Fir extract could have anti-cancer and anti-aging properties

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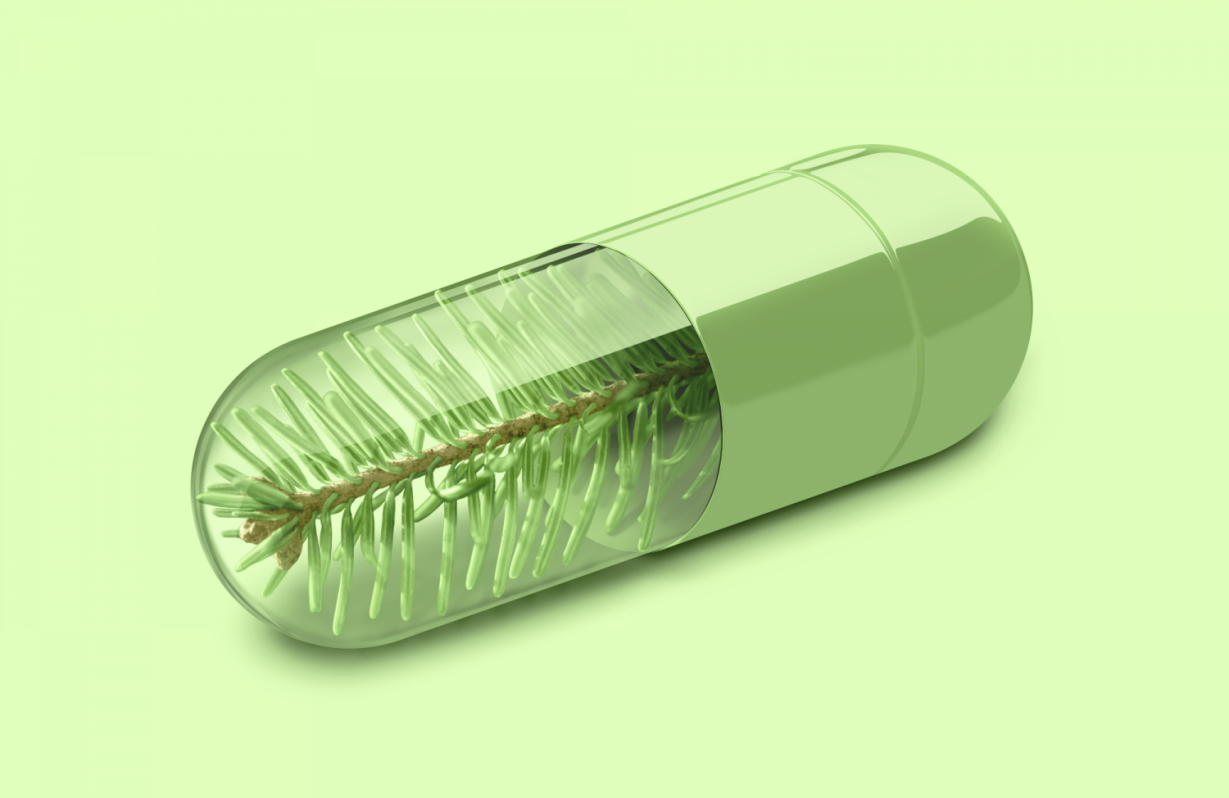

Slider. Credit: MIPT

Scientists from the Engelhardt Institute of Molecular Biology and MIPT have studied the effects of Siberian fir terpenoids on senescent and human cancer cell lines at the genetic level. Research into terpenoids, including their effect on cancers, was initiated by scientists at Initium-

Pharm Ltd. The study was published in the biomedical journal *Oncotarget*, and the results have attracted the interest of geneticists.

Terpenoids are a class of hydrocarbons that are the principal component of gums, balsams, and essential oils. Large volumes of terpenoids are produced by conifers for protection against diseases and invading insects, and in response to unfavorable environmental factors such as exposure to excessive heat, cold or damage. Many compounds of this class could potentially have anti-aging and anti-cancer properties. For example, extracts from the Damask rose, which is rich in a terpenoid called citronellol, have been shown to increase the lifespans of fruit flies by protecting them against iron toxicity and enhancing their resistance to oxidative stress. Betulinic acid, a lupane-type triterpene derived from birch trees, has demonstrated anti-bacterial, antimalarial, and anti-inflammatory properties, as well as cytotoxicity toward cancer cells. Moreover, both the anti-aging and anti-cancer properties have been observed for such terpenoids as ursolic (in apples), maslinic and oleanolic acids (extracted from olive oil).

At present, genuinely new drugs are costly to develop. However, it is much easier to register a drug based on a compound synthesized in the past that has since demonstrated previously unknown properties. The development of such drugs requires far less investment. Trademarked as Abisil, the drug based on Siberian fir terpenoids is now used externally for its anti-inflammatory, wound-healing, and anti-bacterial medicinal properties. The researchers set out to study its anti-aging and anti-cancer properties in greater detail.

Impact on senescent cells

To study the effect of Siberian fir terpenoids on cellular senescence, the scientists used a technique called cell passaging. Passaging, or subculturing, refers to the process of transferring an existing cell culture

to a fresh growth medium. The cells used in the experiment were human connective tissue cells known as fibroblasts. Every two or three days, the cells in a culture form a continuous layer of sufficiently high density, and need to be detached from their growth surface and transferred to a fresh culture medium. Passaging is necessary due to the accumulation of toxic products of cell metabolism and the depletion of nutrients. The number of passages a culture has experienced is a useful characteristic, because it gives an idea of how many divisions the cells in this culture have undergone, and therefore how much they have aged.

The scientists thus used cell passaging to model aging. Variations in the amount of all kinds of RNA produced by a cell (gene expression levels) were used as cell aging markers. These variations in gene activity were compared between cells from different passages—both untreated and exposed to the substance. Having set a twofold change in gene expression levels as the threshold of significance, the researchers obtained the following data: While 43 genes in the fibroblasts from the 13th passage exhibited increased expression (i.e., more RNA was produced by the cells) and the expression of 67 genes was decreased, the number of genes with significantly increased/decreased expression in fibroblasts from the sixth passage was 21 and 16, respectively. This means that as a cell ages, the effect of Siberian fir terpenoids on gene expression becomes more pronounced.

Exposure of cells to the test compound caused an increase in the expression of the two genes *GADD45B* and *GADD45A* by factors of two and 1.5 respectively. Both of them belong to a gene family whose members have been linked to tumor suppression and longevity.

Treatment with Siberian fir terpenoids coincided with an increase in the expression of heat shock genes (the cell's mechanism of response to elevated temperatures) by a factor of 1.5 to three. These genes play a major role in the assembly, folding and transport of complex proteins, as

well as in degrading and recycling unneeded proteins. By analyzing cell pathways induced by Abisil treatment and other cellular mechanisms involved in the experiment, the scientists concluded that the drug is capable of restoring gene expression in senescent cells to the level of younger cells.

Some of the genes showed increased expression

According to a statistics report citing global mortality rates for various types of cancer, pancreatic and colon cancer are the sixth and third deadliest varieties of the disease respectively. The researchers have tested the effect of Siberian fir terpenoids on human cell lines of colon adenocarcinoma (Caco-2) and pancreatic adenocarcinoma (AsPC-1).

The experiment revealed an increased level of expression of the three genes of the GADD45 family, viz., GADD45A, GADD45B, and GADD45G, both in normal fibroblasts and in tumor cell lines (AsPC-1 and Caco-2). Mutations in the GADD45 genes are often accompanied by the initiation and progression of malignancies. In addition, these genes are known to mediate the effects of several chemotherapeutic drugs.

Other genes whose overexpression was observed by the scientists upon exposure of cancer cells to the test compound include DUSP1–2, DUSP4–6, and DUSP8. Genes of the DUSP family are responsible for the suppression of the MAPK signal transduction cascade, which means they act as tumor suppressors and chemotherapy mediators.

The study has thus demonstrated the potential anti-aging and anti-cancer effects of Siberian fir terpenoids, opening up possibilities for their wider application in the future.

More information: *Oncotarget*, 10.18632/oncotarget.13467

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