CHAPTER 5

Objectives Of The Study
AIMS AND OBJECTIVES OF THE STUDY

Ischemic strokes are more prevalent making up approximately 87% of all cases and have been the target of most drug trials. Thrombosis, embolism or systemic hypo-perfusion, all of which result in restriction of blood flow to the brain, can cause an ischemic stroke, which results in insufficient oxygen and glucose delivery to support cellular homeostasis.

Reperfusion defines the restoration of blood flow to an ischemic area and supply of oxygen and metabolic substrates to starved tissues. Reperfusion is the goal of most clinical therapies for cerebral ischemic injury. Unfortunately, the benefits of reperfusion are mitigated by secondary injury to the penumbra, which is in part, related to acute and prolonged inflammatory events. This secondary injury is called I/R injury. It has been paid further attention.

Cerebral ischemia/reperfusion injury is severe and causes mortality and long lasting disability in adults across the globe. Ischemia and reperfusion occurs in various clinical conditions relevant to adults, including myocardial infarction, stroke and circulating shock as well as surgical interventions like organ transplantation and cardiopulmonary bypass.

Reperfusion injury is the brain damage caused by the return of blood flow, resulting in progression of vasogenic edema, hemorrhagic transformation, and an increase in stroke volume. Reperfusion injury of the central nervous system (CNS) may contribute to the morbidity and mortality of stroke, head
trauma, carotid endarterectomy, aortic aneurysm repair and deep hypothermic circulatory arrest.

A good number of neuroprotective pharmacological agents only proved to be effective when applied before the ischemic insult and are less effective or not effective at all when given later in time, i.e. during ischemia or reperfusion. Recent studies suggest that pyrimidine derivatives that has been shown to inhibit lipid peroxidation in biological membrane. Pyrimidine derivatives can protect the brain by their ability to modulate intracellular signals promoting cellular survival. Pyrimidines have received much attention of researchers because of their vasodilator and antioxidant properties in the recent years. Studies on cerebroprotective mechanism of pyrimidine derivatives on cerebral ischemia reperfusion injury are limited. Hence in the present study two pyrimidine derivatives were evaluated for their cerebroprotective activity and the possible underlying mechanisms.

**OBJECTIVES OF THE PRESENT STUDY ARE AS FOLLOWS**

- To evaluate the cerebroprotective actions of pyrimidine derivatives against ischemia reperfusion induced cerebral infarction in rats
- To establish the mechanisms involved in the cerebroprotective actions of pyrimidine derivatives against I/R injury in rats. The following mechanisms were studied in the present investigation.
  - To study the antioxidant role of pyrimidines in the cerebroprotection by estimating lipid peroxidation marker (tissue malondialdehyde (MDA))
and antioxidant enzymes (superoxide dismutase (SOD), catalase (CAT) in brain tissue) in rats subjected to ischemia reperfusion injury.

- To study the anti-inflammatory role of pyrimidines in cerebroprotection by estimating myeloperoxidase (MPO), tumor necrosis factor alpha (TNF-α) and Interleukin-10 (IL-10) in brain tissues of rats subjected to I/R injury.