CHAPTER 1 INTRODUCTION

1.1. Background

Cancer is considered to be an increasingly threatening disease, affecting people of all ages. Cancer is defined as a disease made up of billions of cells, all originating from an initial cell which multiplies clonally, escapes to apoptosis and accumulates genetic (and/or epigenetic) alterations which converge into a neoplastic cell (Trosko 2001). Among non-communicable diseases, it is the second most cause of death among the global population after cardiovascular diseases (Huff 1994; Wiesburger 1999). According to WHO, about 7.6 million people were died due to cancer in 2008 (WHO 2013). It is estimated that by the year 2020 there will be almost 20 million new cancer cases. Siegel et al. (2013) have reported that there will be a total of 16,60,290 new cancer cases and 5,80,350 cancer deaths were projected to occur in the United States in 2013. The magnitude of the problem of cancer in the Indian subcontinent is alarming. In India, it has been estimated that the total number of cancer cases would rise up from 9,79,786 cases in the year 2010 to 11,48,757 cases by the year 2020 (Takiar et al. 2010). The rate of incidence of cancer in India is less than that of the Western countries but due to large population size, the number of cases is more prevalent at any time (Krishnan and Sankaranarayanan 1991). On the whole, cancer is said to be one of the major health problems in India.

Globally there are more than 100 different types of cancer and cancer is considered to be a ‘silent killer disease’ since its symptoms remains to be silent till the disease reaches its advanced stages. It is also lifestyle related, have a long latent period and need specialized infrastructure and human resource for treatment. Despite significant advances in medical technology for
its diagnosis and treatment, it is perhaps the most progressive and devastating disease posing a threat of mortality to the entire world. It bids a big challenge to the oncologists and researchers for treating this disease.

One of the very important treatment strategies of cancer is chemotherapy, a treatment using anticancer drugs. It can be offered alone and also in conjugation with other treatments like surgery and radiation therapy. Nowadays, a vast array of chemotherapeutic drugs is available as a result of extensive research in cancer treatment. Among which, cisplatin (cis-dichlorodiammineplatinum (II)) is considered to be one of the most effective anticancer agents widely used in the treatment of various solid tumors. This cytostatic agent has been used for more than 30 years in the treatment of a wide spectrum of tumours. This platinum containing drug acts and kills cells mainly by damaging DNA and inhibiting DNA synthesis (Basu and Krishnamurthy 2010).

The antitumor activity of cisplatin is believed to be due to its interaction with chromosomal DNA (Liu et al. 2013). Upon treatment, it increases reactive oxygen species (ROS) production and thereby causes an abnormal change in the redox status of cancer cells. ROS production also enhances the sensitivity of cells to cisplatin. Apoptosis in cisplatin treated cells is accomplished by changes in ROS levels, changes in redox status, DNA damage, mitochondrial membrane potential changes and involvement of signaling pathways. Cisplatin-induced apoptotic pathways are complicated, as cisplatin might cause different stresses, such as DNA damaging and oxidative stresses. Various cisplatin induced stress signals can activate each pathway through specific transcription factors that act as the ultimate drug targets. Signaling pathways that regulate apoptosis have significant impact on deciding cellular responsiveness to cisplatin (Torigoe et al. 2005; Kelland 2007; Basu and Krishnamurthy 2010).
Despite its advantages, the success of cisplatin therapy is compromised due to dose-limiting toxicity as well as resistance by tumor cells to cisplatin. These two factors (cisplatin resistance and toxic side effects) remain to be the major obstacle to successful chemotherapy but cisplatin is still used with curative intention, mainly for the treatment of various malignancies such as ovarian, testicular, head and neck, bladder, oesophageal and small cell lung cancer. Cellular resistance to cisplatin could be either intrinsic or acquired (Osman et al. 2000).

Therefore, exploring alternative therapeutic modalities is necessary to overcome drug resistance and dose-limiting toxicity in cisplatin treatment. Since several years, new strategies have been developed to limit the appearance or the development of cancers through chemosensitization to conventional therapies. Co-administration of phytochemicals with strong anticancer activities would help in fixing the problem of cisplatin resistance and host toxicity. Since, the main target for cisplatin in the cell is believed to be DNA and an enhanced antitumour effect is expected from a new combination of cisplatin with a chemosensitizer (Marcu et al. 2003). In the recent past, polyphenols are emerging as potential candidates among phytochemicals which can act as chemosensitizers.

Polyphenolic compounds constitute one of the most numerous groups in the plant kingdom and can be divided into various classes on the basis of their molecular structure, with flavonoids being one of the main groups (Watson et al. 2000; Wenzel et al. 2000). Evidences suggest the use of polyphenols in sensitization of tumor cells to cell death. The chemosensitizing effects of polyphenols could provide a novel strategy to enhance the efficacy of anticancer therapy in combination with chemotherapeutic drugs such as cisplatin. Polyphenols are said to be strange molecules because it can behave both as prooxidants and antioxidants depending upon the cell environment.
They act as prooxidants in cancer cells which could be a contributing factor for cancer cell killing. At the same time they could act as antioxidants in normal cells which would help in the protection of normal cells against the toxicity of chemotherapy drugs. Hence, these plant polyphenols may enhance the tumoricidal effects of chemotherapy and protect normal cells from therapy-induced damage, and increase systemic bioavailability of chemotherapeutic agents (Garg et al. 2005).

Ferulic acid (3-methoxy-4-hydroxycinnamic acid, FA) is a dietary polyphenol that occurs primarily in the seeds and leaves of most plants such as rice, wheat, barley, oat, roasted coffee, tomatoes and citrus fruits. It is one of the highly abundant polyphenols in dietary sources. FA is used in a wide range of cosmetics, such as skin lighteners, sunscreens, anti-aging creams and moisturizers. FA exhibited antioxidant, antihyperlipidemic, hypotensive, antimicrobial, anticarcinogenic, antimelanogenic, radioprotective, antiproliferative and antimetastatic properties in variety of cancer cell lines and animal models. FA, being a polyphenol, has both antioxidant and prooxidant activities (Murukami et al. 2008; Nyaradzo et al. 2009; Karthikeyan et al. 2011). FA also exhibited chemotherapeutic and radiosensitizing properties. Several studies by Sudheer et al. (2007), Srinivasan et al. (2007), Alias et al. (2009) and Bandugula and Prasad et al. (2012) have proved that FA protected both normal cells (in vitro) and animal models (in vivo) against the action of carcinogens and toxic chemicals. Therefore, the dietary polyphenol FA could be employed in chemotherapy to potentiate the action of chemotherapy drugs.

1.2. Rationale of the study

Combining cisplatin with other drugs or chemicals seems to be effective in chemotherapy. The recent research in cancer treatment was in
search for a chemosensitizing agent (preferably from plant origin) which can increase the effect of an anticancer drug and also decrease its side effects.

1.3. **Hypothesis**

The hypothesis of the present study was formulated as ferulic acid, a dietary polyphenol may sensitize cancer cells for cisplatin chemotherapy and protect normal cells from therapy induced damage.