

Popular-scientific abstract

In the last decades, morbidity and mortality rates from liver and pancreas cancers has increased all over the world, including Poland. This is due to low detection, lack of distinct initial symptoms and difficulties with early diagnosis. Despite the use of novel therapies and advances in understanding the molecular basis of tumor induction, average survival rate of patients still remains at the same low level.

In the pathogenesis of hepatic and pancreatic cancers chronic inflammation plays an important role. In the case of liver cancer inflammation results from the chronic HBV/HCV infection followed by oxidative stress. Inflammation and oxidative stress activate multiple signaling pathways eventually leading to increased cancer cells proliferation and avoidance of programmed cell death.

Thus, search for an alternative approach, such as chemoprevention along with the new treatment modalities is still feasible and necessary.

Cancer chemoprevention is a specific strategy of the disease prophylaxis which is defined as the use of natural, synthetic or biological agents to reverse, suppress or prevent either the initial phases of carcinogenesis or the progression of premalignant cells to invasive disease.

Our previous studies have shown that naturally occurring compounds extracted from hop (xanthohumol), grapes (resveratrol) and cabbage (indole-3-carbinol, phenethyl isothiocyanate) have the ability to modulate the signaling pathways in the liver cancer cells, e. g. Nrf2-ARE (Nuclear factor 2-Antioxidant Response Element). In normal cells transcription factor Nrf2 and its associated signaling pathway(s) act as a sensor of oxidative and electrophilic stresses and prevent cells from cellular genomic instability. Activation of Nrf2-ARE pathway triggers induction of expression of various cytoprotective enzymes and proteins. For this reason, this pathway is regarded as an ideal target for chemopreventive agents. On the other hand, the constitutive overexpression of Nrf2 in malignant cells in the liver and the pancreas is associated with tumor progression and resistance to chemotherapy.

The aim of the project is to assess the possibility of modulation of Nrf2-ARE pathway through a combination of natural phytochemicals: xanthohumol, resveratrol, indole-3-carbinol and phenethyl isothiocyanate as a chemopreventive and/or therapeutic strategies designed against cancers of the liver and the pancreas.

Recently it has been suggested that use of combinations of active compounds ensures improved results of chemoprevention or chemotherapy, when compared to application of individual phytochemical alone.

Such a hypothesis may/might be verified experimentally during realization of the proposed research project, moreover the mechanism(s) of action of selected phytochemicals in cancer cells at early and advanced stages of carcinogenesis may be elucidated. The obtained results may/might support in the future the design of new strategies for prevention and/or therapy of hepatic and pancreatic cancers.

A number of studies have indicated that the target of phytochemicals with potential chemopreventive and/or therapeutic activities may not be limited to Nrf2-ARE only, but also other signaling pathways such as NF- κ B and p53 may be equally involved. NF- κ B and p53 play an important role in activation of Nrf2 and carcinogenesis.

In the proposed research evaluation the ability of the most effective combinations of phytochemicals to translocation of Nrf2 to the nucleus and binding to the ARE sequence will be assessed.

In order to elucidate the mechanism of action of the most active combination of phytochemicals, parameters of canonical (protein Keap1, MAPK, GSK-3 β , Fyn kinases, enzymes GSTs, NQO1, HO-1, SOD, CAT, GR, GPx) and non-canonical pathway activation Nrf2 (protein p62) will be evaluated.

The effectiveness of the proposed new chemopreventive/chemotherapeutic strategy will be evaluated *in vivo* in mice transfected with liver and pancreas cancer cells with luciferase reporter gene allowing the cancer development detection.

Overall, the realization of the project will allow to select the new, more efficient phytochemical modulators of the analyzed signaling pathways in liver and pancreas cancer cells and to propose the mechanism(s) of their activity, which might be useful in designing new preventive and/or therapeutic strategies. The obtained results will/would justify further pre-clinical investigation of selected combination(s) compounds and clinical trials. The enlargement of our knowledge of the interaction between Nrf2, NF- κ B and p53 signaling pathways in response to small-molecule modulators is an equally important aspect of the proposed studies.