Chapter 1

Introduction

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Magnaporthe oryzae (Hebert) Barr (anamorph, *Pyricularia oryzae* Cav. or *Pyricularia grisea*) causes the rice blast disease (Wu et al. 2006). *M. oryzae* is a hemibiotrophic, ascomycetous fungus that has been reported to infect more than 50 grass species (Pennisi 2010). Rice blast disease is one of the most devastating of all cereal diseases worldwide and causes harvest losses of 10-30 % of the global rice yield annually (Talbot 2003). Control of this fungal disease remains a major challenge and hence there is need to identify antifungals selectively acting on novel targets.

Anacardic acid (6-pentadecylsalicylic acid) is a bioactive phytochemical found in the nutshell of *Anacardium occidentale* , an angiosperm belonging to the Anacardiaceae family. Traditionally, it has been used as medicine for treatment of gastric ulcers and stomach cancers (Acevedo et al. 2006). Studies reveal that anacardic acid exhibits antimicrobial (Muroi and Kubo 1996), antioxidant (Trevisan et al. 2006) and highly selective antitumor activities (Wu et al. 2011). Anacardic acid is well known for inhibiting histone acetyltransferases (HATs) and has been reported to inhibit p300 and PCAF histone acetyltransferases in vitro. HAT proteins like Tip60 are involved in DNA damage repair process making cells resistant to apoptosis but inhibition of these proteins by anacardic acid makes these cells vulnerable to DNA damaging agents (Sun et al. 2006). Anacardic acid also inhibits catalytic activity of matrix metalloproteinase-2 and matrix metalloproteinase-9 which may be the reason for some of its therapeutic actions (Omanakuttan et al. 2012).

Cell death can be broadly classified into apoptosis and necrosis. Apoptosis is programmed and carefully regulated through many regulatory proteins, while necrosis is believed to be disordered and mostly induced by physical or chemical injuries. Apoptosis or programmed cell death (PCD) is a morphological and biochemical process in which cells commit suicide by activation of intracellular death machinery. Apoptosis is a ubiquitous characteristic of

most of living organisms and has been described in bacteria, plants and animals (Ramsdale 2008). In the past two decades, apoptosis like cell death has been demonstrated in *Saccharomyces cerevisiae* (Madeo et al. 1997) and some of the filamentous fungi (Hamann et al. 2008). Evidence suggests that programmed cell death has existed in unicellular organisms even before evolutionary separation between fungi, plants and animals (Madeo et al. 2002). Apoptosis like cell death has also been demonstrated in filamentous fungi including *Neurospora crassa* (Marek et al. 2003), *Aspergillus nidulans* (Cheng et al. 2003), *Aspergillus fumigatus* (Mousavi and Robson 2004), *Fusarium oxysporum* (Ito et al. 2007) and *Rhizoctonia solani* (Qi et al. 2010). It has also been reported that mild concentrations of hydrogen peroxide induce apoptosis like cell death in *M. oryzae* (Xiao et al. 2011). In fungi, various factors including physical and chemical stress including antifungal compounds have been reported to induce apoptosis-like cell death (Sharon et al. 2009). Apoptosis follows two major pathways; known as the extrinsic and intrinsic pathways, the former is initiated by extracellular ligands and the latter is activated by cell damage or during various developmental stages. So far, there is evidence only for components of intrinsic apoptotic pathway in fungi. However, it is not very clear whether the extrinsic pathway is on the whole missing in fungi or it is regulated by a different set of unidentified proteins (Sharon et al. 2009). In the present study, we demonstrate that the antifungal activity of anacardic acid would be due to induction of apoptosis like cell death. A better understanding of cell death pathways can provide the basis of developing novel antifungal molecules.