory and motor co-ordination by rodent models.

MATERIALS AND METHODS

Animals

150g -200g weighed Wister strain albino rats of both genders were used in the experiment. The rats were served with adlibitum, water, and standard pellet diet in the animal house. They were kept in the central animal house, which was established with the standard laboratory conditions (12/12 h dark-light cycle, 25^{o}c $\pm$ 1^{o}c temperature). All the experiments were conducted by following the guidelines of the Committee for Control and Supervision of Experiments on Animals (CPCSEA), a regulatory body on the animal experiments in India. Rejection criteria to exclude from the experiment consist of any variation in weight and signs of diseases. The institutional ethical committee (IAEC) approved to carrion the experiment.

Drugs

Diazepam (analytical grade), Cilostazol (Pure Chem. Private LTD), Dimethyl Sulfoxide (Pon Pure Chemicals), sprit

Instruments & requirements

Cooks pole climbing apparatus, Electroconvulsive meter, Rotarod apparatus, sprit, cotton, weighing machine, marker.

Grouping of animals

The experiment was conducted 5 and 6 groups (n=6) for evaluation of learning & memory property, motor co-ordination, respectively, Rats were allocated randomly.

Evaluation effects of treatment on learning & memory

Group 1 - Normal saline

Group 2 - Control – MES

Group 3 - Cilostazol (50 mg/kg p.o)

Group 4 - Cilostazol (75 mg/kg p.o)

Group 5 - Cilostazol (100 mg/kg p.o)

Training procedure

Rats of all the groups were subjected to conditioned avoidance response before the induction of Maximal Electric Shock (MES) seizures except group 1. Each rat was positioned individually in a pole climbing apparatus provided with a grid floor which was electrified and conditioned with a buzzer sound. Rats were trained thrice in a day initially to avoid the electroshock (80 V, 5 pulses/sec) applied to the grid floor, intermittently preceded by the beep (conditioned stimulus). Rats that were learned to escape the shock by climbing the pole after training for 14 days were used in the study. Group 1, Group 3, Group 4, Group 5 rats were treated with normal saline, Cilostazol 50 mg/kg p.o, cilostazol 75 mg/kg p.o, cilostazol 100 mg/kg p.o respectively. Rats in all groups were induced seizures with an electroconvulsive meter except Group 1 (Shibnath *et al.*, 2015).

Conditioned avoidance response: Performance after seizure induction

After ensuring recovery from seizures, each rat was positioned exclusively in the pole climbing apparatus for determining the memory retention effect. A fixed number (i.e. 10) of shocks was applied to the electric grid floor, and the number of shocks escaped by each animal of a group was noted and tabulated (Gupta, 2004; Vogel, 2008).

Evaluation of the effects of treatments on motor co-ordination

Group I - Normal saline

Group II - Diazepam (2 mg/kg i.p)

Group III - Cilostazol (10 mg/kg i.p)

Group IV - Cilostazol (20 mg/kg i.p)

Group V - Diazepam (2 mg/kg i.p) + Cilostazol (10 mg/kg i.p)

Group VI - Diazepam (2 mg/kg i.p) + Cilostazol (20 mg/kg i.p)

Procedure

Rats were trained 15 minutes per day on the Rotarod for one week (12 RPM). Rats were positioned on the rod, and the animals that remained for 5 minutes were selected for the study. Rats were accustomed to the experimental environment 30 min before the start of the experiment. The rats were evaluated for motor co-ordination at an interval of 30, 60 minutes after administration of the experimental interventions as mentioned in the grouping of animals. The rotating rod accelerated at a speed of 4-40 RPM for 5 min. If the animal fails more than once to remain on the rotating rod for 5 minutes, then the test was considered positive. The rod was cleaned with a cotton ball soaked in spirit between each procedure. The latency time of each rat fall off from the rod for the first time was noted and tabulated (Gupta, 2004; Kulakarni, 2007; Abada *et al.*, 2013).

Statistical analysis

The outcomes of the experiments were noted and presented as Mean $\pm$ SD. The outcomes were tested by ordinary two way ANOVA followed by Tukey's multiple comparisons test. A $p < 0.05$ was considered statically significant.

Outcomes

Effects of treatment on learning-memory

The Table 1 reflects that group 5 demonstrated a significant difference in NSA out of 10S compared to other groups ($p<0.001$). Group 4 demonstrated a significant difference over group 2 ($p<0.05$) but not over group 3 ($p=0.834$) in NSA out of 10S. Group 3 did not exhibit statistically significant variance over group 2 ($p<0.26$) in NSA out of 10S.

Effects of treatment on motor-coordination

30 min after the drug administration

The Table 2 reflects that the group 4 exhibited a significant variance in latency period of the first fall of the rod over the group 1 ($p<0.001$) and 3 ($p<0.01$). Group 3 did not demonstrate a significant variance in the latency period of the first fall of the rod over group 1 ($p=0.552$). Group 2 demonstrated a significant difference over group 6 ($p<0.001$) but not with group 5 ($p=0.696$). Group 6 demonstrated statistically significant variance over group 2 and 5 ($p<0.001$).

60 min after the drug administration

Table no 2 reflects that group 4 exhibited a significant variance in the latency period of the first fall of the rod over group 1, 3 ($p<0.001$). Group 3 did not demonstrate significant variance over group 1 ($p=0.981$). Group 5 and 6 were exhibited a significant difference in relation to group 2 ($p<0.001$).

DISCUSSION

The present preclinical study was aimed to assess the influence of cilostazol on learning-memory and motor co-ordination by cook's pole climbing technique (condition avoidance reflex), rotarod technique, respectively. The outcomes of the study revealed that cilostazol 100 mg/kg p.o demonstrated a greater significant memory enhancement activity in conditioned avoidance reflex (CAR) (cook's pole climbing) technique when compared to cilostazol 50 mg/kg p.o., cilostazol 75 mg/kg p.o., and MES-control. Cilostazol 50 mg/kg p.o did not produce a significant effect on memory enhancement activity in CAR when compared to MES-control. Still, Cilostazol 75 mg/kg p.o demonstrated a less significant memory enhancement activity in CAR. Cilostazol 20 mg/kg i.p displayed better motor co-ordination performance in both sessions (30 nim and 60 min after the drug administration) of rotarod test when related to cilostazol 10 mg/kg i.p and normal saline. Cilostazol 10 mg/kg i.p did not display a significant response in both sessions of the rotarod test. Diazepam 2 mg/kg i.p demonstrated significant muscle relaxant property in the rotarod test. In relation to diazepam, concomitant use of cilostazol 10 mg/kg i.p and diazepam demonstrated improved motor co-ordination performance in one session that was 60 min after the drug administration. Cilostazol 20 mg/kg i.p + diazepam 2 mg/kg i.p demonstrated a significant improvement in motor coordination performance in both session

Table 1: Effect of experimental interventions on the behaviour of rodents by the cook's pole climbing technique

Groups	Number of Shocks Avoided out of 10 Shocks (NSA out of 10S)
Group 1 (Normal Saline)	9.16 ± 0.75
Group 2 (MES-control)	$0.83 \pm 0.75^{@}$
Group 3 (Cilostazol 50 mg/kg, p.o)	$1.83 \pm 0.75^{@}$
Group 4 (Cilostazol 75 mg/kg, p.o)	$2.33 \pm 0.81^{@\$}$
Group 5 (Cilostazol 100 mg/kg, p.o)	$5.5 \pm 1.04^{@€£©}$

N=6; @=p<0.001 vs control, $=p<0.05 vs MES-control; €=p<0.001 vs MES-control; £=p<0.001 vs cilostazol 50 mg/kg i.p; ©=p<0.001 vs Cilostazol 75 mg/kg, p.o.

Table 2: Effect of experimental interventions on the behaviour of rodents by rotarod technique

Groups	The latency period of the first fall of the rod in sec.		
	Before drug	30 Min After drug	60 min After drug
Group 1 - Normal saline	181.5±2.81	184.5±6.18	191.83±4.79
Group 2 - Diazepam (2 mg/kg i.p)	178.16±6.52	$37.0 \pm 4.64^{@}$	$31.0 \pm 5.40^{@}$
Group 3 - Cilostazol (10 mg/kg i.p)	185.83±5.11	$189.67 \pm 5.53^{\#}$	$194.33 \pm 5.81^{\#}$
Group 4 - Cilostazol (20 mg/kg i.p)	181.83±6.17	$203.3 \pm 11.74^{@\#!}$	$221.0 \pm 9.44^{@\#*}$
Group 5 - Diazepam (2 mg/kg i.p) + Cilostazol (10 mg/kg i.p)	181.67±6.43	$42.16 \pm 5.4^{@*\&}$	$47.1 \pm 3.4^{@\#*\&}$
Group 6 - Diazepam (2 mg/kg i.p) + Cilostazol (20 mg/kg i.p)	179.33±4.22	$82.83 \pm 4.44^{@\#*\&\wedge}$	$72.66 \pm 6.80^{@\#*\&\wedge}$

N=6; @=p<0.001 vs control; #=p<0.001 vs Diazepam; !=p<0.01 vs cilostazol 10 mg/kg i.p; *=p<0.001 vs cilostazol 10mg/kg i.p; &=p<0.001 vs cilostazol 20 mg/kg i.p; ^=p<0.001 vs diazepam (2 mg/kg i.p) + cilostazol (10 mg/kg i.p).

of the study in relation to diazepam 2 mg/kg i.p and Cilostazol 10 mg/kg i.p + diazepam 2 mg/kg i.p. So this reflected the significant relaxant effect of diazepam. Concomitant use of cilostazol 20 mg/kg with diazepam 2 mg/kg was significantly improved the motor co-ordination performance as cilostazol 20 mg/kg itself improved motor co-ordination over normal saline in both sessions.

The improvement in the learning and memory of cilostazol may be due to increase in cyclic adenosine monophosphate (cAMP) levels which ultimately activates a series of the cascade by phosphorylated signalling pathways like CREB-BDNF-TrkB-PI3K/Akt (cAMP response element-binding protein- Brain-derived neurotrophic factor - phosphoinositide 3 kinase -protein kinase B) (Jiang *et al.*, 2017). These are responsible for neuron survival, maturation and neuronal transmission in the hippocampus was demonstrated in ischemia/reperfusion-induced cognitive deficits rats via PI3K-Akt1/caspase-3 pathways (Qi *et al.*, 2016). The cAMP/PKA/CREB is responsible for Neuroprotection by inhibiting neuronal cell apoptosis and post-stroke axonal regeneration (Zheng *et al.*, 2019; Gao *et al.*, 2020). These signalling pathways also up-regulate Bcl-2 and (cyclooxygenase-2) COX-2 expressions leading to improvement in learning and memory (Watanabe *et al.*, 2006). Insulin-like growth factor I (IGF-I) play a significant role in angiogenesis and neurogenesis in the hippocampus, which was elevated by cilostazol, can improve memory (Zhao *et al.*, 2010). An increase in glucose uptake by cilostazol via vasodilatation may prevent amyloid β-protein-induced impairment of glucose transport in neurons of mild Alzheimer disease receiving acetylcholinesterase inhibitors (Lee *et al.*, 2019). Rababa et al. study results revealed that cilostazol could normalise biomarkers levels like (superoxide dismutase (SOD) and glutathione peroxidase (GPx)) in hippocampus without improvement in the learning and memory functions due to inadequate memory impairment by streptozotocin administration (Rababa'h *et al.*, 2019). In contrast, the present study supported by Kyoung JaKwon et al. study demonstrated improvement of spatial memory in hypoperfused diabetes mellitus-induced dementia or vascular dementia by activation of CREB phosphorylation and BDNF expression (Kwon *et al.*, 2015).

Improvement in motor function by cilostazol

may result due to an increase in cAMP-induced monoaminergic facilitation (Hedya *et al.*, 2018; Mitoma and Konishi, 1996). The present study was supported by Shuichi Yanai et al., where cilostazol was tested against normal ageing in mice. According to Yanai et al., cilostazol improved spatial memory in 23 months aged mice with no difference in memory of cilostazol-treated aged mice and untreated middle-aged mice (Yanai *et al.*, 2018). A cohort study conducted by shu-yu Tai et al. also supported the present study and revelled that cilostazol may reduce dementia by influencing cerebral circulation and Aβ metabolism (Tai *et al.*, 2017). Influence of cilostazol on memory impairment and hyperactivity was demonstrated through oral administration in a well-established Ts65Dn mouse model of Down syndrome with several symptoms of patients of a down syndrome like cognitive impairment, an undersized span of attention, low muscle tone and supported the present study (Tsuji *et al.*, 2020).

CONCLUSION

The present self-funded study concludes that cilostazol has improved the learning and memory performance after MES convulsions. It also improved motor co-ordination against diazepam induced sedative muscle relaxation. Further extensive clinical research should be done to evaluate the safety and efficacy of cilostazol use as a Neuroprotective agent.

Conflict of Interest

The authors declare that they have no conflict of interest for this study.

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REFERENCES

Abada, Y. K., Nguyen, H. P., Schreiber, R., Ellenbroek, B. 2013. Assessment of Motor Function, Sensory Motor Gating and Recognition Memory in a Novel BACHD Transgenic Rat Model for Huntington Disease. *Plosone*, 8(7):e68584.

Al, F. 2018. Dementia: A Review. *J Clin Psychiatr Neurosci*, 1(3):27–34.

Chattipakorn, S. C., Thummasorn, S., Sanit, J., Chattipakorn, N. 2014. Phosphodiesterase-3 inhibitor (cilostazol) attenuates oxidative stress-induced mitochondrial dysfunction in the heart. *Journal of Geriatric Cardiology : JGC*, 11(2):151–157.

Draper, B., Withall, A. 2016. Young onset dementia. *Internal Medicine Journal*, 46(7):779–786.

Ferrucci, L., Cooper, R., Shardell, M., Simonsick, E. M., Schrack, J. A., Kuh, D. 2016. Age-Related Change in Mobility: Perspectives From Life Course Epidemiology and Geroscience. *The Journals of Gerontology Series A: Biological Sciences and Medical Sciences*, 71(9):1184–1194.

Gao, X., Zhang, X., Cui, L., Chen, R., Zhang, C., Xue, J., Zhang, L., He, W., Li, J., Wei, S., Wei, M., Cui, H. 2020. Ginsenoside Rb1 Promotes Motor Functional Recovery and Axonal Regeneration in Post-stroke Mice through cAMP/PKA/CREB Signaling Pathway. *Brain Research Bulletin*, 154:51–60.

Gupta, S. K. 2004. Drug screening methods: Preclinical Evaluation of New Drugs. 2nd edition. New Delhi. Jaypee Brothers Medical Publishers (P) Ltd. New Delhi. ISBN-9788184486186. 688p.

Hedya, S. A., Safar, M. M., Bahgat, A. K. 2018. Cilostazol Mediated Nurr1 and Autophagy Enhancement: Neuroprotective Activity in Rat Rotenone PD Model. *Molecular Neurobiology*, 55(9):7579–7587.

Jiang, T., Wang, X., Ding, C., Du, X. 2017. Genistein attenuates isoflurane-induced neurotoxicity and improves impaired spatial learning and memory by regulating cAMP/CREB and BDNF-TrkB-PI3K/Akt signaling. *The Korean Journal of Physiology & Pharmacology*, 21(6):579–589.

Kulakarni, S. K. 2007. Hand book of experimental pharmacology. 3rd edition. Vallabh Prakashan publishers. ISBN 9788185731124. 199pg. .

Kwon, K. J., Lee, E. J., Kim, M. K., Kim, S. Y., Kim, J. N., Kim, J. O., Kim, H. J., Kim, H. Y., Han, J. S., Shin, C. Y., Han, S. H. 2015. Diabetes augments cognitive dysfunction in chronic cerebral hypoperfusion by increasing neuronal cell death: Implication of cilostazol for diabetes mellitus-induced dementia. *Neurobiology of Disease*, 73:12–23.

Lee, J. Y., Lee, H., Yoo, H. B., Choi, J. S., Jung, H. Y., Yoon, E. J., Kim, H., Jung, Y. H., Lee, H. Y., Kim, Y. K. 2019. Efficacy of Cilostazol Administration in Alzheimer's Disease Patients with White Matter Lesions: A Positron-Emission Tomography Study. *Neurotherapeutics*, 16(2):394–403.

Mitoma, H., Konishi, S. 1996. Long-lasting facilitation of inhibitory transmission by monoaminergic and cAMP-dependent mechanism in rat cerebellar GABAergic synapses. *Neuroscience Letters*, 217(2-3):141–144.

Qi, D. S., Tao, J., Zhang, L. Q., Li, M., Wang, M., Qu, R., Zhang, S. C., Liu, P., Liu, F., Miu, J. C., Ma, J. Y., Mei, X. Y., Zhang, F. 2016. Neuroprotection of Cilostazol against ischemia/reperfusion-induced cognitive deficits through inhibiting JNK3/caspase-3 by

enhancing Akt1. *Brain Research*, 1653:67–74.

Rababa'h, A. M., Mardini, A. N., Alzoubi, K. H., Ababneh, M. A., Athamneh, R. Y. 2019. The effect of cilostazol on hippocampal memory and oxidative stress biomarkers in rat model of diabetes mellitus. *Brain Research*, 1715:182–187.

Rao, G. P., Sivakumar, P., Srivastava, S., Sidana, R. C. 2020. Cognitive Therapy and Family Intervention for Patients with Dementia and Psychosis. *Indian Journal of Psychiatry*, 62(8):183–191.

Shaji, K. S., Sivakumar, P. T., Rao, G. P., Paul, N. 2018. Clinical Practice Guidelines for Management of Dementia. *Indian Journal of Psychiatry*, 60(7):312–328.

Shibnath, K., Satheesh, M. N. V., Sarkar, C. N. 2015. Amnesic Potentiality of Diazepam at Low Dose on Administration Via Transcranial Route in Rodents. *International Journal of Pharmaceutical Sciences and Research*, 6(1):300–307.

Tai, S. Y., Chien, C. Y., Chang, Y. H., Yang, H, Y. 2017. Cilostazol Use Is Associated with Reduced Risk of Dementia: A Nationwide Cohort Study. *Neurotherapeutics*, 14(3):784–791.

Tsuji, M., Ohshima, M., Yamamoto, Y., Saito, S., Hattori, Y., Tanaka, E., Taguchi, A., Ihara, M., Ogawa, Y. 2020. Cilostazol, a Phosphodiesterase 3 Inhibitor, Moderately Attenuates Behaviors Depending on Sex in the Ts65Dn Mouse Model of Down Syndrome. *Frontiers in Aging Neuroscience*, 12:1–12.

Vogel, H. G. 2008. Drug Discovery and Evaluation: Pharmacological Assays. 3rd edition. Berlin Heidelberg: Springer-Verlag. ISBN-978-3-540-70995-4. 2068 pg.

Watanabe, T., Zhang, N., Liu, M., Tanaka, R., Mizuno, Y., Urabe, T. 2006. Cilostazol Protects Against Brain White Matter Damage and Cognitive Impairment in a Rat Model of Chronic Cerebral Hypoperfusion. *Stroke*, 37(6):1539–1545.

Wennberg, A. M., Savica, R., Mielke, M. M. 2017. Association between Various Brain Pathologies and Gait Disturbance. *Dementia and Geriatric Cognitive Disorders*, 43(3-4):128–143.

WHO 2017. What are the treatments for dementia? World Health Organization. Accessed on 04 Aug 2020.

WHO 2020. Dementia. World Health Organization. Accessed on: 04 Aug 2020. .

Yanai, S., Ito, H., Endo, S. 2018. Long-term cilostazol administration prevents age-related decline of hippocampus-dependent memory in mice. *Neuropharmacology*, 129:57–68.

Zhao, J., Harada, N., Kurihara, H., Nakagata, N., Okajima, K. 2010. Cilostazol improves cognitive function in mice by increasing the production of insulin-like growth factor-I in the hippocampus. *Neuropharmacology*, 58(4-5):774–783.

Zheng, M., Liu, C., Fan, Y., Shi, D., Jian, W. 2019. Total glucosides of paeony (TGP) extracted from Radix Paeoniae Alba exerts neuroprotective effects in MPTP-induced experimental parkinsonism by regulating the cAMP/PKA/CREB signaling pathway. *Journal of Ethnopharmacology*, 245:112182.