Nutrition and Cancer, 61(6), 891–899

ISSN: 0163-5581 print / 1532-7914 online
DOI: 10.1080/01635580903285114

Routledge
Taylor & Francis Group

Avemar (Wheat Germ Extract) in Cancer Prevention and Treatment

András Telekes and Márta Hegedűs
Bajcsy-Zsilinszky Municipal Hospital, Department of Oncology, Budapest, Hungary

Chang-Hoon Chae
Department of Oral and Maxillofacial Surgery, Sacred Heart Hospital, Hallym University, Seoul, Republic of Korea

Károly Vékey
Chemical Research Center, Hungarian Academy of Sciences, Budapest, Hungary

Many healthy foods are derived from wheat germ. The molecular composition of these products, however, greatly differs as shown by normal-phase HPLC-mass spectrometry analysis; thus, experimental data obtained by one of them is not necessarily true for the other. Avemar is a nontoxic wheat germ extract registered as a special nutriment for cancer patients in Hungary. It shows potent anticancer activity on cell lines by deeply interfering with glucose metabolism and affecting expressions of several kinases. In in vivo experimental models, Avemar is also effective by enhancing the activity of the immune system such as stimulating NK cell activity (by reducing MHC I molecule expression), enhancing TNF secretion of the macrophages, increasing ICAM 1 molecule expression on the vascular endothelial cells. All of these lead to apoptosis of tumor cells. The wide range of biological activity of Avemar probably cannot be explained by only one active ingredient. Since there are numerous experimental data and the clinical benefit repeatedly confirmed Avemar can be one of the most potent and best researched food supplements available for cancer patients.

NUTRITION, NUTRIMENTS, AND CANCER

There is evidence to prove that in the background of cachexia (often co-occurring with cancer), there is a malfunction of energy supply and storage, which lead to considerable weight loss and feeling weak. It is important to note that the decrease of food intake as a result of tumor related anorexia/cachexia does not necessarily influence the growth of the tumor; therefore, no serious diet has proved to be sensible for cancer patients. The tumor is fully capable of supplying itself with energy for its own growth by consuming the substances of the body itself. Thus, both the decrease in food uptake and the tumor's parasite nature are responsible for the development of the anorexia/cachexia syndrome.

For cancer patients, cachexia represents a predictive factor for survival. The loss of weight by 10% within 6 mo is considered to be critical (1). Patients suffering from such weight loss responded to the treatment to much less an extent than patients with constant or growing body weight. Moreover, the nutritional status exerts deep influence on the activity of the immune system as well.

During the progression of the tumor, patients differ greatly in terms of anorexia and cachexia. For 15–40% of the patients, cachexia is diagnosed at the early stage of the disease and very often in patients who have no other symptoms: just weight loss and feeling weak. The chemotherapy, due to its gastrointestinal toxicity, could contribute to the enhancement of symptoms. A survey showed that 85% of the patients at an advanced stage of the disease suffered from cachexia and anorexia, more than those suffering from pain! It is important to note that there is no positive correlation between weight loss and the size of the tumor. Some patients with relatively small tumors lost substantial weight, whereas others with a big tumor burden never develop cachexia (2).

Finally, data are available to prove that the supply of nutriments does not foster the growth of tumor. Considering all this, it seems that a tumor can ensure its own growth in the body independently of the increase or decrease of food intake. Thus, the role of nutriments in cancer is an important issue. The provision of nutriments should start preferably before the weight loss or straight after it is recognized to avoid or delay the development of cachexia. A nutriment is not expected to suppress tumor growth or to show some other antitumor effect. However, if it does it in a proven and

Submitted 1 May 2009; accepted in final form 25 August 2009.
Address correspondence to András Telekes, Bajcsy-Zsilinszky Municipal Hospital, Department of Oncology, 1106 Budapest, Maglodi u 89-91, Hungary. Phone: +36203396523. Fax: +3614327516. E-mail: andras.telekes@bajcsy.hu

reproducible manner, it is a special advantage and can be of great importance.

AVEMAR—A SPECIAL NUTRIMENT FOR CANCER PATIENTS

Avemar is a chemically transformed natural complex of wheat germ molecules (not identical with wheat germ or germinated wheat), which was registered in 2002 as a special nutriment for cancer patients in Hungary. The aqueous powder contains 63.2% fermented extract of wheat germ and drying aids (35% maltodextrin and 1.8% silicon dioxide). The exact chemical composition of the extract is not entirely known. In fact, this is quite usual in the case of natural products. The manufacturing process of Avemar is standardized to 2,6-dimethoxy-p-benzoquinone content (0.4 mg/g on dry matter basis), but there is no data available regarding permanent composition of other constituents in different manufacturing series. The quality of Avemar is controlled by fingerprint chromatography; each batch is compared to the original one used for experimental studies. The GMP manufacturing technology involves extraction of wheat germs, fermentation of the extract by *Saccharomyces cervisiae,* separation of the fermentation liquid, drying, and granulation. In fact, the manufacturing process is patented (International Application No.: PCT/HU1998/000077).

Avemar is available in pharmacies without prescription. The effects of Avemar are manifold (3–7). On the contrary, it shows no toxicity, mutagenicity, or genotoxicity (8). Moreover, the combination of Avemar with chemotherapeutic agents did not increase the toxicity or reduce antiproliferative activity (9). The role of Avemar in cancer prevention and treatment can be discussed from several aspects.

Molecular Composition of Avemar and Other Wheat Germ Derived Products

Natural extracts typically contain many, often hundreds or thousands, of different molecules. This is the case of Avemar and various other wheat germ derived products. Structural studies on such complex mixtures are usually not directed to determine structure and concentration of each molecular component, as it is mostly unfeasible. There are two typical approaches for characterizing such mixtures. The first is to identify and to quantify certain molecules or molecular types in the extract. This is used when targeting given molecules of biological significance (like resveratrol in wines). The second common approach is to separate the mixture into various fractions and characterize these fractions subsequently. Separation is commonly performed using chromatography. A given fraction is characterized by its retention time, whereas the relative amount of the fractions is characterized by an intensity value (depending on the type of detection, this may be, e.g., absorption of ultraviolet light). The molecular composition of the individual fractions (which may still contain various molecular components) may be characterized, for example, by subsequent spectroscopic analysis.

Current methodologies are often based on an on-line combination of high-performance liquid chromatography (HPLC) with mass spectrometry (HPLC-MS). This allows high separation power and gives structural information on the individual components. These techniques are described in detail in a recent book (10), and these have been used to study the molecular composition of Avemar and other wheat germ derived products.

Altogether, 15 wheat germ derived samples have been studied as shown in Table 1, and three of these were different Avemar batches. Two different analytical approaches have been used, namely, 1) separation of the samples by normal-phase HPLC, followed by mass spectrometric analysis since this method is well suited to isolate the polar molecules present in Avemar; and 2) separation of the samples by reverse-phase HPLC, followed by mass spectrometric analysis, which is well suited to isolate the apolar molecules (11).

The results show that both the polar and the apolar fraction of wheat germ products consist of several hundred different molecules. As an example, the HPLC-MS chromatogram of an Avemar sample is shown in Fig. 1A. Detailed mass spectrometric analysis shows that most peaks in the chromatogram consist of several components.

More significant is the comparison of the molecular composition of different wheat germ derived products. Chromatograms and mass spectra of various products show major differences, whereas the composition of the Avemar batches studied were comparable. For example, the chromatogram of a different wheat germ derived product (a German Weizenkeime sample) under identical conditions is shown in Fig. 1B—indicating large differences in molecular composition compared to Avemar. Characterized by retention time and mass spectra, many different components were identified and quantified. A possible illustration of the variability of the molecular composition of various wheat germ derived products is shown in Fig. 2. This shows the relative amounts of 30 characteristic molecular components identified in the 15 investigated wheat germ derived products. The results clearly show that the composition of various wheat germ derived products is significantly different. Thus, experimental data obtained by one of them is not necessarily true for the other. Bearing this in mind, the most important experimental and clinical effects of Avemar are considered.

Immunological Aspects

After the implantation of skin allografts into mice that had gone through thymus removal, the rejection took much shorter time in the case of mice that had been treated with Avemar than in the case of the control group without Avemar treatment (12). Since the host vs. graft reaction is primarily based on cellular immune response, all this implies an enhanced cellular immune response as a result of Avemar. This is significant because the body's natural antitumor response is also based on the function of the cellular immune system. The primary antitumor

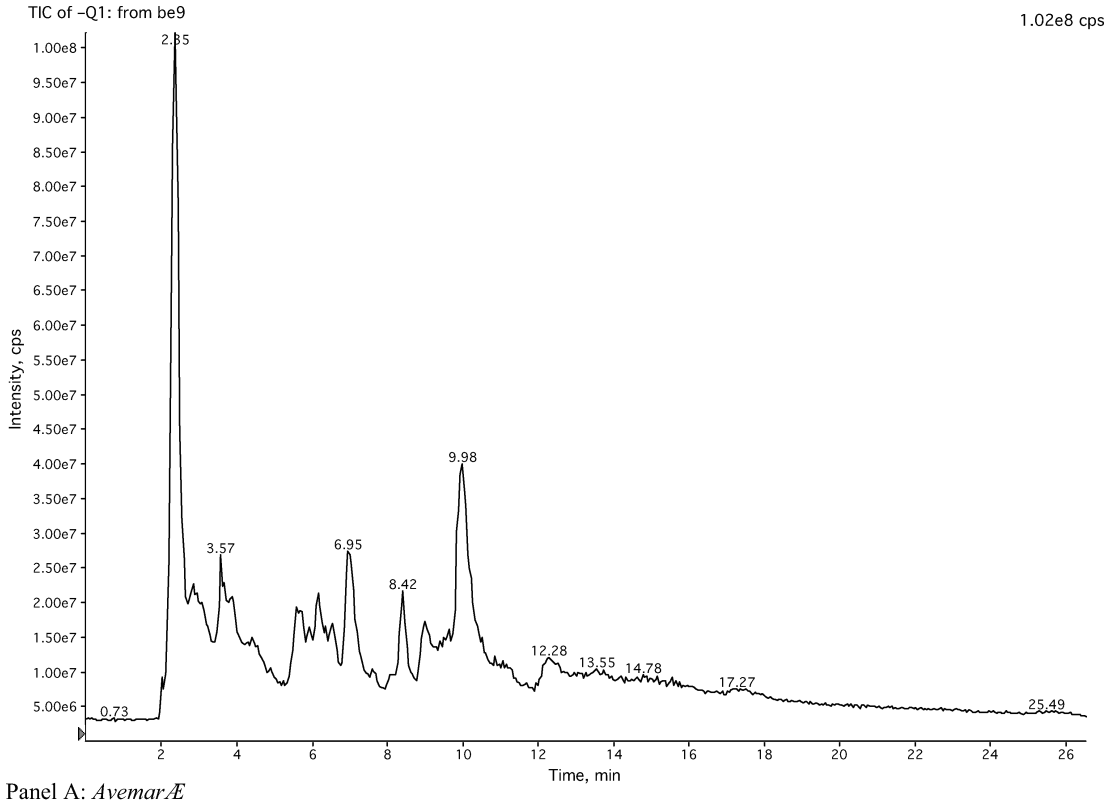
TABLE 1
Characteristics of the investigated wheat germ derived food supplements[a]

Study Code	Product	Identification of the Product
BE/01	Nutritional wheat germ	Manufacturer: Diamant International Mill Ltd. (Baja) Date of production: 2003.10.21.
BE/02	Manna-rax (containing wheat germ)	Distributed by: MANNA-RAX Bt. Best before: 2004.10.26.
BE/03	Yeast powder (*Saccharomyces cerevisiae*)	Manufacturer: BUDAFOK Yeast and Spirit Stock Company. Best before: 2003.11.30.
BE/04	Avemar	Manufacturer: Biromedicina Stock Company. Date of production: 2003.10.20.
BE/05	Wheatgrass Capsule	Manufacturer: Akvapol Stock Company. Distributer: Kombucha Hungary Ltd. Best before: 2004.08.01.
BE/06	Vollgran Weizenkeime	Manufacturer: <DR: GRANDEL> GMBH, Augsburg. Date of production: 2003.05.
BE/07	Manna-rax (100% wheat germ)	Distributed by: MANNA-RAX Bt. Best before: 2004.10.26.
BE/08	Green Wheatgrass Cocktail (Dr. Steinberger)	Manufacturer: Dr.-Steinberger Nachf., Unkel, Germany. Best before: 2005.05.28.
BE/09	Avemar	Manufacturer: Biromedicina Stock Company. Date of production: 1998.09.15.
BE/10	Manna-rax (Szentgyörgyi powder)	Distributed by: MANNA-RAX Bt. Best before: 2004.02.09.
BE/11	Wheat germ Capsule	Manufacturer: Splendor Ltd. Best before: 2004.10.28.
BE/12	Kombucha concentrate containing wheatgrass	Manufacturer: Akvapol Stock Company. Distributer: Kombucha Hungary Ltd. Best before: 2004.03.23.
BE/13	Weizenkeime (die naturlische, kraftspendende Zusatznahrung)	Manufacturer: BIOREX AG (CH-9642 Ebnat-Kappel) Date of production: 2003.05. charge: 08020500
BE/14	Avemar	Manufacturer: Biromedicina Stock Company. Date of production: 2002.10.
BE/15	Immunovet (wheat germ derived animal food supplement)	Manufacturer: Biropharma Ltd. Date of production: 2003.07.

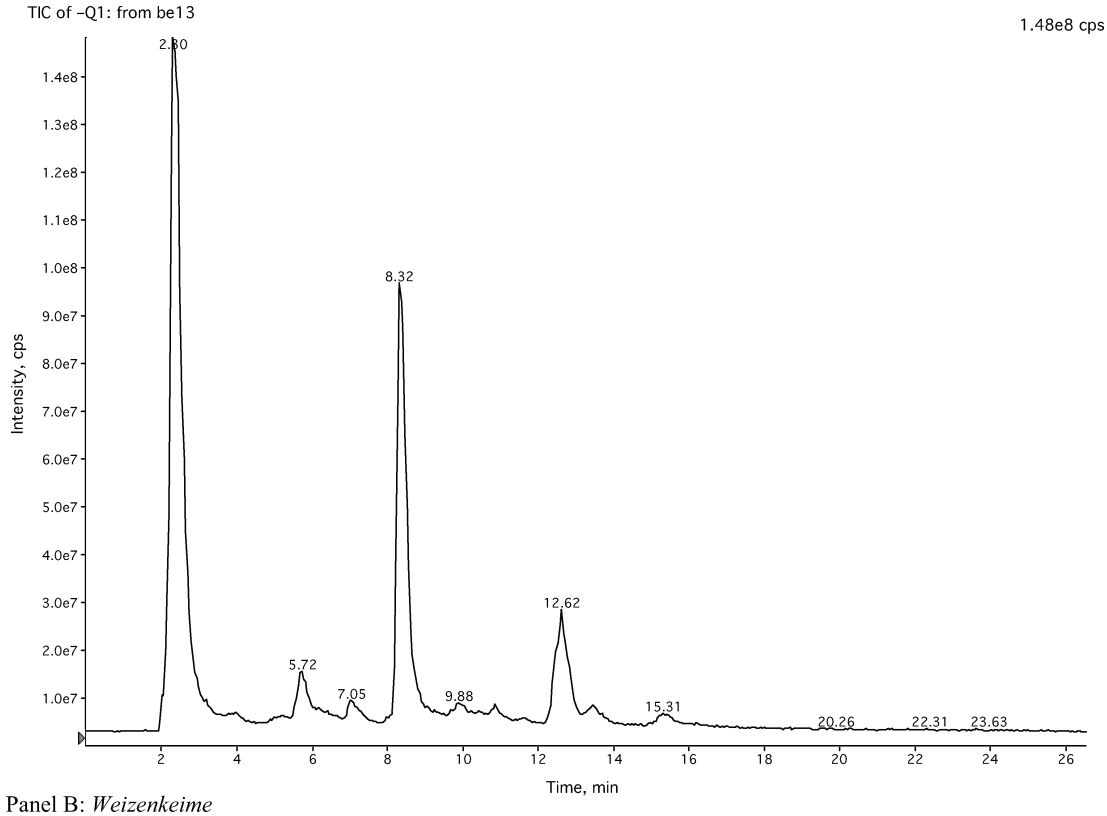
[a] All products were commercially available and used within the valid warranty period.

response depends on the activity of the natural killer (NK) cells. The activity of these cells is enhanced by the decreased level of main histocompatibility complex class 1 (MHC-I) antigens. The presence of MHC-I antigens on the cell surface makes it possible for the immune cells to recognize a cell as "self." MHC-I antigens can be found on the surface of every cell with a nucleus including the tumor cells. The MHC-I molecule complex contains peptide fragments of endogen proteins dissociated within the cells, which stabilize the link between the MHC-I alpha and beta microglobulin peptide chains. The recognition of the MHC + peptide by the immune cells is considered to be the basic "cognitive" movement of immune reaction. Due to Avemar treatment, the expression of MHC-I molecules has decreased 90% on the surface of Jurkat T cells and 69% on Raji Burkitt lymphatic cells (13). This considerable decrease in the level of MHC-I antigens as a result of the treatment could be the trigger of the NK cells to kill the tumor cells. Moreover, in SLE-induced mice Avemar produced a shift toward Th1 (cellular immunity) response by enhancing IL-2 and IFN cytokine production while reducing Th2 (antibody related) immune response by decreasing IL-4 and IL-10 production (14).

The second important area of natural immune reaction to tumor cells is the activity of macrophages (mononuclear phagocite). Macrophages are present in every organ and tissue, and their task is phagocitoses and to produce biologically active molecules (oxygen radicals and cytokines). The most important of cytokines produced by the macrophages is the TNF-α, the main mediator of antitumor defense, which plays a significant role in local inflammations and adhesive processes. The TNF-α is capable of killing the tumor cells both directly (induction of apoptoses, production of oxygen radicals) and indirectly (retardation of tumor angiogenesis, increase of other antitumor reactions). In human THP-1 myeloid leukemia, Avemar—together with lipopolysaccharide and phorbol myrisil acetate—has increased the TNF-α production in a dose-related manner. The immunoglobulin-like intracellular adhesive molecule (ICAM-1, CD54) has a role in connecting cells and also in the immigration of white blood cells from the blood stream. The most important part of effective immune reaction is the transfer of immune cells to the inflamed area or to the site of the tumor. TNF-α increases the production of ICAM-1 molecules and therefore helps the lymphocytes find their "target." Avemar by itself can



Panel A: *AvemarÆ*



Panel B: *Weizenkeime*

FIG. 1. Panel A: Total ion chromatogram of an Avemar sample studied by normal-phase HPLC-MS analysis. Panel B: Total ion chromatogram of a German "Weizenkeime" sample studied by normal-phase HPLC-MS analysis.

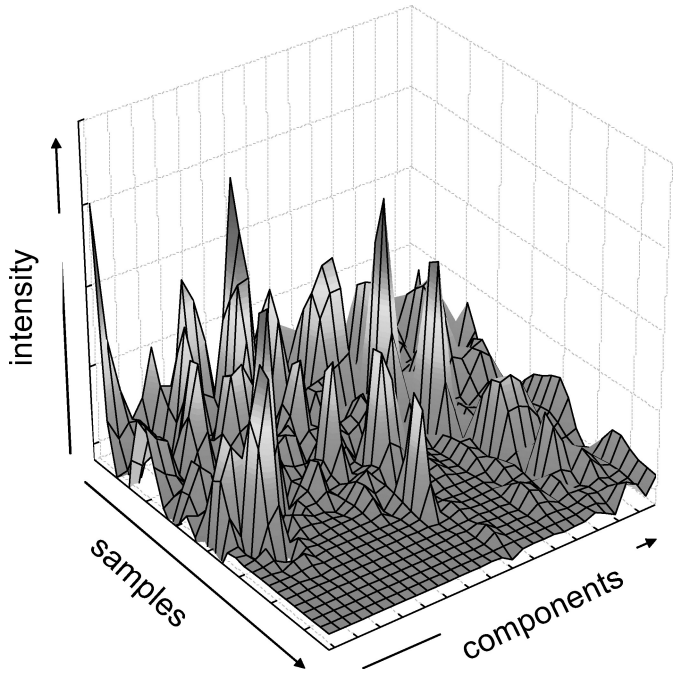


FIG. 2. Three-dimensional representation of the variability of the molecular composition of various wheat grerm derived products.

increase the level of ICAM-1 molecules, and this effect is synergistic to the similar activity that of TNF-α. Therefore, Avemar increases the production of ICAM-1 and may enhance the appearance of white blood cells at the tumor site in a dual way (by itself and by increasing the TNF-α production of macrophages) (15).

Induction of Apoptosis

According to current views, the genetic program of a mammal cell determines the whole life cycle of the cell, including differentiation (i.e., the ability of cells to respond to specific ligands), as well as the programmed death of cells. The ligands attached to the receptors on the surface of the cell cause characteristic intracellular cascade of events on the given cell. An information flow or transfer of signals is created by the receptor-ligand link outside the cell triggering the biological effect inside the cell. Such processes of signal transduction control all the functions of the cell, its metabolism, and death. The specific response to any outside stimulus is all controlled by the genes of the cell.

The programmed death of cells (apoptosis) requires the coordinated function of certain genes, and this is exactly how it differs from cell deaths triggered by other causes (e.g., the necrosis of a cell means the collapse of the intracellular metabolism and the disorganized function of the cell). Apoptosis results in typical morphological changes (e.g., chromatin condensation and fragmentation). When the apoptotic cell dies, it does not affect the neighboring cells (cells dying in any other way usually damage the neighboring cells as well). In some tumors, spontaneous apoptosis can be noted, but it can be induced by chemotherapy, radiation therapy, or immune therapy. Therefore, the antitumor therapy can induce apoptosis of cancer cells, killing the tumor without destroying or damaging the neighboring cells.

Avemar-induced apoptosis in several human cell lines including MCF-7 breast cancer (16), Jurkat acute lymphoid leukemia T cell (17,18), A2058 human melanoma (19), HT-29 colon cancer (20), HL-60 promyelocytic leukemia (21), H9 human lymphoid cell (22), and gastric cancer cell lines (23).

The CD45 is a strongly glycolized receptor that is expressed to a large extent on the surface of the leukocytes and has intracellular phosphatase activity. CD45 has a fundamental role in the intracellular signal transduction of the leukocytes including the apoptosis. Avemar can decrease the CD45 phosphatase activity in Jurkat-T cell lines. Avemar, however, can induce apoptosis in cells that lack in CD45 to the same extent as the parent cell lines. This proves that the apoptosis induction by Avemar does not involve the CD45 system (17). Recent data show that Avemar induces apoptosis of the cells involving the caspase system (18). It is of importance that the induction of apoptosis by Avemar seems to be tumor specific, since in the case of normal peripheral blood mononuclear (PBM) cells, apoptosis does not occur as proven by DNA and FACS analyses. On the other hand Avemar inhibits in dose-related manner the polyclonal mitogen (phytohemagglutinin) induced PBM cell proliferation. This serves as evidence that Avemar-induced inhibition of cell proliferation and the induction of apoptosis have different mechanisms.

Avemar was examined in Jurkat cell lines also with regard to intracellular calcium concentration. As a result of Avemar treatment, an early and transient increase in intracellular calcium concentration occurs. This observation can be explained by the enhanced influx of extracellular calcium into the cells, since in the presence of calcium chelator EGTA Avemar does not alter the intracellular calcium concentration. It is of interest that the Avemar-induced increase of intracellular calcium concentration precedes both the reduction of expression of the MHC-I molecules and the induction of apoptosis (17).

Glucose Metabolism

The genetic program also determines the metabolic capacity of a cell and also its unique characteristics (metabolic profile), as all this depends on the differentiation of the cell. The knowledge of the metabolic profile of cells and the analysis of the changes induced by certain stimuli become the basis for pharmaceutical research and development. The investigation of the metabolic profile of normal and tumor cells and the measurement of the metabolic changes have contributed significantly to the discovery of unknown therapeutic targets as well as to the development of new antitumor agents. The metabolic profile of the Avemar treated and untreated pancreatic adenocarcinoma cell lines was investigated and compared to each other in MIA cell line (24). Cells were incubated with C13 isotopic labeled glucose, and the intracellular sugar metabolism was followed.

Since the carbon atoms of sugar are used in the synthesis of different types of molecules (such as ribose, fatty acids, etc.), the measurement of the amount of isotopic labeled molecules (by gas chromatography and mass spectrometry) provide a method for exact follow-up of the glucose metabolism pathways. The results of these measurements were very noteworthy. Avemar inhibited the glucose uptake of the cancer cells in a dose-related fashion as well as influenced the metabolic pathways of glucose. Namely, Avemar decreased the messenger and ribosomal RNA synthesis and at the same time enhanced the pentose cycle and fatty acid synthesis. The tumor cells primarily need sugar as the source of energy for cell division; therefore, Avemar can reduce the proliferation activity of the cancer cells by reducing the sugar uptake. To maintain the cell functions, the cells require continuous protein synthesis, which is mediated by messenger and ribosomal RNA synthesis. By reducing the available sugar for the synthesis of these nucleic acids (the intracellular sugar is redirected to the enhanced pentose cycle and fatty acid synthesis), Avemar can deeply influence the intracellular metabolism of tumor cells. In other words, Avemar can "pinch" the sugar from the nucleic acid synthesis, leading to reduced chances for survival of the tumor cells. These are direct effects of Avemar on cancer cells and do not require the contribution of the immune system. The inhibition of the use of glucose within the cells is one of the main features of the recently developed anticancer agent Gleevec (Bcr/Abl tyrosine kinase inhibitor) too (25). According to a recent study, Avemar inhibits the glucose-6-phosphate dehydrogenase and transketolase enzyme activity in a dose-dependent way. Since these are the key enzymes of the synthesis of ribose molecules required for the sugar-phosphate chain of the nucleic acids, this observation can further explain the inhibition of nucleic acid synthesis by Avemar. Moreover, Avemar dose and time dependently inhibits two other important enzymes of glucose metabolism such as hexokinase and lactate dehydrogenase, showing significant influence on glucose metabolism (18). Recent report shows that Avemar reversed glucose intolerance in rats fed a high-fat/high-carbohydrate diet (7).

In Vivo Experimental Models

Avemar significantly enhanced the antimetastatic activity of DTIC and 5-FU in the treatment of B16 melanoma and C38 colorectal carcinoma, respectively. In fact, in the untreated control group, 20.0 ± 6.0 (average ± SD) melanoma metastases developed in the lung, whereas this was reduced to 7.0 ± 4.3, 4.0 ± 2.1, and 0.1 ± 0.1 in the case of DTIC, Avemar, and DTIC

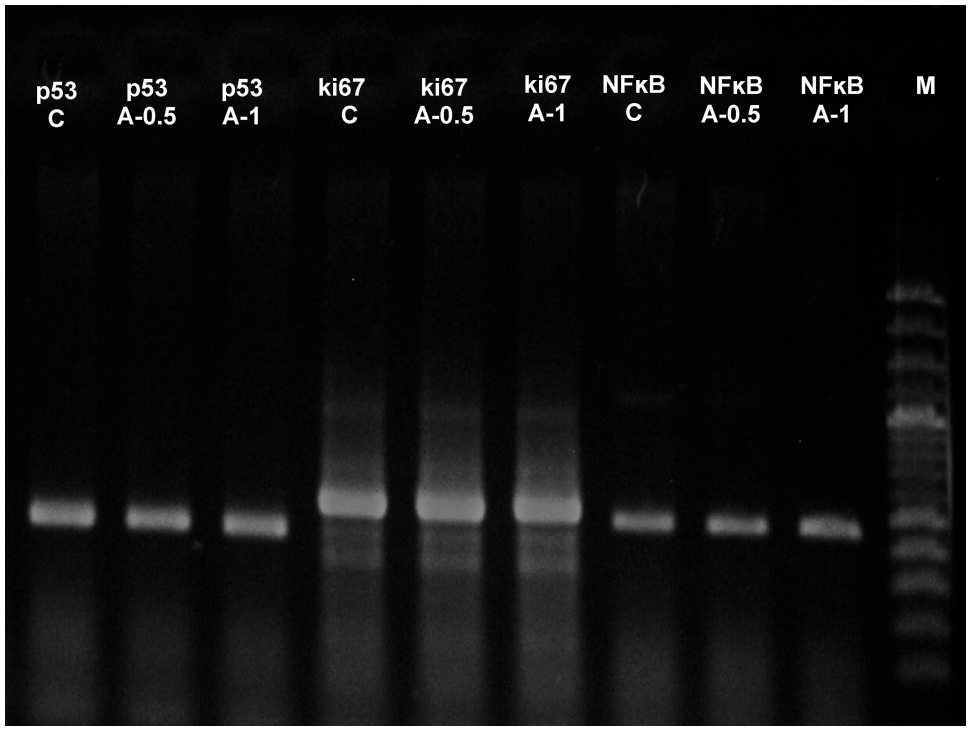


FIG. 3. The effect of 24 h of Avemar treatment on the expression p53, ki67, and NFκB expression, applying real-time polymerase chain reaction (RT-PCR). RT-PCR was carried out to determine gene expressions of p53, ki67, and NFκB. SCC-9 cells were harvested, and total RNA was extracted using easy-BLUE Total RNA Extraction Kit according to the manufacturer's (Intron Biotechnology Co., Republic of Korea) protocol. RT-PCR was carried out by using Maxime RT-PCR PreMix Kit (Intron Biotechnology Co., Seongham, Kyunggi-, Republic of Korea). Primers (*For* and *Rev*) were ordered from Genotech Co., Daejeon, Republic of Korea (p53 *For*: 5′-TTT GGG TCT TTG AAC CCT TG-3′; p53 *Rev*: 5′-GTG GTT TCA AGG CCA GAT GT-3′; ki67 *For*: 5′-AAC AAG GGG AAG GGA AGA GA-3′; ki67 *Rev*: 5′-CCA GGT AAC CCA GAG CAC AT-3′; NFκB *For*: 5′-TCT GTG TTT GTC CAG CTT CG-3′; NFκB *Rev*: 5′-GTG ACC TCA CCA TTC CCA AC-3′). The RT-PCR reaction was run on the Hybaid PCR Thermal Cycler (Hybaid Co., MA, USA) using standard conditions. C, control; M, size markers.

+ Avemar, respectively. In the case of colorectal cancer, 185 ± 104[35] liver metastases developed (average ± SD [SEM]), but this was decreased to 16 ± 17[6], 41 ± 34[11], and 2 ± 4[1] in the case of 5-FU, Avemar, and 5-FU + Avemar, respectively (19).

In the case of transplanted estrogen receptor positive (ER+) mouse mammary carcinoma Avemar proved to be equally effective as standard endocrine treatments (tamoxifen, examestan, anastrasol). This result was confirmed in the case of human xenograft (T47/D) as well. Moreover, the efficacy of Avemar was independent from estrogen receptor expression since Avemar was equally effective in ER+ (T47/D and ER– (MDA-MB-231) human xenografts, namely, the inhibition of tumor growth was 49% and 52%, respectively (26).

Other Experimental Data

Avemar inhibited azoxymethane induced chemical carcinogenesis in F344 rats. In fact, both the percentage of animals developing colon cancer (83.0% vs. 44.8%; $P < 0.001$) and the number of tumors per animal [2.3 ± 0.21; range = 1–8 vs. 1.3 ± 0.17; range = 1–3 (as expressed as mean ± SEM)] were reduced significantly when azoxymethane was applied concomitantly with Avemar and compared to the carcinogen agent alone (27).

Avemar induces changes in the kinase expression panel of cells. In K562 human leukemia cells, changes in kinase expression was declared when Avemar treatment resulted in a twofold change in mRNA copy number and the SD of the 3 parallel samples was relatively small (2 × STDEV = AVERAGE). More than 500 kinase genes were studied (Kinase OpenArray™); 16 and 30 of them were found to be decreased and increased, respectively. Many of the kinases in which expression was altered are known to participate in signal transduction, apoptosis, cell migration, or regulation of cell cycle (28).

The p53, Ki67, and NF-κB expression had been investigated on the human tongue squamous cell carcinoma (SCC-9, ATCC No: CRL-1629™) cell line regarding the effect of Avemar. As shown in Fig. 3, 24 h of Avemar treatment, in the investigated doses, such as Avemar 0.5 mg/ml (A-0.5) and 1.0 mg/ml (A-1), did not alter the expression of these genes compared to untreated controls on RT-PCR. Since Avemar inhibited the cell proliferation of SCC-9 in a dose-dependent manner (and A-1 showed a significant effect), as shown in Fig. 4, the antitumor activity of Avemar might not include these pathways.

Clinical Data

There are 4 completed clinical studies investigating Avemar in cancer patients. In an open-label cohort trial, colorectal cancer patients were enrolled who received standard oncology treatment. In fact, 104 patients served as control and 66 patients

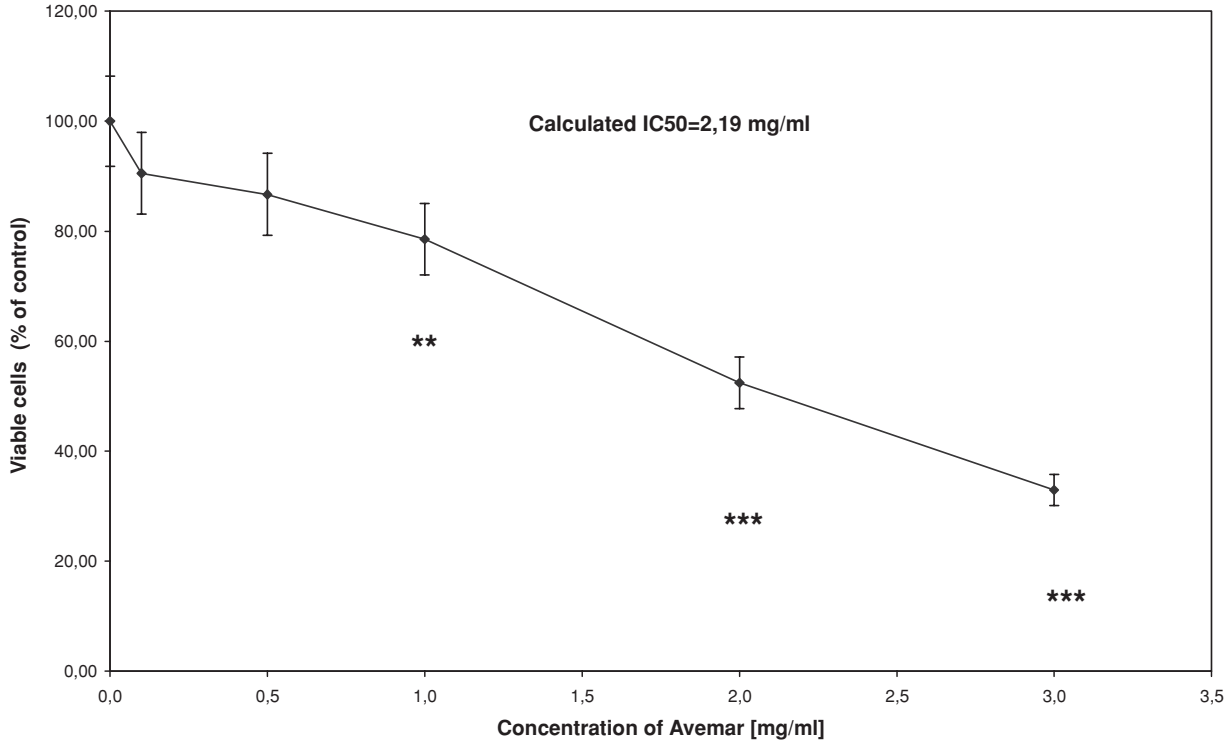


FIG. 4. The effect of Avemar on the proliferation of human tongue squamous cell carcinoma cells (SCC-9) using MTT assay. SCC-9 cell cultures were treated with increasing doses of Avemar for 24 h as indicated on the x-axis; their viability and proliferation were determined by formazan dye uptake and expressed as percent of untreated control cell proliferation. The MTT assay was carried out as triplet measurements in 4 sessions on 2 independent occasions. Bar represents the standard error of the mean; **, $P < 0.01$, ***, $P < 0.001$ (1-sample t-test).

were also receiving Avemar (9 g once daily). The results showed significantly enhanced survival and reduced metastases formation in the Avemar treated group even though the prognostic factors of the patients were worse in this arm. This result, however, should be interpreted with caution, since patient allocation in the treatment groups were not made by proper randomization (29). In another prospective randomized study, 42 stage III melanoma patients participated after radical removal of the primary tumors and the regional lymph-node metastases. Following 4 courses of DTIC treatment, patients were randomly allocated to either receiving 1 yr treatment of Avemar (19 pts) or just observation (23 pts). Time to relapse and the estimated 1-yr survival in the Avemar treated and control groups were 8.9 and 4.2 mo and 54.5% and 38.9%, respectively (30). After a 7-yr-long follow-up period of the treated patients, log-rank analysis still showed significant differences in favor of Avemar group regarding both progression free survival (PFS) and overall survival (OS). Namely, mean PFSs were 55.8 mo vs. 29.9 mo, and the mean OSs were 66.2 mo vs. 44.7 mo in the Avemar and control groups, respectively (31). In the third study, a cohort of 55 evaluable head and neck cancer patients were studied. They were assigned to two groups; both were treated with adequate anticancer therapy, but one of them also received Avemar for 2 mo (26 patients). The oxidative stress was measured at entry and after 2 mo. Avemar (9 g once daily below 80 kg body weight and twice daily above) significantly decreased oxidative stress and increased quality of life (32). The last open-label and matched-pair study was carried out in pediatric cancer patients. Eleven pairs of patients were compared regarding the incidence of treatment related febrile neutropenia. Although no progression on the malignancy was observed in any patients, the incidence of febrile neutropenia differed significantly in favor of the Avemar group (altogether 121 chemotherapy cycles) compared to the control group (altogether 106 chemotherapy cycles) treated with identical chemotherapy regimens but not receiving Avemar. The difference was significant (24.8% vs. 43.4%, $P < 0.05$). The investigational group of patients received 6 g/m^2 Avemar twice daily (33).

CONCLUSION

Wheat (*Triticum vulgare*) is one of the most important staple food stock in certain regions of the world. The germ of the wheat is usually removed in the milling process to yield flour but retained in whole-wheat products. The germ is rich in certain vitamins including vitamin E and biologically active molecules such as benzoquinones. Wheat germ is not known to pose any health hazard since it has been part of the human diet for centuries. The molecular composition of fermented wheat germ extract (Avemar) is unique and largely different from other wheat derived food supplements. The mass spectra of different batches of Avemar is, however, comparable. Thus, data obtained by applying Avemar are unlikely to be true for other wheat germ derived products. In addition, Avemar showed no toxicity in different tests or clinical trials. On the other hand, experimental studies have shown many effects including immunologic, cytotoxic, metabolic, and signal transduction. These effects lead to the inhibition of tumor cell proliferation and increase survival of tumor-bearing animals. Although Avemar influenced the expression of several kinases in the K562 human leukemia cell line, it did not alter the expression of p53, Ki67, and NF-κB in the SCC-9 human squamous cell line. Avemar alters the glucose metabolism of cancer cells in several ways such as reducing glucose uptake, shifting the use of glucose derived carbon atoms from ribose synthesis to pentose cycle and fatty acid synthesis, and inhibiting key enzymes of glucose metabolism. All of these lead to reduced nucleic-acid synthesis in tumor cells. Avemar also exerts beneficial effects on the immune system. It enhances the activity of the NK cells by reducing the amount of MHC-I molecules on the cell membrane. It increases the TNF secretion by macrophages and enhances the expression of ICAM-1 molecules in the vascular endothelial cells, helping white blood cells to leave the vascular system at tumor site. The fact that Avemar reduces the effect of a chemical carcinogen might be a special advantage to patients concerning the carcinogen effect of chemotherapeutic agents. Avemar induces apoptosis, as observed in several tumor cell lines, but it is still not verified whether this is a direct or an indirect effect. Finally, the antitumor activity observed in cell lines is also observed in in vivo experiments. The reduction of metastasis formation by the combination of Avemar and cytotoxic agents seems especially noteworthy. However, the precise mechanism of action of Avemar is still not entirely clarified, but a complex mechanism of action is envisioned with probably more than one active ingredient. Since benefits were observed in small clinical trials, further large scale, double blind, randomized, and placebo-controlled clinical studies are warranted.

ACKNOWLEDGMENT

We thank Tamás Nagy for statistical aid and valuable comments.

REFERENCES

1. Blackburn GL, Bistrian BR, Maini BS, Schlamm HT, and Smith MF: Nutritional and metabolic assessment of the hospitalized patient. *JPEN* **1,** 11–22, 1977.
2. Telekes A and Horváth Zs: The mechanism and treatment of cachexia and anorexia related to cancer (in Hungarian). *Háziorvosi Továbbképzõ Szemle* **5,** 381–386, 2000.
3. Johanning GL and Wang-Johanning F: Efficacy of a medical nutriment in the treatment of cancer. *Alternative Therapies* **13,** 56–63, 2007.
4. Telekes A, Resetár Á, Bálint G, Blazsó G, Falkay G, et al.: Fermented wheat germ extract (Avemar) inhibits adjuvant arthritis. *Ann NY Acad Sci* **1110,** 348–361, 2007.
5. Bálint G, Apáthy Á, Gaál M, Telekes A, Resetár Á, et al.: Effect of Avemar—a fermented wheat germ extract—on rheumathoid arthritis: preliminary data. *Clin Exp Rheumatol* **24,** 325–328, 2006.

6. Boros LG, Nichelatti M, and Shoenfeld Y: Fermented wheat germ extract (Avemar) in the treatment of cancer and autoimmune diseases. *Ann NY Acad Sci* **1051,** 529–542, 2005.
7. Iver A and Brown L: Fermented wheat germ extract (Avemar) in the treatment of cardiac remodeling and metabolic symptoms in rats*. Evid Based Complement Alternat Med* **Jul 21** [Epub ahead of print], 2009.
8. Heimbach JT, Sebestyen G, Semjen G, and Kennepohl E: Safety studies regarding a standardized extract of fermented wheat germ. *Int J Toxicol* **26,** 253–259, 2007.
9. Szende B, Marcsek Z, Kocsis Z, and 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* **19,** 343–349, 2004.
10. Vékey K, Telekes A, and Vertes A: *Medical Applications of Mass Spectrometry.* New York: Elsevier, 2008.
11. Nagy K and Vékey K: Unpublished results.
12. Hidvégi M, Rásó E, Tömösközi-Farkas R, Lapis K, and Szende B: Effect of MSC on the immune response of mice. *Immunpharmacology* **41,** 183–186, 1999.
13. Boja R, Székely I, Szűcs K, Ion G, and Monostori É: Effect of Avemar on the signal transduction and viability of Jurkat T cells (in Hungarian). *Magyar Egészségpiac* **3,** 120–121, 2000.
14. Ehrenfeld M, Blank M, Shoenfeld Y, and 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* **10,** 622–627, 2001.
15. Telekes A, Kiss-Tóth E, Nagy T, Qwarnstrom E E, Kúsz E, et al.: Synergistic effect of Avemar on proinflammatory cytokine production and Ras-mediated cell activation. *Ann NY Acad Sci* **1051,** 515–528, 2005.
16. Marcsek Z, Kocsis Z, Jakab M, Szende B, and Tompa A:. The efficacy of tamoxifen in estrogen receptor-positive breast cancer cells is enhanced by a medical nutriment. *Cancer Biother Radiopharm* **19,** 746–753, 2004.
17. Fajka-Boja R, Hidvégi M, Shoenfeld Y, Ion G, Demydenko D, et al.: Fermented wheat germ extract induces apoptosis and downregulation of major histocompatibilitz complex class I proteins in tumor T and B cell lines. *Int J Oncol* **20,** 563–570, 2002.
18. Comin-Anduix B, Boros LG, Marin S, Boren J, Callol-Massot C, 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* **277,** 46408–46414, 2002.
19. Hidvégi M, Rásó E, Tömösközi-Farkas R, Szende B, Paku S, et al.: MSC, a new benzoquinone containing natural product with antimetastatic effect. *Cancer Biother Radiopharm* **14,** 277–289, 1999.
20. Illmer C, Madlener S, Horvath Z, Saiko P, Losert A, et al.: Immunologic and biochemical effects of the fermented wheat germ extract Avemar. *Exp Biol Med* **230,** 144–149, 2005.
21. Saiko P, Ozsvar-Kozma M, Madlener S, Bernhaus A, Lackner A, et al.: Avemar, a nontoxic fermented wheat germ extract, induces apoptosis and inhibits ribonucleotide reductase in human HL-60 promyelocytic leukemia cells. *Cancer Lett* **250,** 323–328, 2007.
22. Saiko P, Ozsvar-Kozma M, Graser G, Lackner A, Grusch M, et al.: Avemar, a non toxic fermented wheat germ extract, attenuates the growth of sensitive and 5-FdUrd/Ara-C cross resistant H9 human lymphoma cells through induction of apoptosis. *Oncol Rep* **21,** 787–791, 2009.
23. Lee SN, Park SN, and Lee KE: Cytotoxic activities of fermented wheat germ extract on human gastric carcinoma cells by induction of apoptosis (Abstract). *J Clin Oncol* **23,** 4254, 2005.
24. Boros LG, Lapis K, Szende B, Tömösközi-Farkas R, Balogh Á, et al.: Wheat germ extract decreases glucose uptake and RNA ribose formation but increases fatty acid synthesis in MIA pancreatic adenocarcinoma cells. *Pancreas* **23,** 141–147, 2001.
25. Boros LG, Cascante M, and Lee WNP: Metabolic profiling of cell growth and death in cancer: applications in drug discovery. *Drug Discov Today* **7,** 18–26, 2002.
26. Tejeda M, Gaal D, Szucs I, and Telekes A: Avemar inhibits the growth of mouse and human mammary carcinomas comparable to endocrine treatments. *J Clin Oncol* **25,** 21132, 2007.
27. Zalatnai A, Lapis K, Szende B, Raso E, Telekes A, et al.: Wheat germ extract inhibits experimental colon carcinogenesis in F-344 rats. *Carcinogenesis* **22,** 1649–1652, 2001.
28. Telekes A and Rásó E: Changes in the kinase expression panel of K562 human leukemia after Avemar treatment (Abstract). *J Clin Oncol* **25**, 14143, 2007.
29. Jakab F, Shoenfeld Y, Balogh Á, Nichelatti M, Hoffman A, et al.: A medical nutriment has supportive value in the treatment of colorectal cancer. *Br J Cancer* **89,** 465–469, 2003.
30. Demidov LV, Manziuk LV, Kharkevitch GY, Artamonova EV, and Pirogova NA: Antimetastatic effect of Avemar in high-risk melanoma patients (Abstract). *18th UICC International Cancer Congress*. Oslo, Norway: 30 June–5 July, 2002, p. 48, 2002.
31. Demidov LV, Manziuk LV, Kharkevitch GY, Pirogova NA, and 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 7-year follow-up. *Cancer Biother Radiopharm* **23,** 477–482, 2008.
32. Sukkar SG, Cella F, Giuseppe M, Rovera G M, Nichelatti M, 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 newbenzoquinone-rich product derived from fermented wheat germ (Avemar). *Mediterr J Nutr Metab* **1,** 37–42, 2008.
33. Garami M, Schuler D, Babosa M, Borgulya G, Hauser P, et al.: Fermented wheat germ extract reduces chemotherapy-induced febrile neutropenia in pediatric cancer patients. *J Pediatr Hematol Oncol* **26,** 631–635, 2004.