The Effects of Quercetin on Antioxidant Status and Tumor Markers in the Lung and Serum of Mice Treated with Benzo(a)pyrene

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Chemoprevention has emerged as a very effective preventive measure against carcinogenesis. Several bioactive compounds present in fruits and vegetables have revealed their cancer curative potential on benzo(a)pyrene (B(a)P)-induced carcinogenesis. In the present study, the efficacy of quercetin on the level of lipid peroxides, activities of antioxidant enzymes and tumor marker enzymes in B(a)P-induced experimental lung carcinogenesis in Swiss albino mice was assessed. In lung cancer bearing animals there was an increase in lung weight, lipid peroxidation and marker enzymes such as aryl hydrocarbon hydroxylase, gamma glutamyl transpeptidase, 5'-nucleotidase, lactate dehydrogenase and adenosine deaminase with subsequent decrease in body weight and antioxidant enzymes—superoxide dismutase, catalase, glutathione peroxidase, glutathione-S-transferase, glutathione reductase, reduced glutathione, vitamin E and vitamin C. Quercetin supplementation (25 mg/kg body weight) attenuated all these alterations, which indicates the anticancer effect that was further confirmed by histopathological analysis. Overall, the above data shows that the anticancer effect of quercetin is more pronounced when used as a chemopreventive agent rather than as a chemotherapeutic agent against B(a)P-induced lung carcinogenesis.

Key words quercetin; benzo(a)pyrene; tumor marker; lipid peroxidation; antioxidant; flavonoid

Lung cancer is the most common cause of cancer deaths in developed countries and both men (80—90%) and women (40—50%) worldwide of which about 90% are associated with tobacco use.1,2 Over one million people around the world are likely to be killed by lung cancer due to increased tobacco habit.3 The polycyclic aromatic hydrocarbons (PAH) and N-nitrosamines are the two major classes of tobacco-related inhaled carcinogens. The PAH including Benzo(a)pyrene (B(a)P), a potent tobacco carcinogen (amount of B(a)P per cigarette is 18—50 ng)4 is a significant pro-carcinogenic substance, which requires metabolic activation to electrophilic reactive metabolites for its carcinogenic activity.5 It is well established that B(a)P after sequential metabolic activation principally by cytochrome P450 generates 7,8-diol-9,10-epoxide-benzo(a)pyrene, which is believed to be the ultimate carcinogenic metabolite of B(a)P5 that leads to the formation of DNA adducts. During metabolic processes, B(a)P in cigarette smoke can be directly or indirectly metabolized into free radicals.5

Chemoprevention offers a novel approach to control the incidence of lung cancer. The search for new chemopreventive and antitumor agents that are more effective and less toxic has kindled great interest in phytochemicals.7 A recent international report concluded that high dietary intake of alkaloids and flavonoids reduce further risk of developing lung cancer. The main mechanism responsible for this reduced risk is the strong antioxidant effect of these substances. 8 Quercetin [3-ol-2-[3,4-dihydroxyphenyl]-3,5,7-trihydroxy-4H-1-benzopyran-4-one], one of the most abundant of the naturally occurring flavonoid and dietary nutrient found in onion, grapes, green vegetables etc. has been shown to possess potent antioxidant and antiproliferative effects against various malignant cells,9,10 is also a potent cytochrome P450 inhibitor. It has a wide spectrum of anticancer properties including inhibition of the growth of cells derived from human cancers such as those of stomach,11 colon,12 prostate13 and breast.14 Additionally, it suppresses the growth and development of uterine cervical cancer,15 melanomas16 and intestinal tumors17 in whole mice. Quercetin terminates chain radical reactions by donating hydrogen atoms to the peroxyl radical forming of a quercetin radical which in turn reacts with free radicals thus terminating the propagating chain.18 It is known to protect against oxidative damage by quenching free radicals and oxygen species or enhancing antioxidant enzymes.19 These enzymes reduce carcinogen-DNA interaction by providing a large nucleophilic pool for the electrophilic carcinogen.

Hence, our present research aims to demonstrate the preventive effects of quercetin against the B(a)P induced lung carcinogenesis by assessing lipid peroxidation (LPO), antioxidant tissue defense system and marker enzymes such as aryl hydrocarbon hydroxylase (AHH), gamma glutamyl transpeptidase (γ-GT), 5'-nucleotidase (5'-ND), lactate dehydrogenase (LDH) and adenosine deaminase (ADA) in serum and lung.

MATERIALS AND METHODS

Animals Healthy male Swiss albino mice (6—8 weeks old) were used throughout the study. The animals were purchased from Tamil Nadu Veterinary and Animal Sciences University (TANUVAS), Madhavaram, Chennai, India and maintained in a controlled environmental condition of temperature and humidity on alternatively 12 h light/dark cycles. All animals were fed standard pellet diet (Gold Mohor rat feed, M/s. Hindustan Lever Ltd., Mumbai) and water ad libitum.

Chemicals Benzo(a)pyrene, Quercetin, reduced glutathione and Bovine serum albumin were purchased from Sigma Chemical Company (St. Louis, MO, U.S.A.). All other chemicals were procured from SRL Chemicals (Mumbai, India).

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Experimental Protocol The experimental animals were divided into five groups, each group comprising of six animals. Group I served as normal control. Group II animals were administered with B(a)P (50 mg/kg body weight dissolved in corn oil, orally) twice a week to induce lung cancer by 16th week. One week prior to the first dose of B(a)P, group III (pre-treated) animals were administered with quercetin (25 mg/kg body weight, dissolved in 0.1% DMSO, intra peritoneally) twice a week for consecutive weeks. Quercetin was administered intra peritoneally as when administered orally; it was poorly absorbed from digestive tract and did not have a greater influence on the organ. Group IV animals were post treated with quercetin (as in Group III) but from 8th week of B(a)P induction till the end of the experiment (16th week). Group V animals were treated with quercetin alone (as in Group III) for 16 weeks to study the cytotoxicity (if any) induced by quercetin. The pre and post treatment of quercetin were used to study the chemopreventive and/or chemotherapeutic efficacies of quercetin in the experimental animals.

Biochemical Analysis At the end of the experimental period, the animals were anesthetized with diethyl ether followed by cervical decapitation. The serum was separated from the collected blood. Lung tissues were immediately excised, weighed and then homogenized in 0.1 M Tris–HCl buffer (pH 7.4). Both homogenates and serum were taken for the analyses described below. Total protein was estimated by the method of Lowry et al. Lipid peroxides was estimated by the method of Ohkawa et al. Superoxide dismutase (SOD), catalase (CAT), glutathione-S-transferase (GST), glutathione peroxidase (GPx), glutathione reductase (GR), reduced glutathione (GSH), & glutamyl transpeptidase (δ-GIT), vitamin E and vitamin C. The marker enzymes aryl hydrocarbon hydroxylase (AHH) was estimated from digestive tract and did not have a greater influence on the organ. Group V did not show any significant changes when compared with control animals (Group I).

Figure 2 shows the histological analysis of lung section of control and experimental groups. Lung from control (Group I) animals revealed a normal architecture cells with small uniform nuclei (Fig. 2a). Lung cancer bearing animals (Group II) revealed loss of architecture, alveolar damage as seen from hyperchromatic and irregular nuclei in the cells of alveolar wall (Figs. 2b, c). Cancer bearing animals pretreated with quercetin (Group III) exhibited reduced alveolar damage with near normal architecture (Fig. 2d). Group IV animals post treated with quercetin showed slightly reduced alveolar damage (Fig. 2e). Control animals treated with quercetin showed no appreciable change of histopathological abnormalities as that of control animal (Fig. 2f).

Table 1 shows the body weight and lung weight of different groups of mice that were sacrificed at the end of the study. The final body weight of the B(a)P administered (Group II) animals was found to be significantly (p<0.05) lowered and the lung weight was significantly increased (p<0.05) that of untreated control (Group I) animals. Treatment with quercetin increased (p<0.05) the final body weight and significantly lowered lung weight in Group III (pre-treated) and Group IV (post-treated) animals. Table 2 shows the activities of antioxidant enzymes in lung tissues of various experimental groups of animals. Highly significant (p<0.05) reductions in the activities of antioxidant enzymes (SOD, CAT, GPx, GST, GR, GSH, vitamin E and vitamin C) were observed in the cancer bearing animals (Group II). These adverse changes were reversed to near normal values in Group III (quercetin pre-treated) and Group IV (quercetin post-treated) animals. Table 3 represents the effect of quercetin on the activities of marker enzymes in serum of control and experimental groups. The activities of marker enzymes AHH, γ-GT, 5′-ND, LDH and ADA were found to be significantly (p<0.05) increased in lung cancer bearing animals (Group II), that were reversed to near normally in quercetin pre and post treated animals (Group III and IV). However no significant difference was observed between the quercetin alone treated (Group V) and control (Group I) animals.

Figure 1 shows the extent of LPO in the serum and lung of control and experimental groups of animals. In B(a)P induced (Group II) animals, there was a significant (p<0.05) increase in the levels of lipid peroxides when compared with normal control (Group I) animals. Whereas in Group III (quercetin pre-treated) and Group IV (quercetin post-treated) animals there was a significant (p<0.05) decrease in the levels of lipid peroxides when compared with tumor bearing (Group II) animals. However, quercetin alone treated animals
ADA in lung of control and experimental animals. All the above marker enzymes were found to be significantly increased \((p<0.05)\) in lung cancer bearing (Group II) animals when compared with control (Group I) animals. Significantly

**Table 1. Effect of Quercetin on the Body Weight and Lung Weight Control and Experimental Animals**

<table>
<thead>
<tr>
<th>Particulars</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
<th>Group V</th>
</tr>
</thead>
<tbody>
<tr>
<td>Body weight (g)</td>
<td>28±3.95</td>
<td>20±3.11**</td>
<td>26±3.67**</td>
<td>23.3±3.81* (\pm)NS</td>
<td>29.1±3.80</td>
</tr>
<tr>
<td>Lung weight (mg)</td>
<td>285±28.2</td>
<td>325±35.6**</td>
<td>295±28.2**</td>
<td>323.6±32.6* (\pm)NS</td>
<td>256.6±32.6</td>
</tr>
</tbody>
</table>

Each value is expressed as mean±S.D. for six mice in each group. Statistical significance: *\(p<0.05\), NS, not significant. a) Group II compared with Group I. b) Group II compared with Group III and Group IV. c) Group III compared with Group IV.

**Table 2. Effect of Quercetin on the Activities of Antioxidant Enzymes in Lung of Control and Experimental Animals**

<table>
<thead>
<tr>
<th>Particulars</th>
<th>Group I</th>
<th>Group II</th>
<th>Group III</th>
<th>Group IV</th>
<th>Group V</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOD</td>
<td>4.31±0.53</td>
<td>2.61±0.29**</td>
<td>4.21±0.44**</td>
<td>3.96±0.42* (\pm)NS</td>
<td>4.68±0.56</td>
</tr>
<tr>
<td>CAT</td>
<td>249±35.3</td>
<td>123±21.2**</td>
<td>220±52.1**</td>
<td>164±21.0* (\pm)NS</td>
<td>252±35.3</td>
</tr>
<tr>
<td>GPx</td>
<td>42.50±5.62</td>
<td>22.31±3.08**</td>
<td>34.63±9.24**</td>
<td>33.76±5.11* (\pm)NS</td>
<td>43.56±5.38</td>
</tr>
<tr>
<td>GST</td>
<td>232.28±8.4</td>
<td>144±25.7**</td>
<td>203±28.4**</td>
<td>224±35.3* (\pm)NS</td>
<td>235±28.5</td>
</tr>
<tr>
<td>GR</td>
<td>2.94±0.42</td>
<td>1.79±0.14**</td>
<td>2.63±0.28**</td>
<td>2.24±0.24* (\pm)NS</td>
<td>3.04±0.42</td>
</tr>
<tr>
<td>GSH</td>
<td>1.51±0.14</td>
<td>0.98±0.14**</td>
<td>1.42±0.15**</td>
<td>1.13±0.14* (\pm)NS</td>
<td>1.53±0.14</td>
</tr>
<tr>
<td>Vit E</td>
<td>0.58±0.07</td>
<td>0.34±0.04**</td>
<td>0.49±0.05*</td>
<td>0.39±0.04* (\pm)NS</td>
<td>0.53±0.09</td>
</tr>
<tr>
<td>Vit C</td>
<td>0.47±0.05</td>
<td>0.30±0.04**</td>
<td>0.39±0.05*</td>
<td>0.33±0.04* (\pm)NS</td>
<td>0.48±0.05</td>
</tr>
</tbody>
</table>

Each value expressed as mean±S.D. for six mice in each group. SOD, units/min/mg protein; CAT, \(\mu\)mol of \(H_2O_2\) consumed/min/mg protein; GPx, \(\mu\)mol of GSH oxidized/min/mg protein; GST, \(\mu\)mol of 1-chloro-2,4-dinitrobenzene conjugated/min/mg protein; GR, \(\mu\)mol NADPH oxidized/min/mg protein; GSH, \(\mu\)g/mg protein; Vitamin E, \(\mu\)g/mg protein; Vitamin C, \(\mu\)g/mg protein. Statistical significance: *\(p<0.05\), NS, not significant. a) Group II compared with Group I. b) Group II compared with Group III and Group IV. c) Group III compared with Group IV.
formed/min/mg protein; 5 ties of SOD39) and CAT40) in various carcinogenic conditions enzyme systems. Several reports have cited decreased activation of superoxide radical, which is generated by various source of hydrogen peroxide is mainly SOD-mediated dismutates and catalyses the breakdown of hydrogen peroxide. The peroxide mediated LPO. CAT is widely distributed in all tis-

sue against the cytotoxic effects of B(a)P.

quercetin treatment could have protected the normal cell/tis-

sue against the cytotoxic effects of B(a)P.

The products of LPO include malondialdehyde that has been

tated chain reactions initiated in the membrane

lipids.43) It is the most significant antioxidant of its kind in

tissue keeps up the cellular levels of vitamin C and vitamin E in active form. Vitamin E is the major lipid soluble peroxy radical scavenger, which can limit LPO by terminating chain reactions initiated in the membrane lipids.43) It is the most significant antioxidant of its kind in animal cells and can protect against carcinogenesis and tumor growth.43) Vitamin C, which prevents oxidative damage to cell membrane induced by aqueous radicals also exists in interconvertible forms and participates in neutralizing free radicals.43) In the present study, the lung cancer bearing animals showed decrease in the activities of enzymic antioxidants SOD, CAT, GPx, GST, GR and non-enzymic antioxidants GSH, vitamin E and vitamin C. Quercetin supplementation significantly increased all the above antioxidants which may be due to the ability of quercetin to interact with hydroxyl, superoxide, alkoxyl and peroxyl radicals thereby subsequently scavenging them. Hence, it is suggested that the quercetin treatment could have protected the normal cell/tissue against the cytotoxic effects of B(a)P.

Analysis of tumor marker enzymes serves as an indicator of cancer response to therapy. Distribution of many biochemical, immunological and molecular properties of the host has been observed in B(a)P mediated cancer conditions.46) The marker enzymes such as AHH, γ-GT, 5’-ND, LDH and ADA are specific indicators of lung cancer.40,47) Chen and Liu48) reported that AHH is one of the useful biomarkers in early diagnosis of lung cancer. It is responsible for the activation

(\(p<0.05\)) decreased in the activity of these marker enzymes was observed in quercetin pre and post treated (Group III and IV) animals. Group V animals showed no significant difference in the enzyme activities when compared with controls.

DISCUSSION

Reactive oxygen species (ROS) and organic free radical intermediates formed from many carcinogens are suggested to be involved in the initiation and progression of carcinogenic transformation.36) The B(a)P is a very effective carcinogen with a capability to induce enormous amounts of free radicals, which in turn react with lipids causing LPO.37) The products of LPO include malondialdehyde that has been reported to be involved in formation of tumors.38) In the present study, increased LPO in Group II cancer bearing animals may be due to the excessive free radicals produced by administr-ation of B(a)P, whereas significantly decreased levels of lipids peroxides was seen in quercetin treated Group III and IV animals. This clearly shows that quercetin inhibits LPO thereby limiting the formation of LPO products which are involved in carcino genesis.

Antioxidant status has been suggested as a useful tool in estimating the risk of oxidative damage induced carcinogenesis. It is responsible for the activation of superoxide and hydrogen peroxide mediated LPO. CAT is widely distributed in all tissues and catalyses the breakdown of hydrogen peroxide. The source of hydrogen peroxide is mainly SOD-mediated dismutation of superoxide radical, which is generated by various enzyme systems. Several reports have cited decreased activities of SOD39) and CAT40) in various carcinogenic conditions that may be due to the increased LPO. GPx is a well known first line of defense against oxidative stress and its activity was decreased in various cancerous conditions.41) The observed decline in the activity of GPx may be attributed to the reduction in the levels of reduced glutathione and increase in the level of peroxides during lung carcinogenesis. After GSH has been oxidized to GSGG, the recycling of GSSG to GSH is accomplished mainly by GR using NADPH as its source of electrons. GSH is present in high concentration in the cells, it protects cells from free radical attack and this reduced glutathione in tissues keeps up the cellular levels of vitamin C and vitamin E in active form. Vitamin E is the major lipid soluble peroxy radical scavenger, which can limit LPO by terminating chain reactions initiated in the membrane lipids.43) It is the most significant antioxidant of its kind in animal cells and can protect against carcinogenesis and tumor growth.43) Vitamin C, which prevents oxidative damage to cell membrane induced by aqueous radicals also exists in interconvertible forms and participates in neutralizing free radicals.43) In the present study, the lung cancer bearing animals showed decrease in the activities of enzymic antioxidants SOD, CAT, GPx, GST, GR and non-enzymic antioxidants GSH, vitamin E and vitamin C. Quercetin supplementation significantly increased all the above antioxidants which may be due to the ability of quercetin to interact with hydroxyl, superoxide, alkoxyl and peroxyl radicals thereby subsequently scavenging them. Hence, it is suggested that the quercetin treatment could have protected the normal cell/tissue against the cytotoxic effects of B(a)P.

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### Table 3. Effect of Quercetin on the Activities of Marker Enzymes in the Serum of Control and Experimental Animals

<table>
<thead>
<tr>
<th>Particulars</th>
<th>Group I (Control)</th>
<th>Group II (B(a)P)</th>
<th>Group III (B(a)P)+25 mg of quercetin as pre treated</th>
<th>Group IV (B(a)P)+25 mg of quercetin as post treated</th>
<th>Group V 25 mg of quercetin</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHH</td>
<td>0.61±0.08</td>
<td>0.90±0.07</td>
<td>0.65±0.09</td>
<td>0.74±0.06</td>
<td>0.59±0.07</td>
</tr>
<tr>
<td>γ-GT</td>
<td>1.31±0.14</td>
<td>2.18±0.28</td>
<td>1.55±0.21</td>
<td>1.75±0.39</td>
<td>1.29±0.14</td>
</tr>
<tr>
<td>5’-ND</td>
<td>3.24±0.42</td>
<td>5.87±0.70</td>
<td>3.88±0.42</td>
<td>4.41±0.56</td>
<td>3.25±0.42</td>
</tr>
<tr>
<td>LDH</td>
<td>1.45±0.14</td>
<td>2.67±0.28</td>
<td>1.62±0.14</td>
<td>1.86±0.14</td>
<td>1.53±0.13</td>
</tr>
<tr>
<td>ADA</td>
<td>243±29.6</td>
<td>374±49.1</td>
<td>250±35.4</td>
<td>310±42.9</td>
<td>246±28.2</td>
</tr>
</tbody>
</table>

Each value is expressed as mean±S.D. for six mice in each group. AHH, μmol of p-nitroaniline formed/min/mg protein; γ-GT, nmol of p-nitroaniline formed/min/mg protein; 5’-ND, nmol of Pi liberated/min/mg protein; LDH, μmol of pyruvate liberated/min/mg protein; ADA, μmol of NH3 liberated/mg protein/h. Statistical signif-
cance: *p<0.05, NS, not significant. a) Group II compared with Group I. b) Group II compared with Group III and Group IV. c) Group III compared with Group IV.

### Table 4. Effect of Quercetin on the Activities of Marker Enzymes in Lung of Control and Experimental Animals

<table>
<thead>
<tr>
<th>Particulars</th>
<th>Group I (Control)</th>
<th>Group II (B(a)P)</th>
<th>Group III (B(a)P)+25 mg of quercetin as pre treated</th>
<th>Group IV (B(a)P)+25 mg of quercetin as post treated</th>
<th>Group V 25 mg of quercetin</th>
</tr>
</thead>
<tbody>
<tr>
<td>AHH</td>
<td>0.54±0.07</td>
<td>0.86±0.11</td>
<td>0.60±0.08</td>
<td>0.71±0.09</td>
<td>0.52±0.07</td>
</tr>
<tr>
<td>γ-GT</td>
<td>1.23±0.12</td>
<td>1.98±0.27</td>
<td>1.37±0.15</td>
<td>1.53±0.21</td>
<td>1.21±0.13</td>
</tr>
<tr>
<td>5’-ND</td>
<td>1.90±0.28</td>
<td>2.78±0.37</td>
<td>2.07±0.28</td>
<td>2.68±0.36</td>
<td>1.87±0.22</td>
</tr>
<tr>
<td>LDH</td>
<td>1.16±0.15</td>
<td>1.94±0.28</td>
<td>1.34±0.15</td>
<td>1.56±0.21</td>
<td>1.16±0.50</td>
</tr>
<tr>
<td>ADA</td>
<td>438±56.5</td>
<td>624±84.8</td>
<td>487±56.5</td>
<td>542±70</td>
<td>440±56.5</td>
</tr>
</tbody>
</table>

Each value is expressed as mean±S.D. for six mice in each group. AHH, μmol of fluorescent phenolic metabolites formed/min/mg protein; γ-GT, nmol of p-nitroaniline formed/min/mg protein; 5’-ND, nmol of Pi liberated/min/mg protein; LDH, μmol of pyruvate liberated/min/mg protein; ADA, μmol of NH3 liberated/mg protein/h. Statistical signif-
cance: *p<0.05, NS, not significant. a) Group II compared with Group I. b) Group II compared with Group III and Group IV. c) Group III compared with Group IV.
of B(a)P and other PAHs in cigarette smoke leading to carcinogenesis.\textsuperscript{49} The AHH activity was increased in lung cancer bearing animals. This elevation was found to be significantly inhibited upon quercetin supplementation during initiation and post initiation period.

\textgamma-\textit{GT} activity serves as a specific marker for the prognosis of carcinogenic events. \textgamma-\textit{GT} is not only useful in diagnosis but also has extraprotective value in malignancies such as lung cancer and malignant melanoma. An increased level of \textgamma-\textit{GT} was observed in cancer cells.\textsuperscript{50} This elevation may indicate the basic tumor burden. A decreased level of \textgamma-\textit{GT} was observed in quercetin treated animals when compared with lung cancer bearing animals, which indicates decreased tumor burden in quercetin treated animals.

Increased activity of 5'-ND seems to have originated from the proliferating tumor cells,\textsuperscript{51} a fast moving 5'-nucleotide phosphodiesterase is found to be elevated in metastases to liver from tumor of the lung and breast.\textsuperscript{52} In the present study, the elevated activity of 5'-ND was observed in cancer bearing animals and upon administration of quercetin to lung cancer bearing animals the activity of 5'-ND was brought down to near normal values indicating its antitumour and/or antiproliferative effect on lung cancer.

LDH is recognized as a potential tumor marker enzyme in assessing the proliferation of malignant cells. LDH is a fairly sensitive marker for solid neoplasms and elevated activity of the enzyme was reported in serum of lung cancer patients.\textsuperscript{53} The possible reason for elevated levels of LDH may be due to higher glycolysis in cancerous conditions, which is the only energy producing pathway for the uncontrolled proliferating malignant cells.\textsuperscript{54} Decrease in LDH activity on treatment with quercetin protected against abnormal cell growth by changing the permeability of membrane or by affecting cellular growth.

Increased ADA activity may be a compensatory mechanism against toxic accumulation of its substrates due to accelerated purine and pyrimidine metabolism in the cancerous tissues and cells.\textsuperscript{55} It has been reported that the patients with lung cancer were shown to have elevated serum ADA levels.\textsuperscript{56} In the present study increased ADA activity was observed in lung cancer bearing animals. Upon quercetin treatment, the activity of this enzyme was brought back to near normalcy highlighting the antiproliferative/antitumour property of quercetin.

From these observations it can be concluded that the anticancer effect of quercetin is more pronounced when used as an chemopreventive agent rather than as a chemotherapeutic against B(a)P induced lung carcinogenesis in mice by attenuating LPO, by scavenging free radicals and by enhancing the activity of antioxidants, which in turn detoxify free radicals. Histopathological observations were in correlation with biochemical parameters carried out in our study that further support the anticancer effect of quercetin.

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\textbf{REFERENCES}

39) Vinodhikumar R., Ravikumar V., Shivashangari K. S., Kamaraj S., De-