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# EFFECTS OF CONCOMITANT ADMINISTRATION OF GINGER EXTRACT WITH SODIUM VALPROATE AGAINST MAXIMAL ELECTROSHOCK AND PENTYLENETETRAZOLE-INDUCED SEIZURES IN LABORATORY ANIMALS

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## ABSTRACT

Sodium valproate is an anticonvulsant used in the treatment of epilepsy, while ginger (*Zingiber officinale*) is a well-known and widely used herb, spice and condiment. Its therapeutic benefits have been utilized in many traditional medicines. It was previously reported to have anticonvulsant effect. In this study, ginger was co-administered with sodium valproate for possible synergistic anticonvulsant effect using maximal electroshock test (MES) and pentylenetetrazole (PTZ) induced seizure models in chicks and mice. Two doses of sodium valproate (100 and 200 mg/kg) were co-administered with different doses of ginger (50, 100 and 200 mg/kg) in chicks and mice. There was no significant synergistic effect in protection against MES seizures but there was significant synergistic effect in protection against pentylenetetrazole induced seizures at doses of 100 and 200 mg/kg of the ginger extract. The results provide a lead for potential benefit of ginger as an adjunct in the treatment of epilepsy.

**Keywords:** *Ginger, Sodium valproate, Pentylenetetrazole, Maximal electroshock, Seizure*

## INTRODUCTION

Epilepsy is a chronic brain disorder characterized by spontaneous recurrent seizures due to abnormal neural excitation in the brain (Shimada et al. 2014). It is thought to be the most common neurological disorder affecting more than sixty five million people worldwide (Katsarou et al. 2017; Lukawski et al. 2018), with about 80% of the affected individuals resides in low and middle income countries like sub-Saharan Africa and Latin America (Espinosa-Jovel et al. 2018). The prevalence has been estimated to be 5–10 per 1000 population (Łukawski, et al. 2018) and the incidence tend to be higher in males than females (Fiest et al. 2017).

Epilepsy is a major public health problem especially in low income countries like sub-Saharan Africa where 75% of the affected people cannot afford the treatment (Espinosa-Jovel et al. 2018), and can cause serious physical and psychological consequences, including premature death, traumatic injury, and mental disorders (Fisher et al. 2005; Ba-

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Diop et al. 2014). Even among those receiving treatment, 30% of them are refractory to the existing antiepileptic drugs (Doeser et al. 2015) and about 30–40% of epileptic patients are affected by numerous adverse effects (Zhu et al. 2014).

Sodium valproate is an anticonvulsant used in epilepsy, bipolar disorder, neuropathic pain and migraine prophylaxis but it is known to cause adverse effects such as gastrointestinal effects, pancreatitis, hepatitis, weight gain and sedation (Carmody and Zawab 2014). The limited efficacy, cost and intolerable side effects of sodium valproate and other antiepileptic drugs are still matters of concern to patients and clinicians (Manchishi 2018). Combinations of two or more antiepileptic drugs of different mechanism of actions may improve efficacy and tolerability in the treatment of epilepsy (Sarhan et al. 2015), but their combinations can also cause harmful interaction. Besides, combination therapy is strongly recommended strategy in the treatment of refractory epilepsy because combination therapy could result in synergistic anticonvulsant effect and minimize adverse effects associated with antiepileptic drugs (AEDs) by lowering their doses (Gavzandarounkola and Sayyah 2016).

Herbal extracts are commonly used in traditional medicine in Africa owing to their easy accessibility, low toxicity, efficacy and affordability (Tambe et al. 2015) and have always been part of epilepsy treatment (Manchishi 2018). Herbal products are candidates to be included in combination therapy of epilepsy due to their considerable safety and lower side effects (Abdel-Wahab and Metwally 2011). Patients using AEDs for the management of epilepsy especially in African rural communities, often take herbal preparations as alternative medicine or in the form of supplements without considering the risk of potential interactions. Generally, AEDs have high propensity to interact (pharmacokinetic or pharmacodynamic) with other drugs including herbal preparations (Landmark and Patsalos 2008). Some of these herbal extracts can be used as adjuvants to AEDs, offering additive or synergistic effects while others can completely prevent seizure on their own (Manchishi 2018). Combination of AEDs with these herbal extracts has the potential of improving the antiepileptic effect.

*Zingiber officinale* (Ginger) is a well-known and widely used herb that possesses health-promoting properties (Ajayi et al. 2013). It is one of the most widely used spice and condiment, an integral part of many traditional medicines, reportedly used for dementia and other diseases (Baliga et al. 2011). The hydroethanolic extract of ginger is reported to have anticonvulsant effects (Hosseini et al. 2016; Hosseini and Mirazi 2014). The present study seeks to evaluate possible additive or synergistic anticonvulsant effects of the combination of sodium valproate and ginger extract.

## MATERIALS AND METHODS

### Collection and identification of Plant material

The ginger (*Zingiber officinale*) rhizomes were collected on 4th November, 2017 from a farm in Kachia, Kaduna State, Nigeria. The plant material was authenticated at the herbarium section, Department of Botany, Ahmadu Bello University, Zaria, Kaduna State, Nigeria by comparing with existing specimen and the Voucher Specimen Number (2099). The plant materials were washed, thinly sliced, dried under shade, size reduced to powder and extracted with water using cold maceration for 24 hours with occasional shaking. The extract was filtered using Whatman filter paper. The filtrate was dried using water bath (45-50$^{o}$C) and the dry extract stored in desiccators and subsequently referred to as “ginger extract”. Fresh aqueous solutions of the extract were prepared for each study.

### Experimental Animals

Swiss mice (18-25 g) of either sex used in the studies were procured and housed in the Animal House of Pharmacology and Therapeutics department, Faculty of Pharmaceutical Sciences, Ahmadu Bello University, Zaria-Nigeria. Day old ranger’s cockerels used in the studies were obtained from National Animal Production Research Institute (NAPRI), Zaria. The animals were kept in standard cages and maintained under standard hygienic conditions, at 27 ± 20c, humidity (60 ± 10 %) with 12 hours day and night cycle, with food and water *ad libitum*. Ethical approval was sought and obtained from Ahmadu Bello University Committee on Animal use and Care (ABUCAUC/2017/021). All experiments were in accordance with the standard protocols of National Institute of Health (NIH, 2015) guidelines for use and care of laboratory animals.

### Equipments and Reagents/Drugs

Pentylenetetrazole, sodium valproate (Sigma-Aldrich), Phenytoin sodium (Sanofi synthelabo, France), Ugobasile electroconvulsive machine (Model 7801, Italy), analytical balance AE240 (Mettler Instrument Corporation, USA) were used in the study.

### Acute Toxicity Study of Ginger Extract

The acute toxicity study was carried out using limit test in accordance with the procedure earlier described (OECD 420). A total of six mice were used for the study. The mice were divided into two groups of 3 mice each for Phase I and Phase II studies. In Phase I and Phase II studies, the mice were administered with the extract at dose of 2,000 and 5,000 mg/kg body weight respectively. Prior to dosing the animals were fasted (food but not water withheld for 3 hours). Administration was in a single oral dose using an oral cannula. The animals in Phase I was observed for 48 hours before proceeding to Phase II.

All the animals were observed individually for 14 days after treatment.

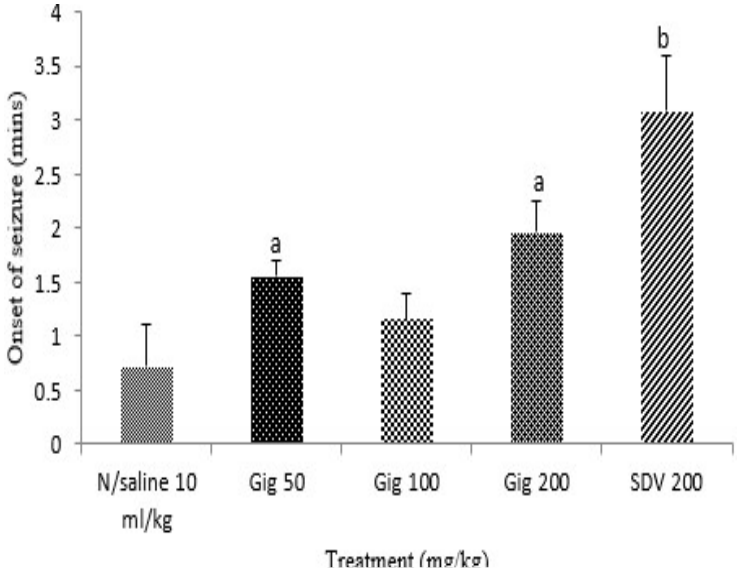


Figure1: Effect of Aqueous Extract of *Zingiber officinalis* (Gig) on Onset of Seizure in Pentylenetetrazole-Induced Seizure in Mice, SDV=sodium valproate, a=p < 0.05, b= p <0.01

**Anticonvulsant Studies**

**Maximum Electroshock-Induced Convulsion in Chicks**

The ginger extract was investigated for anticonvulsant effect using the method of Sayyah et al. (2002). Forty-eight day old cockerels were randomly divided into six groups each containing eight chicks (n=8). One control group received normal saline (10 ml/kg);

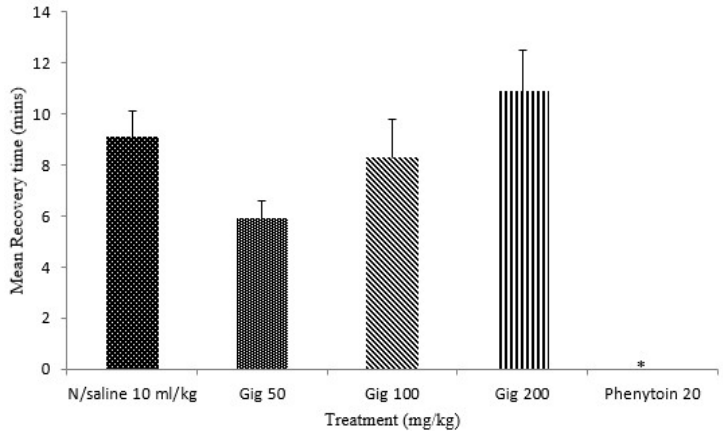


Figure 2: Effect of aqueous extract of Zingiber officinalis (Gig) on mean recovery time in maximal electroshock -induced seizure in mice, *= p<0.01

four other groups received 50, 100, 200 and 400 mg/kg of the ginger extract while the remaining group received phenytoin 20 mg/kg (positive control. All treatments were administered intraperitoneally 30 minutes before maximal electroshock was administered to induce seizure in the chicks using Ugobasile electroconvulsive machine (Model 7801) connected to Claude Lyons stabilizer with corneal electrodes placed on the upper eyelids of the chicks. The shock duration, frequency and pulse width were set and maintained at 0.80s, 200 pulse per second and 0.8 ms respectively with current of 90 mA. Suppression of tonic hind-limb extension (THLE) or increase in latency or onset of the THLE was taken to indicate anticonvulsant activity (Sayyah et al. 2002).

**Pentylenetetrazole-Induced Seizure in Mice**

The method of Swinyard et al. (1989) was employed in this study. Thirty-six mice were divided into six groups, each containing six mice (n=6). The mice in control group received normal saline (10 mL/kg) intraperitoneally; those in treatment groups were administered 50, 100, 200 and 400 mg/kg of the ginger extract while the remaining group received sodium valproate 200 mg/kg (positive control), all intraperitoneally. Thirty minutes post-treatment, the mice in all the groups received pentylenetetrazole 85mg/kg s.c. and were observed over a period of 30 minutes for myoclonic jerks and tonic-clonic convulsion. The onset, recovery time and percentage of protections against tonic-clonic convulsion were observed and recorded.

**Interactive Studies**

**Maximum Electroshock-Induced Convulsion in Chicks**

The method previously described by Sayyah et al. (2002) was used for the study. Seventy-two (72) day old cockerels were randomly divided into nine groups each containing eight chicks (n=8). Two doses of sodium valproate (100 and 200 mg/kg) were co-administered with different doses of ginger extract (50, 100 and 200 mg/kg). One control group received normal saline (10 mL/kg); six other groups simultaneously received combinations of ginger extract and sodium valproate as follows; ginger 50 + sodium valproate 100, ginger 100+ sodium valproate 100, ginger 200 + sodium valproate 100, ginger 50 + sodium valproate 200,ginger 100 + sodium valproate 200, and ginger 200 + sodium valproate 200 while the remaining two groups received only sodium valproate in doses of 100 and 200 mg/kg, all drugs administered intraperitoneally 30 minutes before maximal electroshock was administered to induce seizure in the chicks. The mean recovery time from seizure and percentage protection against hind limb tonic extension seizure (HLTE) were observed and recorded.

**Pentylenetetrazole-Induced Seizure in Mice**

The method of (Swinyard et al. 1989) was employed in this study. Fifty-four mice were divided into nine groups each containing six mice (n=6).The mice in the control group received normal saline (10 mL/kg);

six other groups simultaneously received combinations of ginger extract and sodium valproate as follows; ginger 50 + sodium valproate 100, ginger 100 + sodium valproate 100, ginger 200 + sodium valproate 100, ginger 50 + sodium valproate 200, ginger 100 + sodium valproate 200, and ginger 200 + sodium valproate 200. While the remaining two groups received only sodium valproate in doses of 100 and 200 mg/kg, and all drugs were administered intraperitoneally. Thirty minutes post-treatment, the mice in all the groups received pentylenetetrazole 85 mg/kg s.c. and were observed over a period of 30 minutes for myoclonic jerks and tonic-clonic seizure. The time taken for the onset of clonic seizure, mean recovery time from the seizure and percentage protection against mortality were observed and recorded.

**Statistical Analysis**

Results were expressed as mean ± standard error of mean (mean ± SEM) and percentage protection. The difference between the control and the test groups were analyzed for statistical difference using One Way ANOVA followed by Bonferroni's post hoc t-test for multiple comparisons. Values of $p \leq 0.05$ were considered significant.

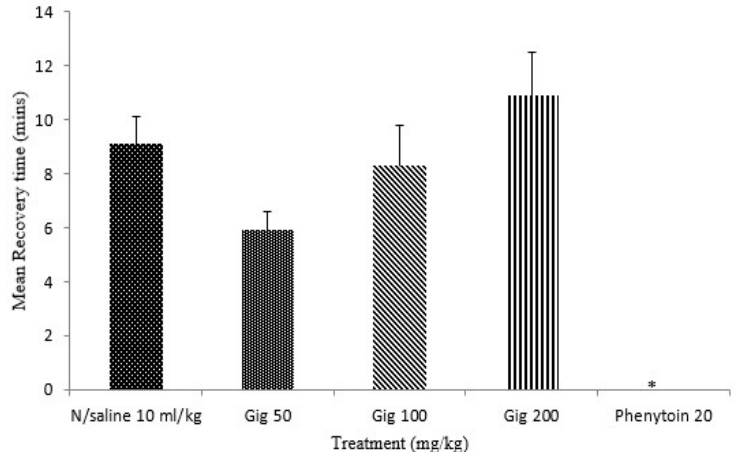


Figure 3: Effect of aqueous extract of *Zingiber officinalis* (Gig) on protection against hind limb tonic extension seizure (HLTE) in maximal electroshock -induced seizure in mice.

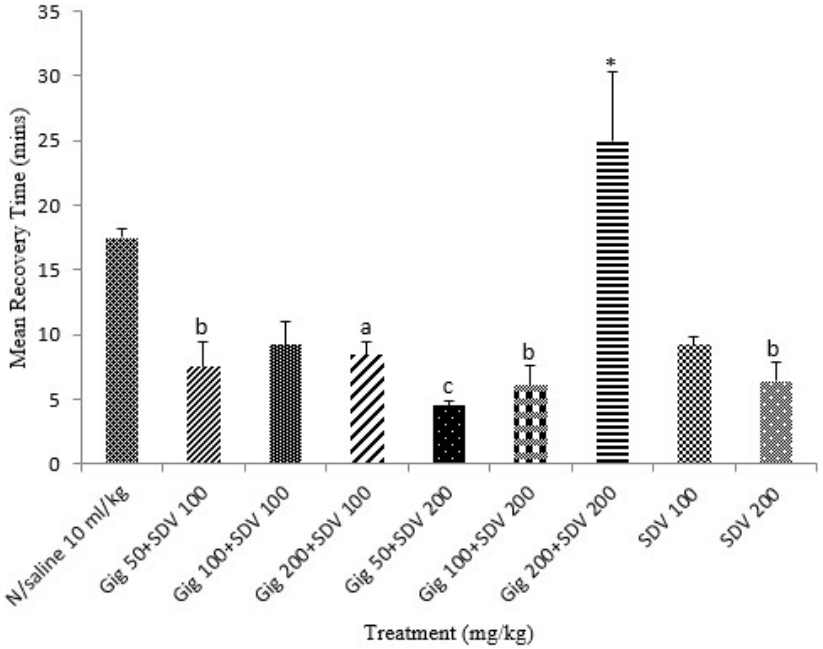


Figure 4: Effects of co-administration of aqueous extract of *Zingiber officinalis* (Gig) with Sodium valproate (SDV) on mean recovery time from seizure in maximal electroshock -induced seizure in Chicks. Mean ± SEM significant at a= $p<0.05$, b= $p<0.01$, c= $p<0.001$ as compared to N/saline, * $p< 0.05$ compared to SDV 200

## RESULTS

**Acute Toxicity Study**

There was no mortality recorded in both the groups of the mice that received 2,000 and 5,000 mg/kg body weight of the extract 48 hours and 14 days after administration.

**Effect of the Extract on Pentylenetetrazole-Induced Seizure in Mice**

The extract at 50 and 200 mg/kg significantly ($p <0.05$) increased the onset of seizure but did not protect against tonic seizure compared to sodium valproate 200 mg/kg which produced 33.33% protection against tonic seizure. Sodium valproate 200 mg/kg also significantly ($p < 0.01$) increased the onset of seizure (Figure 1).

**Effect of the Extract on Maximal Electroshock-Induced Seizures (MES) in Chicks**

The extract produced 37.5%, 25% and 12.5% protection against seizure at doses of 50, 100, and 200 mg/kg body weight respectively but the standard drug (phenytoin 20 mg/kg) produced 100% protection against seizure (Figure 2). However, there was no significant difference in the mean recovery time from hind limb tonic extension seizure (Figure 3).

**Effect of Co-Administration of Ginger Extract With Sodium Valproate on Maximal Electro-Shock-Induced Seizures (MES) in Chicks**

The co-administration of the extract with sodium valproate in the combinations of Gig 50 + SDV 100, Gig 200 + SDV 100, Gig 50 + SDV 200 and Gig 100 + SDV 200 significantly ($p < 0.01$) decreased

mean recovery time from hind limb tonic extension seizure (HLTE) when compared with the normal saline group but not significant when compared with the group that received sodium valproate 200 mg/kg body weight. However, the combination of Gig 200 + SDV 200 significantly ($p < 0.05$) increases the mean recovery time from (HLTE) seizure when compared with the sodium valproate group (Figure 4). The combinations of the ginger extract with sodium valproate; Gig 50 + SDV 100 produced 25% protection, Gig 100 + SDV 100 and Gig 200 + SDV 100 produced 12.5% protection, while Gig 50 + SDV 200, Gig 100 + SDV 200 and Gig 200 + SDV 200 produced 75%, 75%, and 50% protection against (HLTE) seizure. The standard drug (sodium valproate) at the doses of 100 and 200 mg/kg produced 50% and 75% protection respectively against (HLTE) seizure in maximal electroshock-induced seizure in chicks (Figure 5).

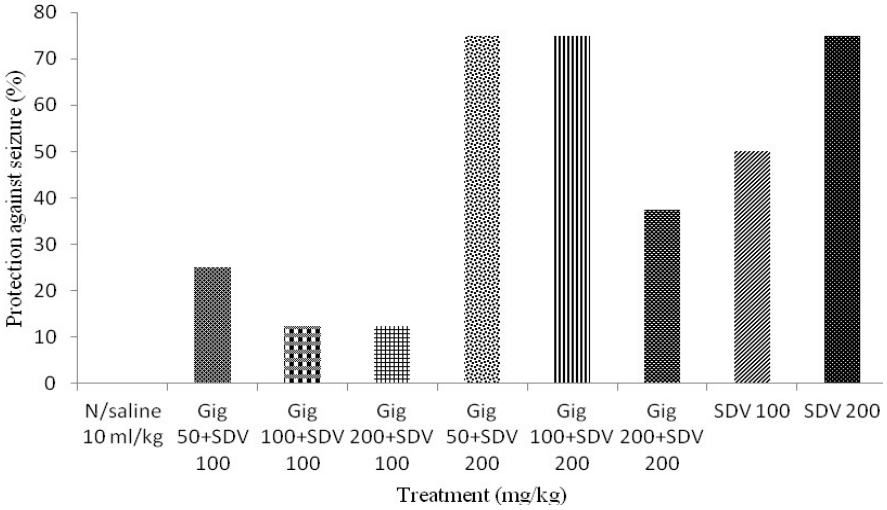


Figure 5: Effects of co-administration of aqueous extract of *Zingiber officinalis* (Gig) with Sodium valproate (SDV) on protection against the hind limb tonic extension seizure (HLTE) in maximal electroshock -induced seizure in mice.

**Effect of Co-Admininis-tration of Ginger Ext-ract with Sodi-um Valproate on Pentylenetet-razole-Induced Seizure in Mice**

The co-administration of the extract with sodium valproate (Gig 100+SDV 200) significantly ($p < 0.05$) prolonged the onset of seizure when compared to normal saline group. There were also significant decreases ($p < 0.05$) in the mean recovery time from tonic seizure when the combination of the extract at 100, and 200 mg/kg with sodium valproate 100mg (Gig 100+SDV 100, Gig 200+SDV 100) were administered compare to the administration of sodium valproate 100mg only. Also, Gig 50+SDV 100, and SDV 100 significantly ($p< 0.05$) prolonged the mean recovery time from tonic seizure when compared with SDV 200 (Figure 6). The co-administration of the extract at 50, 100 and 200 with sodium valproate 100mg (Gig 50+SDV 100, Gig100+SDV 100, Gig 200+SDV 100) produced 33.33%, 66.67%, and 66.67%, protection against mortality respectively as compared to 83.33% produced by SDV 100. However, Gig100+SDV 200 and sodium valproate 200 mg/kg produced complete (100%) protection against mortality (Figure 7).

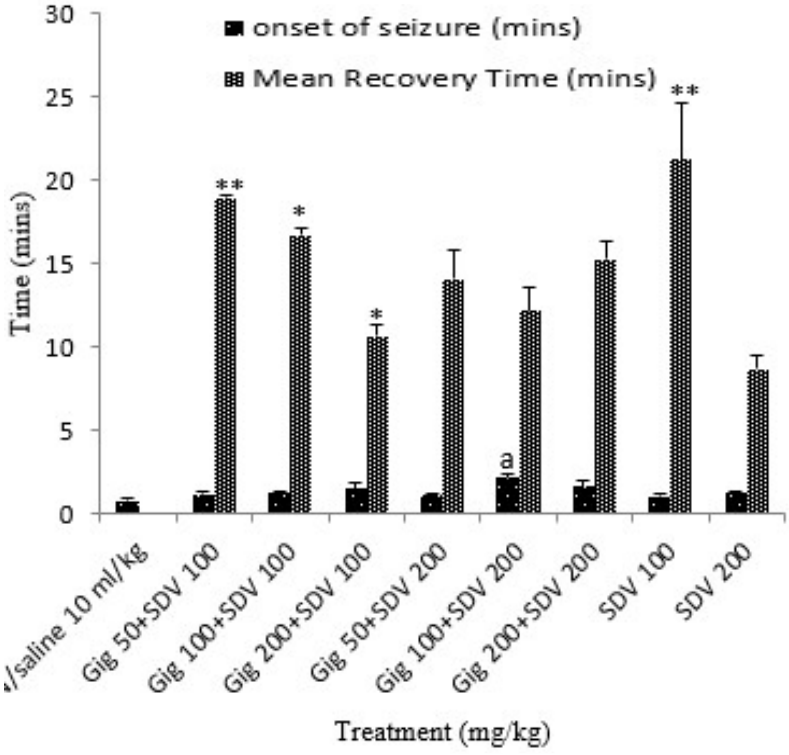


Figure 6: Effects of co-administration of aqueous extract of *Zingiber officinalis* (Gig) with Sodium valproate (SDV) on onset of seizure and mean recovery time in pentylenetetrazole-induced Seizure in mice. Mean ± SEM significant at a= $p<0.05$ compared to N/saline, * $p<0.05$ compared to SDV 100, **$p< 0.05$ compared to SDV 200.

## DISCUSSION

From the results of the acute toxicity study, oral median lethal dose ($LD_{50}$) of the extract might be greater than 5,000 mg/kg and the extract can be categorized as substance of relatively low acute toxicity hazard (OECD, 2001).

The results of the present studies indicate that aqueous extract of *Zingiber officinalis* (ginger extract) possesses anticonvulsant activity in mice and chicks. The anticonvulsant effects of ginger extract observed in this work is in agreement with the previous studies done by (Hosseini and Mirazi 2014; Hosseini et al. 2016). However, in this study different doses of ginger extract were administered 30 minutes before the induction of seizures unlike in the previous studies where ginger extract was administered to the animals 2 hours and 24 hours before PTZ-induced seizure. The observed anticonvulsant effect might be possibly through the interaction of ginger extract with inhibitory and excitatory system, antioxidant mechanisms, oxidative stress and calcium channel inhibition (Hosseini and Mirazi 2014).

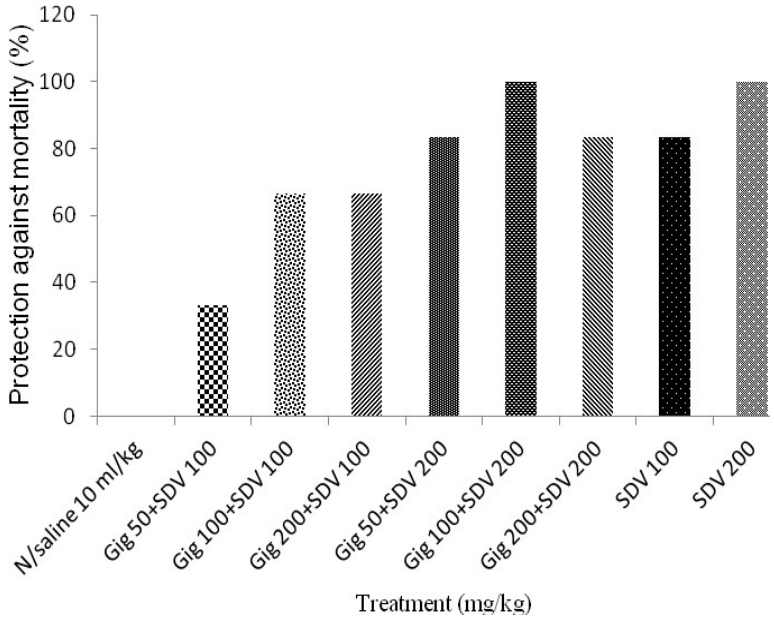


Figure 7: Effects of co-administration of aqueous extract of *Zingiber officinalis* (Gig) with Sodium valproate (SDV) on protection against mortality in pentylenetetrazole-induced seizure in mice.

Pentylenetetrazole (PTZ) is a chemoconvulsant that induce convulsion or seizure by inhibiting the action of GABA at GABAA receptors (Vasconcelos et al. 2007). The increase in the onset of seizure by the extract in the PTZ-induced seizure test is an indication that the extract may exert its effect by enhancing GABAergic neurotransmission at GABAA receptors. However, sodium valproate at 200 mg/kg produced a protection against PTZ-induced seizure and the effect produced by sodium valproate is better than that of the extract. Sodium valproate produced its anticonvulsant effect by blocking voltage-dependent sodium channels, facilitating the inhibitory effects of gamma-aminobutyric acid (GABA), and reduces low threshold (T-type) calcium currents for seizure (Macdonald and Kelly 1995).

Maximal electroshock induced-seizure model of epilepsy represents tonic-clonic type of seizure (grandmal seizure). In this study, ginger extract at the lower doses produced moderate protection against tonic-clonic seizure but as the doses increases, the protection becomes weaker. However, phenytoin 20 mg/kg (the standard drug used) produced complete protection against tonic-clonic seizure in all the animals tested compare to ginger extract that produced complete seizure protection in less than half of the animals tested. Phenytoin produced its anticonvulsant effect by reducing neuronal excitability through blocking or inhibition of voltage-gated sodium and calcium channels (Deshmukh et al. 2011). There was a decrease in mean recovery time from seizure in the animals that received ginger extract at the low dose but not significant. The moderate protection against hind limb tonic-clonic extension by ginger extract in this study indicates that the extract can inhibit or prevent seizure discharge within the brain stem seizure substrate (Browing 1992). Thus, it may be beneficial to epileptic patients in increasing seizure threshold, decreasi-ng the severity and frequency of myoclo-nic or tonic-clonic seizure at lower doses.

The co-administration of AEDs such as sodium valproate with herbal extracts can increase the potential for interactions; synergism or potentiation and side effects due to enzyme induction and/or inhibition (Kr et al. 2014). Previously, Ginkgo biloba was reported to enhance the anticonvulsant and neuroprotective effects of sodium valproate (Abdel-Wahaband Metwally, 2011). In this study, the co-administration of sodium valproate and ginger extract in both maximal electroshock-induced seizure and PTZ-induced seizure test in the animals though significantly increased the onset of seizure but did not produce a synergistic anticonvulsant effects. The results of this study shows that at lower doses combination of sodium valproate and ginger extract, there were better protection against seizure than at higher doses. Probably, using lower doses combin-ations could have produced better anticonvulsant effect. Besides, sodium valproate like other AEDs is known to have complex interaction with other drugs through enzyme induction or inhibition (Kr et al. 2014). The interactions could also occur at the level of drugs absorption, distribution, metabolism or excretion (pharmacokinetic interactions) or at the site of action (pharmacodynamic interaction). Effects of such interactions could be additive, synergistic or inhibitory to the anticonvulsant activity of sodium valproate.

Sodium valproate is metabolized by the liver cytochrome $P_{450}$ enzymes. Any altered metabolic capacity of these enzymes by another drugs or substrates by induction or inhibition would affect its anticonvulsant

effects (Landmark and Patsalos 2008). It is possible that concomitant administration of sodium valproate and ginger extract in this study resulted in pharmacokinetic interactions at the level of metabolism. Ginger extract could function as cytochrome $P_{450}$ substrates, resulting in the inhibition or induction of the metabolizing enzymes for sodium valproate. Such enzyme induction could lead to increase in the clearance of sodium valproate which could reduce its therapeutic effect (Gorman 2012).

However, the inhibition of the metabolizing enzymes for sodium valproate by ginger extract could delay its clearance, prolong its effect and cause toxicity.

Herbs are generally known to be multi-component products, containing therapeutically active ingredients and excipients (Izzo 2012). Previous studies show that ginger contains over 400 different compounds (Prasad and Tyagi 2015) and the major constituents in ginger rhizomes are carbohydrates, lipids, terpenes (zingiberene, β-bisabolene, α-farnesene, β-sesquiphellandrene, α-curcumene), and phenolic compounds like gingerol, paradols, and shogaol (Prasad and Tyagi 2015; Grzanna et al. 2005). The anticonvulsant activity of ginger extract might be attributed to the presence of one or some of these bioactive compounds. More so, any of these active compounds in ginger rhizome could be responsible for the pharmacokinetic interaction with sodium valproate altering its plasma concentration, absorption and metabolism.

Similarly, the inhibition or induction of drug transporters like P-glycoprotein (P-gp) by co-administered drugs, or herbal constituents may result in pharmacokinetic interactions leading to unexpected toxicities or under treatment (Marchetti et al. 2007). In this study, it is possible that one or some of the constituents of ginger extract acted as transporter substrates resulting in induction of P-gp thereby reducing the plasma concentration of sodium valproate hence decrease in anticonvulsant effect. The nature of the interaction in this study could also be in the form of pharmacodynamic interaction due to altered sensitivity at site of action occasioned by the concomitant administration of sodium valproate and ginger extract thus resulting in decrease effect instead of additive or synergistic anticonvulsant effect (Gorman, 2012).

Pharmacodynamic interactions between sodium valproate and other drugs can have potentially beneficial effects, such as the therapeutic synergism of valproic acid combined with lamotrigine, or adverse effects, such as the reciprocal potentiation of neurotoxicity when combined with sodium channel blocking antiepileptic drugs (Zaccara and Perucca, 2014). In this study, co-administration of sodium valproate with ginger extract did not significantly enhances its anticonvulsant effect (synergism) but rather the extract at high doses reduces its effect.

**Conclusion**

Findings from this study suggested the potential benefit of ginger as an adjunct to sodium valproate in the treatment of epilepsy but concomitant administration of sodium valproate and ginger extract.

**Acknowledgements**

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**Conflict of Interest**

None declared.

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