Various oncogenes are associated with deregulation in cell proliferation, apoptosis and cell survival, leading to cancer. Aberrant activation of PI3K-AKT signaling is known modulator of cancerous growth. Overproduction of ROS in tumor microenvironment due to higher metabolic activity is further increased owing to oncogenic signaling pathways. Oxidative stress is a major contributor of cancer development, upregulates expression of oncogenic signaling; down regulates apoptosis as well as induces inflammation and angiogenesis. Targeting deregulated signaling pathways in cancer should regulate cellular processes like cell proliferation, survival or angiogenesis towards prevention of carcinogenesis. Present study was aimed to analyze oncogenic signaling pathway and its correlation with ROS production, cell survival, apoptosis, angiogenesis and energy metabolism during lymphoma growth in mice. Further, the study reveals anticarcinogenic role of quercetin (QUE) in Non-Hodgkin’s T-cell lymphoma (Dalton’s Lymphoma-DL) bearing mice. Accumulation of ascite fluid in peritoneum of mice is a hallmark of lymphoma growth. Therefore, ascite cells were used for experimental purpose to study the effect of QUE in prevention of cancer progression.

**Experimental Strategies**

1. Induction of Dalton’s lymphoma in mice
2. Treatment of Dalton’s lymphoma bearing mice with three different doses of quercetin through i.p.
3. Effect of QUE on DL mice
   i. Lymphoma growth in terms of body weight, volume of ascite fluid accumulation, life span and cell proliferation
   ii. Apoptosis
      • Morphological assessment
      • Intrinsic and extrinsic pathway
   iii. Level of ROS
   iv. PKC signaling
      • Total PKC activity
      • Level of PKCα and PKCδ
      • Expression of classical, novel and atypical isoenzymes
   v. PI3K-AKT signaling pathway
      • Expression, level and phosphorylation of p85α
      • Expression and level of p110α
• Level and phosphorylation of AKT
• Expression and level of tumor suppressor p53 and PTEN
• Phosphorylation of PDK1
• Phosphorylation of AKT downstream protein- BAD, GSK-3β, mTOR, NF-kB

vi. Inflammation: level of COX-2 and iNOS
vii. Glycolytic metabolism: expression and activity of LDH-A
viii. Angiogenesis: expression of VEGF

4. Anti-carcinogenic action of QUE on HepG2 cells

5. Effect of H$_2$O$_2$ on modulation of PI3K-AKT signaling pathway in DLA cells in vitro

6. Effect of QUE on modulation of PI3K-AKT signaling pathway in H$_2$O$_2$ induced DLA cells in vitro

**Salient Findings**

The results obtained from different parameters studied here to investigate the effect of QUE in ascite cells of Dalton’s lymphoma bearing mice are summarized below in detail.

1. QUE decreased body weight and volume of ascite fluid, whereas improved longevity of DL mice.

2. Decreased cell viability, glycolytic metabolism and induced apoptosis were observed after QUE treatment.

3. Accumulation of ROS and activity of PKC were declined after QUE treatment. This was correlated with modulation of conventional, novel and atypical PKC isoenzymes, especially decreased PKCα and induced PKCδ level.

4. Anti-carcinogenic activity of QUE was suggested by reduced cell proliferation, survival and increased apoptosis in HepG2 cells.

5. QUE treatment to DL mice caused suppression of PI3K-AKT signaling via decreased level of downstream cell survival factors; p-BAD, p-GSK-3β, p-mTOR; and via increased level of tumor suppressor p53 and PTEN.

6. Angiogenic inducer VEGF-A was downregulated by QUE in DL mice. QUE decreased level of NF-κB mediated inflammatory factors iNOS and COX-2.

7. Exposure of H$_2$O$_2$ caused hyperactivation of PI3K-AKT signaling in terms of increased phosphorylation of PI3K, AKT and PDK1 as well as declined level of tumor suppressor
PTEN in ascite cells in vitro. This was consistent with increased level of cell survival factors p-BAD and TNFR1.

8. Effect of QUE was found similar to that of PI3K inhibitor (PI-103) in H2O2-induced ascite cells in vitro. Reduced phosphorylation of AKT, PDK1 and decreased level of cell survival factors p-BAD, TNFR1 as well as increased level of tumor suppressor PTEN was observed by both PI-103 & QUE.

9. QUE shows dose dependant response at all parameters studied. Anti-carcinogenic action of QUE was exhibited at translational and post-translational modification level in DL mice.

Modulation of carcinogenic signaling pathway by QUE is depicted below.

**Conclusion**