

Mini-review-article

Dietary supplements: Innocent or potentially carcinogenic?

E. Roumelioti, P. Karkalousos, M. Trapali

Laboratory of Chemistry, Biochemistry, Cosmetic Science, Department of Medical Laboratories, University of West Attica, Aigaleo, Greece

Key words: dietary supplements, cancer, β -carotene, folic acid, PUFA.

Accepted for publication (Final version): May 03, 2022

SUMMARY. *Consumption of dietary supplements has increased in recent decades. Below, it is analyzed the conditions under which the dietary supplements and their ingredients have been associated with a possible increase in cancer risk and poor prognosis of the disease. The need for careful use of supplements and their safe administration, with a view to ensuring health by recognizing potential risks, is the ultimate goal of this work.*

INTRODUCTION

Dietary supplements, depending on their ingredients, can be categorized as: vitamins, trace elements, plant origins, amino acids and nutrients that increase the daily dietary intake such as enzymes and other extracts (6).

Corresponding author: Dr Maria Trapali, Laboratory of Chemistry, Biochemistry, Cosmetic Science, University of West Attica, Panepistimioupoli I, Ag. Spyridonos, Aigaleo GR-12210, Greece. E-mail: mariatrapali66@yahoo.gr

Send reprint requests to the publisher: Dr Helen S. Plessa, 9A Kanari Str., GR-15239, N. Penteli, Athens, Hellas, E-mail: pharmakonpress@pharmakonpress.gr, Tel. + 30210-9756332

VITAMIN SUPPLEMENTS

Regarding vitamin supplements, *beta-carotene* supplements have not been found to support any protective effect against various types of cancer (15,26,37). On the contrary, their long-term intake has been linked to lung cancer, prostate cancer, while some findings also indicate a link with bladder cancer, which is still under investigation (1,15,26). The risk of lung cancer due to consumption of β -carotene supplements increases more in male smokers (8), especially for cell lung cancer (1). Long term daily consumption of β -carotene in doses of 20-30 mg increases the risk of lung cancer in male smokers. It is recommended that the daily doses should not exceed 7 mg (15). The form of β -carotene contained in supplements acts pro-oxidizing in male smokers, increases oxidate stress levels and promotes development of toxic substances in tissues (26). High doses of β -carotene can affect pre-cancerous lesions and affect cell apoptosis (8).

Long -term administration of *vitamins B6 and B12* increases the risk of lung cancer in people who smoke or have been smokers (1,9). B12 supplements, also, increases the risk of adenocarcinoma and small cell lung cancer (17) and inhibit chemotherapy, especially for breast cancer patients (3). High doses of B6 and B12 are able to promote faster cell growth and ultimately lead to carcinogenesis (9). In general, it

is stipulated that B6 should not exceed 20 mg while B12, 55 mg per day (1).

Supplements that contain *vitamin E* have not been found to provide protection against cancer (34,37,46). In contrast, intake of vitamin E is likely to increase the risk of prostate cancer (31,33,46) and lung cancer, especially to women. Long term administration for more than ten years, at doses that exceed 215 mg per day, increases the risk of lung cancer (1). In addition, their use is not indicated during chemotherapy and radiotherapy as it could restore cellular oxidative damage to cancer cells (46). When it is consumed simultaneously with other supplements, such as vitamins A, C, β -carotene and coenzyme Q10, it could increase the risk of cancer recurrence (3).

Consumption of *folic acid* supplements increases the risk for any type of cancer (4), especially in cases with pre-existing cancer (30,37). Overdose of folic acid is able to deteriorate the progression of pre-existing cancers that may not yet be diagnosed (4,7,53). The most commonly associated cancers are prostate cancer (18,37,53), especially for men over the age of 57 years and with pre-cancerous lesions in the prostate. In the case of prostate cancer, the risk increases even more when daily long-term consumption of folic acid supplements ranging from 0.4-1 mg (53).

In addition, there is evidence that folic acid supplements can increase the risk of breast cancer in menopausal women who have taken very high doses of this supplement for a long period (37). Long-term doses higher than 400 μ g per day showed an increase of risk for breast cancer (47). Moreover, folic acid supplements have not been observed that to offer any form of protection on colon cancer (37,47). On the contrary, in high concentration it may increase the risk of the disease (4,19,29,30). Consumption during chemotherapy treatment has been shown to possibly inhibit the effect of antiplatelet drugs and reduce the function of cytotoxic cells (19,21,30,47).

POLYUNSATURATED FATTY ACIDS

Dietary polyunsaturated fatty acids (PUFAs) are associated with increased risk of prostate cancer and higher mortality rate is observed after consumption of supplements containing *omega-3*

fatty acids than these with *omega-6-fatty acids* (10, 22). It has been found, also, that they are associated with other types of cancer, such as breast cancer, as well as to increase cancer mortality in general (22).

INORGANIC INGREDIENTS

Studies have found that some trace elements supplements, such as *selenium*, are not recommended for use as a chemoprotective factor against cancer (51) because, when administered in high doses, they can act as pro-carcinogens in the body. The most commonly observed type of cancer that has been linked with trace elements supplements is prostate cancer (36). There is evidence that trace elements supplements increase the risk of high-grade malignancies, as they have been found to increase the risk of DNA damage, especially, in the prostate tissue (33).

Recent findings highlight the negative effect of *iron* supplementation during chemotherapy as regards to the outcome of the treatment. Iron supplements are able to both increase cancer mortality and possible recurrence of the disease, as iron is thought to play a very important role in tumor progression due to its effect on the microenvironment (3).

HERBAL SUPPLEMENTS

The most widely used herbal supplements with a link to cancer that have been identified as genotoxic carcinogens are those containing: pyrrolizidine alkaloids, alkenylbenzenes and aristolochic acids (44). *Supplements containing alkaloids* have been implicated in liver cell necrosis and liver cancer (40,41,50,52). Alkenylbenzene supplements have also been associated with an increase in liver cancer (2,12,16,45,50). Supplements containing aristolochic acids are associated with the development of primary or secondary cancer (25,35,50). In particular, they increase the risk of urinary cancer (13) and renal cell carcinoma (5,11, 42). It causes a rare type of cancer with malignant lesions occurring in both the renal pelvis and upper ureter (39) while the International Agency for Research on Cancer (IARC) has placed aristolochic acids in the category of carcinogens (35,50).

Researches have shown that *coumarin supplement* consumption can increase the incidence of cancer in humans, but more research is needed due to their majority being conducted only to mice and not on human population (23). Coumarin supplements significantly increase the incidence of tumors in experimental animals. These tumors were detected, mainly, in cancer of kidneys, liver and cholangiocarcinoma in both male and female mice, while tumors in the lung and squamous cell carcinoma were found mainly in male rats (24). Although coumarin, under normal conditions, inhibits cell proliferation and causes apoptosis, in some cases it links to cell proliferation (23). That's why the German Federal Institute recommends that coumarin supplements should not exceed 0.1 mg per body weight (24).

It is argued by many scientists that *soy supplements* have benefits only in Asian population, in whom soy has already been introduced into their diet from a very early age, while women in the Western world may have a negative effect (28). Soy supplements have been linked to increased breast cancer risk (14,38,55). Isoflavones in soy supplements can affect the way breast mammalian epithelial cells proliferate in premenopausal women (55). Blood tests have shown that soy supplementation can affect premenopausal women, because the Ki-67 proliferation index, which is used to detect breast cancer, has been found to increase (28). Soy supplements may further elevate the risk of breast cancer in women with pre-existing history of breast cancer (49). In addition, soy supplements can affect chemotherapy, due to the diverse biological action of isoflavones (43), and how they associate with the risk of prostate cancer. So far, it has been found that soy supplements do not have a protective effect against prostate cancer (38).

Green tea supplements may interfere with cancer treatment when drugs with active substance bortezomib are used (20,27,54). French epigallocatechin-3(EGCG) contained in tea can reduce or even completely inhibit bortezomib protease (27,54). In particular, consumption of even 10 μ M was able to inhibit the action of the active substance bortezomib (27). Also, green tea supplements are recommended to be avoided during radiotherapy as it can affect cell apoptosis,

offering protection to cancer cells from ionizing radiation (48).

REFERENCES

1. Alsharairi, N. A., 2019. The Effects of Dietary Supplements on Asthma and Lung Cancer Risk in Smokers and Non-Smokers: A Review of the Literature. *Nutrients*, p. 725.
2. Al-Subeihi, A. et al., 2011. Physiologically based biokinetic model of bioactivation and detoxification of the alkenylbenzene methyleugenol in rat. *Toxicology in Vitro: Volume 25, Issue 1, February*, pp. 267-285.
3. Ambrosone, C. B. et al., 2019. Dietary Supplement Use During Chemotherapy and Survival Outcomes of Patients With Breast Cancer Enrolled in a Cooperative Group Clinical Trial (SWOG S0221). *Journal of Clinical Oncology*, 19 December, p. 804–814.
4. Baggott, J. E., Oster, R. A. & Tamura, T., 2012. Meta-analysis of cancer risk in folic acid supplementation trials. *Cancer Epidemiology*, February, pp. 78-81.
5. Bara Jr, T. et al., 2017. A systematic review of the possible carcinogenic role of the aristolochic acid. *Romanian Journal of Morphology & Embryology*, p. 41–44.
6. Binns, C., Lee, M. K. & Lee, A., 2017. Problems and Prospects: Public Health Regulation of Dietary. *Annual Reviews*, 22 December, p. 403–420.
7. Bjelakovic, G. et al., 2013. Is folic acid supplementation to food benefit or risk for human health?. *Pteridines: Volume 24 Issue 3-4, 5* 5 October.
8. Bohn, T. et al., 2019. β -Carotene in the human body: metabolic bioactivation pathways - from digestion to tissue distribution and excretion. *Nutrition Society*, 12 February, pp. 68-87.
9. Brasky, T. M., White, E. & Chen, C.-L., 2017. Long-Term, Supplemental, One-Carbon Metabolism-Related Vitamin B Use in Relation to Lung Cancer Risk in the Vitamins and Lifestyle (VITAL) Cohort. *Journal of Clinical Oncology*, 20 October, p. 3440–3448.

10. Brasky, T. et al., 2013. Plasma phospholipid fatty acids and prostate cancer risk in the SELECT trial. *JNCI: Journal of the National Cancer Institute*, Volume 105, 10 July, p. 1132–1141.
11. Chen, C.-H. et al., 2012. Aristolochic acid-associated urothelial cancer in Taiwan. *Proceedings of the National Academy of Sciences of the United States of America*, 22 May, pp. 1-6.
12. Dang, H. & Quirino, J. P., 2021. Analytical Separation of Carcinogenic and Genotoxic Alkenylbenzenes in Foods and Related Products (2010–2020). *Toxins*, 28 May, pp. 1-25.
13. Dietz, B. & Bolton, J. L., 2007. Botanical Dietary Supplements Gone Bad. *Chem Res Toxicology*, April, p. 586–590.
14. Doerge, D. R., 2011. Bioavailability of soy isoflavones through placental/lactational transfer and soy food. *Toxicology and Applied Pharmacology: Volume 254, Issue 2*, 15 July, pp. 145-147.
15. Druesne-Pecollo, N. et al., 2010. Beta-carotene supplementation and cancer risk: a systematic review and metaanalysis of randomized controlled trials. *International Journal of Cancer*, 21 April, pp. 172-184.
16. Eisenreich, A. et al., 2021. Alkenylbenzenes in Foods: Aspects Impeding the Evaluation of Adverse Health Effects. *Foods*, 10 September.
17. Fanidi, A. et al., 2018. Is high vitamin B12 status a cause of lung cancer?. *International Journal of Cancer*, 29 November, pp. 1499-1503.
18. Figueiredo, J. C. et al., 2009. Folic Acid and Risk of Prostate Cancer: Results From a Randomized Clinical Trial. *JNCI: Journal of the National Cancer Institute: Volume 101, Issue 6*, 18 March, p. 432–435.
19. Figueiredo, J. C. et al., 2010. Folic acid and prevention of colorectal adenomas: a combined analysis of randomized clinical trials. *International Journal of Cancer*, 17 December, pp. 192-203.
20. Furlow, B., 2017. Green Tea and Cancer. *Cancer Therapy Advisor*, 26 May.
21. Gonen, N. & Assaraf, Y. G., 2012. Antifolates in cancer therapy: Structure, activity and mechanisms of drug resistance. *Drug Resistance Updates: Volume 15, August*, pp. 183-210.
22. Hanson, S. et al., 2020. Omega-3, omega-6 and total dietary polyunsaturated fat on cancer incidence: systematic review and meta-analysis of randomised trials. *British Journal of Cancer: volume 122, 29 February*, pp. 1260-1270.
23. Hsieh, C. J. et al., 2019. Cancer Hazard Identification Integrating Human Variability: The Case of Coumarin. *International Journal of Toxicology*, December, pp. 501-552.
24. Iwata, N. et al., 2016. The Relation between Hepatotoxicity and the Total Coumarin Intake from Traditional Japanese Medicines Containing Cinnamon Bark. *Frontiers in Pharmacology*, 20 June.
25. Jadot, I., Declèves, A.-E., Nortier, J. & Caron, N., 2017. An Integrated View of Aristolochic Acid Nephropathy: Update of the Literature. *International Journal of Molecular Sciences*, 29 January.
26. Jeon, Y.-J. et al., 2011. Effects of beta-carotene supplements on cancer prevention: meta-analysis of randomized controlled trials. *Nutrition and Cancer*, 7 October, pp. 1196-1207.
27. Jia, L. & Liu, F.-T., 2013. Why bortezomib cannot go with 'green'?. *Cancer Biology & Medicine*, 10 December, pp. 206-213.
28. Khan, S. A. et al., 2012. Soy isoflavone supplementation for breast cancer risk reduction: a randomized phase II trial. *Cancer Prevention Research*, 5 February, pp. 309-319.
29. Kim, Y.-I., 2005. Nutritional epigenetics: impact of folate deficiency on DNA methylation and colon cancer susceptibility. *The Journal of Nutrition Q Volume 135, Issue 11, November*, p. 2703–2709.
30. Kim, Y.-I., 2007. Folic acid fortification and supplementation--good for some but not so good for others. *Nutrition Science*, November, pp. 504-511.
31. Klein, E. A. et al., 2011. Vitamin E and the Risk of Prostate Cancer: Updated Results of The

- Selenium and Vitamin E Cancer Prevention Trial (SELECT). National Institute of Health, 12 October, p. 1549–1556.
32. Kopp, T., Abdel-Tawab, M. & Mizaikoff, B., 2020. Extracting and Analyzing Pyrrolizidine Alkaloids in Medicinal Plants: A Review. *Toxins*, 13 May.
33. Kristal, A. R. et al., 2014. Baseline selenium status and effects of selenium and vitamin e supplementation on prostate cancer risk. *JNCI: Journal of the National Cancer Institute*, 22 February.
34. Lin, J. et al., 2009. Vitamins C and E and Beta Carotene Supplementation and Cancer Risk: A Randomized Controlled Trial. *JNCI: Journal of the National Cancer Institute*, 7 January, pp. 14-23.
35. Li, X.-L. et al., 2020. Aristolochic Acid-Induced Genotoxicity and Toxicogenomic Changes in Rodents. *World J Tradit Chin Med*, pp. 12-25.
36. Mandair, D. et al., 2014. Prostate cancer and the influence of dietary factors and supplements: a systematic review. *Nutrition & Metabolism*, 16 June.
37. Martínez, M. E. et al., 2012. Dietary Supplements and Cancer Prevention: Balancing Potential Benefits Against Proven Harms. *Journal of the National Cancer Institute*, 25 April, pp. 732-739.
38. Messina, M., 2016. Soy and Health Update: Evaluation of the Clinical and Epidemiologic Literature. *Nutrients*, 24 November, pp. 1-42.
39. Miyazaki, J. & Nishiyama, H., 2017. Epidemiology of urothelial carcinoma. *International Journal of urology*, 24 October, pp. 730-734.
40. Moreira, R., Pereira, D. M., Valentão, P. & Andrade, P. B., 2018. Pyrrolizidine Alkaloids: Chemistry, Pharmacology, Toxicology and Food Safety. *International Journal of Molecular Sciences*, 5 June.
41. Neuman, M. G. et al., 2015. Hepatotoxicity of Pyrrolizidine Alkaloids. *Journal of Pharmacy and Pharmaceutical Sciences*, 26 November, pp. 825-843.
42. Ng, A. et al., 2017. Aristolochic acids and their derivatives are widely implicated in liver cancers in Taiwan and throughout Asia. *Science Translation Medicine*, 18 October.
43. Pabich, M. & Materska, M., 2019. Biological Effect of Soy Isoflavones in the Prevention of Civilization Diseases. *Nutrients*, July, pp. 1-13.
44. Prinsloo, G., Steffens, F., Vervoort, J. & Rietjens, I., 2019. Risk assessment of herbal supplements containing ingredients that are genotoxic and carcinogenic. *Critical Reviews in Toxicology*, Volume 49, 19 December, pp. 567-579.
45. Punt, A. et al., 2009. Use of Physiologically Based Biokinetic (PBBK) Modeling to Study Estragole Bioactivation and Detoxification in Humans as Compared with Male Rats. *Toxicological Sciences*, August, pp. 248-259.
46. Rock, C. L. et al., 2012. Nutrition and physical activity guidelines for cancer survivors. *CA: A Cancer Journals for Clinicians*, 4 March, pp. 243-274.
47. Smith, D., Kim, Y.-I. & Refsum, H., 2008. Is folic acid good for everyone?. *The American Journal of Clinical Nutrition*, 1 March, pp. 517-533.
48. Thomas, F. et al., 2011. Green Tea Extract (Epigallocatechin-3-Gallate) Reduces Efficacy of Radiotherapy on Prostate Cancer Cells. *Urology*, 14 June.
49. Touillaud, M. et al., 2019. Use of dietary supplements containing soy isoflavones and breast cancer risk among women aged >50 y: a prospective study. *The American Journal of Clinical Nutrition*, 4 March, pp. 597-605.
50. van den Berg, S. et al., 2011. Levels of Genotoxic and Carcinogenic Compounds in Plant Food Supplements and Associated Risk Assesment. *Scientific Research*, November, pp. 989-1010.
51. Venkateswaran, V. & Klotz, L., 2010. Diet and prostate cancer: mechanisms of action and implications for chemoprevention. *Nature Reviews Urology* volume 7, 20 July, pp. 442-453.

52. Wiedenfeld, H., 2011. Toxicity of Pyrrolizidine Alkaloids – a Serious Health Problem. *Journal of Marmara University Institute of Health Sciences* Volume: 1, 2 November, pp. 79-87.
53. Wien, T. N. et al., 2012. Cancer risk with folic acid supplements: a systematic review and metaanalysis. *BMJ OPEN*, 12 January, pp. 1-13.
54. Wolf, C. et al., 2021. Interactions in cancer treatment considering cancer therapy, concomitant medications, food, herbal medicine and other supplements. *Journal of Cancer Research and Clinical Oncology*, 17 April.
55. Xiao, C. W., 2008. Health Effects of Soy Protein and Isoflavones in Humans. *The Journal of Nutrition*: Volume 138, June, p. 1244–1249.