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Neuroprotective Potential of the Methanolic Leaf Extract of *Launaea taraxacifolilia* and Oil of *Dennettia Tripetala* Seed in Sub-chronic Lead Toxicity in Offspring of Rats

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ABSTRACT

Background: The development of childhood intellectual disabilities as a result of lead poisoning is a major public health concern. In South West Nigeria, *Dennettia tripetala* (DT), a promising nootropic as well as Launaea taraxacifolia (LT), a reported antidote in lead induced hepatotoxicity, are widely consumed. Tocopherol (Vitamin E), Vitamin C and Di-Mercapto Succinic Acid (DMSA) has also been reported to be useful in the management of lead poisoning. The possible neuro-protective effect of both plants, together with tocopherol and Vitamin C in lead-induced memory deficit is yet to be determined. This study evaluated the possible Neuro-protective effect of the methanolic extract of the oil of *Dennettia tripetala* G. Baker (*Annonaceae*) seed, (DT) and the leaf of *Launaea Taraxacifolilia* (Asteraceae) (LT) as well as their combination with tocopherol or Vitamin C and DMSA on lead-induced memory deficit in rat's offspring.

Materials and Methods: Female rats were administered lead acetate (30 mg/kg p.o) during gestation and lactation period. After weaning, the neonates were randomly divided into groups, and were orally administered DT or LT only, and their combinations with Vitamin C or Tocopherol (Vitamin E) and DMSA. This was followed by subjecting the animals to Spontaneous object recognition and Y-maze tests to evaluate memory deficit as well as the effect of the drugs on memory deficit.

Results: Results showed that the extract of DT and LT, Tocopherol /Vitamin C and their combination ameliorated lead- induced memory deficit.

Conclusion: Tocopherol and Vitamin C appeared to promote the memory enhancing activity of the extract DT/LT respectively, suggesting that they act via similar pathways.

Keywords: Lead poisoning, Tocopherol, Neuro-protective, Vitamin c, *Dennettia tripetala*, *Launaea taraxacifolilia*, Y-maze tests

INTRODUCTION

Various reports have attested to the fact that lead exposure during pregnancy and/or lactation affects not only the mother, but the offspring thus leading to congenital abnormalities, long term cognitive and behavioural deficits among other conditions. Such exposures, in addition to direct contacts, have been estimated by WHO (2014) to contribute to about 600,000 new cases of intellectual disabilities yearly. Furthermore, in 2017, lead exposure accounted for 1.06 million deaths, and in 2016 it accounted for 63.2% of idiopathic developmental intellectual disability [1-12].

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Additionally, WHO still identifies it as one of 10 chemicals of major public health concern that workers, children and women of reproductive age should be protected from, hence, forming a global alliance with the United Nations Environment Programme, to eliminate lead paint which is a major source of exposure by 2020 [13]. Other sources of children's exposure are lead added to petrol, from an active industry such as mining, solder in food cans, ceramic glazes, drinking-water systems with lead solder and lead pipes, in product such as herbal and traditional medicines, cosmetics and toys, lead in electronic waste (e-waste), in the food chain *via* contaminated soil [14,15].

Even though lead appears to cause injury at all Blood Lead Levels (BLL) to the developing human brain, neuro-behavioural damage has been associated with blood levels lower than 5 µg/dL. Chandran and Cataldo (2010) stated that for every rise greater than 10 µg/dL of BLL, there is a decline of 2 to 3 points in a child's Intelligence Quotient (IQ) scores although recent studies have suggested that this relationship may not be linear.

Recently, lead poisoning crisis was discovered in Zamfara State, Nigeria in March, 2010 killing about 400 children and the root cause of the crisis was identified as unsafe mining and ore processing [16]. A similar scenario was reported in Niger State in May, 2015 [17]. Also, according to a CNN report on the 13th of February 2016, some researchers discovered elevated levels of lead in drinking water in Michigan State, United States of America. These events indicate that, even though many countries have initiated means to lower the level of lead in the environment, human exposure remains a public health concern worldwide [14].

Although, the biochemical and molecular mechanisms of lead toxicity is poorly understood, studies have shown its ability to elicit oxidative stress due to the decrease in antioxidant function such as thiol-containing antioxidants and a consequent increase in quantity of free radicals such as hydroxyl radical, as one of the mechanisms through which exposure results in neurotoxicity in the brain. Lead induced learning and memory impairment is preventable by Vitamin E and other antioxidants. Flora et al. (2003), presumed that supplementation of antioxidants could be an alternative method for chelation therapy. Salehi et al. (2015), also demonstrated that the co-administration of lead and Vitamin E in rats counters the neurotoxic effect of lead. According to Lyn (2006), antioxidants may have synergistic relationship with pharmacological chelating agents [18-23].

Dennettia tripetala G. Baker (*Annonaceae*), also known as pepperfruit is widely consumed in South Eastern Nigeria [24]. Also, its wide use in the management of oxidative stress related diseases was supported by Aderogba et al. (2011), who demonstrated that the methanolic leaf extract has free radical scavenging properties [25].

The ethanolic extract of the leaf, fruit and seed of *Dennettia tripetala* has been shown to contain ß-Phenylnitroethane (BPNE, 1-nitro-2-phenylethane), thought to be responsible for the neuro-pharmacological effects of the oil, exhibited a dose-dependent hypnotic, anticonvulsant and anxiolytic effect. The dried seed contains 87.4% BPNE which is greater than the dried fruits and fresh leaves content at 78.1% and 62.9% of BPNE respectively. Also, using the Y-maize test, the seed oil and BPNE exhibits high memory promoting activity [26,27].

Launaea taraxacifolia (*Asteraceae*) also known as wild lettuce is widely distributed in tropical and temperate regions although it is extensively cultivated in Western part of Nigeria [28]. Adebisi (2004), stated that the plant has high nutritional and medicinal value, because it contains minerals, vitamins, flavonoids, among other nutrients. Sofowora (2008), alluded that it is among the least utilized vegetables in South Western Nigeria even though, it is known traditionally as an antidote for snake bite, lactation stimulant (Odugbemi et al., 2008), antiemetic (Achigan et al., 2009) and other purposes. Eluwole et al. (2018) supported its ethno medical use in the management of poisoning because it ameliorated and prevented the effect of hepatotoxicity induced by lead poisoning. Furthermore, concluded that LT reversed lead-induced histological alternations to the liver and kidney [29-35].

Also, its neuro-protective effect, anti-inflammatory (Bello et al., 2018), anticancer, antimalarial, and antiviral have been reported [36-40].

This study determined the neuro-protective effect of the methanolic extract oil and leaf of *Dennettia tripetala* G. Baker (*Annonaceae*) seed, (DT) and *v* (*Asteraceae*) (LT) respectively in the offspring of rats on sub chronic lead administration. In addition, it evaluated the neuro-protective effect of the combination of DT, tocopherol and DMSA, as well as LT and Vitamin C.

METHODS

Animal Selection

Female rats weighing between 180 g-200 g were used. The animals were kept under natural light/dark cycle, housed in cages under conventional laboratory condition, and fed with standard laboratory chow and clean water was given. They were mixed with adult male rats for two weeks to achieve copulation. The research followed standard animal handing procedures as stipulated by The "Principle of Laboratory Animal Care" [41].

Extraction Procedures for DT AND LT

The essential oil from DT seeds was carried out according to Oyemitan et al. (2008). The Powdered leaf (500 g) of LT was extracted with 1.5 L of absolute methanol in a Soxhlet extractor set at 55°C for 72 hours. The filtrate generated was concentrated to dryness in a rotary evaporator under enough pressure to prevent decomposition of its active components. The extract concentrate yield was 44.4 g (8.88%) powered leaves [42].

Experimental Protocol

The female rats were given 30 mg/kg of lead acetate during gestation and lactation period. After weaning, the offspring were divided into two groups-DT and LT.

DT: Offspring were further divided into 9 groups (n=6); group I: Served as the control and received distilled water, group II: Received no treatment, group III: DT only (100 mg/kg), group IV: Vitamin E only (150 mg/kg), group V: DMSA (30 mg/kg)+Vitamin E (150 mg/kg), group VI: DMSA (30 mg/kg)+DT (100 mg/kg), group VII: DT (100 mg/kg)+Vitamin E. (150 mg/kg), group VIII: DMSA (30 mg/kg)+DT (100 mg/kg)+Vitamin E (150 mg/kg)

and group IX: DMSA only (30 mg/kg). All drug administration was through the oral route.

On the other hand, LT: Offspring were divided into six groups. (n=6); group I: Served as the control and received distilled water, group II: Received no treatment, group III: LT only (100 mg/kg), group IV: LT only (200 mg/kg), group V: Vitamin C and group VI: Vitamin C+LT (100 mg/kg).

Determination of the Dose of DT

After weaning, the offspring of lead-exposed mothers were divided into 3 groups (n=6). They were subjected to the spontaneous object recognition test and the Y-maze test. Three doses 100 mg/kg, 250 mg/kg and 500 mg/kg were orally given to the groups respectively for 5 days. Then, they were again subjected to the tests. This 100 mg/kg was chosen because, it produced a better activity.

Spontaneous Object Recognition Test (SOR)

The test is performed in an open field apparatus (100 cm × 100 cm × 46 cm high). The procedure consists of three phases: Habituation phase, sample phase and choice phase.

In the habituation phase, the animal was allowed to explore the empty box for 40 minutes to facilitate habituation to the apparatus. The amount of exploration indicated by the number of line crossing was measured. Then, the animal was removed from the apparatus, and two identical objects were placed in the box at two opposite ends. The animal was returned into the box, and the time spent exploring each of the objects was noted for a period of 10 minutes (Sample phase).

After, 8 hours, one of the previous objects used, and a novel but identical object was placed in the box. The old object was placed in its former position, and the novel in the position of the replaced object. The time spent exploring each of the objects was noted for a period of 3 minutes (choice phase).

The difference in the time spent exploring the novel object and the familiar object (d1) is calculated. The proportion of the time spent exploring the novel object (d1) to the total exploration time (e2) in the choice phase is then calculated. Recognition index is then the percentage of the proportion obtained. That is, (d1/e2) × 100 [43].

Y-Maze Test (Y-M)

The Y-maze used has wooden walls that are 8 cm high. Its arms consist of three identical compartments, labelled A, B and C respectively which are symmetric to each other. The animal was placed in the arm of the apparatus labelled ''A'' and the movement of the animal in the apparatus was observed for 10 minutes. An arm entry is defined as the body of the animal (with or without the tail) completely entering into an arm compartment. The number and sequence of arm entry were manually recorded. An alternation consists of entering three deferent arms consecutively. The percentage alternation is computed by dividing the number of alternations the animal made by the total number of arms entered minus two. The resulting number is multiplied by hundred [44].

Statistical Analysis

The data obtained from the tests were reported as mean (± SEM). One way ANOVA followed by post-hoc analysis using Newman Keuls test for multiple comparisons was used to analyze the data obtained from the tests immediately after weaning the animals. Paired T test was used to compare the data obtained immediately after weaning and after five days of drug administration. Significant difference was taken as $p<0.05$. GraphPad Prism Version 5.04 (GraphPad oftware Inc., La Jolla, USA) was used to compute the data analysis.

RESULTS

100 mg/kg, 250 mg/kg and 500 mg/kg of the DT was administered to three groups of animals (n=6) respectively. 100 mg/kg produced the highest mean values for the parameters measured after five days of administration (**Table 1**).

In the determination of percentage alternation in the DT grouped rats (**Figure 1**) using the Y-maze model after drug administration, there was a significant difference between the group that was administered lead only and the other groups. Vitamin E had the highest mean (79.28 ± 6.31) after administration while Pb only group had the least value (37.54 ± 4.22). One way ANOVA revealed a significant difference ($p<0.05$) in the mean values. The post-hoc analysis also indicated a significant difference ($P<0.05$) between the Pb only group and the other groups. However, no significant difference ($p>0.05$) was indicated between DT and the other groups. In the LT group (**Figure 2**) on the other hand, the control group (offspring of rats not exposed to lead) had the highest mean percentage alternations at 93.33(± 6.67), which was followed by the LT+Vitamin C group (87.67 ± 6.23), while the Pb only group had 21.33(± 3.67) which was the least mean value. Statistical analysis using Dunnet Test indicated a significant difference in the mean values obtained and between the Pb only group and other groups ($p<0.05$).

Table 1: The effect of the dose of DT after three weeks of postnatal exposure to lead *via* breast milk on SOR, Y-M and line crossing

Dose (mg/kg)	Recognition Index (%)	Alternations (%)	Line Crossing (%)
100	70.83 ± 15.02	68.89 ± 17.36	46 ± 12.66
250	11.11 ± 11.11	45.28 ± 17.36	17.67 ± 5.61
500	19.04 ± 19.05	42.12 ± 21.35	24.67 ± 15.41

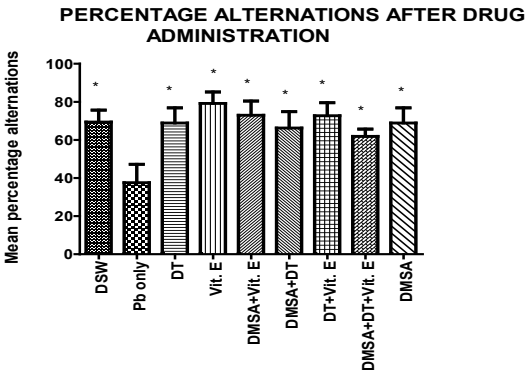


Figure 1: The effect of *Dennettia tripetala* extract (100 mg/kg), Vitamin E and DMSA on mean percentage alternations in lead poisoned rats using the Y-Maze model. Each bar represents the mean (± standard error of mean) obtained after the administration of the drugs. KEY: DSW=Distilled water, Pb only=animals exposed to lead only, DT=Dennetia tripetala extract, Vit E=Vitamin E, DMSA=Dimercaptosuccinic acid. *=Significant difference ($p<0.05$) compared with Pb only.

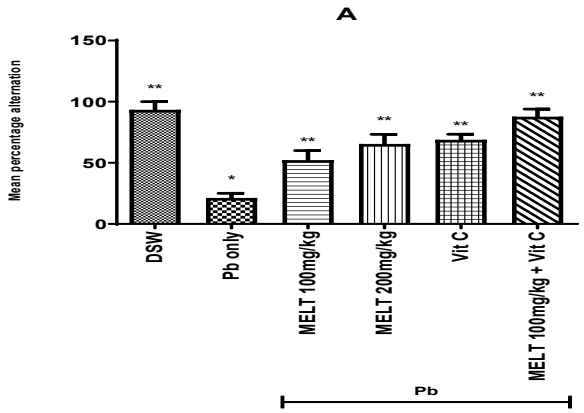


Figure 2: The effect of the Methanolic extract of LT (MELT) (100 mg/kg and 200 mg/kg), Vitamin C and a combination of Vitamin C and MELT (100 mg/Kg) on the mean percentage alternations in lead poisoned rats using the Y-maze model. Each bar represents the mean (± standard error of mean) obtained after the administration of the drugs. KEY: DSW=Distilled water, Pb only=Lead only, MELT 100 mg/kg=MELT at 100 mg/kg, MELT 200 mg/kg=MELT at 200 mg/kg, Vit C=Vitamin C. *=Significant difference ($p<0.05$) compared with Pb only.

The control group (rats, whose mothers were not administered lead) had the highest mean 93.33 (± 6.67), followed by those administered MELT (100 mg/Kg) and Vitamin C 87.67 (± 6.23), while the group that was administered Lead only had the least value 21.33 (± 3.67). The Dunnet Test showed a significant difference ($p<0.05$) between the value obtained for the Lead only and the other groups.

The mean values of line crossing obtained in the DT groups (**Figure 3**) for the distilled water only group and Vitamin E group was 85.83 (± 18.18) while DT+Vitamin E group was 85.17 (± 14.47) which were the highest values. No significant difference ($p>0.05$) between the Pb only group and other groups was observed. Similarly in the LT group (**Figure 4**), Vitamin C and distilled water group had the highest mean values at 98.67 (± 9.26) and 97.67 (± 7.8) respectively. Also, there was a significant difference between the Pb only group and the distilled water group whereas the other groups indicated no significant difference.

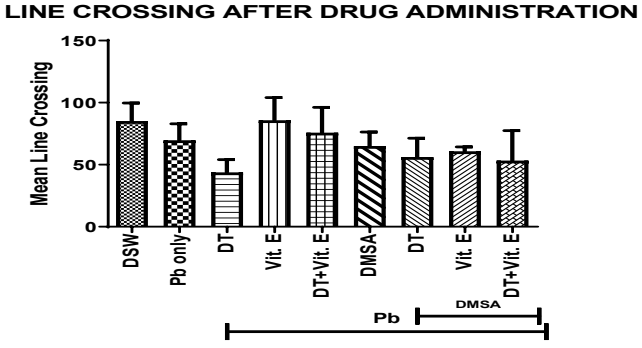
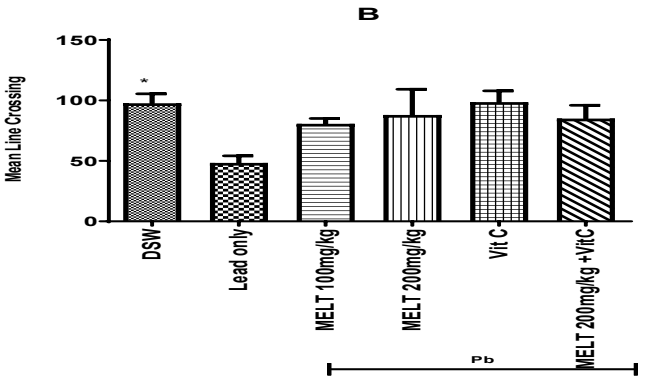


Figure 3: The effect of DT extract (100 mg/kg), Vitamin E and DMSA on the number of line crossing in rats exposed to maternal lead toxicity. Each bar represents the mean (± standard error of mean) obtained after the administration of the drugs. (n=6). KEY: DSW=Distilled water, Pb only=animals exposed to lead only, DT=Dennetia tripetala extract, Vit E=Vitamin E, DMSA=Dimercaptosuccinic acid. *=significant difference ($p<0.05$) compared with Pb only. ** =very significant difference ($p<0.01$) compared with Pb only.



From the percentage recognition index obtained after drug administration, DT only group, had the highest mean recognition index values of 61.61 (± 15.16) respectively.

Figure 4: The effect of the Methanolic extract of LT (MELT) (100 mg/kg and 200mg/Kg), Vitamin C and a combination of Vitamin C and MELT (100 mg/Kg) on the number of line crossings in lead poisoned rats using the open field box. Each bar represents the mean (± standard error of mean) obtained after the administration of the drugs. KEY: DSW=Distilled water, Pb only=Lead only, MELT 100 mg/Kg =MELT at 100 mg/Kg, MELT 200 mg/Kg=MELT at 200 mg/Kg, Vit C =Vitamin C. *=significant difference ($P<0.05$) compared with Pb only (**Figure 5**).

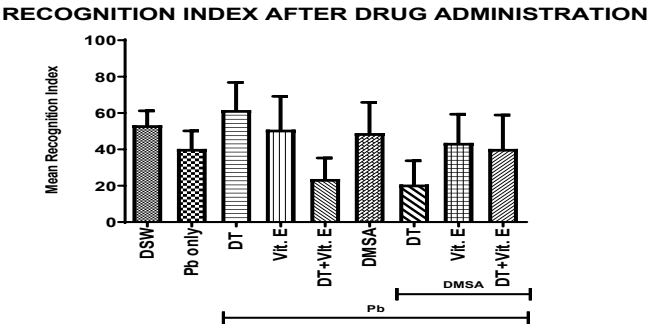


Figure 5: The effect of *Dennettia tripetala* extract (100 mg/kg), Vitamin E and DMSA on the recognition index in lead poisoned rats after five days of drug treatment using the spontaneous object recognition test. Each bar represents the mean (± standard error of mean) obtained before the administration of the drugs (n=6). KEY: DSW=Distilled water, Pb only=animals exposed to lead only, DT=Dennetia tripetala extract, Vit E=Vitamin E, DMSA=Dimercaptosuccinic acid. *=significant difference ($P<0.05$) compared with Pb only.

DISCUSSION

It has been established that lead exposure during pregnancy and/or lactation causes long term cognitive sequelae and behavioural deficits in the offspring. Furthermore, WHO (2010) suggests that any amount of lead exposure can cause injury to the developing brain [45-47]. *Dennettia tripetala* G. Baker (*Annonaceae*) seed (DT) has been shown to have memory enhancing activity because of its high BPNE content. Likewise, Launaea taraxacifolia (*Asteraceae*) (LT) has been reported to show neuroprotective effect (Owoeye et al., 2016) as well as being useful in ameliorating the effect of lead-induced hepatotoxicity. This study therefore, evaluated the effect of *Dennettia tripetala* G. Baker (*Annonaceae*) extract and Launaea taraxacifolia (*Asteraceae*) extract on memory impairment induced by sub chronic exposure of adult female rats to lead. The offspring of such animals were selected for the study.

The result of the mean percentage alternation using the Y-maize model obtained for the DT group showed that the

value obtained for the lead only group was significantly lower than those of the other groups. The group that was given Vitamin E only had the highest value, which was closely followed by the DT+Vitamin E group. This observation is in agreement with studies by Salehi et al. (2015) where Vitamin E has been reported to counteract the negative effect of lead on learning and memory mainly due to its antioxidant property. Also, Aderogba et al. (2011) demonstrated the free radical scavenging property of DT. The mean value obtained in the DT+Vitamin E group was higher than that of the DT only group, indicating that in addition to its potential to reverse and inhibit lead induced memory deficit, it may possess a synergistic effect on Vitamin C [48].

In addition, in the LT group, all the groups had mean values that were significantly higher than that obtained for the lead only group. Similarly, the combination of LT at 100 mg/kg+Vitamin C showed a higher mean percentage alternation than the LT only group at 100 mg/kg and 200 mg/kg, and Vitamin C only. In line with the results obtained from the DT group, Vitamin C has been reported by Ibrahim Abdulwaliyu et al. (2018), to be useful in the management of lead poisoning just as LT leafs have been reported to have antioxidant properties [49,50].

Furthermore, the mean line crossing in the open field test obtained for the DT group indicated that the group administered Vitamin E only, and the distilled water only group, had similar values, while the DT+Vitamin E group had higher values than the DT and Vitamin E only groups respectively. Similarly, the LT group showed that the Vitamin C only group, distilled water group and LT at 200 mg/kg had the highest values respectively. Certain studies suggest that Sub-chronic lead toxicity can cause locomotion hypoactivity because lead interferes with catecholaminergic and dopaminergic transmission same as observed in the LT group as there was a significant difference between the unexposed rats (distilled water only group) and the lead only group which had a higher value. On the other hand, Azzaroui et al. (2019), reported that sub-chronic lead exposure causes hyperactivity in rats as seen in the DT group where there was no significant difference between the lead only group and other groups. Also, the DT only group had the least value which is in line with Oyemitan et al. (2009), which stated that DT had an inhibitory effect on the adrenergic pathway of mice which results in decrease in locomotion.

A recognition index test was carried out for the DT group, in which the DT only group and the Vitamin E only group had the highest mean values. High intake of Vitamin E has been associated with less cognitive decline with age. Zandi et al. (2004), also demonstrated its neuro-protective property against free radical generating molecules. Additionally, DT has been reported by Oyemitan et al. (2019), to have nootropic activity.

Lead has been reported to induce changes in exploratory activity and motor skills. Hypoactivity and hyperactivity may occur due to altered dopamine neurotransmission [51]. These authors also reported that pups born to pregnant mice administered lead acetate had an increased exploratory activity because of the associated neuro-developmental deficits, while rats directly administered with lead, had a decrease in activity. Needleman (2004), reported that lead produced a deficit in IQ scores, attention and language in children. Needleman et al. (1990), also concluded that childhood lead exposure results in deficits in central nervous system functions that persist into adulthood [2].

Y-maze model and spontaneous object recognition test measures the memory capability of the animals, while line crossing is used to indicate the extent of exploration. These tests explore the innate tendency of animals to explore novel objects and environment.

CONCLUSION

In conclusion, DT and LT appears to ameliorate lead-induced memory deficit and their action is promoted by Vitamin E and C respectively as observed in the Y-maize test, indicating that the extracts and the Vitamins may act *via* similar pathways.

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None.

CONFLICT OF INTEREST

We have no conflict of interest to disclose.

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