Beneficial Effects of Turkey Tail on Colorectal Cancer Treatment

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Colorectal Cancer (CRC) is the second leading cause of malignant tumor-related deaths across the globe. Also, it is the third most diagnosed cancer type (Zhicheng He et al., 2022). According to the American Cancer Society, in 2024, the incidence rate of new cancer cases was 2,001,140, and the mortality projection was about 611,720 cases in the United States. Colorectal cancer was the fourth leading cause of cancer death in the 1990s below the age of 50, however, currently is the number one cancer death in men, and the second in the USA among cancer-related deaths (Siegel et al., 2024). Patients diagnosed with CRC stage-1 have a 90% chance of a five-year survival rate. However, patients diagnosed with CRC with stages -3,4 have a significantly lower chance of 5-year survival rate, down to 67%. And, about 90% of CRC mortality rates are due to metastasis of the cancer (Jian et al., 2022).

Therefore, the prevention, diagnosis, and treatment of CRC are continuously studied. Current medical treatment of CRC includes radiotherapy, surgical procedures by resection of the tumor location in the colon part, and chemotherapy. However, many medications have side effects with higher cytotoxicity by lowering the quality of life of CRC patients.

In some cultures, like Japanese & Chinese, the cancer treatment plan includes incorporating the traditional methods by administering patients various herbs, cocktails, and mushrooms. The diverse pharmacological activities of natural products obtained from plants, microorganisms, animals, and fungi led to the discovery of new drugs. Researchers always look for those compounds that could be able to kill cancer cells, without harming other non-cancerous cells(He et al., 2022).

In Chinese Medicine, *Trametes versicolor (formerly Coriolus versicolor)* has been used

for enhancing immunity and treating cancer for thousands of years. Additionally, *Trametes versicolor* is a medicinal mushroom and has been known for its longevity-enhancing and health-promoting properties(He et al.,2022). Scientific name: *Trametes versicolor* – also known as *Coriolus versicolor*, *has several colors.* It grows on logs and stumps of deciduous trees, and It is found throughout the world. A common name of *Trametes versicolor* is Turkey tail, which is a polypore(*genus of Fungi*) mushroom that resembles the tail feathers of a turkey.

Trametes versicolor's two well-studied components such as polysaccharide Krestin (PSK) and polysaccharide peptide (PSP) were used in the treatment of CRC. In fact, in China and Japan, these two molecules of *Trametes versicolor* are used as an additional therapy for cancer (He et al., 2022). They were offered in the treatment of cancers such as breast, cervical, liver, lung, and prostate cancer as a chemotherapeutic agent (Jian et al., 2022).

Previous studies have shown that polysaccharide Krestin (PSK) and polysaccharide peptide (PSP) of *Trametes versicolor* have similar peptide moieties as beta-glucan backbone has. Beta-glucan has been identified as effective in assisting white blood cells to kill cancer cells (VE & Liu., 2000).

Furthermore, Jian and his colleagues, in 2022, studied the mechanisms of action through which PSP inhibits CRC growth in vitro. In addition, the cytotoxicity of PSP was explored by using human CRC cell lines (HCT116 and HT29). For methods of the experiment were used in real-time PCR, western blot, and immunofluorescence were used to examine the expression of epidermal growth factor receptor (*EGFR).* Also, programmed cell death-ligand 1 (*PD-L1*), activator of transcription 3 (*STAT3*), *c-Jun*, and *NF-κB* in the PSP-treated CRC cells. The synergic effect of T-cell killing was evaluated using the terminal-deoxynucleotidyl

transferase-mediated nick-end labeling (TUNEL) method.

The result of this study showed the significant inhibition of CRC (HCT116 and HT29) cells in vitro. In addition, PSP reduced the phosphorylation activities of EGFR PD-L1 which are responsible for the cell's survival activities. So, in this case, inhibiting EGFR and PD- L 1 of CRC by PSP is a good indication that PSP is a powerful anti-agent. And, PSP has increased the activity of T cells killing the CRC cells. Thus, in conclusion, Jian and his colleagues state that PSP can be used as a prophylactic and therapeutic agent in the treatment of CR cancer.

According to Ying He and his colleagues, the polysaccharide Krestin (PSK) and polysaccharide peptide (PSP) of *Trametes versicolor* weigh from 100 to 500 kDa and they tend to be highly heterogeneous in the mixture. He argues that first, PSK's and PSP's molecular weight makes research very challenging. The second disadvantage of PSK & PSP is that they do not get digested in the mammalian gut and lead to poor absorption making the product less effective. However, PSK and PSP components still have a strong inhibitory effect against cancer cell proliferation.

In 2021, the same research team, Ying He and his colleagues, discovered a novel protein molecule *Musirin* from polysaccharide Krestin (PSK) and polysaccharide peptide (PSP) powder. This molecule weighs significantly lighter 12 kDa than polysaccharide Krestin (PSK) and polysaccharide peptide (PSP) 100-500 kDa. Furthermore, researchers tested Musarin's anticancer activities using multiple colorectal cell lines and its cellular pathways.

For the methods and materials they used CRC cell lines (HCT116, HT 29), and they cultured in DMEM (Dulbecco's Modified Eagle Medium) (T84 and Caco2), RPMI 1640 (WiDr, Colo320DM, colo205, HCT-15, SW620, SW480, SW1116), all had 10% FBS. In parallel, for the

reference, they also used a normal cell from epithelial cells(FHs74) and was cultured in X-46 medium which had 10% FBS & 30 ng/mL EGF. All were incubated at 37 C.

In this study, researchers studied the purification & characterization of *Musarin,* its digestion and absorption, proliferation and cytotoxic effect, its effect on CRC metastasis, tumorigenic assays, DNA sequencing & structure analysis, vitro RNase activities, transcription expression profile, and tyrosine kinase inhibition. All were tested using different chemical reactions along with various biological agents. They used statistical analysis, One-way ANOVA, two-way ANOVA, or Student's *t*-test was performed using Prism (GraphPad Software).

Results of the study showed that PSP's ultra purification with the size of less than 30,000 Da and more than 3000 Da has the significant ability to decrease the CR cell growth and it has an anti-tumor effect.

They identified that *Musarin* inhibits colorectal cell proliferation in a dose-dependent manner (from 0.1 to 10 μg/mL). The results also showed that *Musarin* did not show any cytotoxicity while treating the colorectal cell. *Musarin* targets CRC stem cell proliferation by 82% in just 4 days of treatment.

Furthermore, it was identified that *Musarin* can decrease the size & weight of CRC tumors in vivo in mouse models. In the oral administration of *Musarin* to mice, the average tumor size & weight decreased from ~2000 mm3 in size and ~1 g to ~400 mm3 and ~0.3 g, Side effects such as skin rash and hair loss were not observed, suggesting its low cytotoxicity.

Tyrosine kinase is one of the signaling molecules that stimulate cancer cell signaling, growth, and division. In this study, Musarin was able to stop Tyrosine Kinase activity in

colorectal cancer cells.

A mutation in the gene of EGFR (epidermal growth factor receptor) can lead to cancer. This study identified that Musarin can also inhibit EGFR-RAS signaling pathways thereby interrupting the colorectal cancer cell growth activities.

In 2019, researchers Roca-Lema et al., published a paper where they looked at the effect of two combined mushrooms such as *Trametes Versicolor and Grifola Frondosa* in the treatment of colon cancer cells. Additionally, they were interested to see their oncogenic effect, inhibition of cell proliferation, migration, and invasion of the CRC. They tested their cytotoxicity and wound healing assays as well. Statistical analysis was used to see the statistical significance via GraphPad Prism software applying ANOVA or Kruskal-Walli. Shapiro-Wilk test for normal distribution & Levene test to determine the equality of variances.

For the materials and methods, they extracted both *Grifola frondosa* and *Trametes versicolor*, LoVo cells from metastatic sites, and HT-29, a colorectal adenocarcinoma cell line with an epithelial morphology.

CRC cells were treated with 10, 50, 100, 250, or 1000μg/ml of extracts from *Trametes versicolor* or *Grifola frondosa* for 24, 48, or 72 h. *Trametes versicolor* Vs *Grifola frondosa* effects were explored separately as well with different concentrations.

Application of 10 μg/ml of TV extract to LoVo cells (from metastatic sites) resulted below:

- in 24h did not show the effect
- in 48h was a slightly reduction

- in 72h was a significant reduction

In contrast, *Trametes versicolor* extract, *and Grifola frondosa* extract, showed the earlier effect on LoVo cells, with endpoint reduction similar, however, its cytotoxicity was higher on HT-29 cells than *Trametes versicolor* extract. In conclusion, the mixture of *Trametes versicolor* & *Grifola frondosa* extracts was capable of directly inhibiting colon cancer cell growth, they have the strongest antitumor effect, which also stops metastasis of CRC. Also, the combination extract of *Trametes versicolor* & *Grifola frondosa* showed an anti-proliferative and anti-migratory action in human colon cancer cells, suggesting that this combo is the best in the treatment of colon cancer.

In conclusion, 5 peer-reviewed articles were reviewed. All the papers studied the anticancer effect of the *Trametes versicolor*, commonly known as mushroom Turkey tail. Since *Trametes versicolor* was widely used in Asian traditional medicine for enhancing immunity & longevity, researchers have looked closely at its components. In 2022, Zhicheng He and his colleagues summarized the *Trametes versicolor* studies against colon cancer treatment.

Two components of *Trametes versicolor* such as polysaccharide Krestin (PSK) and polysaccharide peptide (PSP) showed their anti-colorectal cancer tumor growth by inhibiting the EGFR cascade activities.

Ying He and his colleagues, argued for the polysaccharide Krestin (PSK) and polysaccharide peptide (PSP) molecules making research more challenging due to their heavy molecular weight, poor solubility, and poor digestion in the mammalian gut. As an answer to their argument, they discovered a novel protein molecule from *Trametes versicolor* called *Musarin*. Musarin was identified with less molecular weight, and it showed stronger inhibition of

colorectal cancer cell growth in vivo and in vitro.

In the study of Roca-Lema et al., (2019), they looked *at Trametes versicolor* combined with another mushroom *Grifola frondosa*. They concluded that the combined extract of two powerful mushrooms showed a significant antitumor effect, suggesting that the mixture of *Trametes versicolor* & *Grifola frondosa* can cure colorectal cancer.

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