Fermented wheat germ extract: a dietary supplement with anticancer efficacy

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REVIEW

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 Avé. 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

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 Ca^{2+}, 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 effect of Avemar was 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

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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).

POTENTIATION OF CHEMOTHERAPEUTICS AND SIDE EFFECT REDUCTION

FWGE as an adjunct has been shown to potentiate chemotherapeutic drugs in combating various cancers. It was reported that continuous supplementation of conventional drugs with Avemar (9 g/daily) for more than 6 months is beneficial to patients with colorectal cancer in terms of overall and progression-free survival (16). The combined effect of tamoxifen (an antagonist of the estrogen receptor in breast tissue) and Avemar on the human breast adenocarcinoma MCF-7 cell line was investigated. The estrogen-receptor activity of the cells was decreased by the treatment, as manifested by a higher apoptosis rate (17). An open-label, matched-pair clinical trial was conducted to test the efficacy of cytotoxic drugs and Avemar. The combination therapy reduced the incidence of febrile neutropenia (fever with a significant fall in the number of white blood cells) in children with solid cancers (18). A randomized trial was conducted to compare the effect of dacarbazine (an alkylating agent) combined with FWGE on the survival of melanoma patients (19). After 1 year of administration of FWGE and a 7-year-long follow-up period, cancer progression and overall survival were measured. Both parameters showed improvement in the supplemented group over the control group. Progression-free survival duration increased from 29.9 months to 55.8 months, whereas overall survival duration increased from 44.7 months to 66.2 months (19). The in vitro antiproliferative activity of FWGE in combination with fluorouracil, oxaliplatin or irinotecan was evaluated against a broad spectrum of human tumor cell lines (20). The combination induced apoptosis, and the antitumor activity was strongest against neuroblastoma cell lines. The cytotoxic activity varied from additive to synergistic (20). The activity of Avemar in combination with cisplatin was investigated against a range of advanced-stage epithelial ovarian cancer cell lines. It exhibited synergistic antiproliferative effects against the studied cell lines via promotion of apoptosis (21).

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).

It was reported that oral administration (3 g/kg body weight) of Avemar enhanced blastic transformation of splenic lymphocytes in mice (22). The same treatment shortened the survival time of skin grafts in a co-isogenic mouse skin transplantation model, pointing to the immune-reconstructive effect. Combined treatment consisting of Avemar with fluorouracil and dacarbazine significantly enhanced the antimetastatic effect in mouse colon carcinoma C38 and mouse melanoma B16 models (22).

The effect of Avemar on the blastic transformation of peripheral blood lymphocytes of mice was examined (24). In a B10LP to C57Bl skin graft system, Avemar restored the immune function. Oral administration at a dose of 3 g/kg enhanced the blastic transformation of splenic lymphocytes in mice. The same treatment shortened the survival time of skin grafts in a co-isogenic mouse skin transplantation model (24).

The effect of Avemar on the trend of autoantibody production was assessed in treatment-naive mice with systemic lupus erythematosus induced by idiotypic manipulation (27). When given in the pre-immunization period, Avemar downregulated autoantibody production, an effect that continued even after the therapy was stopped. The mice showed a normal erythrocyte sedimentation rate and white blood cell count, and less than 100 mg/dL of protein in the urine. From the results it was inferred that Avemar can ameliorate the clinical manifestations of systemic lupus erythematosus by inhibiting the Th2 response (27).

An in vivo experiment was conducted on mice inoculated with tumor 3LL-HH and it was reported that Avemar, when combined with cytostatic drugs such as endoxan, navelbine and doxorubicin, does not alter the tumor growth inhibitory effect, toxicity or antiproliferative effect of the drugs (28).

The clinical and experimental outcome of Avemar treatment in cancer was reviewed and the effect on certain autoimmune conditions was documented (29). It was reported that Avemar treatment induced the synthesis of ICAM-1 and promoted its induction of TNFs. Further, from the study of HeLa cells it turned out that Avemar treatment increased the activity of stress kinases in a concentration-dependent way, resulting in the activation of enhancer-binding protein AP-1 (30). Also, nuclear factor kappa-light-chain enhancer of activated B cells (NF-κB)-sensitive reporters were activated by Avemar (30).

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).

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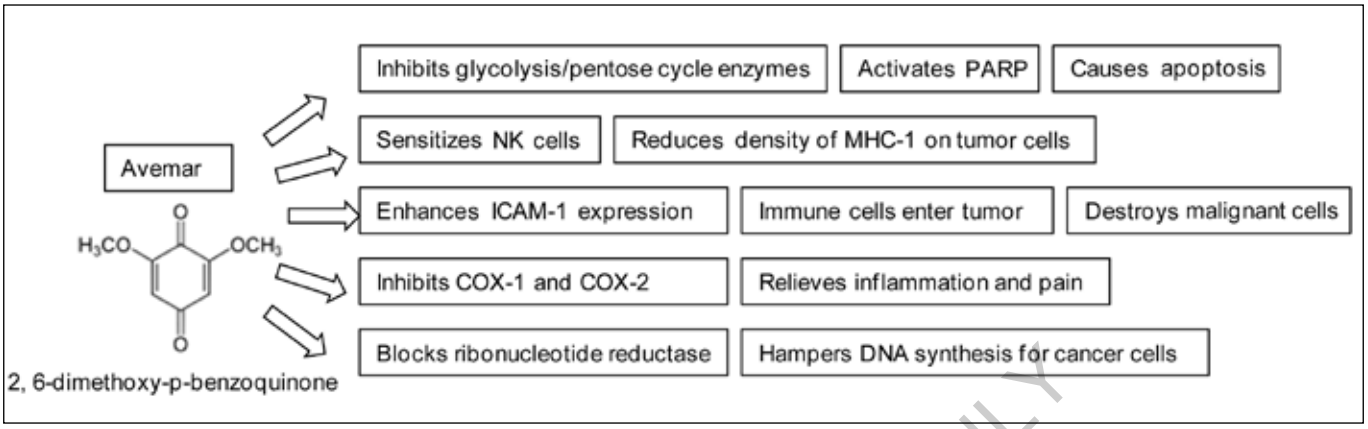

Fig. 1 - *Mechanisms by which fermented wheat germ extract controls cancer.*

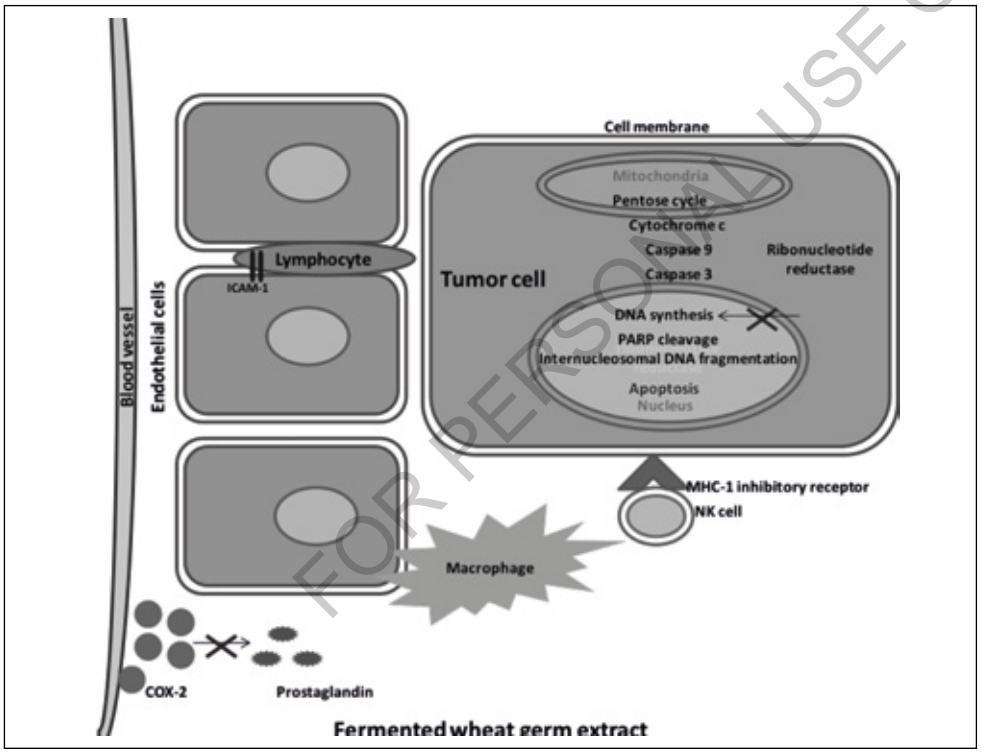

Fig. 2 - *Illustration of the anticancer pathways of fermented wheat germ extract.*

FUTURE DIRECTIONS

Nuruk, a traditional Korean fermentation starter for beverages, shows radical scavenging activity (31). It contains 2,6-dimethoxy-p-benzoquinoe. 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.

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

1. Heimbach JT, Sebstyen G, Semjen G, Kennepohl E. Safety studies regarding a standardized extract of fermented wheat germ. Int J Toxicol 2007; 26: 253-9.
2. Iyer A, Brown L. Fermented wheat germ extract (avemar) in the treatment of cardiac remodeling and metabolic symptoms in rats. Evid Based Complement Alternat Med 2011; 2011: 508957.
3. Dubna S, Rada V, Llkova E, Horejsova V, Havlik J. Growth of bifidobacteria in a fermented wheat germ medium. Acta Alimentaria 2010; 39: 293-8.
4. Bálint G, Apáthy A, Gaál M, et al. Effect of Avemar–a fermented wheat germ extract–on rheumatoid arthritis. Preliminary data. Clin Exp Rheumatol 2006; 24: 325-8.
5. Telekes A, Resetar A, Balint G, et al. Fermented wheat germ extract (avemar) inhibits adjuvant arthritis. Ann N Y Acad Sci 2007; 1110: 348-61.
6. Farkas E. Fermented wheat germ extract in the supportive therapy of colorectal cancer. Orv Hetil 2005; 146: 1925-31.
7. Telekes A, Hegedus M, Cahe CH, Vekey K. Avemar (wheat germ extract) in cancer prevention and treatment. Nutr Cancer 2009; 61: 891-9.
8. Mueller T, Voigt W. Fermented wheat germ extract – nutritional supplement or anticancer drug? Nutr J 2011; 10: 89.
9. Zalatnai A, Lapis K, Szende B, et al. Wheat germ extract inhibits experimental colon carcinogenesis in F-344 rats. Carcinogenesis 2001; 22: 1649-52.
10. Boros LG, Lapis K, Szende B, et al. Wheat germ extract decreases glucose uptake and RNA ribose formation but increases fatty acid synthesis in MIA pancreatic adenocarcinoma cells. Pancreas 2001; 23: 141-7.
11. Fajka-Boja R, Hidvegi M, Shoenfeld Y, et al. Fermented wheat germ extract induces apoptosis and downregulation of major histocompatibility complex class I proteins in tumor T and B cell lines. Int J Oncol 2000; 20: 563-70.
12. Comin-Anduix B, Boros LG, Marin S, et al. Fermented wheat germ extract inhibits glycolysis/pentose cycle enzymes and induces apoptosis through poly(ADP-ribose) polymerase activation in Jurkat T-cell leukemia tumor cells. J Biol Chem 2002; 277 : 46408-14.
13. Illmer C, Madlener S, Horvath Z, et al. Immunologic and biochemical effects of the fermented wheat germ extract Avemar. Exp Biol Med (Maywood) 2005; 230: 144-9.
14. Saiko P, Ozsvar-Kozma M, Madlener S, et al. Avemar, a non-toxic fermented wheat germ extract, induces apoptosis and inhibits ribonucleotide reductase in human HL-60 promyelocytic leukemia cells. Cancer Lett 2007; 250: 323-8.
15. Saiko P, Ozsvar-Kozma M, Graser G, et al. Avemar, a non-toxic fermented wheat germ extract, attenuates the growth

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of sensitive and 5-FdUrd/Ara-C cross-resistant H9 human lymphoma cells through induction of apoptosis. Oncol Rep 2009; 21: 787-91.
16. Jakab F, Shoenfeld Y, Balogh A, et al. A medical nutriment has supportive value in the treatment of colorectal cancer. Br J Cancer 2003; 89: 465-9.
17. Marcsek Z, Kocsis Z, Jakab M, Szende B, Tompa A. The efficacy of tamoxifen in estrogen receptor-positive breast cancer cells is enhanced by a medical nutriment. Cancer Biother Radiopharm 2004; 19: 746-53.
18. Garami M, Schuler D, Babosa M, et al. Fermented wheat germ extract reduces chemotherapy-induced febrile neutropenia in pediatric cancer patients. J Pediatr Hematol Oncol 2004; 26: 631-5.
19. Demidov LV, Manziuk LV, Kharkevitch GY, Pirogova NA, Artamonova EV. Adjuvant fermented wheat germ extract (Avemar) nutraceutical improves survival of high-risk skin melanoma patients: a randomized, pilot, phase II clinical study with a 7-year follow-up. Cancer Biother Radiopharm 2008; 23: 477-82.
20. Mueller T, Jordan K, Voigt W. Promising cytotoxic activity profile of fermented wheat germ extract (Avemar®) in human cancer cell lines. J Exp Clin Cancer Res 2011; 30: 42.
21. Judson PL, Al Sawah E, Marchion DC, et al. Characterizing the efficacy of fermented wheat germ extract against ovarian cancer and defining the genomic basis of its activity. Int J Gynecol Cancer 2012; 22: 960-7.
22. Hidvegi M, Raso E, Tomoskozi Farkas R, Lapis K, Szende B. Effect of MSC on the immune response of mice. Immunopharmacol 1999; 41: 183-6.
23. Sukkar SG, Cella F, Rovera GM, et al. A multicentric prospective open trial on the quality of life and oxidative stress in patients affected by advanced head and neck cancer treated with a new benzoquinone-rich product derived from fermented wheat germ (Avemar). Mediterranean Journal of Nutrition and Metabolism 2008; 1: 37-42.
24. Hidvegi M, Raso E, Tomoskozi-Farkas R, et al. MSC, a new benzoquinone-containing natural product with antimetastatic effect. Cancer Biother Radiopharm 1999; 14: 277-89.
25. Jakab F, Mayer, Hoffmann A, Hidvegi M. First clinical data of a natural immunomodulator in colorectal cancer. Hepatogastroenterol 2000; 47: 393-5.
26. Hidvegi M, Raso E, Tomoskozi-Farkas R, Paku S, Lapis K, Szende B. Effect of avemar and avemar + vitamin C on tumour growth and metastasis in experimental animals. Anticancer Res 1998; 18: 2353-8.
27. Ehrenfeld M, Blank M, Shoenfeld Y, Hidvegi M. AVEMAR (a new benzoquinone-containing natural product) administration interferes with the Th2 response in experimental SLE and promotes amelioration of the disease. Lupus 2001; 10: 622-7.
28. Szende B, Marcsek Z, Kocsis Z, Tompa A. Effect of simultaneous administration of Avemar and cytostatic drugs on viability of cell cultures, growth of experimental tumors, and survival tumor-bearing mice. Cancer Biother Radiopharm 2004; 19: 343-9.
29. Boros G, Nichelati M, Shoenfeld Y. Fermented wheat germ extract (Avemar) in the treatment of cancer and autoimmune diseases. Ann N Y Acad Sci 2005; 1051: 529-42.
30. Telekes A, Kiss-Toth E, Nagy T, et al. Synergistic effect of Avemar on proinflammatory cytokine production and Ras-mediated cell activation. Ann N Y Acad Sci 2005; 1051: 515-28.
31. Lee SJ, Cho SW, Kwon YY, Kwon HS, Shin WC. Inhibitory effects of ethanol extracts from Nuruk on oxidative stress, melanogenesis, and photo-aging. Mycobiol 2012; 40: 117-23.
32. Yoo JG, Kim DH, Park EH, Lee JS, Kim SY, Kim MD. Nuruk, a traditional Korean fermentation starter, contains the bioactive compound 2,6-dimethoxy-1,4-benzoquinone (2,6-DMBQ). J Korean Soc Appl Biol Chem 2011; 54: 795-8.
33. Rizzello CG, Mueller T, Coda R, et al. Synthesis of 2-methoxy benzoquinone and 2, 6-dimethoxybenzoquinone by selected lactic acid bacteria during sourdough fermentation of wheat germ. Microb Cell Fact 2013; 12: 105.