ACCSCIENCE PUBLISHING

Eurasian Journal of Medicine and Oncology

EDITORIAL

From the Editor's desk

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Citation: Kaina B. From the Editor's desk. *Eurasian J Med Oncol.* 2025;9(3):1-3.
doi: 10.36922/EJMO025360369

Received: August 21, 2025

Accepted: September 1, 2025

Published online: September 23, 2025

Two articles have appeared in this volume of the *Eurasian Journal of Medicine and Oncology* that I would like to address. The work by Rauf *et al.*[1] describes two natural compounds isolated from *Pistacia chinensis*. This tree is found primarily in China and is planted as a street tree in temperate zones worldwide due to its attractive fruit and beautiful autumn foliage. Two flavonoids were extracted from the tree's bark. The flavonoids are polyphenols, and their chemical structures are described in the manuscript. *In silico* analyses showed that the phytochemicals, designated as compound 1 and compound 2, bind to several target proteins, including mechanistic target of rapamycin (mTOR) and protein kinase B 1 (encoded by *AKT1*). They could therefore potentially influence the phosphoinositide 3-kinase (PI3K)–AKT–mTOR pathway. If this binding has an inhibitory effect, it could lead to reduced protein synthesis and, consequently, inhibition of cell growth and proliferation. It could also contribute to increased levels and activation of tumor suppressor protein p53 through targeting mouse double minute 2 homolog (MDM2), as well as to the activation of pro-apoptotic proteins such as BCL2, thereby stimulating pro-apoptotic signaling. A third effect is based on the inhibition of autophagy by mTORC1, which may also be inhibited. In summary, pro-apoptotic processes could be promoted, and cells could be specifically driven to undergo cell death.

In light of this scenario, the authors also investigated cell death using the glioblastoma cell line U87MG. In the 3-(4,5-di methyl thiazol-2-yl)-2,5-diphenyltetrazolium bromide (MTT) assay, the flavonoids showed a positive effect, which is interpreted as anti-cancer activity. However, it must be noted that the MTT assay is a metabolic assay and reflects both proliferation inhibition and actual cell death. Unfortunately, these toxicity studies were not extended, and the authors did not assess apoptosis or, where applicable, necroptosis. Therefore, it remains unclear whether the effects observed through the MTT assay are due to genuine cell death or simply reflect growth inhibition.

This is clearly a limitation of the work. Observing a growth-inhibitory or cytotoxic effect on a tumor cell line should not immediately lead to the conclusion that a substance has "anti-cancer activity." Such a conclusion requires evidence that the substance is selectively active against tumor cells and not toxic to non-transformed cells. This implies that a broad panel of cell lines should be tested. Animal experiments are also necessary before claims of anti-cancer activity can be made. The term "activity on cancer cell lines" would be more precise and appropriate in this context.

Nevertheless, the study is interesting because it reports the identification of a new group of natural compounds with potential relevance for cancer therapy. In future research, it would be worthwhile to characterize the effects at both the cellular and molecular levels in detail, to answer important open questions. For example, in the toxicity prediction assay, one of the compounds tested positive in the Ames test. This could indicate that at least one of the substances has genotoxic potential. Genotoxic effects are clearly linked to cytotoxicity, as p53-dependent apoptotic signaling pathways are activated through DNA damage.[2] In fact, some natural compounds that exert cytotoxic effects on glioblastoma cells, such as curcumin[3] and fisetin,[4] exhibit this mechanism. The cytotoxic effect of the flavonoids could potentially be harnessed for adjuvant therapy or to enhance the activity of existing anti-cancer drugs.

Another interesting aspect that could be explored in future studies is whether the substances exhibit senolytic or senomorphic activity. This is plausible, as the PI3K–AKT–mTOR axis is a major driver of the senescence-associated secretory phenotype (SASP) and helps to maintain the senescent state: mTORC1 promotes translation of interleukin-1 alpha and other SASP regulators. Sustained mTOR activity supports the enlarged, metabolically hyperactive phenotype of senescent cells. Furthermore, AKT activity prevents apoptosis, allowing these damaged cells to persist.[5,6] Thus, this pathway, which is linked to both induction and maintenance of senescence, is crucial, and its inhibition represents a clear therapeutic target. Overall, while the study has limitations, it is likely to stimulate further research on these intriguing flavonoids isolated from *P. chinensis*.

Another study that caught my attention reports on the link between diet and pancreatic cancer.[7] In this case–control study, the authors surveyed 101 pancreatic patients and 314 controls from Jordan about their eating habits and carefully analyzed their responses. They concluded that the extensive consumption of three types of food is associated with an increased risk of pancreatic cancer: (i) yogurt, (ii) white and processed cheese, and (iii) cooked red meat (from veal and lamb) and cooked chicken.

The observation that yogurt and cheese, both generally considered healthy foods, may support pancreatic cancer development is surprising. What might explain this? It should be noted that the overall data are very heterogeneous and, as the authors carefully summarize, there are studies that do not support such a relationship for yogurt and cheese. Could it be that yogurt and cheese are produced differently in Jordan compared to other countries, where these dairy products are not associated with enhanced cancer risk? Is the chemical composition, or the ingredients added or formed during the preparation of yogurt and cheese in Jordan, different from those in other countries? It is also possible that certain microbes or fungi contaminated the dairy products, or are even part of the fermentation process, and produce toxins that are genotoxic.

An example from a completely different context may be illustrative: nicotine-derived N-nitrosamines in tobacco, which are at least partially responsible for the carcinogenic effects of both smokeless and smoked tobacco, and are formed during the fermentation of tobacco leaves.[8] In this case, the carcinogens arise as a result of the preparation process. While this is an extreme example, there are plenty of others involving microbial and fungal contamination of food that impact the incidence of cancer.

The link between high-temperature cooked meat and increased cancer risk is well established. Specifically for pancreatic cancer, this study reported that total consumption of red meat is associated with a 65% increased risk. Possible causes include food-borne heterocyclic aromatic amines, polycyclic aromatic hydrocarbons, heme iron metabolites in red meat, and/or aromatic amino acids. All of these are plausible contributors. However, two meta-analyses, each involving a very large number of patients, concluded that there is no clear relationship between the consumption of red or processed meat and the risk of pancreatic cancer (for references see the paper I am referring to). That said, subgroup differences within cohorts may exist, as indicated by findings from a multiethnic cohort study. A more refined analysis revealed that even relatively small amounts (100–120 g/day) of red and processed meat may be significantly associated with increased pancreatic cancer risk (as discussed in the study from Jordan).

In contrast to red meat, chicken is generally not considered a risk factor for cancer such as colorectal carcinomas. However, this study concludes that "a large intake of poultry may increase the risk of pancreatic cancer." The potential cause could again be food-borne aromatic amines, which are highly carcinogenic and formed during high-temperature cooking. Clearly, the methods of red meat and poultry preparation in Jordan warrant further investigation. Experimental and field studies could assess the actual levels of carcinogenic compounds in these foods.

The current investigation also offers a glimmer of hope. Cooked fish showed a negative correlation with pancreatic cancer, suggesting it may offer some protective effects. Although the overall data on this are not entirely consistent, the study demonstrates that the diverse dietary patterns present in Jordan have a profound effect on health. Dietary recommendations, possibly promoting a mixed diet rich in vegetables, may be an effective strategy to reduce cancer incidence in Jordan.

Conflict of interest

Bernd Kaina is the Editor-in-Chief of this journal. The author declares that he has no known competing financial interests or personal relationships that could have influenced the work reported in this paper.

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