Fermented wheat germ extract: a dietary supplement with anticancer efficacy

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Fermented wheat germ extract: a dietary supplement with anticancer efficacy

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Introduction: Recent times have witnessed an unprecedented surge in phytochemical-based dietary supplements for the alleviation of various forms of cancer. Fermented wheat germ extract (tradename Avemar or MSC) has proven efficacy in this regard.

Materials and Methods: To review the current status and future scope of fermented wheat germ extract, the PubMed and ScienceDirect databases have been explored.

Results: This product of high health repute is obtained by fermenting Triticum vulgaris grains with baker’s yeast, Saccharomyces cerevisiae. The bioactive ingredients responsible for the anticancer activity have been identified as 2,6-dimethoxy-p-benzoquinone and 2-methoxy benzoquinone. The progression of cancer is inhibited by immune modulation and antimetastasis.

Conclusions: This review focuses on the potential of Avemar as a supportive option to complement conventional cancer treatment, on the pitfalls encountered in this vision, and on the possibilities of widening the therapeutic spectrum.

Keywords: Fermented wheat germ extract, Avemar, Benzoquinone, Anticancer, Immunomodulation

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INTRODUCTION

Fermented wheat germ extract (FWGE) is a biologically active compound derived from wheat. It is a tiny but the most vitamin- and mineral-dense part of the cereal kernel. Avemar is the only patented FWGE, the name being derived from “Avemar pulvis”. Avemar pulvis is a powder consisting of an aqueous extract of fermented wheat germ, with the drying aids maltodextrin and silicon dioxide, standardized to contain approximately 200 mg/g of the natural constituent 2,6-dimethoxy-p-benzoquinone. It was reported that Avemar pulvis as a supplement administered to cancer patients at doses of 8.5 g/day is free of any adverse effect (1).

Avemar’s development was inspired by the work of the Hungarian scientist Dr Albert Szent-Györgyi, awarded the 1937 Nobel Prize in Medicine for describing the essential role of vitamin C in the metabolism. It was invented by Máté Hidvégi in the early 1990s. The compound is obtained by fermenting Triticum vulgaris grains with Saccharomyces cerevisiae. 2,6-Dimethoxy-p-benzoquinone and 2-methoxy benzoquinone are 2 key ingredients of Avemar. Avemar has garnered reputation as an adjunct therapy and is registered as a special nourishment for cancer patients in Hungary. It is distributed in the United States under the brand name Avè. It has established beneficial roles against metabolic syndromes. Also, Avermar’s benefits as a prebiotic source and antiinflammatory agent have gained credence. It has been shown that rat models of hypertension and diet-induced obesity respond well to Avemar treatment. The supplement improved cardiac function by decreasing collagen deposition in the ventricular myocardium and decreasing plasma malondialdehyde concentrations (2). Further, it reversed glucose intolerance, normalized systolic blood pressure and decreased visceral fat deposition in rats fed a high-fat/high-carbohydrate diet (2). It proved useful as an animal–protein-free culture medium for bifidobacteria growth (3). The potency of Avemar in
Fermented wheat germ extract: a dietary supplement with anticancer efficacy

pain management for rheumatoid arthritis patients was investigated and a reduction of steroid dosages to half was reported (4). Its capacity to inhibit cyclooxygenase (COX-1 and COX-2) and its additive effect on the analgesic diclofenac in rat models have been reported (5).

However, its action against cancer has received the most attention. Avemar has been recognized as a medical nutriment for cancer patients in the Czech Republic, Bulgaria and Romania, and approved as a dietary supplement in the United States. In the sections below, the recently validated anticancer effects of FWGE will be discussed.

Cancers, ranging from mild to malignant forms, disrupt normal life and claim millions of lives. Conventional therapies have proven insufficient in wiping them out. Therapeutic potency of FWGE has been observed against colon, blood, breast, oral, ovary and skin cancers. The role of Avemar in the treatment of colorectal cancer has been reviewed (6). When supplemented to patients undergoing postoperative chemo-radiotherapy, it significantly reduced recurrences, metastases and deaths. Cancer–cell-specific induction of caspase-3-mediated cleavage of poly ADP ribose polymerase (PARP) was identified to be the underlying mechanism (6). It was reported that Avemar bolsters immunity by stimulating natural killer (NK) cell activity, enhancing tumor necrosis factor (TNF) secretion from macrophages, and increasing intercellular adhesion molecule 1 (ICAM-1) expression on vascular endothelial cells. These modulations in the immune profile aid in the apoptosis of cancer cells (7).

Further, it was found that the beneficial effect of FWGE is mediated through interference with anaerobic glycolysis, the pentose cycle, and ribonucleotide reductase (8).

INHIBITION OF TUMOR GROWTH

Important research findings highlighting the efficacy of FWGE as an antidote to cancer will be discussed below. Avemar was given to rats by gavage at a dose of 3 g/kg daily, followed by injection of azoxymethane to induce colon carcinogenesis. Supplementation of Avemar was continued until the rats were sacrificed 32 weeks later. Tissue analysis revealed a conspicuous decrease in the number of aberrant crypt foci, indicating a chemopreventive effect of Avemar (9).

Melanoma inhibitory activity (MIA) is a small secreted protein that promotes the metastatic behavior of malignant cancers (10). It was observed that MIA pancreatic adenocarcinoma cells treated with 0.1, 1, and 10 mg/mL FWGE showed a dose-dependent decrease in cell glucose consumption. The synthesis of cell palmitate and the 13C enrichment of acetyl units were also significantly increased with all doses of FWGE. It was inferred that tumor propagation is controlled by regulation of glucose carbon redistribution between cell–proliferation-related and cell–differentiation-related macromolecules (10).

The molecular and cellular mechanisms of the in vitro antitumor effects of FWGE were analyzed using T and B tumor lymphocytic cell lines (11). FWGE stimulated tyrosine phosphorylation of intracellular proteins and the influx of extracellular Ca2+, resulting in the elevation of their intracellular concentration. Apoptosis of 20-40% cells was detected upon 24 hours’ incubation with FWGE. The key component was identified to be 2,6-dimethoxy-p-benzoquinone (11).

The effect of Avemar on Jurkat leukemia cell viability, proliferation, cell cycle distribution, apoptosis and the activity of key glycolytic/pentose cycle enzymes (that control carbon flow for nucleic acid synthesis) was reported. When incubated for 72 hours at concentrations higher than 0.2 mg/mL, it inhibited the growth of more than 50% of cells (12).

The antiproliferative effects of Avemar were also studied in the human colon carcinoma HT-29 cell line and it was reported that 7 days of incubation was capable of causing inhibition (13). Incubation of cells with 3200 µg/mL Avemar for 24 hours caused necrosis in 28% and apoptosis of 22% of the cells. The cell-cycle progression of HT-29 cells occurred in the G1 phase of the cell cycle. Also, it inhibited the activity of ribonucleotide reductase, the enzyme responsible for de novo DNA synthesis as well as COX-1 and COX-2 (13).

The antiproliferative effects of Avemar were also investigated in human promyelocytic leukemia HL-60 cells (14). After 24, 48 and 72 hours of incubation, it inhibited the growth of the cells in a dose-dependent manner. Induction of apoptosis occurred in approximately 85% of tumor cells. Also, Avemar attenuated the progression from G2-M to G0-G1 phase of the cell cycle and significantly reduced the in situ activity of ribonucleotide reductase (14).

Avemar’s effects on sensitive and 5-FdUrd/Ara-C cross-resistant human lymphoma H9 cells have been investigated as well (15). After 48 and 72 hours of incubation, it
inhibited the growth of both types of cells, though IC50 was achieved at different doses. Treatment with 300 µg/mL induced apoptosis in 48% of sensitive cells, while 200 µg/mL resulted in apoptosis of 41% of resistant cells. Growth arrest of both types of H9 cells occurred mainly in the S phase of the cell cycle (15).

IMPROVEMENT OF QUALITY OF LIFE

The anorexia-cachexia syndrome is a metabolic disorder associated with cancer, leading to weight loss, fatigue, anemia, weakness and inflammation. It was reported that Avemar in combination with antineoplastic agents (fluorouracil and dacarbazine) markedly decreased the toxic side effects of the drugs, as manifested by decreased weight loss (22). The effects of Avemar in head and neck cancer patients were investigated. After 2 months of treatment, a significant fall in the level of oxidative stress quantified by circulating hydroperoxides was observed. Avemar proved capable of attenuating the anorexia-cachexia syndrome triggered by oxidative stress (23).

ANTIMETASTASIS

Metastasis is the spread of cancer from one organ to another via the blood or the lymphatic system. A significant inhibitory effect of Avemar was observed against 3 metastasis models (Lewis lung carcinoma 3LL-HH, mouse melanoma B16 and human colon carcinoma xenograft HCR-25). Immunomodulatory, cell-adhesion inhibitory, apoptosis-enhancing and antioxidant actions were credited for this effect (24). A clinical study was conducted to assess whether Avemar offers therapeutic benefit in colorectal cancer. Intake of Avemar by patients who had undergone curative surgery prevented new metastases (25).

IMMUNE ENHANCEMENT

Evidence from several studies reinforces the immunomodulatory role of Avemar. The tumor growth- and metastasis-inhibiting effects of Avemar alone or in combination with vitamin C were investigated (26). The combined treatment significantly inhibited metastasis formation in all the applied tumor models, i.e. Lewis lung carcinoma 3LL-HH, melanoma B16, a rat nephroblastoma RWT-M and a human colon carcinoma xenograft HCR25 implanted in mice. Apart from the synergistic effect, Avemar alone could exert a pronounced inhibitory effect on metastases. It was suggested that the observed metastasis-inhibiting effect of this preparation may be mainly due to its immune-stimulatory properties (26).
MOLECULAR TARGETS

Several crucial targets of FWGE have been identified in recent times. The COX-1 and COX-2 enzymes, major histocompatibility complex class 1 (MHC-1) proteins, ICAM-1 and ribonucleotide reductase have been recognized as key targets. FWGE nonselectively inhibits COX-1 and COX-2 and relieves inflammation and pain in cancer patients. MHC-1 on tumor cells makes them appear noncancerous. High density of MHC-1 on tumor cells was reduced by FWGE, mediated by sensitization of NK cells. The inner cells of the vessels of some tumors have a smaller amount of ICAM-1 than normal cells. FWGE makes more ICAM-1 on the cells of the vessels, thus helping the leukocytes destroy the malignant tumor cells in the surrounding tissues. FWGE blocks the enzyme ribonucleotide reductase, which hampers DNA synthesis for cancer cells. PARP is an enzyme that plays a pivotal role in repairing the DNA chains. If PARP does not work well, it leads to DNA fragmentation and subsequent apoptosis. Avemar inhibits PARP, therefore DNA repair in cancer cells is also impaired. It has been shown that Avemar does not allow cancer cells to produce DNA. Also, it diverts the metabolic pathway to build fat from glucose, helping to decrease the life-threatening cachexia syndrome. Research has already proved that preventing weight loss or at least reducing its speed is beneficial enough to prolong life in patients suffering from cancer. Avemar promotes immunity by augmenting the production of cancer-suppressing cytokines. The intensive chemotherapy-depleted immune cells could be replenished by the supplementation. The fact that Avemar nonselectively inhibits COX-1 and COX-2 enzymes may partly explain its antiinflammatory activities (5). The mechanisms of anticancer actions are presented in Figure 1. The cancer pathways interrupted by FWGE are illustrated in Figure 2.

ADVERSE EFFECTS

FWGE has been accorded GRAS (Generally Recognized As Safe) status. So far, no major side effects of its consumption have come forth. Still, the few benign reports of health risks must be taken into account. FWGE use is not recommended during pregnancy or radiation therapy and after organ transplantation (19). Mild gastrointestinal side effects have been observed in a few colorectal cancer patients (6).
**FUTURE DIRECTIONS**

Nuruk, a traditional Korean fermentation starter for beverages, shows radical scavenging activity (31). It contains 2,6-dimethoxy-p-benzoquinone. FWGE contains the same component, so it could be a source of antioxidant (32). The possibility of 2-methoxy benzoquinone and 2,6-dimethoxybenzoquinone production by sourdough lactic acid bacteria fermentation has been explored (33).

Lactobacillus plantarum LB1 and Lactobacillus rossiae LB5 were selected based on the highest enzyme activity. The sourdough-fermented wheat germ was characterized based on microbiological, physicochemical and biochemical features. During incubation, the release of nonglycosylated and physiologically active 2-methoxy benzoquinone and 2,6-dimethoxybenzoquinone was almost completed during 24 hours. Compared with the control, the concentration of the above bioactive compounds increased 4- and 6-fold.

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**Fig. 1 - Mechanisms by which fermented wheat germ extract controls cancer.**

<table>
<thead>
<tr>
<th>Mechanism</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Inhibits glycolysis/pentose cycle enzymes</td>
<td>Activates PARP</td>
</tr>
<tr>
<td>Causes apoptosis</td>
<td></td>
</tr>
<tr>
<td>Sensitizes NK cells</td>
<td>Reduces density of MHC-1 on tumor cells</td>
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<tr>
<td>Enhances ICAM-1 expression</td>
<td>Immune cells enter tumor</td>
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<tr>
<td>Destroys malignant cells</td>
<td></td>
</tr>
<tr>
<td>Inhibits COX-1 and COX-2</td>
<td>Relieves inflammation and pain</td>
</tr>
<tr>
<td>Blocks ribonucleotide reductase</td>
<td>Hampers DNA synthesis for cancer cells</td>
</tr>
</tbody>
</table>

**Fig. 2 - Illustration of the anticancer pathways of fermented wheat germ extract.**
Fermented wheat germ extract: a dietary supplement with anticancer efficacy

When assayed for antiproliferative activity, sourdough-fermented wheat markedly affected human germ cell tumors, colon carcinoma and ovarian carcinoma (33). As mentioned earlier, the capability of Avemar to reverse glucose intolerance, normalize systolic blood pressure and decrease visceral fat deposition in rats fed a high-fat/high-carbohydrate diet has been reported (2). Its potential role in attenuating chronic hypertension, diabetes or metabolic syndrome-induced cardiovascular symptoms along with metabolic abnormalities such as glucose intolerance and obesity requires further investigation (2).

CONCLUSION

The encouraging findings to date seem to favor the inclusion of Avemar as a complementary and alternative medicine against cancer. The product may be used as an adjuvant in the therapy for malignant neoplasia. More placebo-controlled clinical trials are warranted to explore hidden efficacies and ensure the lack of toxicity. Though Avemar has already established itself as a potent cytotoxic agent, there is always scope for improvement. Fermentation of wheat germ by novel GRAS microbes may augment its efficacy. Avemar has shown efficacy against head and neck, breast, ovary, colorectal and oral cancer as well as melanoma and leukemia, and this might be extended to other forms of cancer.

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REFERENCES


