Ali et al. (2011) said cancer has become a big threat to human beings globally. As per Indian population census data, the rate of mortality due to cancer in India was high and alarming with about 8, 06,000 existing cases by the end of the last century. Cancer is the second most common disease in India responsible for maximum mortality with about 0.3 million deaths per year. This is owing to the lack of preventive measures and poor diagnostic and treatment methods. All types of cancers have been reported in Indian population including the cancers of skin, lungs, breast, rectum, stomach, prostate, liver, cervix, esophagus, bladder, blood, mouth etc. The causes of such high incidence rates of these cancers may be due to both internal (genetic, mutations, hormonal, poor immune conditions) and external or environmental factors (food habits, industrialization, over growth of population, social etc). In addition to this, efforts have also been made to predict the effect of increasing number of cancer patients on the Indian economy.

The total cancer cases are likely to go up from 979,786 cases in the year 2010 to 1,148,757 cases in the year 2020. The tobacco-related cancers for males are estimated to go up from 190,244 in the year 2010 to 225,241 in the year 2020. Similarly, the female cases will go up from 75,289 in the year 2010 to 93,563 in the year 2020. For the year 2010, the number of cancer cases related to digestive system, for both males and females, are estimated to be 107,030 and 86,606 respectively. For, head and neck cancers, the estimates are 122,643 and 53,148 cases, respectively and for the lymphoid and hematopoietic system (LHS), for the year 2010, are 62,648 for males and 41,591 for females. Gynecological-related cancers are estimated to go up from 153,850 in 2010 to 182,602 in 2020. Among males and females, cancer of breast alone is expected to cross 100,000 cases by the year 2020. (Takiar et al., 2010).
Danaei et al. (2005) proposed that 7 million deaths from cancer worldwide in 2001, and estimated 2·43 million (35%) were attributable to nine potentially modifiable risk factors. Of these, 0·76 million deaths were in high-income countries and 1·67 million in low-and-middle-income nations. Among low-and-middle-income regions, Europe and Central Asia had the highest proportion (39%) of deaths from cancer attributable to the risk factors studied. 1·6 million of the deaths were attributable to these risk factors were in men and 0·83 million in women. Smoking, alcohol use, and low fruit and vegetable intake were the leading risk factors for death from cancer worldwide and in low-and-middle-income countries. In high-income countries, smoking, alcohol use, and overweight and obesity were the most important causes of cancer. Sexual transmission of human papilloma virus is a leading risk factor for cervical cancer in women in low-and-middle-income countries.

TRAIL and its receptors are attractive targets for anticancer therapy owing to their ability to trigger apoptosis selectively in cancer cells but not normal cells. To date, many combinatorial strategies, such as chemotherapy or radiotherapy, have given encouraging results for overcoming TRAIL resistance in preclinical models. Naturally occurring compounds can restore tumor cell sensitivity to TRAIL-induced cell death with no apparent toxicity towards normal cells. Both extrinsic and intrinsic pathways can be modulated by polyphenols, the activation of which largely depends on the cell type, the particular polyphenolic compound, and the conditions of treatment. The large variety of polyphenol cellular targets could prove useful in circumventing TRAIL resistance (Jacquemin et al., 2010).

The ability of TRAIL to induce apoptosis in a large number of tumors has stimulated interest in TRAIL as a tumor therapeutic agent. Although TRAIL mRNA
is expressed in a number of tissues, its functional significance to various organs is unknown. Because tumors rarely develop in the eye, we have examined this organ for functional TRAIL expression. Our analysis revealed that TRAIL mRNA and protein are constitutively expressed on numerous ocular structures, including the cornea and retina. More importantly, ocular tissue displays functional TRAIL as determined by in vitro killing of TRAIL-sensitive tumor cell lines. Previous studies have shown that ocular tissue also expresses functional Fas ligand (FasL). To assess the contribution of TRAIL and FasL for tumor cell killing in the eye, cell lines susceptible to both TRAIL and FasL were examined. Ocular tissue kills via either ligand, suggesting a compensatory mechanism between TRAIL and FasL. Collectively, these results provide physiological evidence for ocular TRAIL expression, and suggest a role for this molecule in tumor surveillance in an immune privileged site (Lee et al., 2002).

During the last decade, the cytokine TRAIL (APO2-L or TNF-related apoptosis-inducing ligand) and agonistic antibodies targeting TRAIL receptors have gained considerable interest in cancer therapy, due to their ability to induce tumor regression in preclinical studies with no significant side effects (Ashkenazi et al., 2008).

Thorburn, 2004 said that apoptosis pathways activated by death receptors of the tumor necrosis factor (TNF) family such as Fas, TNFR1, or the TRAIL receptors DR4 and DR5 are implicated in diverse diseases. Cell killing from such receptors occurs because of recruitment to the receptor of the adaptor protein FADD, which in turn recruits the pro form of caspase-8. Aggregation of pro-caspase-8 leads to its auto-activation and subsequent activation of effector caspases such as caspase-3. The apoptotic signal can be amplified through the mitochondria and inhibited through the
action of competing molecules such as the inhibitor c-FLIP, which binds to the receptor complex in place of caspase-8. This simple mechanism explains much of the cell death that is induced by death receptors. However, recent studies indicate that we must incorporate new information into this model.

Tumor necrosis factor apoptosis inducing ligand (TRAIL, Apo2L) is a type II membrane bound TNF family ligand that is highly homologous to cytotoxic FasL, displays widespread expression and is up-regulated on lymphocyte activation (Pitti et al., 1996; Wiley et al., 1995). Crystal structures have shown that, like other TNF ligands, it occurs as a trimer. It can be cleaved from the membrane by cysteine proteases to generate a soluble form of the ligand (Wajant et al., 2001).

The crystal structure of a complex between TRAIL and DR5, revealed the trimeric ligand interdigitated with three monomeric receptors (Mongkolsapaya et al., 1999b; Hymowitz et al., 1999; Cha et al., 2000). The receptors are positioned neatly at the interfaces between the ligand monomers with the contact surface in the second and third Cysteine Rich Domain (CRD). Such crystal complexes of other members of this family led to the ligand induced trimerisation model, in which the incoming trimeric ligand recruits three receptor molecules. This induced juxtaposition of the intracellular receptor domains is then sensed inside the cell and facilitates the recruitment of downstream signaling components, triggering the internal signalling cascade. The ligand-induced trimerisation model was consequently widely accepted and became the paradigm for receptor triggering in the TNFR superfamily. However, studies of both Fas and TNFR1 defined a ligand-independent oligomerisation domain in the extracellular region, termed the pre-ligand assembly domain (PLAD). These observations invoked consideration of an alternative model for receptor triggering, in
which the receptors could associate prior to ligand binding (Siegel et al., 2000; Chan et al., 2000).

Polyphenols are the products of secondary metabolism in plants. They play a role in defense mechanisms against pathogens or radiations and give plants their colors. They are found in fruits and vegetables, but also in wine, tea, coffee, chocolate and many other plant-derived products (D’Archivio et al., 2007). These compounds are known for their beneficial effects against a large number of diseases, including cardiovascular or neurodegenerative diseases, osteoporosis and cancer (Ramos, 2008).

The biological activity of polyphenols is mainly attributed to their antioxidant properties, which is strictly related to their chemical structure (Depeint et al., 2002). Polyphenols prevent reactive oxygen species (ROS)-induced DNA damage by scavenging free radicals (reactive oxygen, nitrogen and chlorine species) and by inactivating metal catalysts by chelation, decreasing their oxidative activity. Their ability to interact with other reducing compounds and to inhibit redox active transcription factors may also contribute to the antioxidant properties of these molecules as well as to their ability to regulate gene expression. Paradoxically, in addition to their antioxidant effects, polyphenols have also been shown to exert pro-oxidant effects that could also be responsible for their anticancer properties (Depeint et al., 2002). For example, owing to the presence of its hydroxyl groups, the flavonoid quercetin was shown to inhibit proliferation and to induce apoptosis of malignant cells through the generation of intracellular superoxide (Sakao et al., 2009).

The members of the tumor necrosis factor (TNF) superfamily of cytokines play important roles in the regulation of various T-cell functions. Likewise, induction of cell death by apoptosis is indispensable for the normal functioning of the
immune system. There are two major pathways of apoptosis induction. The intrinsic, or mitochondrial, pathway is regulated by the activation and interaction of members of the Bcl-2 family. The extrinsic, or death receptor, pathway is triggered by certain TNF family members when they engage their respective cognate receptors on the surface of the target cell. Hence, cell-to-cell-mediated death signals are induced by activation of these death receptor–ligand systems. Besides TNF itself and the CD95 (Fas/APO-1) ligand (FasL/Apo1L), the TNF-related apoptosis-inducing ligand (TRAIL/Apo2L) belongs to the subfamily of ligands that is responsible for extrinsic induction of cell death. Depending on their status of stimulation, TRAIL can be expressed by various cells of the immune system, amongst them natural killer (NK) cells, T cells, natural killer T cells (NKT cells), dendritic cells and macrophages. TRAIL has been implicated in immunosuppressive, immunoregulatory and immune-effector functions. With respect to pathological challenges, TRAIL and its receptors have been shown to play important roles in the immune response to viral infections and in immune surveillance of tumors and metastases (Falschlehner et al., 2009).

The first hint at understanding the function of TRAIL in the immune system came when it was discovered that TRAIL is expressed on a variety of cells of the innate and adaptive immune systems. Yet, the expression of TRAIL was found to depend on the stimulation status. TRAIL is up-regulated on monocytes and macrophages after stimulation with lipopolysaccharide (LPS) and interferon-b (IFN-b). Interferon-c (IFN-c), in turn, can induce the expression of TRAIL on the surface of monocytes, dendritic cells (DCs) and natural killer (NK) cells. Surface bound TRAIL is one of the effector mechanisms of NK cells, as only combined neutralization of TRAIL, CD95L and perforin can block NK cell-mediated killing of
tumor cell lines in vitro. These results were confirmed in an in vivo model, where TRAIL plays a critical role in NK cell-mediated and IFN-c-dependent suppression of tumor cell growth. Furthermore, it was demonstrated that IFN-c induces TRAIL on NK cells in vivo and that it is this induction of TRAIL that is required for the IFN-c-mediated prevention of the formation of primary experimental tumors and experimental metastasis. A subpopulation of NK cells in adult mouse liver was shown to express TRAIL constitutively as a result of the autocrine production of IFN. During development, TRAIL is predominantly expressed in fetal and neonatal mouse liver NK cells. Some of the TRAIL+ immature NK cells remain in the liver of adult mice and its retention is dependent on IFN-c, but not on interleukin (IL)-12, IL-18 or host pathogens. TRAIL could also be detected on IFN-c-producing killer dendritic cells (IKDCs), an important finding that provides an intriguing link between the innate immune system and the adaptive immune system (Chan et al., 2006; Taieb et al., 2006). Expression of TRAIL at the mRNA level was shown in human peripheral blood lymphocytes following activation with a monoclonal anti-CD3 or phorbol 12-myristate 13-acetate (PMA)/ionomycin. Increased expression of TRAIL was detected on CD4+ and CD8+ human peripheral blood T cells after T-cell receptor (TCR) stimulation, in combination with type I IFNs. In contrast to CD95L, surface expression of TRAIL was not strongly induced by stimulation with TCR/CD3 alone. The enhancement of TRAIL expression depended on the costimulation with interferon-a (IFN-a) or IFN-b. Ehrlich et al. (2003) reported that IFN-b did not induce TRAIL on phytohaemagglutinin (PHA)- and IL-2-stimulated T cells. This difference could be attributed to the different culture conditions and to the activation status of the
T cells. LPS, in combination with PHA and IL-2, also led to the up-regulation of TRAIL in a type I IFN-dependent manner (Ehrlich et al., 2003).

Kalimuthu et al. (2013) said Apoptosis, the major form of cellular suicide, is central to various physiological processes and the maintenance of homeostasis in multicellular organisms. A number of discoveries have clarified the molecular mechanism of apoptosis, thus clarifying the link between apoptosis and cell survival factors, which has a therapeutic outcome. Induction of apoptosis and inhibition of cell survival by anticancer agents has been shown to correlate with tumor response. Cellular damage induces growth arrest and tumor suppression by inducing apoptosis, necrosis and senescence; the mechanism of cell death depends on the magnitude of DNA damage following exposure to various anticancer agents. Apoptosis is mainly regulated by cell survival and proliferating signaling molecules. As a new therapeutic strategy, alternative types of cell death might be exploited to control and eradicate cancer cells.

Szliszka et al. (2010) showed Chalcones antitumor effects. Tumor necrosis factor-related apoptosis-inducing ligand (TRAIL) is a naturally occurring anticancer agent that induces apoptosis in cancer cells and is not toxic to normal cells. Cytotoxic and apoptotic effect of five chalcones in combination with TRAIL on prostate cancer cells was evaluated by the MTT and LDH assays. The apoptosis was determined using flow cytometry with annexin V-FITC. Our study showed that all five tested chalcones, chalcone, licochalcone-A, isobavachalcone, xanthohumol, butein markedly augmented TRAIL-mediated apoptosis and cytotoxicity in prostate cancer cells and confirmed the significant role of chalcones in chemoprevention of prostate cancer.
Shankar et al. (2007) has reported that curcumin enhanced the apoptosis-inducing potential of TRAIL in androgen-unresponsive PC-3 cells and sensitized androgen-responsive TRAIL-resistant LNCaP cells. Curcumin inhibited the expressions of Bel-2, Bel-XL, survivin and XIAP, and induced the expressions Bax, Bak, PUMA, Bim, and Noxa and death receptors (TRAIL-R1/DR4 and TRAIL-R2/DR5) in both cell lines. Over expression of dominant negative FADD inhibited the interactive effects of curcumin and TRAIL on apoptosis. Treatment of these cells with curcumin resulted in activation of caspase-3, and caspase-9, and drop in mitochondrial membrane potential, and these events were further enhanced when combined with TRAIL. Curcumin inhibited capillary tube formation and migration of HUVEC cells and these effects were further enhanced in the presence of MEK1/2 inhibitor PD98059.

The combined treatment of flavonoids and TRAIL can be a promising chemoprevention and/or new therapy against malignant tumors. Cytotoxic effect of dietary flavonoids in combination with TRAIL on HeLa cells. It was found that treatment with noncytotoxic concentration of some flavonoids significantly sensitizes to TRAIL induced death in HeLa cells. Flavone, apigenin and genistein markedly augmented TRAIL mediated cytotoxicity against HeLa, whereas kaempferol and quercetin produced no effect (Szliszka et al., 2008).

Szliszka et al. (2011) demonstrated that EEP sensitizes TRAIL-resistant prostate cancer cells. The main phenolic components detected in Brazilian green propolis are artepillin C, quercetin, kaempferol and p-coumaric acid. Brazilian propolis and its bioactive components markedly augmented TRAIL-mediated apoptosis and cytotoxicity in prostate cancer cells. Brazilian EEP enhanced the
expression of TRAIL-R2 and the activity of NF-κB in LNCaP cells. The co-treatment of prostate cancer cells with 100 ng/ml TRAIL and 50 µg/ml EEP increased the percentage of apoptotic cells to 65.8±1.2% and caused a significant disruption of ∆Ψm in LNCaP cells. Brazilian EEP helped cells overcome TRAIL resistance by engaging both intrinsic and extrinsic apoptotic pathways and regulating NF-κB activity. The data demonstrate the important role of Brazilian green propolis and its bioactive compounds in prostate cancer chemoprevention through the enhancement of TRAIL-mediated apoptosis.