Chapter-I

Introduction
Stroke remains one of the major devastating among neurological diseases, often causing death or severe long-term disability with astronomical financial repercussions on health systems across the globe (Mukherjee and Patil, 2011; Nijasri and Walter, 2007). According to the World Health Organisation, over 15 million people a year, equating to one in every 400 people, suffer a stroke worldwide, out of which approximately 33.3% die and among the survivor 50% are left with permanent disabilities, placing a burden on family and community. (Broderick JP. 1998; Tuhrim S. 2002 Mackay and Mensah, 2004). The prevalence of people affected are over the age of 65 years, but all ages are at a risk of having a stroke (Mackay and Mensah, 2004). Clinical features of stroke include hemiplegia, movement disorders, somatosensory impairments, spatial neglects, learning and memory, and tactile extinction (Cenci et. al., 2002). Due to its huge socioeconomic burden, with overall increases in life expectancy, one can predict that stroke will continue to be a tremendously challenging disease (Durukan and Tatlisumak, 2007).

The two main types of stroke are ischemic and hemorrhagic. Approximately 85% of all stroke is ischemic in nature characterised by the sudden interruption of cerebral blood flow (CBF), results from thrombolic or embolic occlusion of a major cerebral artery, most often the middle cerebral artery (MCA) or its branches (Brott and Bogousslavsky, 2000; Durukan and Tatlisumak, 2007). The remaining 15% are hemorrhagic stroke which result from a burst blood vessel in the brain or on its surface (Richard Green et al., 2003). Cerebral ischemic/reperfusion injury can be characterized into two distinct regions, the infarct core and penumbra (Liu et al., 2012). In general, the infarct core is an area with severe occlusion of blood flow, rapid excitotoxicity, necrotic cell death and irreversible neuronal cell damage (Tang et al., 2007). Whereas penumbra is the area surrounding the infarct core and receives marginal circulation (between 10 and 20 ml/ 100g/ min) from collateral blood vessels (Ginsberg and Pulsinelli, 1994). The penumbra originates from delayed cell death by apoptosis and necrosis and the ischemic injury depends initially on the extent, severity, and duration of the perfused deficit. The degree of ischemia is also determined by the distribution of collateral blood vessels (Tang et al., 2007).

Cerebral ischemia triggers a cascade of pathophysiological mechanisms that lead to ischemic cell damage. Among the pathophysiological changes that are postulated to occur (Fig. 1.1) as a consequence of ischemia are free radical productions (Chan, 1996, 2001), excitotoxicity (Arundine & Tymianski, 2004), disruption of ionic influx, enzymatic changes, stimulation of the inflammatory process (Allan & Rothwell, 2001; Del Zoppo, 2009), endothelin release, activation of platelets and leukocytes, endothelial dysfunction and apoptosis (Shin et al., 2006; Mehta et
al., 2007; Ozbal et al., 2008; Yousuf et al., 2009). All of these pathophysiological reactions contribute to the brain injury following the onset of cerebral ischemia.

Fig. 1.1 Schematic flow chart of the mechanisms of cerebral ischemia injury

Restricted blood supply as a consequence of cerebral ischemia leading to reduced availability of glucose and oxygen in the territory of affected vascular bed that brings to all brain cells is loss of the energy substrates and thereby causing cellular energy crisis by slows or stops the synthesis of ATP through glycolysis and oxidative phosphorylation (Sims and Muyderman, 2010; Yang et al., 2000). This shortage of ATP is insufficient to maintain the cellular homeostasis and basic neuro-function, such as sodium-potassium ATPase ($Na^+-K^+$ATPase). Subsequently, inhibition of $Na^+-K^+$ ATPase will lead to loss of ionic gradients and membrane depolarization in both neurons and surrounding cells like astrocytes (Won et al., 2002). This results in increased release of neurotransmitters particularly glutamate from the presynaptic terminals, within 1–2 min after the onset of ischemia. A massive release of excitatory amino acid activates the glutamate receptors and NMDA receptors, leading to membrane depolarization. When NMDA receptors are over stimulated with excess glutamate, it causes a massive influx of $Ca^{2+}$ and thus plays a crucial role in calcium overload (Choi, 1992). The accumulation of intracellular calcium levels play a pivotal role to irreversible neuronal death by
activating several destructive (catabolic enzymes) enzymes (Kristian and Siesjo, 1998; Kirino, 1982) such as proteases, phospholipases, protein kinases, protein phosphatases, endonucleases, ROS generation, mitochondrial Ca$^{2+}$ overload and mitochondrial dysfunction (Nagahiro et al., 1998). Elevated levels of intracellular calcium causes rapid hydrolysis of phospholipids, which results in the accumulation of lysophospholipids (LPLs), diacylglycerides (DAGs) and free fatty acids (FFAs), which degrade cellular structure via the activation of phospholipases (Siesjo, 1993). However, activation of proteases such as calpains can degrade the neuronal skeleton, resulting in membrane blebbing, depolymerization of microtubules and inhibition of axonal transport (Schlaepfer and Zimmerman, 1985).

**Aims and Objectives**

Despite increases in knowledge about pathophysiological mechanisms that occur following cerebral ischemia, it has been a major challenge to develop effective therapeutics strategies for stroke. Even though enormous efforts have focused on the development of drugs to limit ischemia/repurfusion damage caused by acute ischemic stroke. There is as yet no single effective accepted protocol available for the prevention or treatment of cerebral stroke. Fibrinolysis is the only approved and accepted therapy against stroke. However, thrombolytic therapy (Aspirin and tissue-plasminogen activator (rt-PA) is restricted to patients who meet strict eligibility criteria, including a tight 3-hour therapeutic time window (Alberts, 1998, Horn and Limburg, 2001). In recent years considerable attention has been devoted to the approach of neuroprotection by naturally occurring agents as a newer dimension in the management of stroke prevention. Many naturally occurring agents have shown preventive potential as a protective measure for cerebral stroke in a variety of bioassay systems and animal models, having relevance to human disease.

**The study has been done with the following objectives:**

- To study the neurobehavioral, neurochemical, immunohistochemical and histopathological changes associated with cerebral ischemia.
- To study the protective role of some herbs/ herbal drugs/ chemicals/ polymeric nanoparticles on neurobehavioral, neurochemical, immunohistochemical and histopathological changes associated with cerebral ischemia.

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