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Original Research Article

# Effect of Pitavastatin and Gemfibrozil on Motor Coordination by using Rotarod in Mice

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**Abstract**

**Introduction:** An ability to perform a motor task accurately, rapidly, and controlled manner are known as "motor coordination." Neurodegenerative diseases like Parkinson's disease (PD) are characterized by motor incoordination, gait disturbances, and static tremors. Motor control and muscle coordination also decrease with age, and other diseases are reflected by down neuromotor functions. Pitavastatin and gemfibrozil both causes lipid lowering effects by different mechanisms of action. Few studies positively report skeletal muscle contraction behavior with statin use. In the drug-repurposing process, hidden therapeutic functions of the drugs are uncovered using different approaches.

**Aim and Objectives:** Present study was done to assess the motor coordination effect of pitavastatin and gemfibrozil in Comparison to diazepam using Balb-c mice in the rotarod behavioural model.

**Material and Methods:** 20 balb/c mice were divided into 4 groups. The rotarod was used to evaluate the motor coordination effect. The fall-off time was compared among 4 groups. Observations were analyzed by using paired t-tests, ANOVA, and post hoc Tukey's test.

**Results:** Pitavastatin (30mg/kg) and gemfibrozil (60mg/kg) make a decline in the fall-off time at all period of time with significant results at 60 and 120 minutes.

**Conclusion:** In the present study we concluded that both pitavastatin and gemfibrozil possess muscle relaxant properties. Our study fails to conclude any positive effect of pitavastatin and gemfibrozil on motor coordination. However further studies are needed to confirm that hypothesis.

**Keywords:** Balb-c mice, Drug repurposing, Gemfibrozil, Motor coordination, Pitavastatin, and Rotarod



## Introduction

An ability to perform a motor task accurately, rapidly, and controlled manner is known as "motor coordination [1]. The cerebellum coordinates voluntary movements for balanced motor activities [2]. Cholesterol is an essential molecule required for the growth of neurons and synapses [3]. Cholesterol is abundantly present in the CNS and known for its versatility [4]. Neuro-degenerative diseases like Parkinson's disease (PD) are mainly occurs by the waste of dopaminergic neurons. Parkinson's disease is characterized by diminished movements, gait disturbances, and static tremors [5].

According to [Diagnostic and Statistical Manual of Mental Disorders Fifth Edition (DSM-5)], motor skills abnormalities are one of the features related to Neurodevelopmental disorders (NDDs). Early detection of motor impairment might be an indication of a genetic disorder [6]. Motor coordination is the major component to form posture and balance of the body. Including motor coordination, seven components are identified that are involved in postural control. These seven components are sensory organization, central predictive set, limits of stability, head-eye balance, the musculoskeletal system, motor coordination, and environmental reconstruction [7]. Children with developmental coordination disorder (DCD) are at enormous risk for depression, anxiety, and obesity [8]. Recently, studies suggest that the development of motor functions might be linked to cognitive developments linked to the prefrontal cortex and cerebellum [9].

Motor coordination plays a vital role in interacting with the other person. It has been demonstrated that interlinkage at the level of body movements is a key to social exchanges [10]. Motor control and muscle coordination also decrease with age, and other diseases are reflected by down neuromotor functions [11]. To date, many therapies are used for improving motor coordination disorders like; Occupational therapy, Physical therapy, Task-oriented interventions, Methylphenidate, and dietary supplementation with fatty acids. Although there are some unanswered questions like how much the benefits rather than harm? and which interventions result in the best outcomes [12]. Few studies suggest the co-existence of psychiatric symptoms and motor incoordination. Based on that, it is essential to investigate the other challenges faced by motor coordination impairment patients [13]. Myopathies could be linked with statin use according to some evidence-based research [14] besides that, there are no sufficient pieces of evidence available in support [15]. Although few studies positively report skeletal muscle contractile role with statin use, the majority report no lousy effect of statins on skeletal muscle contractility [16]. Drug repurposing is a different approach to recognizing the new indications for already approved drugs [17]. Pharmaceutical companies, repurposing technology companies, and academics or research institutes are the key players in repurposing [18]. In this process, hidden therapeutic functions of the drugs are uncovered using different approaches [19]. In the present research we tested the outcomes of pitavastatin and gemfibrozil effect on motor coordination.

Pitavastatin, first discovered in Japan, and flourish by Kowa pharmaceuticals Tokyo, as a

hypolipidemic drug belongs to 3-hydroxy3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitor (statin) family [20]. The main action of pitavastatin is to decrease serum triglycerides and total cholesterol by enhancing the overexpression of hepatocellular LDL (low-density lipoprotein) receptors. Simultaneously it also inhibits hepatocellular VLDL (very low-density lipoprotein) release [21]. Recent studies support the protective role of statins in Parkinson's disease, which is characterized by a neurodegenerative disorder [22] α-Synuclein is a protein present abundantly in the nerve terminal. Aggregation of this protein plays an important role in increasing cholesterol levels. Statins diminished the levels of cholesterol (promoter of α-syn aggregation), providing additional evidence in favor of the action of statins in the management of PD [23] few pieces of literature support the positive role of statins on motor skills in contrast to most of them in favor of adverse effects on muscles.

Gemfibrozil is an FDA-approved drug that causes a decrease in serum triglyceride and total cholesterol levels and increases high-density lipoprotein [24]. Study shows that gemfibrozil also reduces the motor deficit and nigrostriatal pathology in the MPTP mouse model of Parkinson's disease (PD) via the Peroxisome proliferator-activated receptor (PPAR)-alpha-dependent astrocytic GDNF pathway [25]. The protective role of motor inadequacy in Parkinson's disease is proven based on experimental evidences, However, the positive role of gemfibrozil on normally acting muscle is a matter of further discussion. The rotarod test is arguably the most widely used determinant of motor function, as it rapidly provides easily interpretable results for investigators with little or no behavioural expertise [26].

## Material and Methods

**Animal** Our research was done in the Department of Pharmacology & Therapeutics, King George's medical university, Lucknow. Ethical clearance was procured from the Institutional Animal Ethics Committee (IAEC). (Ethical approval number-150/IAEC/2021)

20 adult healthy male Balb/c mice weighing 17-24 gm were utilized in the study. Mice were purchased via Indian Institute of Toxicology Research [IITR] Lucknow. IITR is one of the certified centers by the Committee for Purpose of Control and Supervision of Experiments on Animals (CPCSEA) for the breeding and housing of animals. They were housed in appropriate-sized cages in an Institutional animal house maintaining a specific temperature-controlled environment [25±2◦C], humidity (60% ± 10%) with 12 hours light / 12 hours dark cycle. Animals were fed a regular pellet diet with water ad libitum. The regular pellet diet was purchased from Bharat Science Solution Company, Lok Nagar, Unnao, Uttar Pradesh. All animals were permitted to acclimatize to a new environment for two weeks prior the experiments in the institutional animal house of King George medical university. Present validated models of rodents were used to assess the motor coordination properties of pitavastatin and gemfibrozil. Mice will be randomly divided into 4 different groups, each group containing 5 mice.

**Drug treatment:** Tests drugs were solubilized in 0.5% carboxymethylcellulose (CMC) and dissolved in normal saline then given orally (p.o.) by a feeding gavage. Pitavastatin and gemfibrozil were administered to individual mice in group 2, and group 3 subsequently. None of the mice was dead due to treatment till the end of the observation period. Pitavastatin, gemfibrozil, and diazepam were purchased from Gyan Scientific Traders Pvt. Ltd. Authorized company.

**Vehicle:** Pitavastatin and gemfibrozil was dissolved in 0.5%w/v CMC (carboxy-methylcellulose) and administered orally in mice through normal saline. Diazepam was dissolved in normal saline and injected i.p.

**Behavioral model:** Experiment Performed on the rotarod apparatus (Orchid Scientific company, serial no. Rotarod/18-19-09) made in India, consisting of a plastic drum (3cm diam., 30cm long) with a non-smoothy surface. The drum was separated into five equal segments by four discs, enabling five mice to run on the drum at the same time. The platform is equipped with sensors that allow the device to stop rotation and record the ending time of the test when mice contact the platform [27] The mice were habituated to handling any stress during testing. Animals remaining on Rotarod (22 rpm) for 60 sec or more in three consecutive trials were selected 1 day before the actual day of training.

**Table 1: Animal grouping**

| Activity To Be Tested | Groups | Treatment |
|---|---|---|
| Motor Coordination | Group 1 | Normal Saline |
| | Group 2 | Tab Pitavastatin30 Mg/Kg Bw |
| | Group 3 | Tab Gemfibrozil 60 Mg/Kg Bw |
| | Group 4 | Inj Diazepam 5 Mg/Kg Bw |

## Measurement of motor coordination effect

The mice were separated into 4 groups, each group consists of five mice (n=5). Animals that stay on the rotarod between 1-5 minutes were included and others were excluded. An appropriate speed (22 rpm) on the rotarod is used in the study. The animal was placed one by one on the rotarod more than one mouse at a time were placed. The mean training data was taken at 0 min as a control performance time (Basal reading). The mice were given control, standard, and both test drugs and falling time were assessed again after a duration of 0, 30, 60, 90, and 120 min. The fall-off time from the rotating rod was noted.

**Statistical analysis:** The calculated data were revealed as MEAN ± SD from 5 mice. Final outcome was subjected to statistical analysis by applying one-way ANOVA followed by post hoc Tukey's test to enumerate the significant difference if any among the sets. $P<0.05$ was considered significant. Paired t-test used for calculating intragroup comparison. Data were analyzed by using excel sheet and SPSS.

## Results

### Assessment of effect on motor coordination (Fall-off time)

Motor coordination was assessed by duration of stay on the rotating rod and by measuring "fall-off time". Group 1: Control, Group 2: Pitavastatin (Test drug 1), Group 3: Gemfibrozil (Test drug 2), Group 4: Diazepam (Standard). The intergroup comparison of "fall-off" time between groups was done using ANOVA and has been summarized in table 2 and graphically in figure 1

The decrease in fall-off time from the rotating rod was indicative of a compromise of motor coordination.

**Table 2: Intergroup comparison of "Fall-Off" Time (seconds) at 0, 30, 60, 90, 120 minutes**

| Group | 0 min | | 30 min | | 60 min | | 90 min | | 120 min | |
|---|---|---|---|---|---|---|---|---|---|---|
| | Mean | SD | Mean | SD | Mean | SD | Mean | SD | Mean | SD |
| Group 1(NS) | 269 | 10.70 | 264.4 | 7.22 | 265.6 | 39.43 | 267.4 | 11.67 | 266 | 5.51 |
| Group 2 (Test 1) | 261.4 | 7.50 | 260.8 | 7.52 | 256.2 | 43.55 | 261.8 | 5.94 | 263.2 | 6.85 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Group 3 (Test 2) | 255.4 | 8.79 | 252 | 11.93 | 245.2 | 69.34 | 256 | 10.37 | 251.6 | 5.38 |
| Group 4 (Standard) | 241.8 | 9.09 | 241.6 | 23.61 | 241.2 | 21.87 | 223.4 | 8.95 | 244 | 5.69 |
| Anova | F = 7.99 p = 0.001* | | F = 2.04 p = 0.14 | | F = 0.22 p = 0.87 | | F = 17.31 p = 0.00003* | | F = 12.10 p = 0.0002* | |

N=20, n=5 in each group. Values are expressed as Mean ± SD posthoc Tukey's test was applied to find the significant difference after the application of one-way ANOVA

F = 7.99; P =0.001* (0 min),
F = 2.04; P = 0.14 (30 min),
F = 0.22; P = 0.87 (60 min),
F = 17.31; P = <0.001*(90 min),
F = 12.10; P = <0.001*(120 min).

**Table 3: Between-Group Comparison "Fall-off" time (Tukey HSD test)**

| Group | 0 min | | | 30 min | | | 60 min | | | 90 min | | | 120 min | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Mn diff | SE | ' p' | Mn diff | SE | ' p' | Mn diff | SE | ' p' | Mn diff | SE | ' p' | Mn diff | SE | ' p' |
| 1vs 2 | 7.6 | 4.06 | 0.56 | 3.6 | 7.11 | 0.98 | 9.4 | 23.3 | 0.99 | 5.6 | 4.73 | 0.83 | 2.8 | 2.94 | 0.90 |
| 1vs 3 | 13.6 | 4.06 | 0.12 | 12.4 | 7.11 | 0.61 | 20.4 | 23.3 | 0.92 | 11.4 | 4.73 | 0.35 | 14.4 | 2.94 | 0.01 |
| 1vs 4 | 27.2 | 4.06 | 0.001 | 22.8 | 7.11 | 0.14 | 24.4 | 23.3 | 0.88 | 44 | 4.73 | 0.0004 | 22 | 2.94 | 0.0003 |
| 2vs 3 | 6 | 4.06 | 0.72 | 8.8 | 7.11 | 0.81 | 11 | 23.3 | 0.98 | 5.8 | 4.73 | 0.82 | 11.6 | 2.94 | 0.057 |
| 2vs 4 | 19.6 | 4.06 | 0.01 | 19.2 | 7.11 | 0.26 | 15 | 23.3 | 0.96 | 38.4 | 4.73 | 0.0001 | 19.2 | 2.94 | 0.001 |
| 3vs 4 | 13.6 | 4.06 | 0.12 | 10.4 | 7.11 | 0.73 | 4 | 23.3 | 0.99 | 32.6 | 4.73 | 0.0008 | 7.6 | 2.94 | 0.29 |

*Statistically significant

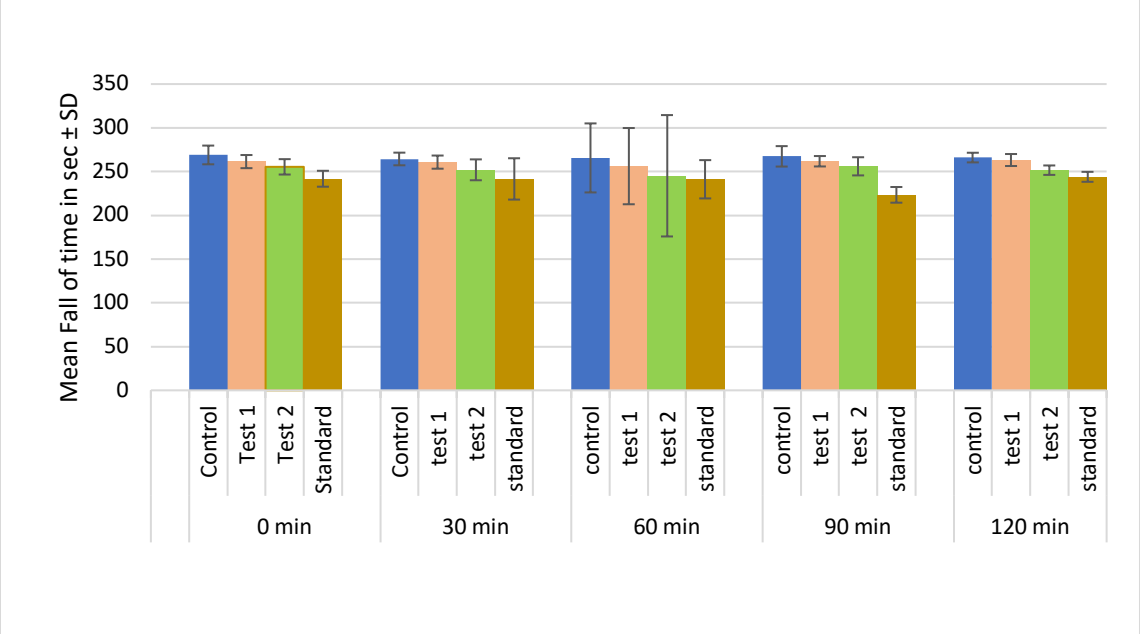


**Figure 1: Mean fall off time in seconds**

## Intergroup comparison

At 0 min, fall-off time on rotarod of group 1 (269 ± 10.70), group 2 (261 ± 7.50), group 3 (255.4 ± 8.79), and group 4 (241.8 ± 9.09) were found to be comparable.

At 30 min, fall-off time on rotarod is comparatively lower in group 4 (241.6 ± 23.61) followed by group 3 (252 ± 11.93) and group 2 (260.8 ± 7.52) while higher in group 1 (264.4 ± 7.22). On exploring between-group differences, no significant difference was found.

At 60 min, fall-off time on rotarod is comparatively lower in group 4 (241.2 ± 21.87) followed by group 3 (245.2 ± 69.34) and group 2 (256.2 ± 43.55) while higher in group 1 (265.6 ± 39.43). On exploring between-group differences, no significant difference was found.

At 90 min, fall-off time on rotarod is comparatively lower in group 4 (223.4 ± 8.95) followed by group 3 (256 ± 10.37) and group 2 (261.8 ± 5.94) while higher in group 1 (267.4 ± 11.67). On exploring between-group differences, a significant difference was established between groups 1 vs group 4; group2 vs group 4, and group 3 vs group 4.

At 120 min, fall-off time on rotarod is comparatively lower in group 4 (244 ± 5.69) followed by group 3 (251.6 ± 5.38) and group 2 (263.2 ± 6.85) while higher in group 1 (266 ± 5.51). On exploring between-group differences, a significant difference was established among groups 1 vs group 3; group 1 vs group 4, and group 2 vs group 4.

**Table 4: Intragroup Change in Baseline (0 min) "Fall-off" time (Paired 't-test)**

| Group | Time period | Mean change | % BL change | 't' | 'p' |
|---|---|---|---|---|---|
| Group 1 | 30 m | -4.6 | -1.73 | -0.62 | 0.56 |
| | 60 m | -3.4 | -1.28 | -0.15 | 0.88 |
| | 90 m | -1.6 | -0.59 | -0.16 | 0.87 |
| | 120 m | -3 | -1.12 | -0.47 | 0.66 |
| Group 2 | 30 m | -0.6 | -0.23 | -0.115 | 0.91 |
| | 60 m | -5.2 | -2.02 | -0.21 | 0.83 |
| | 90 m | 0.4 | 0.15 | 0.07 | 0.94 |
| | 120 m | 1.8 | 0.68 | 0.53 | 0.62 |
| Group 3 | 30 m | -3.4 | -1.34 | -0.42 | 0.69 |
| | 60 m | -10.2 | -4.15 | -1.1 | 0.33 |
| | 90 m | 0.6 | 0.23 | -0.6 | 0.94 |
| | 120 m | -3.8 | -1.51 | -1.06 | 0.34 |
| Group 4 | 30 m | -0.2 | -0.08 | -0.01 | 0.98 |
| | 60 m | -0.6 | -0.24 | -0.05 | 0.95 |
| | 90 m | -18.4 | -8.23 | -4.39 | 0.01* |
| | 120 m | 2.2 | 0.90 | 0.54 | 0.61 |

*Statistically significant

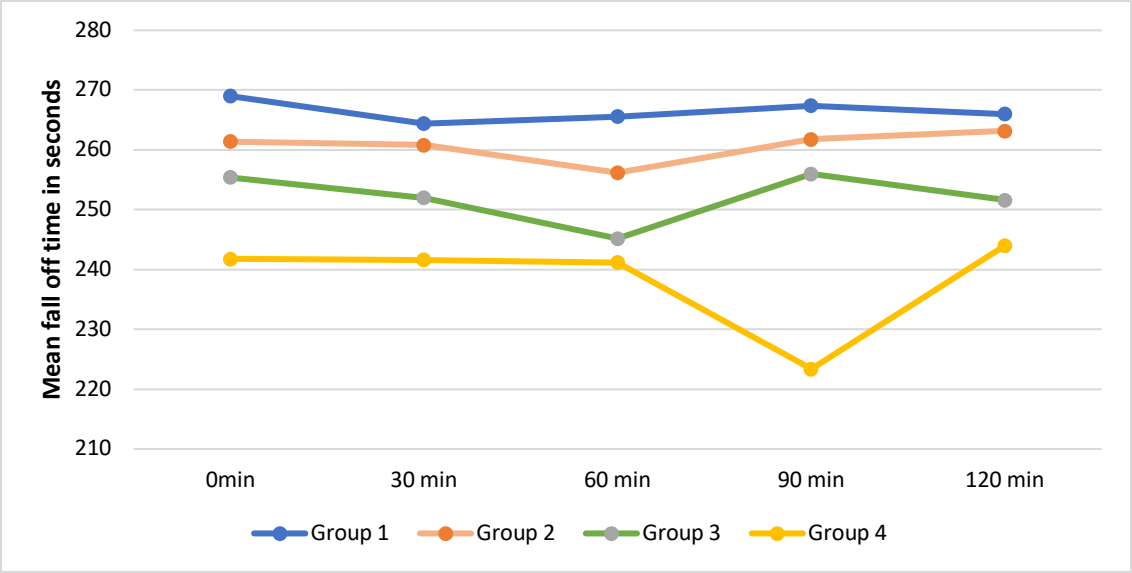


**Figure 2: Mean fall-off time in seconds**

As observed in the above graph Fall-off time of Group 1, and Group 2, is almost a straight line while that of Group 4 shows a tremendous decline at 90min, thereafter a subsequent improvement at 120min. Group 3 also shows a slight decline at 60 min there after a subsequent improvement at 90 min with a decline at 120 min. overall both tests' drugs show a lower graph in comparison to the control group at all periods.

### Intragroup comparison

The range of percentage change in Intragroup baseline fall-off time in Group 1 was 0.59% to 1.73%, in Group 2 was 0.15% to 2.02%, in Group 3 was 0.23% to 4.15%. Fractional percentage change in baseline fall-off time was noticed at 30 min, 60 min, 90 min, and 120 min in all 3 groups. None of the changes were significant statistically.

In Group 4, fall-off time was lower than baseline at all periods of observation (30 min, 60 min, 90 min, and 120 min). At 30min, 60 min, and 120 min changes were not found to be significant and the percentage change in baseline fall-off time was fractional (0.08%, 0.24%, and 0.90% subsequently). At 90 min fall-off time was 8.23% at baseline, this change was found to be significant statistically.

### Discussion

Dunham and Miya (1957) first described Fixed-speed rotarod (FSRR) for testing neurological deficits in rodents [28]. In behavioral studies for the evaluation of motor coordination activities, the rotarod test has been selected wisely [29]. It may help in quantitative tests to assess the efficacy of therapeutic strategies. We can observe the quick fall of animals with motor coordination deficits as compared to an animal with normal motor function [30]. The training was given to the mice on the constant speed rotating rod. The speed was increased gradually, so the mice learn to stay on the rod for a designated time frame. On the day of final testing, the trained mice were firstly marked properly then after weighing calculating doses were given to each mouse. Then mice were placed gently on the rotarod, which was set at the constant speed of 22 rpm. After placing the mouse on each compartment, the start button was pressed for each mouse so the countdown was started from 0 seconds. The duration was recorded from start to fall from the rod on the touch-sensitive platform for 0, 30, 60, 90 120 minutes.

The standard drug diazepam showed a reduction in fall-off time as compared to control and both test drugs and was statistically

significant. Fall-off time was slightly earlier in test drugs as compared to the saline treated group. The percentage alteration in the baseline of diazepam was maximum at 90 min (8.23 %) and the value was significant and followed by Gemfibrozil at 60 min (4.15%), but the value was not significant.

We all know that benzodiazepine facilitates GABA which is an inhibitory neurotransmitter in CNS. The centrally acting skeletal muscle relaxant shows a dose-dependent relaxant effect which must be responsible for the early fall-off time. It was found in some studies that gemfibrozil and pitavastatin protect nigral neurons, normalized striatal fibers, and neurotransmitters and improves locomotor activities. Despite that, a decrease in the fall-off time of the gemfibrozil and pitavastatin group may be due to some other mechanism that causes muscle weakness and shows relaxant properties. Some studies have shown that statins may induce instability in the myocyte cell membrane which triggers the stimulation of intracellular proteolytic cascades and modification in the protein degradation system.

## Conclusion

Both pitavastatin and gemfibrozil at their respective dose of 30 mg/kg BW and 60 mg/kg BW showed a derangement in motor coordination on the rotarod test. The falling time is more than the standard drug diazepam while less than the control group. hence, it can be concluded that pitavastatin and gemfibrozil possess muscle relaxant properties but the effect was less than diazepam. The present study fails to conclude any positive effect of pitavastatin and gemfibrozil on motor coordination. However further research is needed to make a solid conclusion, as we know that the individual study is only a contribution to making novel orchestrations.

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