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Anti-carcinogenic and neuroprotective potentials of quercetin: Friend or foe?

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Abstract
Quercetin (3,5,7,3',4'-pentahydroxy flavone) is the extensive class of polyphenolic flavonoids ubiquitously found in plants such as apples, onions, seeds, tea, berries etc. It has diverse biological activities including anti-proliferative, apoptotic, prevents oxidant injury and cell death by several mechanisms which includes scavenging oxygen radicals, protecting against lipid peroxidation and chelating metal ions. Our studies proved that quercetin induces cell cycle arrest and regulates uPA and uPAR mRNA expression in prostate cancer cells. Quercetin reverses the EGF induced epithelial mesenchymal transition, migration and invasion in prostate cancer. Apart from antioxidant property, quercetin acts as a neuroprotectant through restoration of Purkinje cells of cerebellum and pyramidal cells of cerebral cortex of PCB treated adult male rats. Behavioral analysis claims drastic revitalization of cognitive function like learning and memory on treatment with quercetin. Thus quercetin prevents prostate cancer metastasis in prostate and breast cancer cells. It also prevents the degeneration in the brain regions in PCB treated rats. Depend on the nature of the cell quercetin acts as friend and foe.

Keywords: anti-cancer, neuroprotectant, antioxidants, PCB toxicity

Introduction

Quercetin is a plant flavonoid which is widely distributed in plants and exhibits a wide spectrum of biological activities such as antioxidant, antitumor, anti-inflammatory, antimicrobial, antiviral and spasmolytic effects (Formica and Regelson, 1995; D'Andrea, 2015; Scambia *et al.*, 1990; Wright *et al.*, 2010; Boesch-Saasatmasndi *et al.*, 2011) [23, 19, 57, 80, 15]. In the cardiovascular system, quercetin has been shown to prevent atherosclerotic plaque formation, prevent platelet aggregation and promote relaxation of cardiovascular smooth muscle. Dual effects of quercetin on contraction in cardiac and skeletal muscle preparations (Apisariyakul *et al.*, 1999) [6]. Quercetin (3,3', 4',5,7- pentahydroxyflavone) is a ubiquitous flavonol in human diets found especially in fruits, vegetables, tea and red wine (Formica and Regelson, 1995) [23]. In addition to antioxidant activity, the putative health effects of quercetin have been attributed to bio activities such as the induction of apoptosis, antimutagenic actions, modulation of the cell cycle and inhibition of angiogenesis and angiotensin – converting enzyme II (Tan *et al.*, 2003) [65]. The effects of quercetin may be mediated substantially by its metabolites (Graf *et al.*, 2006) [25].

Upon absorption in the gastrointestinal tract, quercetin is metabolized by phase II enzymes in gastric and intestinal epithelial cells and conjugated metabolites are further metabolized in the liver and kidney (De Boer *et al.*, 2005) [20]. The B ring catechol structure is methylated at the 3' or 4' hydroxyl site by catechol – o – methyl transferase (COMT), resulting in the formation of isorhamnetin and tamarixetin, respectively (Van der Woude *et al.*, 2004) [68]. Quercetin metabolites appear to accumulate in tissues even after short term ingestion of quercetin rich vegetables (Manach *et al.*, 1997) [43].

Quercetin is a dietary polyphenol because it can exert biphasic dose responses on cells depending on its concentrations. 40-100µM of quercetin are observed as the effect of cancer prevention and they are likely to mediates its antioxidant properties. Pro–oxidant effects are present at cellular concentrations of 40 - 100µM. However, at higher concentrations, many novel pathways in addition to ROS contribute to its effects (Vargas and Burd, 2010) [69]. The potent bioactivity of quercetin has led to vigorous studies on neuroprotection and cancer prevention are discussed in this review.

Quercetin could be used in both the prevention and treatment of cancer and that diet would likely fulfil the concentration requirements for prevention, but supplementation could be necessary for therapeutic responses. Quercetin's ability to interact with electrons at high concentrations plays a central role in its mechanism of action, mainly by the activation of proteins and DNA damage leading to the induction of many downstream pathways.

Malignant tumors results from uncontrolled cell growth are due to mutations. Mutations are result of DNA damage which is commonly incurred through exposure to reactive oxygen species (ROS). Quercetin is able to donate electrons to ROS (Awad *et al.*, 2000) [8] and thereby reduce their availability to damage cellular DNA (Metodiewa *et al.*, 1999) [44]. This is the primary mechanism by which quercetin exerts antioxidant and neuropreventive effects on the cell. Quercetin is able to increase cytotoxicity in tumor cells and oxidative stress usually at greater than 40 µM concentrations; it is able to do

this by becoming ROS itself and by increasing damage or apoptosis pathways in the transformed cell. These benefits rely on ROS and the quercetin concentration to produce either anti or pro – oxidant effects.

Quercetin is consumed daily by millions of people through nuts, tea, vegetables and herbs in the diet. It is available as a commercial dietary supplement and it is now being included in functional foods. Quercetin is generally recognized as safe in oral dosages of 1000mg / day (Harwood *et al.*, 2007) [30] or in intravenously administered dosages of 756mg / day. Upto 60% of orally ingested quercetin is absorbed and the average dietary intake or quercetin is between 6 and 31 mg daily. It is normally found in the glycosylated form. Digestion of most dietary quercetin, in the form of quercetin glycosides begins in the oral cavity with some cleavage of the glycosides catalyzed by β –glycosidase. Hydrolysis of quercetin by β – glycosidase results in different metabolites of quercetin depending on what the original glycoside was. These metabolites include not only free quercetin but also conjugates such as glucuronidase, O-methylated products and sulphate forms(Murota and Terao, 2003) [47]. This conjugation of quercetin is reported to occur throughout the process of digestion and absorption (Murota and Terao, 2003) [47]. Animal studies demonstrated that blood contains mostly quercetin metabolites after quercetin ingestion wheras only the organs involved in quercetin metabolism are kidney, liver and intestine can contain significant amounts of free quercetin in addition to methylated forms. Therefore, studies suggest that quercetin distribution and absorption depend on its form (Bieger *et al.*, 2008) [14].

Antioxidant mechanism of quercetin

Recent study looking at quercetin's antioxidant mechanism in colorectal adenocarcinoma cells ($Caco_2$)found that treatment consisting of 1µM concentrations of quercetin led to decreased double stranded DNA breaks but that higher concentrations of quercetin increased double stranded DNA breakage (Min and Ebeler, 2009) [45]. Quercetin also has the ability to work synergistically with other systems of antioxidant to decrease oxidative stress in the body. When quercetin exerts its antioxidant power it can advance to the semiquinone or even the O – quinine state (Kim and Jang, 2009) [35]. Our earlier studies on PCB induced oxidative stress has been decreased on the ventral prostate after quercetin supplementation (Vijayababu *et al.*, 2000). Quercetin is able to chelate ROS, react with hydrogen peroxide to reduce ROS and use GSH mediated reduction in order to return ROS to their reduced states (Kim and Jang 2009) [35]. This cocooperativity with GSH is likely one mechanism by which quercetin can protect the cell from mutagenesis. Long-term high dose may be able to cause cellular damage.

Pro oxidant mechanisms of quercetin

Quercetin is able to act as a pro oxidant at concentrations greater than 40µM which is agreement with Watjen *et al.*, (2005). Therefore, quercetin could likely be used as an adjuvant to current chemotherapies and if quercetin is activated (oxidized) by enzymes in tumor cells, the dose needed for the pro oxidant or anti – tumor responses could be considerably lower(Thangasamy *et al.*, 2008) [67].

Mitochondrial apoptotic pathway

Apoptosis or programmed cell death is now studied as a cascade of caspases and endonucleases responsible for the proteolytic cleavage of cellular proteins leading to the characteristic apoptotic features like plasma membrane blebbing, cell shrinkage, chromatin condensation and fragmentation (Vermeulen *et al.*, 2005) [71]. Caspases, family totaling of 14 members are synthesized as inactive zymogens, which is proteolytically cleaved as two aspartate residues to generate the active mature enzyme. The generation of active caspases interacts with specific adapter molecules to facilitate their own auto processing. It is now active initiator caspases in turn cleave and activate the downstream executioner caspases. These then cleave their target substrates to orchestrate the proteolytic dismantling of the cell (Henson *et al.*, 2001; Green and Evan, 2002) [32, 27]

This sequence of activation of caspases has been broadly categorized into two pathways, the extrinsic pathway characterized by the engagement of cell surface death receptors (DRS). Caspases 8/10 are initiator caspases in extrinsic pathway and they share a same homology with dead effectors domain (Green and Evan, 2002) [27] and the intrinsic pathway involving key mitochondrial events such as anti-apoptotic protein Bcl_2, Bclxl and proapoptotic protein Bax, Bak, Bad and Bid (Green and Reed 1998) [28], regulating the release of cytochrome c from mitochondria to cytosol. In both cases, an initiator caspase, interacts with a specialized adaptor molecule, which mediates activation and ultimately activates he downstream executioner Caspases. These are the activity of Caspases which ensures the destruction of the cell.

Thus, the mitochondrial apoptotic pathway is initiated via Bcl_2 associated x protein (Bax) and or Bcl_2 homologous antagonist /killer (Bak) proteins that bring about an increase in the mitochondria outer – membrane pore size. This allows for cytochrome C among other pro apoptotic proteins to leak out into the cytoplasm, it is able to combine with apoptotic protease activating factor 1 (APAF – 1) and undergo a conformational change, thus forming the apoptosome. The apoptosome then enlists caspase 9 in order to activate the so called executioner proteins, caspase 7 and caspase 3. Cell death is subsequently carried out by these caspase proteins (Hao *et al.*, 2005) [29].

Quercetin is known inducer of apoptosis in multiple cancer cell lines such as melanoma cells (Thangasamy *et al.*, 2007; 2008) [66, 67]; lung cancer (Jagtop *et al.*, 2009); gastric cancer (Wang *et al.*, 2011) [76], Salivary adenoid cystic carcinoma (Sun *et al.*, 2010) [63] He La cell (Jang *et al.*, 2010), Pancreatic cancer cells (Zhou *et al.*, 2010) [81] heptoma cell line (Grands – Serrano *et al.*, 2006) [26], prostate cancer cells Pc_3 and LNCaP (Vijayababu *et al* 2005; 2006, Senthilkumar *et al.*, 2010;2011) [74, 61, 62]. Quercetin inhibits the proliferation of cancer cells; breast cancer (Cho *et al.*, 2006) [18], lung carcinoma cells and nasopharyngeal carcinoma cells (Ong *et al.*, 2004) [52]. Quercetin enhances TRAIL induced apoptosis in PC3 cells via increased protein stability of death receptor 5 (Jung *et al.*, 2010) [34]. Earlier studies in our laboratory demonstrated that quercetin induced growth inhibition and cell death in prostate carcinoma cells are associated with increase in p^{21} and hypophosphorylated retinoblastoma proteins expression (Vijayababu *et al.*, 2005) [74].

Insulin like growth factors (IGFs), IGF receptors and IGF binding proteins (IGFBPs) constitute the IGF system. Insulin like growth Factors, IGF I, IGF II modulate a diverge range of biological activities including mitogenic actions. $IGFBP_3$ has direct IGF dependent effects on cellular functions. Further we investigated at the mRNA levels of IGF I, IGF II and $IGFBP_3$ expression. Quercetin decreased the IGF I and IGF II mRNA and increased $IGFBP_3$mRNA expression (Senthilkumar *et al.*, 2010) [62]. Our previous studies showed increased secretion of $IGFBP_3$ and and decreased IGF I and IGF II by quercetin treatment (Vijayababu *et al.*, 2006) [72, 73, 75].

Quercetin treatment has been associated with anti-proliferative effects (Lamson and Brignall 2000) [41] and induction of apoptosis in cancer cells but not in normal cells (Nair *et al.*, 2004) [50]. Our recent study demonstrated that quercetin induces apoptosis through activating intrinsic and extrinsic mediated apoptosis as well as down regulate IGF system and its signaling molecules in androgen independent prostate cancer cells (PC3) (Senthilkumar *et al.*, 2010) [62]. Prostate cancer is the most commonly diagnosed malignancy of men. Advance prostate cancer is first treated through chemical or surgical castration because a large percentage of the cancer cells are androgen dependent. The large majority of patients however relapse with a few years of treatment because of the emergence of androgen independent type. There is a great need for novel therapeutic strategies that target the molecular basis of androgen independent chemo resistant prostate cancer.

Development of hormone insensitivity in patients who have been on long term androgen ablation therapy for prostate cancer is associated with reinforcement of the PI3K–AKT pathway (Pfeil *et al.*, 2004) [54]. Increase of p – AKT expression particularly at serine 473, has been shown to correlate with higher Gleason score and is an excellent predictor of poor clinical outcome in PCa patients (Kreisberg *et al.*, 2004) [39]. Activation of PI3K / AKT promotes cell survival, cell migration, proliferation and cytoskeletal rearrangement. Complete activation of the catalytic activity of AKT requires phosphorylation of threonine residues at 308 and a serine residue at 473. It is possible that AKT shows partial activation with phosphorylation at the threonine 305 position. Phosphorylation at ser 473 is the key for the complete activation of AKT. PI3K / AKT signalling can also increase cyclin D1 levels through enhanced mTOR mediated protein translation. Phosphatase and tensin homolog deleted on chromosome ten (PTEN) genewas lost or mutated in a large number of human cancers including prostate cancer (Steck *et al.*, 1997). A number of therapeutic agents have been observed to induce cyclin D 1 degradation in vitro (Alao 2007) [3]. Induction of cyclin D1 degradation is a useful therapy for cancer.

PTEN is a key negative regulator of PI3K, and it is either mutated or lost in human prostate cancer cells. Anti-apoptotic effects of PI3K are due its activation of ser / threonine protein kinase AKT. We observed that quercetin inhibits AKT phosphorylation (Senthilkumar *et al.*, 2010) [62]. Previous reports also support that quercetin decreased phosphorylation of AKT and expression of survivin in prostate cancer cells (Kim *et al.*, 2008) [36]. Decrease in PI3K levels is also one of the reasons for decreased P – AKT. Our study proved that PI3K expression significantly decreased after quercetin treatment. This argument is supported by Gamet – Payrastre*et al.*, (2008) [24] that quercetin is an inhibitor of PI3K. PI3K and AKT may be processing molecular targets in the management of prostate cancer. We have studied the combination of PI3K inhibition (LY 294002) and quercetin on pAKT was observed. PI3K – AKT and its associated regulatory signalling pathways are potential targets for therapeutic intervention and molecular based approaches for management of prostate cancer in humans. By inhibit the activation of AKT -1, quercetin can promote apoptosis via several pathways. Decrease in pAKT decreases the phosphorylating Bad on the serine 136 as a result total Bad increases. In the recent study, Bad significantly increased after quercetin treatment. Thus quercetin serves as a potent inhibitor of PI3K / AKT pathway.

Cyclin D1 is known as proto-oncogene whose gene amplification and protein over expression are frequently observed in tumor cells. It actsas a mitogenic signal senors and is expressed as a delayed early response to many mitogenic signals. Cyclin – Dependent Kinases (CDKs) 4 and 6 are cyclin D1 binding partners. Activated cyclin D1 / CDK 4 and cyclin D1 /CDK6 complex phosphorylate the retinoblastoma protein to induce the expression of target genes essential for S phase entry resulting in facilitation of the progression from G1 to S phase (Takahshi-Yanaga and Susaguri, 2008). Defects in DNA replication are implicated as early and casual events in malignancy. Quercetin decreases cyclin D1 expression on PC cells (Senthilkumar *et al.*, 2010) [62]. Our previous studies demonstrated that quercetin increases the expression of P^{21}. It may prevent the binding of cyclin D1 to CDK 4. Pathways responsible for targeting G1 cyclins the proteosomal degradation can be engaged pharmacologically. The importance of cyclin D1 in cancer makes it an attractive target for anticancer therapy and degradation of cyclins as a target for cancer therapy (Kim *et al*. 2008) [36]. Our studies demonstrated that quercetin decreases mRNA expression levels of IGF I, IGF II, IGF IR and protein levels of IGF IR-β, PI3K, p–AKT, cyclin D and induces extrinsic and intrinsic pathway mediated apoptosis in androgen independent prostate cancer cells.

Progression of prostate cancer is facilitated autocrine / paracrine growth factors and their signalling cascade promotes prostate cancer cell growth, survival and migration. Alterations of growth factors and their receptors may lead to the development of cancer. Epidermal Growth Factor Receptor (EGFR) over expression is driven by gene amplification and is associated to carcinomas with high invasive potential. Growth factors and their receptors are over expressed in advanced prostate cancer including EGF, transforming growth factor TGF alpha and beta, fibroblast growth factor (FGF) and IGF. The urokinase plasminogen activator (UPAR/UPA) system plays a major role in extra cellular matrix proteolysis and tumor invasion. Secreted UPA binds to its cell membrane associated receptor and converts serum plasminogen to plasmin. Plasmin is a serum protease that can degrade basement membrane proteins. UPA binding to UPAR activates various pathways, including the ras – extracellular signal regulated kinase pathway (ERK) which control cancer cell migration, growth and invasion (Aguirre Ghiso *et al.*, 1999) [2].

UPA expression was not present innormal prostate cancer (LNCap) but increased UPA expression was found in androgen independent prostate cancer cells (Pakneshan *et al.*, 2003; Senthilkumar *et al.*, 2011) [61]. UPA can activate nuclear localization of cFos and cJun transcription factors which are necessary for cell cycle progression (Weber *et al.*, 1997) [79]. Ras is a small GTP binding protein, which is the common upstream molecule of several signaling pathways including Raf / MEK /ERK. EGF receptor (Erb B -1) mediated Ras activation was reported in 40% of prostate tumors. Ras and its effectors may be appropriate targets for therapeutic intervention. The role of NF Kappa β activation in cell survival has been well documented in various cancer systems. NFκβ is a cell survival factor which can be activated by many types of stimuli including tumor necrosis factor, EGF, UV radiation etc.

AKT was found to phosphorylate and activate NFκβ also phosphorylate and inactivate GSK-3. GSK in turn phosphorylates and degraded the β catenin during apoptosis. β–catenin is a transcription factor known to promote survival by regulating the expression of other survival genes such as c–myc (He *et al.*, 1998), Dunn *et al.*, (2002) [21] studied that IGF can up regulate UPA transcription directly through the AP -1 and its sites in the UPA promoter. Our recent study also we found that quercetin decreases the UPA and UPAR mRNA expression in PC3 cells. UPA activated the matrix metalloproteases (MMP2 and MMP9) during invasion. In our earlier studies also showed that quercetin down regulates MMP2 and MMP9 protein expression in prostate cancer cells (Vijayababu *et al.*, 2005) [74].

UPAR signalling activates ERK in many cells. Quercetin significantly decreased the mRNA expressions of EGF, EGF-R and phosphorylation of EGF R protein. Thus quercetin decreased the EGF system thereby inhibits cell proliferation of PC3 cells (Senthilkumar *et al.*, 2011) [61]. Ras regulates several cell cycle proteins; it inactivates RB protein through the activation of G1 cdks. This has been shown to occur through the stimulation of cyclin D1 transcription as well as by increasing cyclin D1/cdk kinase activity. Thus, quercetin significantly reduces the Ras and Raf-1 expression thereby reduces the cell cycle progression. c-Fos and c-Jun genes are expressed constitutively in certain tissues. The inducible transcriptional complex AP1 composed of c-Fos and c-Jun proteins is crucial for cell adaptation to many environmental changes. Fos/Jun heterodimers are present in the AP-1 transcription factor complex and both c-Fos and c-Jun are capable of transforming cells. Increased activity of Jun and AKT phosphorylation in human prostate cancer is positively correlated. JNK and c-Jun phosphorylation was found in PTEN null cells and tissues (Agarwal *et al.*, 2003) [1]. PC 3 cells are PTEN null cells. Quercetin decreased c - Jun, c - Fos and PC JUN protein expression which in turn decreased the regulatory genes transcription thereby inhibit progression of PC3 cells.

P^{38} MAPK can also directly phosphorylate cyclin D1 and promotes proteosomal degradation by ubiquitination. In our study also quercetin increases p^{38} MAPK leads to decrease in cell proliferation and survival. NFκBplays an important role in the apoptotic process. β-catenin levels are regulated by a multiprotein complex containing the tumorsuppressor adenomatous polyposis coli (APC) the scaffolding protein axin and GSK-3-β. Phosphorylation of β catenin by GSK 3 β targets β catenin for ubiquitination and subsequent degradation (Liu *et al.*, 2003). Signals that prevent GSK-3 mediatedβ–catenin phosphorylation cause an accumulation of β catenin in the cytosol and its subsequent translocation to the nucleus.

Several cellular proteins have been activated by AKT. The AKT substrates include components of apoptotic machinery molecules such as BAD, GSK, Caspases 9 transcription factors of the forehead family and IKK which regulates NFκB transcription factor. Transfection with constitutively active GSK -3 induces apoptosis, whereas transfection of cells with kinase inactive GSK-3 blocks apoptosis. GSK phosphorylates β catenin and promotes the degradation by the proteosome during apoptotic processes. Because AKT phosphorylates and inhibits GSK-3, it may lead to stabilization of β catenin. Quercetin significantly decreased the β catenin protein expression (Senthilkumar *et al.*, 2011) [61]. Our previous report showed that quercetin inhibited the phosphorylation of AKT (Senthilkumar *et al.*, 2010) [61] which may consequently inhibit the phosphorylation of GSK -3. Thus we provide evidence that quercetin is a potent sensitizer by down regulating UPA, UPAR,EGF,EGFR mRNA and NFK β,β catenin, Ras, Raf signalling molecules thereby decreasing cell survival, proliferation, migration and invasion of PC3 cells. Thus, quercetin may be useful for the treatment of metastasis of prostate cancer.

Neuroprotectant

Polychlorinated biphenyls (PCBs) are environmental toxicants associated with numerous adverse health effects through widespread bioaccumulation in the biosphere and bio concentration in the food chain (Norstrom *et al.*, 2010). Acute and long-term exposure to PCBs has been reported to cause neurological and non-specific psychological effects such as depression, sleeplessness, memory disturbances, nervousness, fatigue and impotence (Schantz 1996) [58]. The ability of PCBs to accumulate in brain tissue (Caudle *et al.*, 2006) [17] is likely related to their neurotoxicity. PCB induced toxic manifestations are associated with the production of free radicals (Allen and Tresini 2000) [4] which can damage the cellular elements in developing nervous system.

PCBs are used in dielectric fluids in transformer, and capacitors, heat transfer fluids and lubricants (Webb and Mc Call *et al.*, 1972) [78]. Adverse effects of PCB has been extensively studied as endocrine disruptors (ATSDR 2000; Anbalagan *et al.*, 2003) [7], male reproductive disorders (Murugesan *et al.*, 2005; Krishnamoorthy *et al.*, 2007; Selvakumar *et al.*, 2011) [48, 40, 55], carcinogen (ATSDR 2000) [7], immune depressants; thyroid cancer (Bastomky *et al.*, 1974; 1976) [10, 11] hypertension, diabetes (Longnecker *et al.*, 2001) [42] and hepato toxicant (Banudevi *et al.*, 2005) PCBs are neurotoxicant by altering dopaminergic neurotransmission in mammalian forebrain by inhibiting the activity of tyrosine hydroxylase, the rate limiting enzyme in dopamine biosynthesis (Selvakumar *et al.*, 2012) [60], produces toxicity by binding to an aryl hydrocarbon (Ah) receptor by accumulate in brain following in vivo exposure and decrease dopamine content (Kodavanti *et al.*, 1998) [39]. PCBs are

highly toxic to the developing nervous system (Melissa *et al.*, 2009) by disruption of dopamine (DA) function. It interferes with calcium homeostatic mechanism and intracellular second messenger systems (Kodavanti, 2005) [38]. Seelbach *et al.*, (2010) studied the availability of individual PCB congeners to promote brain metastases possibly by disrupting the integrity of the blood brain barrier.

In infants and children, PCBs modify cognitive processes including abnormal reflexes and deficits in memory, learning and IQ (Faroon *et al.*, 2000) [22]. Previous studies in our laboratory demonstrated that PCBs induce oxidative stress in rat brain by decreasing the activities of antioxidant enzymes altering membrane bound ATPase, cholinergic function and decreases the neurotransmitters (Venkataraman *et al.*, 2007; Selvakumar *et al.*, 2013) [40, 59]. In the mammalian brain, the cerebral cortex is a sheet of neural tissue that is outermost to the cerebrum. Cerebellum is an important region balance; cognitive functions such as attention, language, emotional functions such as regulating fear and pleasure responses. It does not initiate movement but contributes coordination, precision and accurate timing (Venkataraman *et al.*, 2007) [40].

Neurotransmitters are endogenous chemicals which transmit signals from a neuron to a target cell across the synapse. They transmit their signals via metabotrophic receptors (GPCR), ionotrophicreceptors (Ligand gated, voltage gated). The major neurotransmitters are dopamine, glutamate, aspartate, gamma butyric acid, glycine, nor epinephrine, epinephrine and serotonin. Dopamine regulates movement, emotion, motivation and feeling of pleasure. Dopamine stabilizes the brain function to regulate flow of information to other parts of the brain and controls movement. It transmits signals via metabotrophic receptors.

Metabotrophic are coupled with seven transmembrane protein G protein coupled receptors (Missale *et al.*, 1998) [46]. There are five types of dopamine receptors. D1, D2, D3, D4 and D5 have been identified in brain regions. D1 like receptors family are excitatory or stimulatory, D2 like receptor family are inhibitory functions. Drd1 receptors are located throughout the brain regions, regulates neuronal growth and development, mediate some behavioural responses and modulate dopamine. Drd2 receptors are present in caudate putamen, nucleus accumbens and olfactory tubule modulates locomotion, reward reinforcement, memory and learning. Drd3 receptors are present in nucleus accumbens, olfactory tubule and island of calleja which modulates locomotion, cognition and emotion. Drd4 receptors are available in the frontal cortex, midbrain, amygdale and the cardiovascular system which regenerates cognition and emotion. Drd5 is present in limbic areas which modulates dopamine (Missale *et al.*, 1998) [46].

Quercetin a flavonoid has been shown to have a beneficial role in neuroprotection (Cho *et al.*, 2006) [18] and it has much stronger antioxidant activity (Ipeo and Lee 2004) [52]. It has potential for treatment of neuroleptic induced extra pyramidal side effects such as from haloperidol (Naidu and Kulkarni 2004) [49]. It increases brain GSH level, hydroxyl radical (OH^+) scavenging capacity and Na^+/K^+ ATPase activity but decreases brain NOS activity and mitochondrial malondialdehyde content which consequently resulted in the improvement of the spontaneous behaviour and cognitive performance and enhancement of brain inherent antioxidant capacity (Pu *et al.*, 2007) [56].

PCBs altered the dopaminergic receptors mRNA expression by producing ROS and disrupting the functional markers of brain such as brain specific creatine kinase, acetyl choline esterase and membrane bound ATPases. Quercetin acts against PCB induced neurotoxicity in cerebral cortex (Pradeepa Kumari *et al.*, 2012), cerebellum (Bavithra *et al.*, 2012, 2017) [12, 13], hippocampus (Selvakumar *et al.*, 2012, 2013) [59, 60] by decreasing oxidative stress by scavenging ROS and brought back the mRNA expression of dopaminergic receptors. Thus quercetin treatment precludes against PCBs induced oxidative stress and protects dopaminergic receptors in rat cerebral cortex, cerebellum and hippocampus.

PCB induced neurodegeneration has also been assessed by histological studies. The degenerative neurons, Pyknotic nuclei with prominent peri - neuronal space, neuronal shrinkage of pyramidal cells on the cerebral cortex, degenerated neuronal morphology of Purkinje and granule cells on the cerebellum, were observed after PCB exposure. Brouwer *et al.*, (1998) [16] studied that PCBs could affect the cerebellar development through their complex actions on the thyroid hormone system. In our earlier study also Anbalagan *et al.*, (2003) [5] demonstrated that PCBs exposure decreased the thyroid hormonal profiles (Murugesan *et al.*, 2005) [48]. In our recent study also morphology of Purkinjee cells of the cerebellum was changed may be due to enhanced free radicals level in PCB exposed rats and the restoration of Purkinje cells with few degenerated neurons in cerebellum of PCB with supplementation of quercetin treated rats reveals that quercetin has scavenged the ROS and protected cerebellum. The same explanation is applicable in both cerebral cortex and hippocampus also. Collectively the data indicate stress plays a key role in the in vivo pathological process of PCBs intoxication. The alterations of dopaminergic receptors may be due to PCBs mediated oxidative stress which is quenched by the anti-oxidative property of quercetin.

Thus, quercetin shows wide spectrum of therapeutic properties as a neuroprotectant and anticancer drug by decreasing the cell survival, proliferation and metastasis of prostate cancer cells. It decreases IGF system components by decreasing IGF I and II and increases IGFBPs. It also decreases PI3K/PAKT, NFKB, β catenin, Ras, Raf–1, c Fos, c Jun, p–c Jun on PC3 cells. It also decreases EGF, EGFR mRNA levels, UPA, UPAR mRNA levels and MMPs on PC3 cells. In vivo studies on prostate cancer as well as on neuroblastoma cell lines are in progress. Further therapeutic values of quercetin in the treatment of prostate cancer and the neural disorders are warranted. Hence uniqueness of quercetin is serves as a friend and foe depends on the nature of the cell its function.

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