CHAPTER II

LITERATURE REVIEWS

Doxorubicin (hydroxyl daunorubicin) consists of four fused rings and positively charged amino sugar. It is an antracycline antibiotic which can be isolated from streptomyces peucetius var. caesius bacterial. Doxorubicin is considered as a commercial drug used in cancer chemotherapy including hematological malignancies, leukemias, scormas, germ cell tumors and carcinomas. The molecular mechanisms have been reported to kill the cancer cells and are classified in three ways;

(i) inserting and bonding into the strands of genetic material (DNA) resulting in inhibition of preventing the cancer cells from making genetic material (DNA and RNA) and proteins.

(ii) interfering with an enzyme called topoisomerase II, which is involved in DNA replication, resulting in the inhibition of stopping cancer cells from growing and multiplying.

(iii) free radicals are formed whose molecules are capable of damaging cancer cells.

Cisplatin, cisplatinum, or cis-diamminedichloroplatinum is a chemotherapeutic drug. It was discovered as a first member of a class of platinum-containing anti-cancer agents including carboplatin and oxaliplatin. These agents react *in vivo* binding and cause crosslinking of DNA, which ultimately triggers apoptosis (Einhorn et al., 1990).

Multiple-drug resistance (MDR) is the major clinical obstacle in cancer therapy such as DU-145 and NCI/ADR-RES cell lines. These cells can be intrinsic, but they are a failure of responses of the first phase of chemotherapy or failure of the second one.

In either case, however, tumors become refractory to a variety of structurally diverse anti-cancer drugs. Failure of clinical chemotherapy may be attributable to pharmacokinetic, tumor environment, or cancer cell-specific issues. The best characterized mechanism of drug resistance to microtubule inhibitors is the over expression of the P-glycoprotein drug efflux pump (Blagosklonny, 1999) and (Licht et al., 2002). In addition, structural and functional alterations in the α- and β-tubulins of tumor cells are also a factor, resulting from either genetic mutations or post-translational modifications. These are associated with an acquired resistance to taxanes and vinca alkaloids (Juliano and Ling, 1976) and (Ueda et al., 1986). Thus, identification of natural and synthetic compounds with therapeutic effects on multiple-drug resistant tumors remains an attractive goal.

Human papilloma virus (HPV) is a small double-stranded DNA virus. It causes hyperproliferative lesions in epithelial tissues leading to malignancy (zur Hausen, 1996)). HPV is present in over 90% of cervical cancer (DiPaolo JA, 2004) and (Parkin et al., 2005). High-risk HPV infection types such as 16 and 18 (HPV16 and HPV18, respectively) are the major risk factor for the development of cervical cancer worldwide, the second most common form of cancer in women (Kaur et al., 1989).

Apoptosis is the process of programmed cell death (PCD) leading to characteristic cell changes and death such as membrane blebbing, cell shrinkage, cell/nuclear fragmentation, chromatin condensation and chromosomal DNA fragmentation. On the other hand, necrosis is a form of traumatic cell death resulting from acute cellular injury. This occurs during an organism's life cell cycle (2004; Proskuryakov et al., 2003).

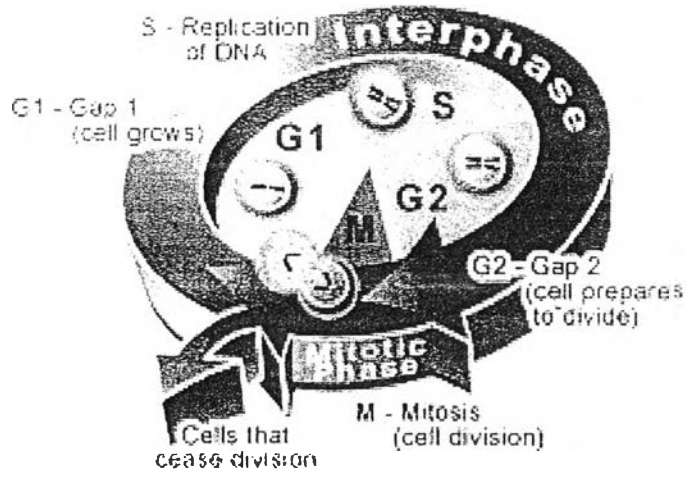

Figure 5. Cell cycle

The cell cycle is the series of events that occurs in a cell causing inhibition of its division and duplication (replication). In eukaryotes, cell cycle can be divided in two main periods:

(i) interphase; involving cell growth, accumulating nutrients needed for mitosis and duplicating its DNA.

(ii) the mitotic (M) phase; when the cell splits itself into two distinct cells, often called "daughter cells", and the final phase called cytokinesis, where the new cell is completely divided.

If the cell division cycle is blocked the cell won't be able to survive. This becomes one of the main targets for developing chemotherapy.

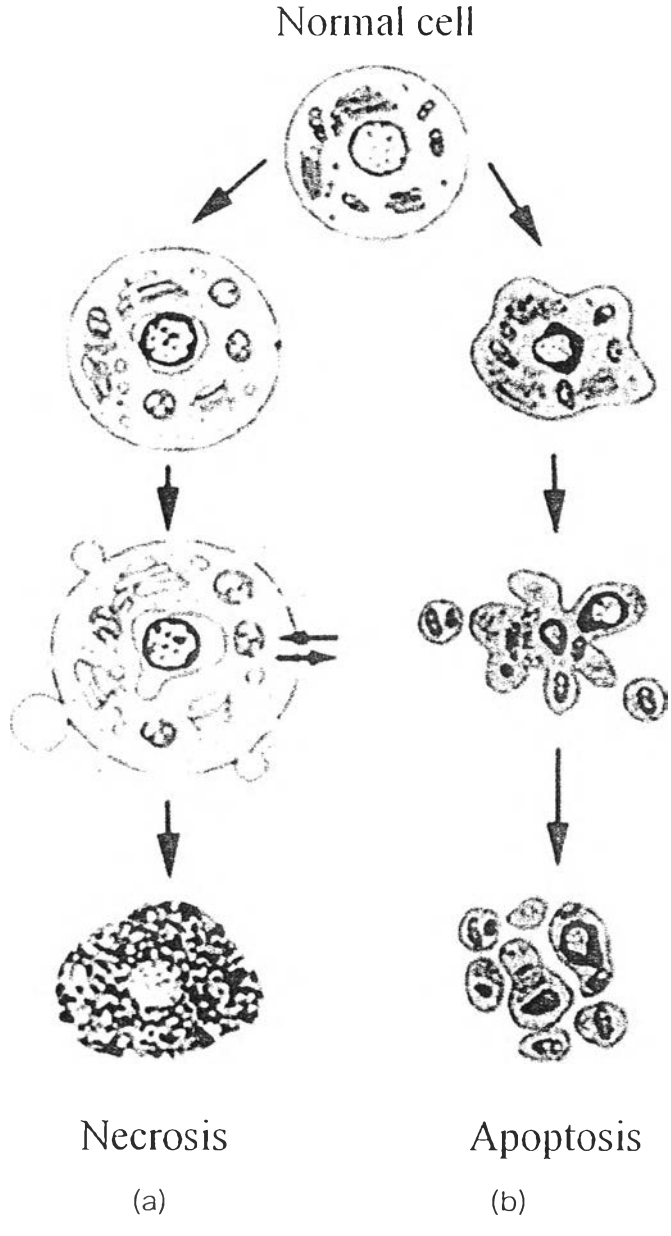

Figure 6. Model of program cell deaths (a) necrosis and (b) apoptosis

Bcl-2 protein was found to be related to regulation of apoptotic pathway. Bcl-2 is also regulated by p53 via the interaction. Thus, over-expression of bcl-2 protein has been reported in many cancer cells such as oral cavity, tongue and nasopharyngeal carcinoma (Han et al., 2001) and (Yu and Zhang, 2008)). The relationships between p53 and bcl-2/bax or between HPV and p53 are unclear, but it is possible that HPV-

associated cell, p53 and bcl-2 all interact within the apoptotic pathway. The phenomenon could be related in these tumors. Thus, targeting the anti-apoptotic Bcl-2 proteins can improve apoptosis and thus overcome drug resistance to cancer chemotherapy.

Anthraquinone, its amino and hydroxyl derivatives, is the largest group of naturally occurring quinines which has been applied in pharmacology, biochemistry and dry chemistry (Hunger, 2003). Anthraquinones are widespread in nature, for example, in bark and roots of certain plants. They show various pharmacological activities including anti-oxidant, anti-microbial, anti-fungal and anti-viral characteristics (Nakanishi et al., 2005). Interestingly, it is one part of many chemotherapeutic drugs, for instance, anthracyclines, mitoxantrone, ametantrone and anthrapyrazoles (Cheng and Zee-Cheng, 1983). Its planarity allows for inserting it in to DNA base pairs in the β conformation, while its redox properties are linked to the production of radical species in biological systems. Thus, the chemical and biological activity of anthraquinones depends on the different substituents of the planar ring system (Krapcho et al., 1991).

Although many researchers have been searching for new anti-cancer agents, cancer's mortality rate is still increasing. The purpose of this research is to modify new anthraquinone derivatives for enhancing cytotoxicity and to study molecular anti-cancer mechanisms.