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Research Article

Zoology

Assessment of Proanthocyanidin's Antioxidant Properties in a Lung Cancer Mice Model

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KEY WORDS

Proanthocyanidins, lung carcinogenesis, urethane, butylated hydroxytoluene (BHT), antioxidants

ABSTRACT

Proanthocyanidins (PCs) are numerous polyphenolic compounds found across a broad range of fruits, nuts, flowers, plant skins, and vegetables. Oxidative stress (OS) is the outcome of prooxidant accumulation, such as reactive oxygen species (ROS), beyond the cell's potential for antioxidants. Organelles may sustain damage by OS, macromolecules, and entire tissues. As a result, we employed a lung cancer mouse model caused by either a low or high dose of urethane/butylated hydroxytoluene to assess the antioxidant effectiveness of PCs. The results indicated that both doses of PACs were able to increase the malondialdehyde (MDA) levels while only the 50 mg/kg dose in G3 reduced the plasma superoxide dismutase (SOD) activity in treated mice, unlike the control group. However, both doses of PACs have elevated the catalase and glutathione reductase (GR) activities in G3 and G4 almost to control levels, particularly in G4. Therefore, we concluded that PACs exert antioxidant activities in a way dependent on dosage and might serve as a natural adjuvant lung cancer treatment exerting antioxidant effect.

Introduction

Lung cancer has one of the most severe rates of morbidity in the world and death from cancer, a malignant tumor. Lung cancer (11.4%) is the second most common cause of malignant tumors globally, subsequent to breast cancer (11.7%) **(Sung et al., 2021)**. A possible explanation for the disease's heterogeneity is its pathologically and clinically significant subtypes. Based on their fundamental histotypes, prognoses, and treatment outcomes, small-cell lung carcinoma (SCLC; 12.9% of cases) and non-small-cell lung cancer (NSCLC; 83.9% of cases) are the two main subtypes of lung malignancies **(Fujimoto and Wistuba, 2014).** The most aggressive and quickly spreading form of lung cancer, small cell lung cancer (SCLC), is mostly thought to be caused by smoking **(Salim et al., 2011).**

Grape seed proanthocyanidin extract (GSPE) is an ingredient made from grape seeds that contain oligomers of proanthocyanidins, epicatechin gallate, epigallocatechin, dimers, trimers, and tetramers of flavone-3-alcohol **(González-Quilen et al., 2021).** The name "proanthocyanidins" refers to a broad class of polyphenolic substances. They can efficiently remove superoxide anion and hydroxyl radicals and scavenge free radicals, and are strong antioxidants. Additionally, they encourage the synthesis of phosphoric and arachidonic acids, which shield lipids from peroxidative deterioration. They act as a potent metal chelator, protecting and stabilizing vitamin C and facilitating its absorption and utilization in the body by chelating metal ions into inert compounds **(Lu et al., 2022).** Human degenerative disorders including diabetes, cancer, and cardiovascular disease are relevant to oxidative stress **(Azuma et al., 2019; Andrade et al., 2021).**

Additionally, GSPE has been shown to have anti-cancer qualities in conditions such as esophageal squamous carcinoma **(Guo et al., 2018)**, hepatocellular carcinoma **(Sherif et al., 2017)**, breast cancer **(Song et al., 2010)**, colon cancer **(Engelbrecht et al., 2007)**, and acute myeloid leukemia.

Thus, the current study evaluates and discusses the evidence supporting the potential effectiveness of proanthocyanidins in treating lung cancer through antioxidant properties in vivo.

Materials and procedures

Chemicals and medications

Urethane 97% and Butylated hydroxytoluene (BHT) were purchased from Acros Organics (New Jersey, USA), Proanthocynadin natural compound

extracted from grape seed (purity 95%). Proanthocynadins (PAC) with a purity of 95% HPLC grade was bought from Cairo, Egypt's Al-Gomhoriya Co. and dissolved in RPMI at different concentrations.

Animals' husbandry and diet

Forty healthy 5–6 week old male Balb–c mice were purchased from The Holding Company for Biological Products & Vaccines (Vaccera), located in Giza, Egypt. The Institutional Animal Care and Use Committee (IACUC) of Tanta University-Egypt Faculty of Science approved the design of the experiment. The Public Health Handbook on the Use and Care of Lab Animals in Research ethical guidelines were followed throughout the protocols for caring for animals **(Council, 2010).**

Experimental design

After 1 week of the animal's acclimatization period facility settings, the animals were split into four groups based on their body weights to reduce standard errors across groups as follows: G1: 10 mice were given doses of saline and corn oil as -ve control group. G2: For seven weeks, 20 mice received intraperitoneal (i.p.) injections of urethane (1 mg/g body weight) dissolved in saline once. A week later, the mice received injections of BHT (125 mg/kg body weight, 150 mg/kg body weight, and 200 mg/kg body weight, once a week) **(Salim et al., 2022, 2023)**. G3: 20 mice were injected with Urethane/BHT by the same protocol as in G2, and then given 50 mg/kg PAC extract orally twice a week till the completion of the trial as a post-treatment after one week. G4: 20 mice were injected with Urethane/BHT by the same protocol as in G2, and subsequently given 100 mg/kg of PAC twice a week orally until the experiment's completion, which is expected to take 20 weeks.

Biochemical analysis for antioxidant enzymes activities and antioxidative stress markers concentrations in liver tissues

The liver was chopped into small pieces, put on ice without compressing the tissue, cleaned with ice-cold isotonic NaCl saltwater, patted dry with filter paper, and weighed. The tissues were homogenized in ice-cold phosphate buffer containing Triton X-100 (50 mM, pH 7.4) 10% (w/v) using Omni international homogenizer (USA) at 22.000 rpm for 20 s each with 10 s intervals. Then, the supernatant was centrifuged at 6000xg in a cooling centrifuge at 4°C for 15 min and we kept the generated supernatant for quick enzyme tests. The oxidative stress parameters and enzyme activity were measured at 25°C using the UV/vis Spectrophotometer (JANEWAY 6505, UK).

Using commercial kits, antioxidant enzyme activity and indicators of oxidative stress were measured (Biodiagnostics, Egypt). MDA was determined utilizing the procedures outlined by **Ohkawa et al. (1979)**. Catalase activity was calculated using the procedure that catalase in the original sample reported, whereas SOD activity was assessed utilizing the technique of **(Nishikimi et al., 1972) (Aebi, 1984).** Measured is the drop in glutathione reductase (GR) absorbance at 340 nm **(Goldberg and Spooner, 1983).**

Statistical analyses

Each experiment was run three times, and the means ± standard deviation are displayed for each. Excel was utilized for statistical analysis and data visualization. $P<0.05$ was applied to assess statistical significance.

Results

Average Weight of the Organs: Absolute, Relative, and Average

Throughout the progression of the experiment, 1 mouse died in G1 in the 9^{th} week , 3 mice died in G2 in 6^{th}, 12^{th}, and 19^{th} Week, 5 mice died in G3 in 9^{th} week (2 mice), 10 th, 15^{th}, and 18^{th} weeks and 5 mice died in G4 in 6 th, 8 th, 11 th and 18^{th} week (2 mice), due to unknown circumstances. The growth curves did not show intergroup differences throughout the experiment (Fig. 1).

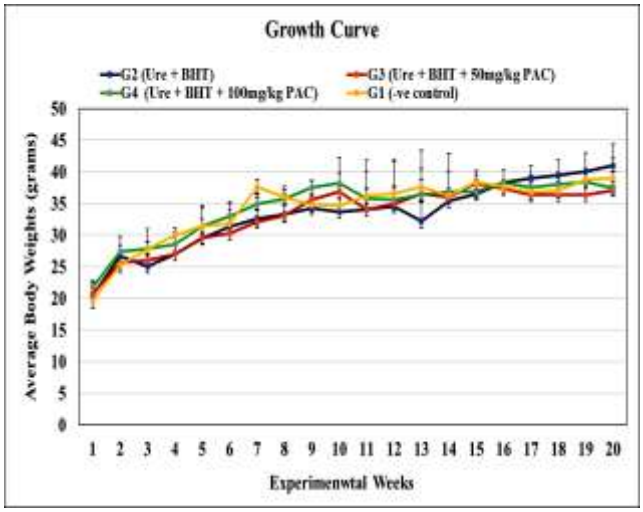

Fig. (1): Growth curves of mice throughout the trial across many groups.

Table (1) shows the average start and ending body weights, and the absolute and relative weights of vital organs of mice in all groups. There were no obvious variations in the ultimate body weights. The relative lung weights were increased in G2 administered Ure + BHT as compared with control. Treatment with 100 mg/kg PAC significantly lowered the relative left and right kidney weights compared to control levels in G1. The relative spleen weights were significantly changed after treatment with both doses of PAC in both G3 & G4. Moreover, the carcinogen administration significantly increased the relative weights in G2 in contrast to a typical control (G1), nevertheless, medication using both doses of PAC did not change relative spleen weights versus G1.

Table (1): Initial, Final Body Weights, Weight Gain, Absolute and Relative Organs Weights

Groups	G1 No treatment (-ve control)	G2 (Ure + BHT) (+ve control)	G3 (Ure + BHT +50 mg/kg PAC)	G4 (Ure +BHT +100 mg/kg PAC)
Initial No. of Mice	10	20	25	25
Final No. of Mice	9	17	20	20
Initial body wt (g)	19.6 ± 2.8[a]	20.5 ± 3.5	19.7 ± 3.2	20.8 ± 3.7
Final body wt (g)	39.0 ± 4.7	40.1 ± 2.6	37.09 ± 5.9	37.4 ± 6.2
Weight gain (g)	19.4 ± 3.7	19.6 ± 3.01	17.39 ± 4.51	16.6 ± 4.95
Liver wt (g)	1.89 ± 0.43 (4.9%)[b]	2.024 ± 0.51 (5.1%)	2.25 ± 0.31 (6.1%)	1.77 ± 0.25 (4.7%)*
Left kidney wt (g)	0.30 ± 0.06 (0.77%)*	0.26 ± 0.04 (0.65%)	0.34 ± 0.04 (0.92%)*,**	0.31 ± 0.07 (0.83%)*
Right kidney wt(g)	0.32 ± 0.06 (0.82)*	0.27 ± 0.04 (0.67)**	0.34 ±0.04 (0.92%)*	0.30 ± 0.07 (0.80)*
Spleen wt (g)	0.34 ± 0.09 (0.87)	0.33 ± 0.24 (0.83%)	0.36 ± 0.10 (0.97%)*	0.23 ± 0.06 (0.62%)*
Testis wt (g)	0.21 ± 0.02 (0.54)	0.25 ± 0.13 (0.62%)**	0.22 ± 0.07 (0.59%)	0.26 ± 0.06 (0.69%)

a: Absolute organ weight values (means ± standard deviation); b: Relative organ weight values are expressed as organ weight/body weight X 100 (%); *: Significance in relation to G1 at P<0.05; **: Significance in relation to G2 at P<0.05.

MDA concentrations, SOD, Catalase, and GR activities in Liver Tissues

Malondialdhyde (MDA) levels

The determined hepatic MDA concentration levels were markedly elevated in the liver tissues of G2 which received the carcinogens Ure and BHT without further treatment as compared with G1. Interestingly, The MDA levels in G4 treated with 100 mg/kg PAC decreased significantly (P<0.05), about twice as much as those in G2. G3 showed that data was almost similar to that of G2.

Superoxide dismutase (SOD) activity levels

When comparing G2 to G1, the SOD activity levels were observed to be noticeably greater (P<0.05) in G2. Treatment with 50 mg/ kg has shown a significant decline in the hepatic SOD levels of activity in relation to G2. Conversely, no discernible variations in SOD activity levels were seen between G4 and G2.

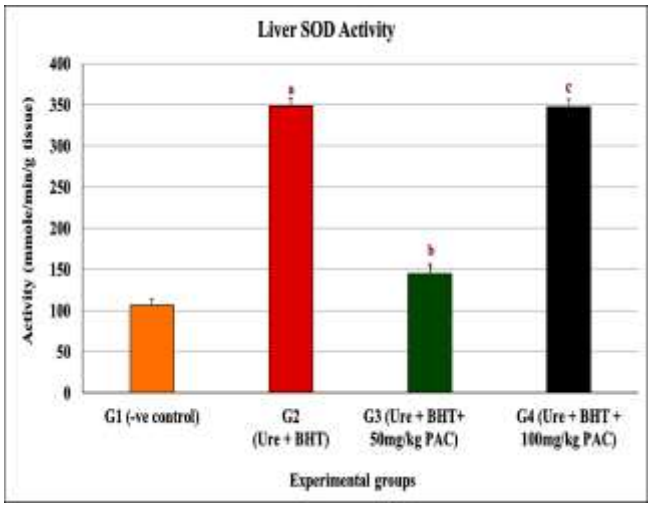

Fig. (2): Antioxidant markers levels in mice liver of MDA concentration levels; n = 6 animals were analyzed. Each analysis was performed in duplicate. Values are percentages means ± S.D; a: Significance vs. G1 at P<0.05; b: Significance vs. G2 at P<0.05; c: Significance vs. G3 at P<0.05.

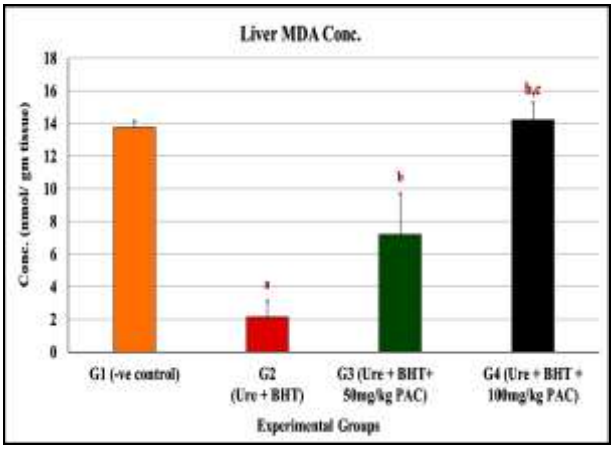

Fig. (3): Antioxidant markers levels in mice liver of SOD activity. n = 6 animals were analyzed. Each analysis was performed in duplicate. Values are percentages means ± S.D; a: Significance vs. G1 at P<0.05; b: Significance vs. G2 at P<0.05; c: Significance vs. G3 at P<0.05.

Catalase (CAT) activity levels

Comparing G2 to G1, there was a discernible decrease in CAT activity levels. On the other hand, when compared to G2, the therapy with both dosages of PAC significantly increased and restored the levels of CAT activity, close to normal levels. The lower dose of PAC in G3 has exerted the most significant modulatory effect as compared with G4.

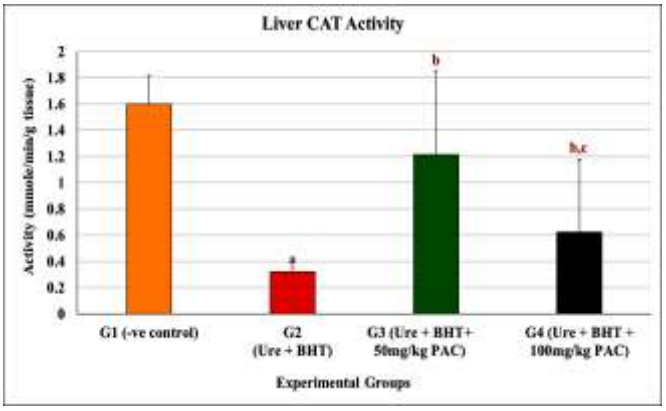

Fig. (4): Antioxidant markers levels in mice liver of catalase activity levels. n = 6 animals were analyzed. Each analysis was performed in duplicate. The values represent percentages means ± standard deviation; a: significance in contrast to G1, b: significance in contrast to G2, and c: significance in contrast to G3.

Glutathione reductase (GR) activity levels

When G2 was given Ure + BHT, GR revealed a considerable drop in G2 when compared to G1's typical control levels. Importantly, A significant and dose-dependent increase was seen in the GR activity levels in both groups treated with PAC at both doses (G3 & G4) as compared with G2. The high dose in G4 showed the most profound increase in restoring GR levels almost to control values.

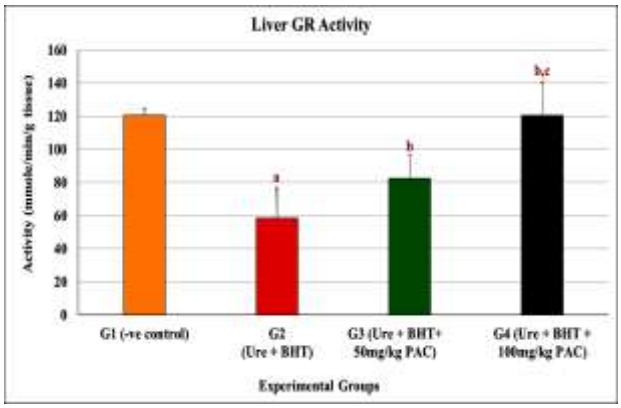

Fig. (5): Antioxidant markers levels in mice liver of GR activity levels. n = 6 animals were analyzed. Each analysis was performed in duplicate. The following values are expressed as percentages means ± standard deviation: a) significance vs. G1 at P<0.05; b) significance vs. G2 at P<0.05; c) significance vs. G3.

Discussion

Oxidative stress (OS) explains an imbalance in which the capability of antioxidant defense mechanisms is out matched by the generation of oxidative species. Redox homeostatic disturbance and macromolecular damage follow from this. One well-known phenomenon that plays a major role in macromolecular damage is free radical

reaction **(Cesselli et al., 2017; Ciccarese et al., 2020).** Overproduction of oxides and radicals, such as reactive nitrogen species (RNS), throws off the oxidant/antioxidant system's delicate equilibrium **(Sharifi-Rad et al., 2020; Nakai et al., 2021).**

By controlling several pathways, Proanthocyanidins prevent OS, enhance antioxidant capacity, and restore normal immune function via removing MDA and ROS, preserving the equilibrium of inflammatory agents and immune cells, and boosting antioxidants and detoxication enzymes **(Longet al., 2016; Han et al., 2019).** Proanthocyanidins upregulate antioxidants like glutathione (GSH), catalase, heme oxygenase-1 (HO-1), SOD, and MDA while reducing the generation of mediators linked to OS, such as MDA and ROS. Proanthocyanidins decrease the production of MDA and its metabolites by blocking the LPO pathway **(Mittal et al., 2003).** Additionally, by inhibiting OS and decreasing LPO, Proanthocyanidins may shield EC function and lower the chance of diabetic vascular problems **(Rodríguez et al., 2022).**

Consistent with our findings, which showed that PAC administration dramatically reduced MDA levels and SOD activity in comparison to G2 in an orderly fashion. Furthermore, compared to G2, the PAC therapy in G3 and G4 dramatically raised the CAT levels and GR activity. It has been demonstrated that PACs can minimize the development of oral squamous cell carcinoma and slow the proliferation of cervical cancer cell lines, in a way dependent on dosage **(King et al., 2007).** Furthermore, dietary PACs prevented the growth of UVB-induced cutaneous cancer by encouraging nuclear excision repair systems to repair damaged DNA and by enhancing DNA repair-dependent immunological activity via effector T cells and dendritic cells **(Katiyar et al., 2017).**

PACs help put a stop to oxidative chain reactions by stabilizing and neutralizing free radicals by providing an electron to their -OH groups linked to the phenolic ring. PAC treatment significantly reduced UVB-induced lipid peroxidation, according to **(Mittal et al., 2003; Nimse and Pal, 2015).**

Furthermore, in rat erythrocytes and lymphocytes, PACs provide defense against lipid peroxidation, free radical generation, and ROS production brought on by cadmium **(Nazima et al., 2016).** Additionally, PAC therapy was shown to limit H_2O_2-induced NSCLC cell survival, as shown by increased Nrf2 target gene expression, oxidative stress generated by H_2O_2, and reduced production of MDA and ROS **(Sun et al., 2017).** When grape

seed proanthocyanidin extract was given to rat models, MDA, NO, and calpain-II protein were reduced and antioxidative enzyme activity was restored in a dose-dependent manner. It improved lens opacity and inhibited the production of lipid peroxidation **(Zhang and Hu, 2012).**

It has been recommended that proanthocyanidins have strong antioxidant properties **(Lai et al., 2018).** Grape seed extract suppressed H_2O_2 induced phosphorylation of the p38 and c-Jun N-terminal kinase (JNK) proteins of the NF-κB and MAPK pathways in human lens epithelial B-3 HLE-B3 cells, preventing cataractogenesis **(Jia et al., 2011).** Rat testicular toxicity can be stopped in q dose-dependent way by using 400 mg/kg of grape seed proanthocyanidin extract **(Zhao et al., 2014).** In rat models, It has been demonstrated that a modest dosage of GSPE's grape seed proanthocyanidin extract reduce oxidative stress and enhances mitochondrial function **(Pajuelo et al., 2012).** In models of obese rats, liver glutathione change was reduced by grape seed proanthocyanidin extract **(Fernández-Iglesias et al., 2014).** In conclusion, further in vitro and in vivo research are required to verify the anticancer treatment of PAC by confirming the molecular link between its anticancer efficacy and oxidative stress signaling pathways.

Appreciation:

The writers express their gratitude to the Tanta University team in Egypt's Faculty of Science, Zoology Department, and Research Laboratory for Molecular Carcinogenesis, for their excellent technical assistance.

Declarations

Data accessibility

This put-out publication includes all of the information gathered or analyzed during this investigation. If more specific information is needed, they can get in touch with the study's coordinator. Mona Elwan (Email address: mona.elwan@science.tanta.edu.eg).

Ethics approval and consent to participate:

Given that the mice study in this work has been authorized by the appropriate ethics committee, it has been completed by the moral standards. The ethical standards of the Public Health Guide for the Care and Use of Laboratory Animals were adhered to while performing treatments on animals. The reference number-based experimental methodology **(IACUC-SCI-TU-0093)** was accepted by the Committee for Institutional Animal Care and the Research Ethical Committee (REC) of Tanta University Faculty of Science. In this investigation, no human samples were used.

Patient consent for publication

Not applicable.

Competing interests

The writers claim to have no overlapping objectives.

Author Contributions

Elsayed I. Salim, conceptualization of the research idea and methodology development, **Mostafa M. El-Hadad**, experimentation, methodology, animal caring, data collection. **El-Sayed I. Salim, Mostafa M. El-Hadad, Mona M. Elwan** analysis of the data and the preparation, proofreading, and the article's editing. Every writer evaluated and approved the final draft.

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تقييم خصائص البروانثوسيانيدين المضادة للأكسدة في نموذج الفئران المصابة بسرطان الرئة

د/ منى محمد علوان- مصطفى محمد الحداد- أ.د/ السيد إبراهيم سالم

قسم علم الحيوان- كلية العلوم- جامعة طنطا

إن البروانثوسيانيدينات (PACs) عبارة عن مركبات بوليفينولية عديدة توجد في مجموعة واسعة من الفواكه والمكسرات والزهور وقشور النباتات والخضروات. إن الإجهاد التأكسدي هو نتيجة لتراكم المؤكسدات مع خلل فى انتاج أنواع الأكسجين التفاعلية (ROS)، بما يتجاوز قدرة الخلية على إنتاج مضادات الأكسدة. وقد تتعرض العضيات والجزيئات الكبيرة والأنسجة بأكملها للتلف. ونتيجة لذلك، استخدمنا نموذجًا لفأر مصاب بسرطان الرئة ناتجًا عن جرعة منخفضة أو عالية من اليوريثين/البوتيلاتيد هيدروكسي تولوين لتقييم فاعلية مضادات الأكسدة في البروانثوسيانيدينات. وأشارت النتائج إلى أن كلتا الجرعتين من PACs كانت قادرة على زيادة مستويات المالونديالدهيد (MDA) بينما أدت الجرعة ٥٠ مجم/كجم فقط في المجموعة الثالثة إلى تقليل نشاط إنزيم ديسميوتاز الفائق في البلازما (SOD) في الفئران المعالجة، على عكس المجموعة الضابطة. ومع ذلك، فقد أدت جرعتا PACs إلى رفع نشاط الكاتالاز و الجلوتاثيون (GR) في المجموعة الثالثة والرابعة إلى مستويات التحكم تقريبًا، وخاصة في المجموعة الرابعة. لذلك، استنتجنا أن PACs لها خصائص مضادة للأكسدة بطريقة تعتمد على الجرعة وقد تعمل كعلاج مساعد طبيعي لسرطان الرئة.