**Journal of Environmental Biology**
p-ISSN: 0254-8704 • e-ISSN: 2394-0379 • CODEN: JEBIDP

JEB®

Original Research Paper
Volume 45 Issue 2 March 2024 pp. 139-144
*DOI:* http://doi.org/10.22438/jeb/45/2/MRN-5226

*J. Environ. Biol.*, 2024

Journal website : www.jeb.co.in ★ E-mail : editor@jeb.co.in

# Exploring the correlation between environmental pesticide exposure and antioxidant level in recently diagnosed cancer patients

**A. Ojha[1]*, P. Sahani[2], S. Shekhar[3] and S.K. Mishra[4]**

[1]*Faculty of Allied Health Sciences, Mahayogi Gorakhnath University Gorakhpur, Gorakhpur-273 007, India*
[2]*Deapartment of Biotechnology, Deen Dayal Upadhyay Gorakhpur University, Gorakhpur-273 009, India*
[3]*Department of Radiotherapy, All India Institute of Medical Sciences, Gorakhpur-273 008, India*
[4]*Deapartment of Biotechnology, Deen Dayal Upadhyay Gorakhpur University, Gorakhpur-273 009, India*

**Received:** 17 January 2024 **Revised:** 06 February 2024 **Accepted:** 20 February 2024

***Corresponding Author Email :** anupama.ojha0@gmail.com ***ORCiD:** https://orcid.org/0000-0003-1652-1073

## Abstract

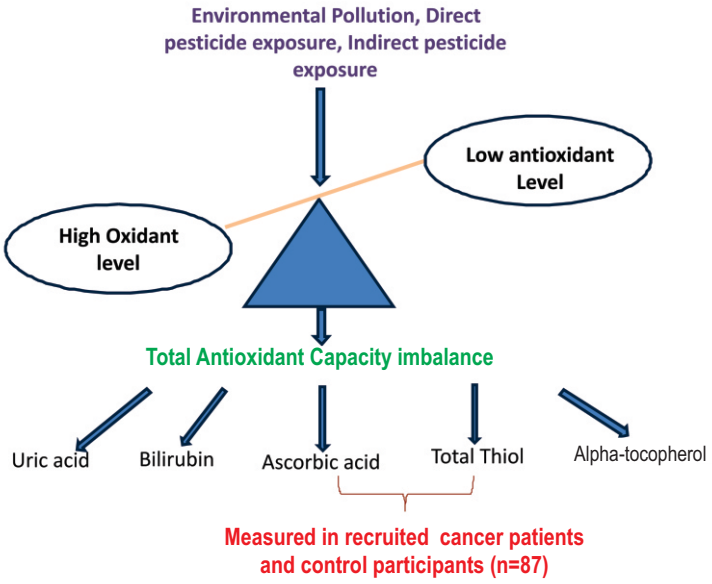
**Aim:** Within biological systems thiol and ascorbic acid are important antioxidant that play roles in the antioxidant defense systems. In this study, we investigated the correlation between environmental pesticide exposure and antioxidant level in recently diagnosed cancer patients.

**Methodology:** Blood samples were collected from 87 participants (48 male and 39 female) including control, gallbladder, blood, and oral cancer patients. Serum total thiol content and antioxidant ascorbic acid levels were measured by biochemical method. We also examined whether there is any correlation between the plasma thiol content and ascorbic acid content in cancer prevention

**Results:** Analysis indicated that most of the cancer patients belonged to middle age and were mostly non-vegetarian. In the present study, it was found that the total thiol content of cancer pateints was high, while the ascorbic acid content was low in cancer patients as compared to control indicating the role of oxidative stress in cancer development.

**Interpretation:** The present study suggests that pesticide exposure may increase the total thiol content and negatively impact ascorbic acid content in cancer patients.

**Key words:** Antioxidant, Blood cancer, Epidemiology, Gallbladder cancer, Oral cancer, Pesticide






**How to cite:** Ojha, A., P. Sahani, S. Shekhar and S.K. Mishra: Exploring the correlation between environmental pesticide exposure and antioxidant level in recently diagnosed cancer patients. *J. Environ. Biol.*, **45,** 139-144 (2024).

## Introduction

It is reported that 20 million new cancer cases and 9.7 million deaths due to cancer in the world in 2022 (IARC report, 2022). India ranks 3rd in the world with 14,61, 427 new cases of cancer with 12,997 cases of gallbladder during the year 2022 (Sathishkumar *et al.,* 2022). Blood cancer is at 13rd position in the world with around 1.24 million cases that occur worldwide annually. Age, diet, genetics, environment, and exposure to carcinogenic chemicals are major factors for causing cancer. Accumulation of damage in DNA by the carcinogenic element can induce cancer at a later stage (Nogueira *et al.,* 2014). Studies have reported that intake of meat, saturated fat, and cholesterol, increases gallbladder cancer incidence (Di Ciaula *et al.,* 2019). In 80% cases the major cause of gallbladder cancer is gallstone which contains high cholesterol and bilirubin. Gallstones lead to inflammation that may later develop into cancer (Espinoza *et al.,* 2016).

Various genetic mutations in KRAS oncogene have been reported in gallbladder cancer in India (Mishra *et al.,* 2022). Similarly, genetic mutation at codons 12, 13 and 61 of KRAS oncogene has also been reported in India (Zhu *et al.,* 2021). Missense mutation in TP53 and PIK3CA and KRAS mutation are also common in gallbladder cancer (Vidaurre *et al.,* 2019). These genetic mutations are mainly caused by carcinogenic substances, like pesticides, present in the environment. Acute or chronic exposure to pesticides such as malathion, carbofuran, triflumuron, acetamiprid, imidacloprid, thiamethoxam, pentachlorophenol, emamectin benzoate, and tembotrione have been reported to cause genetic damage (Alavanja *et al.,* 2014; Kachuri *et al.,* 2020; Moura *et al.,* 2020). Pesticides exposure can lead to the production of various reactive oxidative species (ROS) such as superoxide anion ($O_2$•−) and hydroxyl radical (•OH), etc (Sule *et al.,* 2022; de Souza *et al.,* 2021). These reactive oxygen species are neutralized by the antioxidant defense system of our body. Thiol is an important antioxidant that prevents the destruction of cells and helps against oxidative stress. Thiol has disulfide having an antioxidant ability that maintains homeostasis, enzymatic reactions detoxification, transcription, signal transduction, and cellular signaling mechanism (Ulrich and Jakob, 2019; Di Marzo *et al.,* 2019; Huijskens *et al.,* 2016).

Thiol is present in albumin of plasma proteins, cysteine, glycine, homocysteine, and GSH. Active thiol-disulfide maintains an essential role in antioxidant systems (Durankuş *et al.,* 2022). Vitamin C is used as an anti-cancer agent (Shenoy *et al.,* 2018). The process of formation of beta-amyloid peptide and glutamate–mediated excitotoxicity can be suppressed by the antioxidant ascorbic acid (Reich and Hölscher, 2022). The effect of ascorbic acid on various types of cancer progression depends on oral and intravenous concentration and their expression in tumor cells. Ascorbic acid can exist either in reduced form as L-ascorbate or in oxidized form as dehydroascorbic acid (DHA) (Corpe *et al.,* 2013). The reduced form of ascorbic acid is transported to different cells through the sodium-ascorbate cotransporters SVCT1 and SVCT2, while the oxidized form is transported by glucose-facilitative transporters (Salazar *et al.,* 2016). Conversion of ascorbate to DHA, allows its transfer insidiously in cancer cells via GLUT1 to stimulate the production of intracellular ROS, which ultimately kills the cancer cell. Ascorbic acid in tumor cells increases the expression of GLUT1 in erythrocytes, than normal cells (Vissers *et al.,* 2018). In the present study, we investigated the correlation between environmental pesticide exposure and antioxidant level in recently diagnosed cancer patients.

## Materials and Methods

**Epidemiological studies:** Blood samples were collected from 87 participants (48 male and 39 female) including control, gallbladder, blood, and oral cancer patients. Histologically confirmed 27 patients of Gallbladder cancer, 8 patients of blood cancer, and 29 patients of oral cancer were included in the present study. 23 normal individuals were included as controls. The demographical data of the above patients were obtained in the form of a questionnaire where we collected information about their age, sex, diet pattern, and status of pesticide exposure. A written informed consent was obtained from each patient to participate in our study. Cancer patients of the present study were recruited from Hanuman Prasad Poddar Cancer Hospital and Research Centre Gorakhpur.

**Patient's recruitment:** The present study is the continuation of my previous study Ojha *et al.* (2023) therefore; the patient recruitment section may show similarity with the published one. Our study was divided into seven groups. Group I consists of 23 randomly selected healthy volunteers having no history of any disease. Group II consists of 14 histopathologically confirmed gallbladder cancer patients who were directly exposed to pesticides during their involvement in agricultural activities and group III consists of 13 histopathologically confirmed gallbladder cancer patients who were not directly exposed to pesticides. Group IV consists of 2 patients having blood cancer with exposure to pesticides and Group V consists of 6 blood cancer patients who were not exposed to pesticides. Group VI consists of 15 patients of oral cancer with exposure to pesticides and Group VII consists of 14 oral cancer patients who were not exposed to pesticides. Only recently diagnosed biopsy-proven confirmed cancer cases, who have not received any chemotherapy were included in the present study. The study was approved by the Ethics Committee of the hospital and before blood collection informed written consent was obtained from each patient. The extent of exposure was calculated by using the equation mentioned below:

Number of treatments per year X total year of pesticide application X cultivation area (ha)

Cancer patients who have not worked within the agriculture sector as their main or secondary occupation and had lived in urban and suburban regions were classified under 'No' or

'Without exposure category'.

**Isolation of plasma from blood:** Venous blood (3ml) was collected through needle and was immediately transferred into a plain yellow and EDTA-containing vial (red cap), and stored at 4°C in ice. The plasma was separated through centrifugation of a vial at 1,300 rpm for 20 min at room temperature, later transferred to sterile Eppendorf and re-centrifuged at 3,000rpm for 15 min for removal of residual cellular components. The plasma was collected in cryo-tubes and stored at –20°C until further biochemical analysis.

**Total Thiol estimation by Ellman's reagent:** Tris EDTA Buffer (300µl) was taken in a test tube and to it 20µl DTNB and 730µl of methanol was added. To initiate the reaction 100µl of plasma sample was added with the help of a pipette in all the test tubes, except control. All the test tubes were centrifuged at 3000rpm for 10 min at room temperature and the optical density of supernatant was read at 412 nm. The value of total thiol content is expressed in terms of µg $ml^{-1}$ (Ellman, 1959).

**Estimation of Ascorbic acid:** For ascorbic acid estimation, 125µl of plasma and 125µl of ice cold 10%TCA were taken in the test tube, mixed well, and centrifuged for 20 min at 3500 rpm. DTC treated water (500µl) was mixed with 250µl of the above supernatant and incubated for 3 hrs at 37°C. Ice-cold 65% sulphuric acid (500µl) was added to the above test tube to convert it into an interchangeable product. Tubes were mixed well and cooled and the absorbance was read at 520 nm on a spectrophotometer. The amount of ascorbic acid was calculated from the standard curve of ascorbic acid and was expressed in terms of nmol $l^{-1}$ (Levy, 1943).

**Statistical analyses:** Results were expressed as mean ± standard error (S.E.). Statistical analyses were performed using GraphPad Prism 5 software using a One-way analysis of variance with post hoc Bonferroni's multiple comparison tests applied across all studied groups. Significance was based on p-value < 0.05.

## Results and Discussion

The epidemiological data shows that participants of the control group were not in direct contact with pesticides. Out of 27 gallbladder cancer patients, 14 (6 females and 8 males) of them were occupationally exposed to pesticides and 13 (9 female and 4 male) were unexposed to it. Out of 8 blood cancer patients 2 (1 male and 1 female) patients were occupationally exposed to pesticides, while 6 (3 females and 3 males) were unexposed to it. Among 29 oral cancer patients 15 (2 females and 13 males) were occupationally exposed to pesticides, while 14 (4 female and 10 male) were unexposed to pesticides. The mean age of the clinical patients ranged from 42.82 years to 57.71 years. A comparison of the mean age of cancer patients with normal control showed no significant changes in the age as compared to control, except for gallbladder cancer patients exposed to pesticides. In this study it was observed that gallbladder cancer group, the patients who were exposed to pesticides developed cancer at an early age as compared to unexposed group which was statistically significant ($P<0.05$). It was also found that out of 87 cancer patients, only 14 were vegetarian and 73 were non-vegetarian, 22 consume alcohol, 25 were smoking regularly and the remaining consume gutkha and paan masala occasionally (Table1).

Cancer development in humans can occur at any age of life (Pedretti *et al.,* 2023). The rates of cancer increase as the age increases. In the present study, the average age of cancer patients was 43-58 years, which is in line with earlier studies (White *et al*., 2014; Farhadnejad *et al*., 2019). It was reported that fewer than 25 cases per 100,000 people may suffer from cancer in the age group under 20 years, and about 350 cases per 100,000 people in the age group of 60 years. Diet also plays a major role in causing various types of cancers. Most of the patients of gallbladder and blood cancer were non-vegetarian and it was found that most vegetarian peoples have 14% lesser chance of cancer while non-vegetarian people, especially meat-eaters have a higher chance of colorectal cancer (Kim *et al.,* 2023). A recent study by Oxford University reported that non-vegetarian food plays a significant role in aggravating human cancer whereas vegetarians are associated with the lowest risk of developing cancer. Intake of meat, saturated fat, and cholesterol increases the chance of breast cancer (Law, 2000). Some diets seem to confer protection against cancer (Tantamango-Bartley *et al.,* 2013).

Meat is rich in fat and animal oil and when cooked at high temperatures, may increase the incidence of cancer, especially cancer of prostate, colorectal, colon and stomach (Fliss-Isakov *et al.,* 2018). Worldwide cancer data shows that excessive intake of alcohol also increases the risk of breast cancer, oral cavity cancer, colorectal cancer, esophagus cancer, gallbladder cancer, blood cancer, stomach cancer and liver cancer. Based on the questionnaire we have separated the gallbladder and blood cancer patients into pesticide-exposed and unexposed groups. Various studies establish that exposure to pesticides in humans can cause the development of some cancers particularly, the brain, prostate, kidney, gallbladder, and leukemia. With increased use of pesticides day by day the risk of cancer also increases. Chemicals can disturb and damage the function of various hormones, inflaming tissues, damaging DNA, proteins, and lipid pathways, and turning genes, which can trigger cancer (Pedroso *et al.*, 2022). The organochlorine pesticide has been estimated in the bile of gallbladder cancer patients which shows the association with aetiopathogenesis carcinoma. A higher concentration of benzene hexachloride was found in bile and causes carcinoma of the gallbladder. In the higher carcinoma of the gallbladder the concentration of dichlorodiphenyltrichloroethane increases in the biliary tract. Biliary aldrin and endosulfan concentrations (0.00008 and 0.0103ppm) also cause higher carcinoma of gall bladder cancer (Shukla *et al.,* 2001). In the present study, a 14.2 to 32.25% increase in total thiol content in plasma of gallbladder, blood and oral cancer patients was observed as compared to control patients, however, the increase in total thiol content was not significant to control. It was also

**Table 1:** Epidemiology of control, gallbladder, blood and oral cancer patients

| Type of Patients | Status of pesticide exposure | Total participants | Sex | | Age | Diet | | Lifestyle choices# | |
|---|---|---|---|---|---|---|---|---|---|
| | | | Male | Female | Mean±SE | Vegetarian | Non-vegetarian | Alcohol intake | Cigarette smoke |
| Control | Unexposed | 23 | 9 | 14 | 42.82±3.938 | 6 | 17 | 3 | 2 |
| | Pesticide | 14 | 8 | 6 | 54.13±3.112* | 1 | 13 | 4 | 4 |
| Gall Bladder | Exposed | | | | | | | | |
| Cancer | Pesticide unexposed | 13 | 4 | 9 | 57.57±2.882 | 2 | 11 | 3 | 6 |
| | Pesticide Exposed | 2 | 1 | 1 | 50.17±6.457 | 0 | 2 | 1 | 1 |
| | Pesticide | 6 | 3 | 3 | 55±10 | 0 | 6 | 3 | 3 |
| Blood | Unexposed | | | | | | | | |
| Cancer | Pesticide Exposed | 15 | 13 | 2 | 50.20±3.526 | 2 | 13 | 3 | 4 |
| Oral Cancer | Pesticide Unexposed | 14 | 10 | 4 | 57.71±4.832 | 3 | 11 | 5 | 5 |

*Significant level is based on P<0.05 when compared with control; **Significant level is based on P<0.001 when compared with control; #Remaining patients do not take alcohol and cigarette but other lifestyle choices such as gutkha and other habit can not be denied.

**Table 2:** Estimation of thiol and ascorbic acid content in control, gallbladder, blood and oral cancer patients

| Type of Patients | Status of pesticide exposure | Total Thiol content (µg $ml^{-1}$) | Ascorbic acid (nmole $l^{-1}$) |
|---|---|---|---|
| Control | Not exposed | 0.217±0.016 | 67.27±4.547 |
| Gall Bladder Cancer | Pesticide Exposed | 0.287±0.023 | 44.00±0.0 |
| | Pesticide Unexposed | 0.250± 0.019 | 62.75±5.963 |
| Blood Cancer | Pesticide Exposed | 0.267±0.332 | 59.22±6.011 |
| | Pesticide Unexposed | 0.267±0.011 | 55.40±4.833 |
| Oral Cancer | Pesticide Exposed | 0.247±0.02829 | 29.54±1.595* |
| | Pesticide Unexposed | 0.248±0.02829 | 29.09±1.669** |

*Significant level is based on P<0.05 when compared with control; **Significant level is based on P<0.001 when compared with control.

found that the ascorbic acid content of cancer patients decreased from 6.7% to 58.8% as compared to control. In oral cancer patients, the decrease in ascorbic acid content was statistically significant as compared to control at the level of p<0.05 and P<0.001 (Table 2). Total thiol content is often used as an indicator of oxidative stress in the body where increased levels indicate an imbalance between the production of reactive oxygen species and the body's ability to neutralize them.

In the present study, the level of total thiol decreased in cancer patients as compared to control. The relationship between pesticide exposure, total thiol content, and cancer development is complex and multifactorial. It can be explained that cancer development is a cumulative effect of multiple processes like oxidative stress, activation of oncogenes, suppression of tumor suppressor genes, and many more. Thiols are powerful antioxidant present in the cells in a millimolar concentration in a highly reduced state and have a significant effect on various physiological activities. Glutathione (reduced), homocysteine, or cysteine are the major compounds in our body having a thiol group. Thiol/disulfide homeostasis is involved in detoxification, antioxidant protection, regulation of biochemical reactions, apoptosis, and cellular signaling mechanisms (Go and Jones, 2011). In the case of blood cancer, the plasma has a low thiol and disulfide in-vivo concentrations which are altered in association with various conditions like- aging, smoking, obesity, alcoholism, and others (Cindoglu *et al.,* 2023). The decrease in thiol content may be explained that because of high oxidative stress in cancerous cells thiol may be utilized to protect against oxidative stress thus their level decreases as compared to control (Gào *et al.,* 2020). A study that analyses the total thiol content in blood samples of cancer patients with documented pesticide exposure showed a significant decrease in total thiol levels compared to control, groups, indicating compromised antioxidant capacity and elevated oxidative stress.

Ascorbic acid has potential anticancer properties and recently diagnosed patients may already have lower ascorbic acid levels due to disease itself. The level of ascorbic acid in the plasma of Cancer patients decreased as compared to the control

in the present study which is in accordance to the previous studies. In various studies, the level of ascorbic acid concentrations in cancer patients was deficient in comparison to normal individuals (Huijskens *et al.,* 2016; Liu *et al.,* 2016). The ascorbic acid level in human body plays an important role in gallstones and gallbladder cancers due to their involvement in the conversion of cholesterol into bile acids (Makiuchi *et al.,* 2017). In the case of blood cancer, ascorbic acid concentration in blood is low and can cause diseases like scurvy. They increase the blood antioxidant level up to 30% and also help in natural defense to fight inflammation. When free radical accumulation is high in our body, various antioxidant defenses act to protect against cellular damage. Ascorbic acid is a strong antioxidant that reduces the risk of various types of chronic diseases (Cerullo *et al.,* 2020). In the case of blood cancer, ascorbic acid induces cytotoxicity. Oral doses of ascorbic acid can have anticancer activity through epigenetic modulation (Kaźmierczak-Barańska *et al.,* 2020).

From the present study it can be concluded that the incidence of cancer increases with age. The intake of a non-vegetarian diet and lifestyle choices may predispose to cancer development. The present study suggests that pesticide exposure may increase the total thiol content and negatively impact ascorbic acid content in cancer patients. Studies are needed to understand the precise mechanism through which pesticide exposure affects the total thiol and ascorbic acid content and its role in cancer development. This knowledge can help in developing preventive strategies such as minimizing pesticide use and promoting protective measures for individuals working in pesticide-related occupations. Additionally, biomonitoring studies can provide valuable insights into the potential health effects of pesticide exposure and guide regulatory action aimed at reducing environmental pesticide contamination levels.

## Acknowledgments

Acknowledgement must be given to University Grant Commssion for providing fellowship and financial support for present study (UGC, Grant File No 4-2/2006 (BSR)/BL/18-19/0472 dated, 16th October 2019) in the form of Dr. D. S. Kothari Fellowship to Dr. Anupama Ojha, New Delhi, India.

**Authors' contribution: A. Ojha:** Prepared the manuscript, planned the experiment, obtained ethical permission, performed epidemological data collection and blood collection from cancer patients. **P. Sahani:** Performed experimental work during her summer internship; **S. Shekhar:** Helped in ethical approval and blood collection; **S.K. Mishra:** Given guidance in implementation of ideas, helped in administrative work and done proof reading of the manuscript.

**Funding:** The University Grant Commission, New Delhi, India provided funds for the present study in the form of Dr. D. S. Kothari's Fellowship to Dr. Anupama Ojha (Letter no. UGC, Grant File No 4-2/2006 (BSR)/BL/18-19/0472 dated, 16th October 2019).

**Research content:** The research content of manuscript is original and has not been published elsewhere.

**Ethical approval:** The present study was approved by the Human Ethical Committee of Hanuman Prasad Poddar Cancer Hospital and Research Centre, Gorakhpur (dated 6th January 2021) and written consent was taken from the participants.

**Conflict of interest:** The authors declare "No conflict of interest".

**Data availability:** Data is available with the corresponding author and can be collected whenever required.

**Consent to publish:** All authors have given their consent for the publication of this manuscript.

## References

Alavanja, M.C.R., J.N. Hofmann, C.F. Lynch, C.J. Hines, K.H. Barry, J. Barker, D.W. Buckman, K. Thomas, D.P. Sandler, J.A. Hoppin, S. Koutros, G. Andreotti, J.H. Lubin, A. Blair and L.E. Beane Freeman: Non-Hodgkin lymphoma risk and insecticide, fungicide and fumigant use in the agricultural health study. *PLoS One,* **9**, e109332 (2014).

Cerullo, G., M. Negro, M. Parimbelli, M. Pecoraro, S. Perna, G. Liguori, M. Rondanelli, H. Cena and G. D'Antona: The long history of Vitamin C: From prevention of the common cold to potential aid in the treatment of COVID-19. *Front. Immunol.,* **11**, 574029 (2020).

Cindoglu, C., A. Uyanikoglu, S. Sari, M. Ozkutlu and O. Erel: Thiol-disulfide homeostasis in irritable bowel syndrome. *Eur. Rev. Med. Pharmacol.,* Sci., **27**, 10569-10576 (2023).

Corpe, C.P., P.Eck, J.Wang, H. Al-Hasani and M. Levine: Intestinal dehydroascorbic acid (DHA) transport mediated by the facilitative sugar transporters, GLUT2 and GLUT8. *J. Biol. Chem.,* **288**, 9092–9101 (2013).

de Souza Espindola Santos, A., C.G. Parks, M.M. Senna, L.V.B. de Carvalho and A. Meye: Exposure to pesticides and oxidative stress in Brazilian agricultural communities. *Biomarkers*, **26**, 539-547 (2021).

Di Ciaula, A., G. Garruti, G. Frühbeck, M. De Angelis, O. de Bari, D.Q. Wang, F. Lammert and P. Portincasa: The role of diet in the pathogenesis of cholesterol gallstones. *Curr. Med. Chem.,* **26**, 3620-3638 (2019).

Di Marzo, N., E. Chisci and R. Giovannoni: The role of hydrogen peroxide in redox-dependent signaling: Homeostatic and pathological responses in mammalian cells. *Cells,* **7**, 156 (2018).

Durankus, F., Y. Albayrak, Y. Tokgoz, O.F. Beşer, R. Durankus, S. Cam, E. Sunnetci, O. Akarsu, C. Nural and O. Erel: Investigation of Thiol/Disulfide homeostasis and ischemia-modified albumin levels in children with Wilson disease. *Fetal. Pediatr. Pathol.,* **41**, 576-583 (2022).

Ellman, G.L.: Tissue sulfhydryl groups. *Arch. Biochem. Biophys.,* **82**, 70–77 (1959).

Espinoza, J.A., C. Bizama, P.García, C. Ferreccio, M. Javle, J.F. Miquel, J. Koshiol and J.C. Roa: The inflammatory inception of gallbladder cancer. *Biochim. Biophys. Acta.,* **1865**, 245-254 (2016).

Farhadnejad, H., H. Emamat and H. Zand. The effect of resveratrol on cellular senescence in normal and cancer cells: Focusing on cancer and age-related diseases. *Nutr. Cancer*, **71**, 1175-1180 (2019).

Fliss-Isakov, N., R. Kariv, M. Webb, D. Ivancovsky, D. Margalit and S. Zelber-Sagi: Mediterranean dietary components are inversely associated with advanced colorectal polyps: A case-control study. *World J. Gastroenterol.,* **24**, 2617-2627 (2018).

Gao, X., T. Wilsgaard, E.H.J.M. Jansen, Y. Xuan, A. Anusruti, H. Brenner and B. Schottker: Serum total thiol levels and the risk of lung, colorectal, breast and prostate cancer: A prospective case-cohort study. *Int. J. Cancer,* **146**, 1261-1267 (2020).

Go, Y.M. and D.P. Jones: Cysteine/cystine redox signaling in cardiovascular disease. *Free Radic. Biol. Med.,* **50**, 495-509 (2011).

Huijskens, M.J., W.K. Wodzig, M. Walczak, W.T. Germeraad and G.M. Bos: Ascorbic acid serum levels are reduced in patients with hematological malignancies. *Results Immunol.,* **6**, 8-10 (2016).

Kachuri, L., L.E. Beane Freeman, J.J. Spinelli, A. Blair, M. Pahwa, S. Koutros, S. Hoar Zahm, K.P. Cantor, D.D. Weisenburger, P. Pahwa, J.A. Dosman, J.R. McLaughlin, P.A. Demers and S.A. Harris: Insecticide use and risk of Non-Hodgkin lymphoma subtypes: A subset meta-analysis of the North American pooled project. *Int. J. Cancer,* **147**, 3370-3383 (2020).

Kazmierczak-Baranska, J., K. Boguszewska, A. Adamus-Grabicka and B.T. Karwowski: Two faces of Vitamin C-antioxidative and pro-oxidative agent. *Nutrients,* **12**, 1501(2020).

Kim, J., J. Khil, H. Kim, N. Keum, X. Zhang and E. Giovannucci: Plant-based dietary patterns and the risk of digestive system cancers in 3 large prospective cohort studies. *Eur. J. Epidemiol.,* **38**, 617-627 (2023).

Law, M.: Dietary fat and adult diseases and the implications for childhood nutrition: an epidemiologic approach. *Am. J. Clin. Nutr.,* **72**, 1291S-1296S (2000).

Levy, L. Determination of ascorbic acid in the presence of sulphur dioxide. *Nature,* **152**, 599 (1943).

Liu, M., H. Ohtani, W. Zhou, A.D. Orskov, J. Charlet, Y.W. Zhang, H. Shen, S.B. Baylin, G. Liang, K. Gronbæk and P. A. Jones: Vitamin C increases viral mimicry induced by 5-aza-2'-deoxycytidine. *Proc. Natl. Acad. Sci. USA.,* **113**, 10238-10244 (2016).

Makiuchi. T., T. Sobue, T. Kitamura, J. Ishihara, N. Sawada, M. Iwasaki, S. Sasazuki, T. Yamaji, T. Shimazu and S. Tsugane: The relationship between vegetable/fruit consumption and gallbladder/bile duct cancer: A population-based cohort study in Japan. *Int. J. Cancer,* **140**, 1009-1019 (2017).

Mishra, S., S. Kumari, P. Srivastava, A. Pandey, S. Shukla and N. Husain Genomic profiling of gallbladder carcinoma: Targetable mutations and pathways involved. *Pathol. Res. Pract.,* **232**, 153806 ( 2022).

Moura, L.T.R., C.N.G. Bedor, R.V.M. Lopez, V.S. Santana, T.M.B.D.S.D. Rocha, V.W. Filho and M.P. Curado: Occupational exposure to organophosphate pesticides and hematologic neoplasms: a systematic review. *Rev. Bras. Epidemiol.,* **23**, e200022 (2020).

Nogueira, L., N.D. Freedman, E.A. Engels, J.L. Warren, F. Castro and J.Koshiol: Gallstones, cholecystectomy and risk of digestive system cancers. *Am. J. Epidemiol.,* **179**, 731–739 (2014).

Ojha, A., S. Shekhar, P. Gupta, H. Singh, S. Jaiswal and S. K. Mishra: Study on effect of environmental and occupational pesticide exposure on marker enzymes of malignancies in cancer patients. *Res. Environ. Sci. Toxicol.*, **12**, 1-5 (2023).

Pedretti, L., S. Massa, D. Leardini, E. Muratore, S. Rahman, A. Pession, S. Esposito and R. Masetti: Role of nutrition in pediatric patients with cancer. *Nutrients,* **15**, 710 (2023).

Pedroso, T.M.A., M. Benvindo-Souza, F. de Araújo Nascimento, J. Woch, F.G. Dos Reis and D. de Melo E Silva: Cancer and occupational exposure to pesticides: a bibliometric study of the past 10 years. *Environ. Sci. Pollut. Res. Int.,* **29**, 17464-17475 (2022).

Reich, N. and C. Holscher: The neuroprotective effects of glucagon-like peptide 1 in Alzheimer's and Parkinson's disease: An in-depth review. *Front. Neurosci.,* **16**, 970925 (2022).

Salazar, K., M. Martínez, V. Ulloa, R. Bertinat, F. Martínez, N. Jara, F. Espinoza, E.R. Bongarzone and F. Nualart: SVCT2 overexpression in neuroblastoma cells induces cellular branching that is associated with ERK signaling. *Mol. Neurobiol.,* **53**, 6668-6679 (2016).

Sathishkumar, K., M. Chaturvedi, P. Das, S. Stephen and P. Mathur: Cancer incidence estimates for 2022 & projection for 2025: Result from National Cancer Registry Programme, India. *Indian J. Med. Res.,* **156**, 598-607 (2022).

Shenoy, N., E. Creagan, T. Witzig and M. Levine: Ascorbic acid in cancer treatment: Let the phoenix fly. *Cancer Cell.,* **34**, 700-706 (2018).

Shukla, V.K., A.N. Rastogi, T.K. Adukia, R.B. Raizada, D.C. Reddy and S. Singh: Organochlorine pesticides in carcinoma of the gallbladder: a case-control study. *Eur. J. Cancer Prev.,* **10**, 153-6 (2001).

Sule, R.O., L. Condon and A.V. Gomes: A common feature of pesticides: Oxidative stress-the role of oxidative stress in pesticide-induced toxicity. *Oxid. Med. Cell. Longev.,* **19**, 2022, 5563759 (2022).

Tantamango-Bartley, Y., K. Jaceldo-Siegl, J. Fan and G. Fraser: Vegetarian diets and the incidence of cancer in a low-risk population. *Cancer Epidemiol. Biomark. Prev.,* **22**, 286-294 (2013).

Ulrich, K. and U. Jakob: The role of thiols in antioxidant systems. *Free Radic. Biol. Med.,* **140**,14-27 (2019).

Vidaurre, T., S. Casavilca, P. Montenegro, H. Gomez, M. Calderón, J. Navarro, J. Aramburu, E. Poquioma, Y. Tsuchiya, T. Asai, Y. Ajioka, A. Sato, T. Ikoma and K. Nakamura: Tumor protein p53 and K-ras gene mutations in Peruvian patients with gallbladder cancer. *Asian Pac. J. Cancer Prev.,* **20**, 289-294 (2019).

Vissers, M.C.M. and A.B. Das: Potential mechanisms of action for Vitamin C in cancer: Reviewing the evidence. *Front. Physiol.,* **9**, 809 (2018).

White, M.C., D.M. Holman, J.E. Boehm, L.A. Peipins, M. Grossman and S.J. Henley: Age and cancer risk: a potentially modifiable relationship. *Am. J. Prev. Med*., **46**,S7-15 (2014).

Zhu, G., L. Pei, H. Xia, Q. Tang and F. Bi: Role of oncogenic KRAS in the prognosis, diagnosis and treatment of colorectal cancer. *Mol. Cancer,* **20**, 143 pages (2021).