Chapter 3

AIMS AND OBJECTIVES
Seizures are a result of a shift in the normal balance of excitation and inhibition within the central nervous system (CNS). Stroke, trauma, tumors, stress, hypoxia and infections may alter the basal levels of prooxidants, antioxidants, neurotransmitters and electrolytes, thereby making the brain more susceptible to seizures. Neuropharmacologists and clinicians have investigated the role of oxidative stress in various animal models of epilepsy and in epileptic patients. A few of the antiepileptic drugs (AEDs) have been evaluated for their efficacy in presence of antioxidants. However, there is also a need for isobolographic analysis of drug interactions between AEDs and antioxidants. Therefore, the present drug interaction study of phenytoin (PHT) and sodium valproate (SVP) with N-acetylcysteine (NAC) was undertaken.

Histamine plays an important role in the pathophysiology of epilepsy. Receptor and non-receptor mechanisms are involved in the anticonvulsant effects of clobenpropit (a H3 antagonist). Its effect on histidine decarboxylase (HDC) is an example of the latter. Clinically, neonatal seizures are effectively treated with pyridoxine (an activator of decarboxylase). Therefore studies were also designed to evaluate the combined effects of clobenpropit with pyridoxine.

In view of an important role of calcium ions in the pathophysiology of epilepsy, in vitro studies were designed to find out the levels of intracellular calcium [Ca$^{2+}$] in synaptosomes.
AIMS AND OBJECTIVES

1. To analyze the nature of interactions of PHT and SVP with NAC in the mouse maximal electroshock (MES) test.

2. To assess the effects of PHT, SVP, NAC and their combinations on grip strength and memory in mice.

3. To investigate the effect of MES induced seizures on the content of reduced glutathione (GSH) and malondialdehyde (MDA) in the cerebral cortex of mice and to assess the modulating actions of PHT, SVP, NAC and their combinations on these parameters.

4. To evaluate the effects of PHT, SVP, NAC and their combinations on serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), alkaline phosphatase (ALP) and calcium levels.

5. To study the role of brain histamine in the effects of PHT, SVP, NAC and their combinations against MES induced seizures.

6. To investigate the effects of clobenpropit, pyridoxine and their combinations on MES induced seizures.

7. To study the role of brain histamine in the effects of clobenpropit, pyridoxine and their combinations against MES induced seizures.
8. To evaluate the effects of PHT, SVP and NAC on $[\text{Ca}^{2+}]_i$ levels in mouse brain synaptosomes.

9. To evaluate the effects of histamine $H_3$ receptor ligands (clobenpropit, imetit) and pyridoxine on $[\text{Ca}^{2+}]_i$ levels in mouse brain synaptosomes.