CHAPTER 1

INTRODUCTION

Perpetual research in the field of drug discovery and research has not been able to provide a permanent solution to the problems faced in the treatment of multifaceted and life-threatening diseases such as cancer and Alzheimer's disease. An alarming rise in a number of cancer patients, as revealed by cancer statistics 2016 (Siegel *et al.*, 2016), warrants fresh insights into the field of rational drug research and design to find the missing link. Cancer is a multifactorial process causing behavioral and metabolic alteration resulting in excessive proliferation with the weakening of immune system (Hussain *et al.*, 2003). Various strategies have been formulated for drug synthesis targeting specific genes through therapies in the recent years. The various treatment strategies depend up on the type of cancer, localization of metastasis, age of patient, and size of the cell (Arap *et al.*, 1998). Failure of numerous synthetic and natural drugs may be attributed to weak understanding of mechanism of action of different drugs to produce the desired therapeutic response. In complex diseases such as in cancer, numerous gene networks and receptors get interlinked playing a significant role in such diseases. The phenomenon of cross-talk among different proteins and their adapter molecules makes it hard to hold any single pathway responsible, as more than one pathway might be leading to a debilitating condition (Vogelstein *et al.*, 2004). In such a scenario, an understanding of the various signaling mechanisms operating in healthy and diseased state, becomes of paramount importance. This has given rise to the desperate need to find lead molecules from natural products that can be utilized for rational drug design and the subsequent synthesis (Newman *et al.*, 2007). This is more so in the case of cancer where at times multiple signaling cascades need to be targeted for effective recuperation. In the signaling pathways, stimulated receptors get phosphorylated resulting in the activation of the signaling cascade. One such important receptor is the Receptor Tyrosine Kinase (RTK), a high-affinity cell surface receptor, regulating the physiology of healthy and tumor cells (Cadena *et al.*, 1992). When a ligand binds to this receptor, it stabilizes the receptor dimerization which causes tyrosine trans-phosphorylation and initiates a downstream signaling cascade in normal cells

(Lemmon *et al.*, 2010). Any aberration in the molecules involved in normal signaling pathway may convert healthy cells into cancerous. Activation of phosphoinositide 3-kinase (PI3K) is an important function of RTK (Schlessinger, 2000). PI3K belongs to lipid kinase family responsible for intercellular signaling regulating diverse cellular functions. PI3K activation, along with mTOR and Akt, leads to activation of numerous downstream signals (Kuruvilla *et al.*, 1999). Under RTK stimulation, the intrinsic or extrinsic pathway in apoptosis may get activated and decides the fate of the cell. Apoptosis is a highly complex process modulating cancer signaling cascade with the involvement of caspases, Bax, Bcl-2, and matrix metalloproteinases (MMPs) (Taylor *et al.*, 2008). Literature highlights the role of a number of triterpenes such as celastrol, pristimerin, ursolic acid, platycodin D in PI3K/Akt/mTOR signaling pathway. Medicinal mushrooms such as *Antrodia camphorate, Cordyceps, Albatrellus confluens, Phellinus linteus, Omphalotus illudens*, and *Psilocybin* mushrooms are known for their potency to exhibit anticancerous properties (Wasser, 2014). Triterpenes are mainly known to target the (NF-κB), STAT3 or PI3K/Akt/mTOR pathways (Yeh *et al.*, 2010). Even though mushrooms such as *G. lucidum* have been explored for their potent anticancerous properties, studies exploring their role in PI3K/Akt/mTOR pathway and apoptosis are yet to be carried out. *G. lucidum* and its constituents are known to modulate the phosphorylation of extracellular signal-regulated kinase (ERK1/2), PI3K or Akt (protein kinase B) (Stanley *et al.*, 2005). The current research work is being put forward with an aim to determine the therapeutic potential of this medicinal mushroom, *G. lucidum*, and association of its bioactive constituents in cancer signaling pathways.