1. **Introduction**

1.1 **Skin Cancer**

Skin cancer is a malignant growth on the skin that generally develops in the epidermis (the outermost layer of skin), and usually clearly visible. This makes most skin cancers detectable in the early stages. Unlike many other cancers, including those originating in the lung, pancreas, and stomach, only a small minority of those afflicted actually die of the disease (www.skincancer.org). Skin cancers are the fastest growing type of cancers in the United States. Skin cancer represents the most commonly diagnosed malignancy, surpassing lung, breast, colorectal and prostate cancer. More than 1 million Americans are diagnosed with skin cancer annually (www.cancer.gov). The annual rates of all forms of skin cancer are increasing each year, representing a growing public concern. It has also been estimated that nearly half of all Americans who live to age 65 will develop skin cancer at least once (www.skincancer.org).

1.2 **Types of skin cancer**

Skin cancer is of three common types, each of which is named after the type of skin cell from which it arises. The first being basal cell carcinoma which arises from the basal cell. Second is squamous cell carcinoma (also referred as epidermoid carcinoma) which arises from the squamous cells, which are thin, flat cells that look like fish scales under the microscope. These two are the most common forms of skin cancer. Together, these two are also referred to as non melanoma skin cancers. The third type is referred to as melanoma which is the most serious form of skin cancer because it tends to spread (metastasize) throughout the body quickly.
1.3 Basal cell carcinoma

It is the most common form of skin cancer and accounts for more than 90% of all skin cancers in the US. These cancers almost never spread (metastasize) to other parts of the body. They can, however, cause damage by growing and invading surrounding tissue. A basal cell carcinoma usually begins as a small, dome-shaped bump and is often covered by small, superficial blood vessels called telangiectases. The texture of such a spot is often shiny and translucent, sometimes referred to as "pearly." It is often hard to tell a basal cell carcinoma from a benign growth like a flesh-colored mole without performing a biopsy. Some basal cell carcinomas contain melanin pigment, making them look dark rather than shiny. Superficial basal cell carcinomas often appear on the chest or back and look more like patches of raw, dry skin. They grow slowly over the course of months or years to become sizable. Although spread to other parts of the body (metastasis) is very rare, a basal cell carcinoma can damage and disfigure the eye, ear, or nose if it grows nearby.

1.4 Squamous cell carcinoma (Epidermoid Carcinoma)

It begins in the squamous cells, which are thin, flat cells that look like fish scales under the microscope. The word squamous came from the Latin squama, meaning "the scale of a fish or serpent" because of the appearance of the cells. Squamous cells are found in the tissue that forms the surface of the skin, the lining of the hollow organs of the body, and the passages of the respiratory and digestive tracts. Thus, squamous cell carcinomas can actually arise in any of these tissues. Men are affected more often than women. The earliest form of squamous cell carcinoma is called actinic (or solar) keratosis. Actinic keratoses appear as rough, red bumps on the scalp, face, ears, and back of the hands. They often appear against a background of mottled, sun-damaged skin. They can be quite sore and tender, out of proportion to their appearance. In a patient with actinic keratoses,
the rate at which one such keratosis may invade deeper in the skin to become a fully-developed squamous cell carcinoma is estimated to be in the range of 10%-20% over 10 years, though it may take less time. An actinic keratosis that becomes thicker and tenderer raises the concern that it may have transformed into an invasive squamous cell carcinoma.

1.4.1 Melanoma

Melanoma is the most serious form of skin cancers. However, if it is recognized and treated early, it is nearly 100 percent curable. But if it is not, the cancer can advance and spread to other parts of the body, where it becomes hard to treat and can be fatal. While it is not the most common of the skin cancers, it causes the most deaths. Melanoma is a malignant tumor that originates in melanocytes, the cells which produce the pigment melanin that colors our skin, hair, and eyes. The majority of melanomas are black or brown. However, some melanomas are skin-colored, pink, red, purple, blue or white (www.medicine.net).

1.5 Signs and symptoms of skin cancer

There are a variety of different skin cancer symptoms. These include crabs or changes in the skin that do not heal, ulcers in the skin, discoloration, and changes in existing moles.

- Basal cell carcinoma usually looks like a raised, smooth, pearly bump on the sun-exposed skin of the head, neck or shoulders. Sometimes small blood vessels can be seen within the tumor. Crusting and bleeding in the center of the tumor frequently develops. It is often mistaken for a sore that does not heal.
• Squamous cell carcinoma (SCC) is commonly a red, scaling, thickened patch on sun-exposed skin. Ulceration and bleeding may occur. When SCC is not treated, it may develop into a large mass.

• Most melanomas are brown to black looking lesions. Signs that might indicate a malignant melanoma include change in size, shape, color or elevation of a mole. The appearance of a new mole during adulthood, or new pain, itching, ulceration or bleeding.

1.6 Risk factors leading to skin cancer

• Exposure to ultraviolet (UV) light is a common cause of skin damage and the major cause of skin cancer in humans (de Gruij et al, 1999, Wolf et al, 1996, Soter et al, 1990). Acute effects of UV irradiation include sunburn, inflammation, erythema, immunosupression, DNA damage, and apoptosis; however, the epidermal damage caused by acute UV exposure will generally disappear within 2 week (Matsumura et al, 2004). Chronic or repetitive exposure to UV light on the other hand, while causing similar histological and molecular effects, can lead to photoaging and skin cancer. In the spectrum of UV light, UVB and to a lesser extent UVA are implicated in the development of skin cancer (Akunda et al, 2007).

• Chronic non-healing wounds, especially burns are called Marjolin's ulcers based on their appearance, and can develop into squamous cell carcinoma.

• Genetic predisposition, including "Congenital Melanocytic Nevi Syndrome" (CMNS) is characterized by the presence of "nevi" or moles of varying size that either appear at or within 6 months of birth. Nevi larger than 20 mm (3/4") in size are at higher risk for becoming cancerous.
Introduction

- Skin cancer is one of the potential dangers of ultraviolet germicidal irradiation.

1.7 Treatment of skin cancer

Most skin cancers can be treated by removal of the lesion, making sure that the edges (margins) are free of the tumor cells. These surgical excisions provide the best cure for both early and high-risk disease.

1.7.1 Curettage and desiccation

Dermatologists often prefer this method, which consists of scooping out the basal cell carcinoma by using a spoon like instrument called a curette. Desiccation is the additional application of an electric current to control bleeding and kill the remaining cancer cells. The skin heals without stitching. This technique is best suited for small cancers in non-crucial areas such as the trunk and extremities.

1.7.2 Radiation therapy

Doctors often use radiation treatments for skin cancer occurring in areas that are difficult to treat with surgery. Obtaining a good cosmetic result generally involves 25 to 30 treatment sessions.

1.7.3 Cryosurgery

Some doctors trained in this technique achieve good results by freezing basal cell carcinomas. Typically, liquid nitrogen is applied to the growth to freeze and kill the abnormal cells.

1.7.4 Mohs micrographic surgery

Named for its pioneer, Dr. Frederic Mohs, this technique of removing skin cancer is better termed, "microscopically controlled excision." The surgeon
meticulously removes a small piece of the tumor and examines it under the microscope during surgery. This sequence of cutting and microscopic examination is repeated in a painstaking fashion so that the basal cell carcinoma can be mapped and taken out without having to estimate or guess the width and depth of the lesion. This method removes as little of the healthy normal tissue as possible. Cure rate is very high, exceeding 98%. Mohs micrographic surgery is preferred for large basal cell carcinomas, those that recur after previous treatment, or lesions affecting parts of the body where experience shows that recurrence is common after treatment by other methods. Such body parts include the scalp, forehead, ears, and the corners of the nose. In cases where large amounts of tissue need to be removed, the Mohs surgeon sometimes works with a plastic (reconstructive) surgeon to achieve the best possible post surgical appearance.

1.7.5 Medical therapy

It is using creams that attack cancer cells (5-Fluorouracil--5-FU, Efudex, Fluoroplex) or stimulate the immune system (Aldara). These are applied several times a week for several weeks. They produce brisk inflammation and irritation. The advantages of this method are that it avoids surgery, lets the patient perform treatment at home, and may give a better cosmetic result. Disadvantages include discomfort, which may be severe, and a lower cure rate, which makes medical treatment unsuitable for treating most skin cancers on the face.

In the case of disease that has spread (metastasized) further chemotherapy may be required (Doherty et al, 2005). Scientists have recently been conducting experiments on what they have termed “immune-priming”. This therapy is still in its infancy but has been shown to effectively attack foreign threats like viruses and also latch onto and attack skin cancers. More recently researchers have focused their efforts on strengthening the body's own naturally produced "helper T cells" that identify and lock onto cancer cells and help guide the killer
cells to the cancer. Researchers infused patients with roughly 5 billion of the helper T cells without any harsh drugs or chemotherapy. This type of treatment if shown to be effective has no side effects and could change the way cancer patients are treated (www.cancer.gov). The possibility of metastasis makes it especially important to diagnose squamous cell carcinomas early and treat them adequately.

1.8 Arachidonic acid metabolism

Arachidonic acid (5, 8, 11, 14-eicosatetraenoic acid, 20:4) is a polyunsaturated fatty acid with four isolated cis double bonds. It is predominantly found esterified in membrane phospholipids in all mammalian cells. It is released from the phospholipids in the cell membrane by the action of phospholipases (Brash, 2001). Among the members of the PLA2 family, the cytosolic PLA2 type IV is known to be an important enzyme that selectively releases arachidonic acid from phospholipids (Neumann et al., 2007; Bonventre et al., 1997). The double bonds of polyenoic fatty acids provide the possibility to react with molecular dioxygen. Such oxygenation reactions may be catalyzed by transition metals (non-enzymatic) or by various types of oxygenases to form eicosanoids (Brash, 2001). Eicosanoids (from the Greek eikosi for “twenty”) are a family of oxygenated metabolites of the 20-carbon fatty acid, arachidonic acid (AA), that are released from the source cell and act at nano molar concentrations on target cells, typically via G-protein coupled receptors (GPCRs).

Although originally recognized for their capacities to elicit biological responses such as smooth muscle contraction, edema, and platelet aggregation, eicosanoids are now appreciated to influence processes ranging from inflammation and immune responses to chronic tissue remodeling and cancer (Brock et al., 2007). In fact, for oxygenation of polyenoic fatty acids three major types of oxygenases have been identified: i) cyclooxygenases (COXs) ii)
lipoxygenases (LOXs) and iii) cytochrome P-450 isozymes (Brash, 2001) (Figure 1).

Figure 1. Arachidonic acid metabolism

1.8.1 Cyclooxygenase (COX) pathway

This pathway leads to the formation of cyclisation products of arachidonic acid that include prostaglandins, prostacyclin and thromboxanes. The COX is a bifunctional enzyme and exhibits cyclooxygenase and peroxidase activity. The cyclooxygenase activity introduces two molecules of oxygen into arachidonic acid to form the cyclic hydroperoxy endoperoxide PGG₂, which is subsequently reduced by the peroxidase activity of the enzyme to the hydroxyl endoperoxide, PGH₂ (Smith et al, 1991) (Figure 2). PGH₂ constitutes substrate for further enzymatic modifications leading to the formation of the prostaglandins (PGD₂, PGE₂, PGF₂α), prostacyclin (PGI₂) or thromboxane A₂ (TXA₂) (Smith et al, 1992).
COX-isofoms employ their heme moiety to generate a tyrosyl radical that abstracts hydrogen from C-11 of arachidonic acid. The two isofoms are the target of most prostaglandin synthesis inhibitors, particularly of the nonsteroidal anti-inflammatory drugs (NSAIDs), such as aspirin and indomethacin (Levy, 1997). Prostanoids exert their actions via membrane receptors on the surface of target cells. A family of membrane receptors mediating their actions has been characterized and cloned.

There are eight types and subtypes of receptors for prostanoid that are conserved in mammals from mouse to human (Narumiya et al, 1999): the PGD receptor (DP), four subtypes of the PGE receptors (EP1, EP2, EP3, and EP4), the PGF receptor (FP), the PGI receptor (IP), and the TXA receptor (TP). All are G-protein coupled rhodopsin-type receptors with seven transmembrane domains, and each is encoded by different genes (Matsuoka et al, 2007).
1.8.2 Lipoxygenases (LOX) pathway

This pathway leads to the formation of linear eicosanoids containing conjugated double bond systems. LOXs produce fatty acid hydroperoxides that are rapidly reduced to the corresponding hydroxyl compounds by glutathione peroxidases. LOXs contain one mole non-heme iron per mole enzyme and this transition metal is involved in the rate-limiting step of the LOX reaction, the initial hydrogen abstraction. Following hydrogen abstraction LOXs catalyze the introduction of atmospheric oxygen into the fatty acid chain and it depends on the positional specificity of the enzyme, at which carbon atom oxygen is inserted. (Yamamoto et al., 1992; Kühn et al., 1986) (Figure 3).

![Figure 3: Lipoxygenase pathways](image)

Hence, 5-LOXs generate 5-HPETE (5-hydroperoxy eicosa-6, 8, 11, 14-tetraenoic acid), 12-LOXs generate 12-HPETE (12-S-hydroperoxy eicosa-
tetraenoic acid) and 15-LOXs generate 15-HPETE (15- hydroperoxy eicosa-
tetraenoic acid). 5-HPETEs and 15-HPETEs can be further metabolized to epoxy
leukotrienes, 5, 6-leukotriene A₄ and 14, 15-LTA₄ respectively. 5, 6-epoxy
leukotriene A₄ (5, 6-LTA₄) constitutes the substrate for the cysteinyl leukotrienes
(LTC₄, LTD₄, LTE₄), the mixture of which is known as slow-reacting substances of
anaphylaxis (Lewis et al, 1980). Within the mammalian LOX family, a distinct
subclass of epidermis-type LOX has been characterized that are preferentially
expressed in skin and few other epithelial tissues (Krieg et al, 1998). They include
the human 15-LOX-2 and its mouse orthologue 8-LOX, 12-R-LOX, and eLOX-3.
The epidermal 12-R-LOX and eLOX-3 differ from all other mammalian LOXs in
their unique structural and enzymatic features (Krieg et al, 1999; Kinzig et al, 1999;
Boeglin et al, 1998). Both proteins contain an extra domain located at the surface
of the catalytic subunit. 12-R-LOX represents the only mammalian LOX that forms
products with R-chirality (Epp et al, 2007).

1.8.3 Cytochrome P-450 pathway

This pathway leads to the formation of two principle metabolites: i) Monohydroxylated eicosanoids, most of which do not contain conjugated double
bond systems (20-HETE, 19-HETE, 18-HETE etc), ii) Epoxy fatty acids, which
originate from epoxidation of double bonds to generate epoxyeicosatrienoic acids
(EETs)(5, 6-EET, 8, 9-EET, 11, 12-EET, 14, 15-EET). In contrast to the LOX
reaction cytochrome P-450-catalysed oxygenation involves insertion of atomic
oxygen. In fact, molecular dioxygen is split into two oxygen atoms, one of which is
introduced into the fatty acid substrate and the other one is reduced to water
(Capdevila et al, 1992). Epoxy eicosanoids are rapidly hydrolyzed to
dihydroxylated fatty acids. In tissues like kidney and cornea, cytochrome P- 450
mediated oxygenation of fatty acids results in the formation of biologically active
products and plays an important role in the physiology of these tissues.
1.9 **Arachidonic acid metabolism in skin**

Skin, the largest human body organ, provides a major interface between the environment and the body and is constantly exposed to an array of chemical and physical environmental pollutants (Athar *et al*, 2002). In addition, a large number of dietary contaminants and drugs can manifest their toxicity in skin (Sander *et al*, 2004). These environmental toxicants or their metabolites are inherent oxidants and/or directly or indirectly drive the production of a variety of reactive oxidants also known as reactive oxygen species (ROS) (Cerutti *et al*, 1992). Skin exposure to ionizing and UV radiation and/or xenobiotics/ drugs generates ROS in excessive quantities that quickly overwhelm tissue antioxidants and other oxidant-degrading pathways. Uncontrolled release of ROS is involved in the pathogenesis of a number of human skin disorders including cutaneous neoplasia (Black *et al*, 2004; Briganti *et al*, 2003). One of the most important metabolites driving cutaneous inflammation is the eicosanoids (Bickers *et al*, 2006). Cancer results from disturbances of cellular signal transduction and data processing at the genetic and epigenetic level. Among these metabolic reactions becoming dys-regulated in the course of tumorigenesis, eicosanoid biosynthesis from arachidonic acid seems to play a pivotal role. A steadily increasing body of evidence indicates a causal relationship between cancer development and an abnormal overexpression of eicosanoid-forming enzymes, i.e. cyclooxygenases and lipoxygenases, in a wide variety of human and animal tumors. Besides their role as indicators of neoplastic development, eicosanoids also act as reporters of skin irritation (Marks *et al*, 2000). Many of these AA metabolites are clastogenic and act as tumor promoters in murine models of skin carcinogenesis and are induced following UVB irradiation (Bickers *et al*, 2006). Elevated levels of eicosanoids (prostaglandins and leukotrienes) have been shown to be associated
with a wide array of dermatological diseases, such as psoriasis, UV-induced erythema, and contact sensitivity (Wang et al., 2001).

1.10 COX pathway in skin health and disease

COX is the key enzyme generating prostaglandins from AA. In humans, prostaglandins are involved in diverse physiological functions. At least two isoforms of COX have been cloned and sequenced. COX-1 is a housekeeping isoform constitutively expressed in most tissues, whereas COX-2 is induced by a variety of proinflammatory agents and mitogens. It is known that COX-2 is upregulated following acute UVB exposure, and is increased in human actinic keratoses/papillomas and in both murine and human SCCs (Bickers et al., 2006). In general, COX-1 regulates prostaglandin synthesis associated with cellular homeostasis whereas COX-2 is upregulated in inflammatory conditions and associated with synthesis of proinflammatory prostaglandins (Vane et al., 1994). Much attention has therefore been paid to develop specific inhibitors of COX-2. Recently, normal murine epidermis was found to express COX-1 but not COX-2. However, COX-2 could be induced either by acetone treatment or by topical application of the phorbol ester, TPA (Scholz et al., 1995). This is in contrast to normal human epidermis where COX-2 has been associated with keratinocyte differentiation (Leong et al., 1996). In normal human skin, COX-1 immunostaining is observed throughout the epidermis whereas COX-2 immunostaining was more in differentiated, suprabasilar keratinocytes (Leong et al., 1996). PGE$_2$ is the main AA cyclooxygenase product in human epidermal homogenates (Iversen et al., 2000).

1.11 Celecoxib

Celecoxib, 4-[5-(4-methylphenyl)-3-(trifluoromethyl) pyrazol-1-yl] benzene sulfonamide, C17H14F3N3O2S (MW 381.38) (Figure 4), is a highly specific inhibitor of COX-2 with 7.6 times more selectivity for COX-2 inhibition over COX-1.
This was the first COX-2 inhibitor approved for the use in U.S. for relief of signs and symptoms of rheumatoid arthritis and osteoporosis in adults. In addition to analgesic, antipyretic and anti-inflammatory activity, it has chemopreventive properties against colon cancer. Celecoxib is the only NSAID that has been approved by the FDA (in December 1999) for adjuvant treatment of patients with familial adenomatous polyposis. Since the introduction of celecoxib in 1998, several studies have investigated the molecular targets and clinical effects of the drug. Anticancerogenic effects of celecoxib have been demonstrated in many types of cancers including non-small-cell lung cancer (Chen et al, 2007), gastric cancer (Zhu et al, 2007), lung cancer (Harris et al, 2007), prostate cancer (Anai et al, 2007), bladder cancer (Zhang et al, 2007), chronic myeloid leukemia (Arunasree et al, 2008; Zhang et al, 2006; Subhashini et al, 2005).

Celecoxib exerts its anti-cancerogenic effects in both COX-2-dependent and independent mechanisms. In general, the anticancerogenic mechanisms of celecoxib involve blocking cell cycle progression, angiogenesis, metastasis and inducing apoptosis.
1.12 LOX pathway in skin health and disease

Within the mammalian LOX family, a distinct subclass of epidermis-type LOX has been characterized that are preferentially expressed in skin and few other epithelial tissues (Krieg et al., 1998). They include the human 15-LOX-2 and its mouse orthologue 8-LOX, 12-R-LOX, and eLOX-3. Their differentiation-dependent expression pattern in epithelial tissues suggests a common physiological role in the regulation of proliferation and differentiation of epithelial cells, especially keratinocytes. In humans, the metabolism of arachidonic acid in psoriasis and other proliferative dermatoses is characterized by the accumulation of the unusual metabolite, 12-R-hydroxyeicosatetraenoic acid (12-(R)-HETE) (Baer et al., 1991) (Figure 5A). Formation of 12-(R)-HETE results from the activity of 12-R-lipoxygenase (LOX) in the psoriatic lesions (Boeglin et al., 1998). In normal human skin, 12-R-LOX activity is almost undetectable (Schneider et al., 2004). 12-R-LOX represents the only mammalian LOX that forms products with R-chirality. Unlike all other LOXs, eLOX-3 does not exhibit dioxygenase activity, but functions as a hydroperoxide isomerase (Yu et al., 2003). Both enzymes act in sequence to convert arachidonic acid to 12-R-hydroperoxyeicosatetraenoic acid (12R-HPETE) to the corresponding hepxilin like epoxyalcohol, 8R-hydroxy-11R and 12-R-epoxy eicosatrienoic acid (Figure 5C). This sequence has been hypothesized to be part of a novel LOX pathway in skin that plays an important role in terminal differentiation (Yu et al., 2003; Jobard et al., 2002). Recent genetic studies have identified mutations in the coding regions of 12-R-LOX and eLOX-3 genes in patients with autosomal recessive congenital ichthyosis (ARCI) (Figure 5B), linking for the first time mutations of a LOX gene to the development of a disease (Eckl et al., 2005; Jobard et al., 2002). ARCI is a clinically and genetically heterogeneous group of skin disorders that is associated with hyp-ERKeratosis and impaired skin barrier functions (Traupe, 1989). It was reported that point mutations found in the
LOX genes of the ARCI patients completely eliminated the catalytic activity of the LOX enzymes, indicating that mutational inactivation of either 12-R-LOX or eLOX-3 is causally linked to the ARCI phenotype (Eckl et al., 2005; Yu et al., 2005). The implication of 12-R-LOX and eLOX-3 in ARCI has brought forth the concept that both enzymes function in the same metabolic pathway to convert arachidonic acid via 12-R-HPETE to hepoxilin and trioxilin-like metabolites that are critically involved in keratinocyte differentiation (Lefevre et al., 2006; Yu et al., 2005; Eckl et al., 2005; Jobard et al., 2002) (Figure 5C).

Moreover, very recent studies have shown that the creation of 12-R-LOX-deficient mice results in a severe impairment in barrier function, with the mice dying soon after birth from a defective barrier (Epp et al., 2007) (Figure 6). Among the diHETEs of the 5-LOX pathway are the biologically active leukotrienes (LTs) which have been ascribed an important role in inflammatory skin diseases like psoriasis and atopic dermatitis (Iverson et al., 2000; Sampson et al., 1992; Brain et al., 1985; Grabbe et al., 1984). Overexpression of the LOX isoforms- 8S-LOX and p12-S-LOX occurs in papillomas and SCCs, leading to accumulation of the corresponding metabolites 8S- and 12-(S)-HETE. Both LOX products are known to induce chromosomal damage in primary basal murine keratinocytes.
Figure 5: (A) Patient with psoriasis (B) Patient with Non Bullous Congenital Ichthiosis (NCIE) (C) Metabolic pathway of 12-R-LOX in the maintenance of epidermal lipid barrier (Yu et al, 2005).

However, the amounts of these metabolites formed in tumors are sufficient for the formation of etheno adducts of DNA. Therefore, 8S- and 12-(S)-HETE may generate endogenous mutagens. Nordihydroguarectic acid (NDGA), a potent
common inhibitor of these enzymes, suppresses skin tumor induction in murine models (Muller et al., 2002).

![Figure 6: Macrosopic appearance of wild-type and 12-R-LOX−/− mice at birth, and 2 and 3 h after birth. Note the red, shiny skin and the dehydrated appearance of 12-R-LOX−/− mice (Epp et al., 2007).](image)

### 1.13 Baicalein

The IUPAC name of baicalein is 5, 6, 7-Trihydroxyflavone (Figure 7). Baicalein (BE) is one of the major flavonoids in Scutellaria baicalensis, which has long been extensively used in Chinese herbal medicine. Baicalein is a highly specific inhibitor of platelet-12-LOX. Platelet 12-lipoxygenase is inhibited by baicalein with an IC\(_{50}\) value of 0.12 µM, with minimal inhibition of platelet cyclooxygenase-1 (IC\(_{50}\) = 0.83 mM). Several biological effects of BE such as antiviral, anti-inflammation, anti-hepatotoxicity, and anti-tumor properties have

![Figure 7: Chemical structure of Baicalein](image)
been reported (Chen et al, 2006; Hwang et al, 2005; Huang et al, 2005; Ahn et al, 2001).

In MCF-7 cells, BE suppressed 17β-estradiol-induced transactivation, and induced apoptosis (Po et al, 2002). In lung squamous carcinoma CH27 cells, BE induced cell cycle arrest at the S-phase, followed by the induction of apoptosis (Chow et al, 2006; Lee et al, 2005). It has been reported that baicalein could make an S-phase arrest in cell cycle of lung squamous carcinoma CH27 cells (Lee et al, 2005) and induce apoptosis in many human cancer cell lines, e.g. hepatoma cells - Hep3B and HepG2 (Chen et al, 2005), pancreatic cancer cells- MiaPaCa-2 and AsPC-1 (Tong et al, 2002), breast cancer cells- MCF-7 (Tong et al, 2002) and prostate cancer cell lines (Chen et al, 2001). Although several biological activities of BE have been reported, intracellular molecules involved in modulation of apoptosis induced by BE are still undefined (Chow et al, 2006). A recent report demonstrated that baicalein induced a mitochondria-dependent caspase-3 and caspase-9 activation, and consequently led to apoptotic cell death in human myeloma cells (Ma et al, 2005).