Molecular mechanism of the effects of quercetin on human breast cancer cells

**INTRODUCTION**

Breast cancer originates from the breast tissue, especially from the inner lining of milk ducts or lobules. It results from a multistep process, which involves initiation, promotion and progression. (Kim et al., 2009). The development of breast cancer involves several proteins and genes, namely; CDK 2 (Cyclin dependent kinase), VEGF (Vascular endothelial growth factor), HIF 1 (Hypoxia-inducible factors), AP 1 (Activator protein), p53, p57, cyclin A and B (Sariego, 2010). Environmental and internal factors; for example smoking and oestrogen have been claimed to be the risk factors for breast cancer] (Anuso et al., 2010). Due to drug resistance and poor prognosis, low success rates have been observed in the management of breast cancer that necessitated the use of complementary and alternative medicine (CAM) and natural health products like dietary polyphenols (Jo et al., 2011). One such novel compound is; Quercetin (3, 3’, 4’, 5, 7-pentahydroxyflavone), which is found in a variety of foods including apples, berries, red onions, tea, broccoli and as well as other green leafy vegetables. The chemopreventive effect of quercetin has been hypothesized to result from inhibition of the cell proliferation (cell cycle arrest, apoptosis, etc..) and angiogenesis in breast cancer cells (Kim et al., 2009; Jo et al., 2011).

**Quercetin and cell cycle to inhibit cell proliferation**

Cell cycle comprises of a series of controlled events that
drive the replication of DNA and cell division. It is divided into several phases: G1 phase, S phase, G2 phase and mitosis (Kim et al., 2009). In a study by Chou et al., (2010) quercetin was found to inhibit progression of human breast MCF-7 cancer cells through down regulation of proteins CDK2, cyclin A, D, E, p53 and p57 involved in cell cycle, which resulted in the arrest of cell cycle. Quercetin has also been found to block cell cycle at G2/M through up-regulation of p21 and cyclin B to regulate cell-cycle arrest at the G1 phase and G2/M phase in breast cancer cell lines (Moon et al., 2008). Likewise, in vivo, quercetin inhibited breast cancer cell line proliferation and led to chemoprevention (Miyamoto et al., 2009). It was also reported that quercetin doses ranging from 50 to 200 µM significantly inhibited proliferation when applied to cultured MCF-7 human breast cancer cells for a definite period of time (Duo et al., 2012).

**Quercetin and apoptosis**

Apoptosis is a process of programmed cell death, where a cell is compelled to be obliterated through activation of proteins called caspases. The proteins break down the cellular components needed for the survival of the cell through a cascade of biochemical events that lead to change the cells morphologically changes and eventual disappearance of cell (Green, 2011).

**Apoptosis with regards to breast cancer**

Normal breast development is controlled by a balance between cell proliferation and apoptosis. Breast cancer, which is formed due to tumor growth often results from uncontrolled proliferation. The balance between proliferation and apoptosis is important in determining the overall growth and or regression of the tumors in response to chemotherapy, radiotherapy and, more recently, hormonal interventions (Vakkala et al., 1999).

**Mitochondrial pathway**

The mitochondrial apoptotic pathway is initiated via Bcl-2 and Bcl-2-associated X (Bax) proteins which increase the mitochondrial membrane potential pore-size allowing cytochrome c, among other pro-apoptotic proteins, to leak out into the cytosol. Cytochrome c then activates apoptotic protease activating-factor 1 (APAF-1) and undergoes a conformational change forming the apoptosome. This enlists caspase-9 in order to activate executioner proteins, caspase-7 and caspase-3 to subsequently drive the cell to death (Tan et al., 2009). These workers have further reported that quercetin doses of 40–50 mM induced apoptosis in multiple cancer cell lines (Tan et al., 2009). At 200 – 250 mM doses of quercetin, p53, caspase-9 activation, caspase-3, cytochrome c proteins were up-regulated in vitro, which induced apoptosis in human breast cancer cells MDA-MB-231 (Chien et al., 2009).

**Protein chaperone inhibition pathway**

Quercetin promotes apoptosis by modulating the proliferation and cell maintenance pathways (Bcl-2 and XIAP inhibition) (Kim et al., 2013). However, it is emerging that quercetin directs protein chaperone inhibition and may play an important role in the stimulation to cell death (Aalinkeel et al., 2008). When protein chaperones are unable to perform their duties, cell functionality is decreased and cell death occurs. It was also revealed that quercetin initiates apoptosis via the mitochondrial pathway involves the activation of caspase-3 downstream from caspase-9 (Aalinkeel et al., 2008).

Quercetin also inactivates these protein chaperones, possibly by its ability to inhibit the kinases that aid in HSP induction (Zhang et al., 2009).

The mechanism involves the expression of HSP70 after stimulation by radiation-induced heat in tumor cells. The heat induces the phosphorylation of heat shock transcription factor 1 (HSF1) by either casein kinase 2 (CK2) or calcium/calmodulin kinase II (CamKII). Once phosphorylated, these kinases activate HSF1, which catalyzes the transcription of HSP70. Quercetin can inhibit HSP70 expression but with no effect on HSP27 (Zhang et al., 2009).

**Endoplastic reticulum (ER) stress pathway**

ER is the cellular organelle responsible for the packaging and synthesis of many nutrients. Endoplasmic reticulum stress is also known as the unfolded protein response, as an accumulation of misshapen proteins increases endoplasmic reticulum stress in cells. It was found to initiate mitochondria-mediated apoptosis by increasing inter-mitochondrial calcium concentration (Lee et al., 2006) that leads to increased recruitment of Bax and thus decreasing mitochondrial membrane potential (Li et al., 2008).

This release triggers the activation of caspase-9 and -3, and then cell death. Inhibition of HSP70 in MCF-7, cell lines by quercetin (100 mM) was followed by initiation of the unfolded protein response initiating increased expression of glucose regulated protein 78 (GRP78) (Li et al., 2008). This provides a clue for cells to resist quercetin-induced apoptosis. However, it has been established that when GRP78 is inhibited, there is increased quercetin-mediated apoptosis (Lee et al., 2006). This provides evidence that quercetin may be able to work in collaboration with other compounds in order to mediate cell death via the endoplasmic reticulum stress pathway.
frightening health problem supplementation or another form of treatment(s) should be necessary for therapeutic responses.

References


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