CHAPTER

# 32

# Fermented wheat germ extract as natural support in cancer patients

*Sweta Y. Patel*[1] *and Rajesh K. Patel*[2]

[1]Department of Life Sciences, Hemchandracharya North Gujarat University, Patan, Gujarat, India [2]Bioinformatics and Supercomputer Laboratory, Department of Biosciences (UGC-SAP-Drs-II & DST-FIST-I), Veer Narmad South Gujarat University, Surat, Gujarat, India

## 32.1 Introduction

Cancer is a disease in which a group of abnormal cells grows uncontrollably by disregarding the standard rules of cell division. Normal cells are under the control of signals that dictate whether the cell should divide or die. Cancer cells develop autonomy from these signals, resulting in uncontrolled growth and proliferation (intro to cancer biology). A cell's genetic material (DNA) can be damaged or changed, resulting in mutations that impede normal cell growth and division. Cells do not die when they might, and new cells develop when the body does not require them. The excess cells may combine to form a tissue mass known as a tumor (benign and malignant). Cancer can affect people of all ages and can involve any part of one body (Lalla et al., 2013). There are over 36 different types of cancer, and the majority of them impact males in the form of colorectal, liver, lung, prostate, and stomach cancer, and women in the form of breast, cervical, colorectal, lung, and thyroid cancer (Bray et al., 2018).

Benign tumors may form in various parts of the body, which grow slowly and do not spread or invade other tissues. Therefore they are not cancerous and are not usually life-threatening. However, certain benign tumors can create complications. Some, for example, might become extremely large and create local pressure problems or appear unattractive. Furthermore, some benign tumors that develop from cells in hormone glands can produce too much hormone, which can have negative consequences.

Malignant tumors (cancers) tend to increase and invade nearby tissues and organs, which can cause damage. Tumors usually develop in one original site—the primary tumor. However, malignant tumors may also spread to other body parts to form secondary tumors (metastases). It occurs when certain cells from the primary tumor break off and travel through the bloodstream or lymph channels to the body's other parts without being destroyed by the liver. These secondary tumors may grow, invade, damage nearby tissues, and spread again. All cancers do not form solid tumors. In leukemia, for example, many abnormal blood cells are produced in the bone marrow and circulate in the bloodstream (Lalla et al., 2013).

### *32.1.1 Brief epidemiology of cancer*

In present-day society, cancer is one of the major causes of mortality worldwide. However, it has various reasons, including tobacco for 33%, obesity for 20%, and poor diet for 5%. In addition, hormonal changes, lack of physical activities, chemical carcinogens, excessive alcohol consumption, and some other nongenetic factors, including certain infections, immune system, exposure to ionizing radiations, and environmental pollutants, are other causes of cancer (Anand et al., 2008).

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According to the information provided by the World Health Organization (WHO), in 2020, there were around 10.1 million cancer diagnoses (excluding nonmelanoma skin and other noninvasive cancers) and 5 million cancer deaths globally, in which, lung cancer (1.8 million fatalities), stomach cancer (769,000 deaths), liver cancer (830,000 deaths), colorectal cancer (935,000 deaths), and breast cancer (685,000 deaths) cause nearly 13% of all deaths each year (https://www.who.int/news-room/fact-sheets/detail/cancer). In addition, the WHO also specifies that cancer has become the leading cause of mortality in developed countries and the second most significant cause of death in developing countries. About 400,000 children are diagnosed with cancer each year. In each country, the most common cancers are different. In 23 countries, cervical cancer is the most common type of cancer.

Therefore cancer experts note that "if humans live long enough, they are afflicted by this disease sooner or later" (Zhang et al., 2021). However, research shows that age and cancer have an immunosenescence relation, DNA mistakes accumulate with time and age-related alterations in the endocrine system. Besides, leukemia (34%), brain tumors (23%), and lymphomas (12%) are the three most frequent childhood cancers.

### 32.1.2 Current status of cancer

The American Cancer Society estimates the number of new cancer cases per year and deaths in the United States in the current year. It compiles the most recent cancer incidence, mortality, and survival data. The Surveillance and Epidemiology collected incidence data from the End Results Program, the National Program of Cancer Registries, and the North American Association of Central Cancer Registries are all part of the End Results Program. Data on mortality were compiled by the National Center for Health Statistics. In 2017 the United States was expected to see 1,688,780 new cancer cases and 600,920 cancer deaths. Men have a 20% higher cancer incidence rate than women across all sites, but women have a 40% higher cancer death rate. However, sex discrepancies differ depending on the type of cancer. Thyroid cancer incidence rates, for example, are three times greater in women than in men (21 vs 7 per 100,000 population), despite equal mortality rates (0.5 per 100,000 population), owing mostly to gender disparities in the "epidemic of diagnosis." Over the last decade of available data, the overall cancer incidence rate (2004−13) was steady in women and decreased by around 2% per year in men, while the cancer death rate (2005−14) decreased by about 1.5% per year in both men and women. Between 1991 and 2014, the overall cancer death rate fell by 25%, resulting in approximately 2,143,200 fewer cancer deaths than would have been expected if death rates had remained constant at their high. Although the cancer death rate in Blacks was 15% higher than in whites in 2014, increased access to health care as a part of the Patient Protection and Affordable Care Act may hasten the racial gap; from 2010 to 2015, the proportion of Blacks without insurance halved, from 21% to 11%, as it did for Hispanics (31% − 16%). Gains in coverage for traditionally marginalized Americans will allow current cancer control information to be applied more broadly across all population segments (Siegel et al., 2017).

### 32.1.3 Causes of cancer

Tobacco use is the cause of about 33% of cancer deaths. Another 20% is due to obesity, and 5% is due to poor diet, hormones, lack of physical activity, chemical carcinogens, and excessive alcohol consumption. Other nongenetic factors include certain infections, infection, immune system, exposure to ionizing radiation, and environmental pollutants (Anand et al., 2008). There are two main groups in which the impacted genes fall. Oncogenes are genes that encourage cell division and proliferation. Genes known as tumor suppressors prevent cell division and death. Malignant transformation can occur by forming novel oncogenes, the inappropriate overexpression of normal oncogenes, or the underexpression or disabling tumor-suppressor genes. Changes in multiple genes are typically required to transform a normal cell into a cancer cell (Lalla et al., 2013). Different degrees and processes can lead to genetic alterations. An entire chromosome's gain or loss can occur through mitosis errors. The nucleotide sequence of genomic DNA can alter, and these mutations are more frequent (Nelson et al., 2004) (Fig. 32.1).

### 32.1.4 Mechanisms of carcinogenesis

Mutations in several critical genes can lead to tumors (Vogelstein et al., 1988). For example, mutations in the tumor-suppressor gene p53 are found in about half of human tumor. The p53 protein guards a cell cycle checkpoint, and the inactivation of p53 allows uncontrolled cell division.

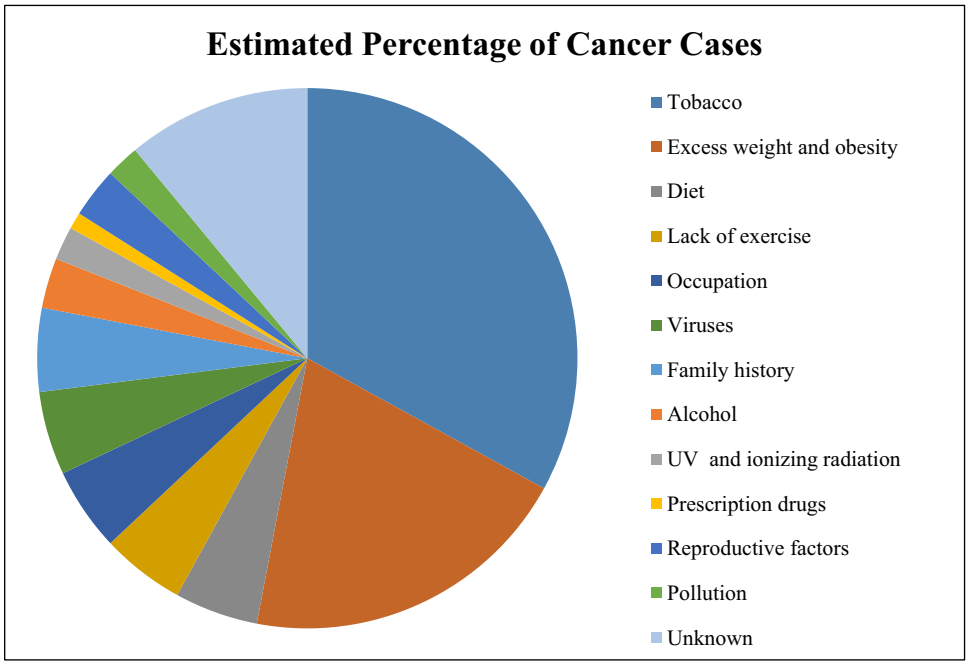


FIGURE 32.1 Estimated percentage of cancer cases caused by identifiable and/or potentially preventable factors (https://cancerprogressreport.aacr.org/progress/cpr22-contents).

DNA Lesions. DNA lesions (damaged bases or chromosome breaks) have a certain probability of giving rise to mutations when the cell divides. Endogenous DNA damage is high (Ames et al., 1993). An exogenous mutagen increases lesions over the background rate of endogenous lesions. The mutagenic effectiveness of a particular lesion depends on its excision rate by DNA repair enzymes and on the probability that it gives rise to a mutation when the cell divides.

Cell division is a critical factor in mutagenesis because when the cell divides, a DNA lesion can give rise to a point mutation, deletion, or translocation (Amestt and Goldt, 1990). Thus an essential factor in the mutagenic effect of an agent is the increment it causes over the background cell division rate in those cells that matter. Those cells that appear to matter most for cancer are the stem cells, which are not discarded, whereas their daughter cells are. Increasing the cell division rate of stem cells increases mutation and, therefore, cancer. As expected, there is little cancer in nondividing cells. Increased cell division, and consequently an increased risk for cancer, can be caused by such diverse agents as increased levels of particular hormones (Henderson et al., 1982), excess calories, chronic inflammation, or chemicals at doses causing cell division (Columbano and Ennas, 1990). Suppose both the rates of DNA lesions and cell division are increased. There will be a multiplicative increase in mutagenesis. For example, by high doses of a mutagen, growing cell division through cell killing and consequent cell replacement. Chronic dosing at high levels of chemicals that do not damage DNA can also cause cell killing, resulting in cell division and thus increasing cancer. Studies of cell division in stem cells, and the signaling systems responsible for the stem cell proliferation, are active and vital research areas (Ames et al., 1995).

Defense Systems. Defense systems such as the glutathione transferases protect DNA against mutagens. These defenses are almost all inducible; thus buffer cells from increments in reactive electrophilic chemicals can cause DNA lesions (Ames et al., 1990). DNA repair enzymes, almost all of which are inducible, buffer the cell against increments in DNA lesions. Therefore the effect of a particular chemical insult depends on each defense's level, which in turn is dependent on the history of exposure. The lack of particular micronutrients can partially disable reasons in the diet (e.g., antioxidants) (Ames et al., 1993).

### *32.1.5 Common cancer symptoms and signs*

Cancer symptoms and signs differ on the type of cancer, where it is located, and where the cancer cells have spread, but the majority of cancer patients typically experience the symptoms and signs including fever, pain,

fatigue, skin alterations (redness, unhealing wounds, jaundice, darkening), unintentional weight loss or increase. In addition to these, more blatant indications of cancer might include tumors or lumps (mass), having trouble swallowing, modifications to or issues with bowel or bladder function, persistent hoarseness or cough—short of breath, chest pain, unexplained bleeding or discharge (https://www.emedicinehealth.com/).

### 32.1.6 Types of cancer based on the origin

Tumorigenesis can result from the abnormal proliferation of any of the different kinds of cells in the body, so more than a hundred distinct types of cancer can vary substantially in their behavior and response to treatment. Thus we can classify tumors based on the types of cells it initiates. Here are some categories, as shown in the National Cancer Institute resource portal, which begins with specific kinds of cells:

**Carcinoma:** Cancers formed from epithelial cells. Many of the most prevalent malignancies, particularly in older persons, are included in this group. Nearly all cancers developing in the breast, prostate, lung, pancreas, and colon are carcinomas.
**Sarcoma:** Connective tissue − related cancers, such as those of the bone, cartilage, fat, and nerve, all of which grow from mesenchymal cells outside of the bone marrow.
**Leukemia**: Leukemia is the name for cancers that start in the bone marrow, which produces blood. Blood cancer.
**Lymphoma and myeloma:** Lymphoma is cancer that starts in the lymphocytes, for example, Hodgkin lymphoma and myeloma begin in plasma cells, also known as multiple myeloma and Kahler disease.
**Melanoma:** This type of cancer begins in the cells, which become melanocytes, specialized cells that make melanin.
**Brain and spinal cord cancers:** The category of cancer-initiating in bones and spinal cord, for example, an astrocytic tumor begins in astrocytes.
**Germ cell tumor:** Pluripotent cells frequently found in the testicles or ovaries give rise to cancers.
**Blastoma:** Cancers formed from embryonic tissue or immature "precursor" cells. Children are more likely than older adults to experience a blastoma (https://www.cancerresearchuk.org/-what-is-cancer/how-cancer-starts/types-ofcancer).

Institute of Medicine, United States, suggests that even though there are many types of cancer, only a few have frequent occurrences. Age, gender, environmental factors, and genetic susceptibility often influence the kind of cancers, incidences, and mortality due to disease (Tevfik Dorak and Karpuzoglu, 2012; White et al., 2014; Ingole et al., 2016).

### 32.1.7 Development of cancer

The recruited normal cells, which form tumor-associated stroma, are active participants in tumorigenesis rather than passive bystanders; these stromal cells contribute to the development and expression of specific hallmark capabilities and a few enabling features to get complete malignancy. These hallmarks include:

**Sustaining proliferative signaling:** Cancer cells can acquire the capability to support proliferative signaling in several alternative ways like cancer cells by deregulating growth-promoting signals, becoming masters of their destinies, and the enabling signals are conveyed in large part by growth factors that bind cell-surface receptors, typically containing intracellular tyrosine kinase domains, which latter proceed to emit signals via branched intracellular signaling pathways that regulate progression through the cell cycle as well as cell growth; often these signals influence yet other cell-biological properties, such as cell survival and energy metabolism.

Cancer cells may produce growth factor ligands themselves, to which they can respond via the expression of cognate receptors, resulting in autocrine proliferative stimulation. Cancer cells may send signals to stimulate normal cells within the supporting tumor-associated stroma, reciprocating by supplying the cancer cells with various growth factors.

Receptor signaling can also be deregulated by elevating the levels of receptor proteins displayed at the cancer cell surface, rendering such cells hyperresponsive to otherwise-limiting amounts of growth factor ligand; the same outcome can result from structural alterations in the receptor molecules that facilitate ligand-independent firing.

**Evading growth suppressors:** After exploiting proliferative growth signals, cancer cells escape the robust programs that negatively regulate the proliferation, such as tumor suppressors such as TP53 and RB (Retinoblastoma associate).
**Resisting cell death:** Elucidation of the signaling circuitry governing the apoptotic program has revealed how apoptosis is triggered in response to various physiologic stresses that cancer cells experience during tumorigenesis; notable among the apoptosis-inducing stresses are signaling imbalances resulting from elevated levels of oncogene signaling,
**Enabling replicative immortality:** Cancer cells require unlimited replicative potential to generate macroscopic tumors, associated with two distinct barriers to proliferation: senescence, a typically irreversible entrance into a nonproliferative but viable state, and crisis, which involves cell death.
**Inducing angiogenesis:** During tumor progression, an "angiogenic switch" is almost always activated and remains on, causing normally quiescent vasculature to sprout new vessels that help sustain expanding neoplastic growths continually.
**Activating invasion and metastasis:** Carcinomas from epithelial tissues progressed to higher pathological grades of malignancy, reflected in local invasion and distant metastasis; the associated cancer cells typically developed alterations in their shape and attachment to other cells and the extracellular matrix (Fig. 32.2) (Hanahan and Weinberg, 2011).

### 32.1.8 *Treatments available for cancer*

Many clinical management systems are available to treat cancer at present. The conventional treatments for cancer as given on the website of NCI include surgery, radiation therapy, chemotherapy, immunotherapy, targeted therapy, hormonal therapy, stem cell therapy, and precision medicine. The treatment type for the individual depends on the stage of the disease. Despite significant advancements and progress, the need to improve cancer therapy without side effects persists (Sultana and Asif, 2017). This need has revitalized the demand for natural and alternative treatments in action.

### 32.1.9 *Natural and alternative therapies*

Ancient manuscripts such as Ayurveda, Siddha, Unani, Egyptian papyrus, and Chinese scriptures describe the application of medicinal herbs for over 4000 years. In various therapeutic systems and indigenous cultures, herbal therapies have unique acceptance even in the current period. India is a rich repository of medicinal plants

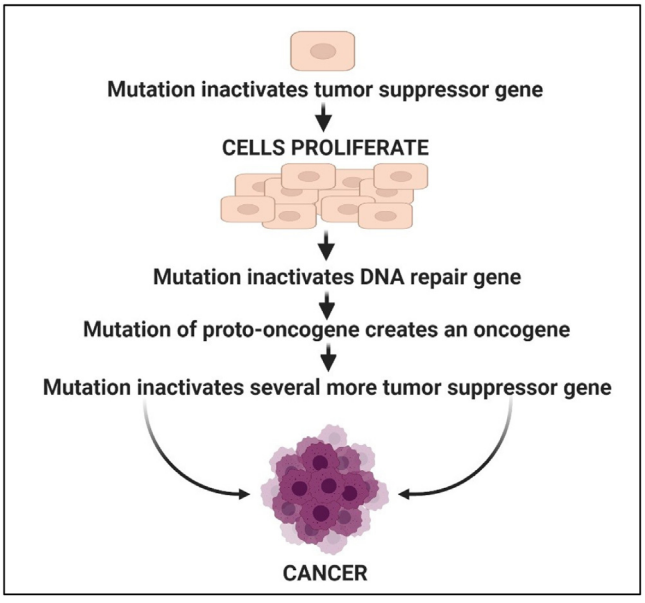


FIGURE 32.2 Development of cancer.

and one of the principal ancient civilizations. Indian Ministry of Ayurveda, Yoga and Naturopathy, Unani, Siddha, and Homeopathy (AYUSH) has codified about 8000 herbal remedies.

Natural compounds from flowering plants play a significant role in cancer chemotherapy (da Rocha et al., 2001). Plants are considered among the primary sources of biologically active chemicals. It has been estimated that about 50% of the prescription products in Europe and the United States originate from natural products or their derivatives (Newman et al., 2003). Out of the 250,000−500,000 plant species on earth, only 1%−10% have been studied chemically and pharmacologically for their potential medicinal value (Verpoorte, 2000). In the Middle East, 700 species of identified plants are known for their medicinal value (Azaizeh et al., 2006). Out of the 2500 plant species recorded in Jordan, more than 100 are listed as endemic and have medicinal potential in folk medicine (Oran et al., 1994).

A comprehensive survey of practitioners and herbalists in Jordan indicated that more than 150 plant herbs are still a traditional source of herbal medicine (Abu-Irmaileh and Afifi, 2003). Medicinal plants are the complete source of life-saving drugs for most of the world's population. Medicinal herbs have been widely used to treat diseases traditionally for several generations. In recent years, the focus on plant research has increased worldwide. A huge potential source of anticancer chemicals is medicinal plants. The significance of medicinal plants, as with many aspects of phytomedicine, rests in the potential access to extremely complex molecular structures that would be challenging to create in the laboratory. Compounds derived from medicinal plants that have antitumor properties may do so through a variety of mechanisms, including interactions with cytoskeletal proteins that are essential for cell division, inhibition of DNA topoisomerase enzymes, antioxidant or antiprotease activity, immune system stimulation, and so on. Worldwide, considerable testing of medicinal plants is still being done to find new, more potent cancer treatments (Dixit and Ali, 2010).

India is the world's leading producer of medicinal plants, widely known as the botanical garden of the world. Medicinal plants are an ancient source of contemporary compounds possessing therapeutic value and may even be utilized in drug development. In total, 80% of the population of developing countries depends on traditional medicines, primarily natural plant products. It is estimated that, in 1997, the world market for over-the-counter phytomedicinal products was US$ 10 billion, with an annual growth of 6.5%. World Health Organization considers phytotherapy in its health programs and suggests fundamental procedures for authenticating drugs of plant origin in developing countries (Rates, 2001). Natural products have played a principal role as new chemical entities (NCEs)—approximately 28% of NCEs between 1981 and 2002 were natural products derived. Natural products give a beginning point for new synthetic compounds, with varying structures and multiple stereo centers demanding synthetically (Balunas and Kinghorn, 2005).

They have minimal toxicity, are cost-effective and pharmacologically active, and supply an easy remedy for several human ailments compared with synthetic drugs that are subject to adulteration and side effects. In addition, the alarming increase in the rate of antibiotic-resistant microorganisms infection has persuaded scientists to search for compounds with potential antimicrobial activity. Antioxidant, antimicrobial, anticancer, antiulcer, antihyperlipidaemic, antiinflammatory, antidiabetic, and antispermatogenic effects have also been reported on several animal models by the crude extracts of plants (Table 32.1).

**TABLE 32.1** List of plants having anticancer activity.

| Sr. no. | Name of plant | Part of plant | Type of cancer | Reference |
|---|---|---|---|---|
| 1. | *Tinospora cordifolia* (Wild) Miers | Stem, roots | Tumor cancer | Jagetia and Rao (2006) |
| 2. | *Ziziphus nummularia* Wight | Root, bark, stem, flowers, and seeds | Mitochondria cancer | Carter and Livingston (1976) |
| 3. | *Andrographis paniculata* (Burm. F.) Nees | Roots and the leaves | Breast cancer | Jada et al. (2007) |
| 4. | *Centella asiatica* Linn | Leaves | Liver, lung, brain, heart, kidney, and spleen cancer | Sharma and Sharma (2005) |
| 5. | *Curcuma longa* Linn | Roots | Breast cancer, liver, lung, leukemia, colon cancer, skin cancer | Sultana et al. (2021) |
| 6. | *Phyllanthus amarus* Schumach. & Thonn | Leaves, roots, and shoots | Oral cancer | Rajeshkumar et al. (2002) |

(*Continued*)

TABLE 32.1 (*Continued*)

| Sr. no. | Name of plant | Part of plant | Type of cancer | Reference |
|---|---|---|---|---|
| 7. | *Annona muricata* Linn | Root, bark, leaf, and fruit. | Lung cancer | Wu et al. (1995) |
| 8. | *Nothapodytes foetida* Miers | Wood | Leukemia, colon cancer | Wall Monroe & Wanl (1996) |
| 9. | *Withania somnifera* (Linn.) Dunal | Roots and leaves | Tumor cancer | Malik et al. (2007), Palliyaguru et al. (2016) |
| 10. | *Cedrus deodara* (Roxb. Ex. D. Don) G. Don | Stem wood | Lung cancer, skin cancer | Shi et al. (2019) |
| 11. | *Boswellia serrata* Roxb | Leaves | Leukemia cancer | Bhushan et al. (2007) |
| 12. | *Achillea wilhelmsii* | Leaves | Colon cancer | Isfahani et al. (2013) |
| 13. | *Allium sativum* | Stem | Breast, larynx, colon, skin, womb, gullet, bladder, and lung | Lau et al. (1990), Thomson and Ali (2005) |
| 14. | *Ammi majus* | Flower | Cardiac cancer | Kooti et al. (2017) |
| 15. | *Ammi visnaga* | Leaves | Hepatic cancer, breast cancer | Arafah et al. (2021), Khalil et al. (2020) |
| 16. | *Artemisia absinthium* L | Flowers | Breast cancer | Sultan et al. (2020) |
| 17. | *Astrodaucus orientalis* | Root | Breast cancer | Hesari et al. (2021) |
| 18. | *Avicennia marina* | Leaves | Breast cancer | Sharaf et al. (2000) |
| 19. | *B. serrata* | Leaves | Leukemia cancer | Mashhadi et al. (2017), Chashoo et al. (2011) |
| 20. | *Camellia sinensis* | Leaves | Prostate cancer | Yang et al. (2019), Yasumoto et al. (1995) |
| 21. | *Citrullus colocynthis* | Fruit | Liver and breast cancers | Ayyad et al. (2012), Hatam et al. (1989), Tannin-Spitz et al. (2007) |
| 22. | *Hordeum vulgare* L. | Seed | Tumor cancer | Seo et al. (2014) |
| 23. | *C. longa* | Shoots | Liver cancer, breast cancer | Ayyadurai et al. (2013), Ranjbari et al. (2013) |
| 24. | *Ferula assa-foetida* | Stems | Liver cancer | Sd et al. (2013) |
| 25. | *Glycyrrhiza glabra* | Root | Breast cancer | Nourazarian et al. (2016) |
| 26. | *Lagenaria siceraria* Standl | Leaves | Lung cancer | Shokrzadeh et al. (2012) |
| 27. | *Lepidium sativum* | Leaves | Leukemia | Shokrzadeh et al. (2012) |
| 28. | *Triticum aestivum* | Seed | Chronic myeloid leukemia | Das et al. (2016) |
| 29. | *Mentha pulegium* | Leaves | Leukemia | Aslani et al. (2013) |
| 30. | *Nigella sativa* | Leaves | Breast cancer | Khalife et al. (2016) |
| 31. | *Olea europae* | Leaves | Colon cancer | Fini et al. (2008) |
| 32. | *Pegaum harmala* L. | Leaves | Breast cancer | Jiménez et al. (2008) |
| 33. | *Rosa damascenes* Mill | Leaves | Breast cancer | Zamiri-Akhlaghi et al. (2011) |
| 34. | *Taverniera spartea* D | Short shoot | Breast cancer | Kooti et al. (2017) |
| 35. | *Eleusine coracana* L | Seed | Breast cancer, colon cancer, leukemia | Kuruburu et al. (2022) |
| 36. | *Urtica dioica* L | Leaves | Prostate cancer | Konrad et al. (2000) |
| 37. | *Zingiber officinale* | Stem | Breast cancer | Rahman et al. (2012) |
| 38. | *Thymus vulgaris* | Stems | Breast cancer and colorectal cancer | Abaza et al. (2015) |
| 39. | *Medicago sativa* L | Leaves | Breast cancer | Kooti et al. (2017) |
| 40. | Saffron *Crocus sativus* L | Leaves | Colorectal cancer | Aung et al. (2007) |

As a result, there is heightening interest in the fermented products of herbal plants. Especially, fermentation can enhance a product's nutraceutical value by breaking down certain undesirable compounds and persuading effective microbial reformation (Kwon and Ha, 2012). Several experiments outlined that fermentation influences the phenolic form of extracts obtained from various plant sources or during the fermentation of plant sources. Several studies described the auspicious cytotoxic activity of fermented wheat germs toward cancer cell lines through in vivo clinical trials (Rizzello et al., 2013). The possible approaches, such as fermented wheat germ extract (FWGE) with antitumor potency, may improve the clinical outcome of current therapy. FWGE obstructs anaerobic glycolysis, pentose cycle, and ribonucleotide reductase. It has notable antiproliferative effects and kills tumor cells by inducing apoptosis via the caspase-poly (ADP-ribose) polymerase pathway (Mueller and Voigt, 2011).

## 32.2 Fermented wheat germ extract

### 32.2.1 History

FWGE was originated by Mate Hidvegi, a Hungarian chemist, in the 1990s. It should not be demented with wheat germ oil. Avemar is a Brand name for FWGE in honor of Ave Maria ("Hail Mary" in Latin), who provided the needed funding for his research.

Avemar was first initiated as a dietary supplement in Hungary in the autumn of 1998. Then, based on the results of animal experiments and toxicological studies, which showed significant anticancer activity and lack of toxicity, the regional research ethics boards of the National Health Council, Hungary, approved the protocols of clinical studies on Avemar. Based on these results, Avemar was registered and approved as a medical nutriment for cancer patients by the National Institute of Food Hygiene and Nutrition, "FodorJózsef" National Centre for Public Health Hungary, on February 6, 2002 (registration number: 503).

The Ministry of Health, Hungary, listed the product under "nonprescription medical nutriments" in its Health Bulletin of July 1, 2002. The retail price of the compound is officially controlled, and the product can only be sold in pharmacies.

The National Institute of Pharmacy, Hungary, qualified the production plant and quality assurance system to fulfill the pharmaceutical manufacturing requirements in 2003 (reference number: 1127–100/38/2003). As a result, Avemar was the first product registered and approved for its oncological indications (https://www.AVEMAR.co).

Avemar is a combination of molecules with a standardized composition carried out from chemically modified natural materials. The main component is wheat germ, from which several other substances are extracted. These substances are then converted through fermentation and biotechnological modification, conforming to the quality standards for pharmaceutical production (GMP, ISO 9001:2000). After their concentration, the active compounds are extracted using various physicochemical activities and then molecularly encapsulated and formulated. The consequence is a seminatural, semisynthetic substance in granular form that must be dissolved in water before being used. Due to its complex nature, Avemar carries several additional molecules except for its main ingredient.

The aqueous powder has 63.2% fermented extract of wheat germ and drying aids (35% maltodextrin and 1.8% silicon dioxide). It is standard in the case of natural products. The GMP manufacturing technology requires extraction of wheat germs, fermentation of the extract by *Saccharomyces cerevisiae*, separation of the fermentation liquid, drying, and granulation. The manufacturing process is patented. It shows no toxicity, mutagenicity, or genotoxicity. Moreover, the combination of Avemar with chemotherapeutic agents did not increase toxicity or reduce antiproliferative activity. Avemar has been treated as an anticancer and immunomodulatory dietary supplement (Telekes et al., 2009).

FWGE is recently utilized as a nutrition supplement for cancer patients. Restricted current data suggest antiproliferative, antimetastatic, and immunological effects that were at least in part exerted by two quinones, 2-methoxy benzoquinone, and 2,6-dimethoxybenzquinone as ingredients of FWGE (Mueller et al., 2011).

### 32.2.2 Mechanisms of action—how Avemar works

Avemar is a plant extract, thus the precise chemical composition is unknown, and the active constituent(s) against cancer has yet to be determined. The methoxy-substituted benzoquinones are promising possibilities for Avemar's active components. Avemar's anticancer activities have been documented. Many cancer patients use

Avemar as a cancer treatment, therefore understanding its mode of action is critical, both for explaining any adverse effects that may arise from its use and for identifying potential novel pathways that lead to favorable outcomes in cancer patients (Johanning, 2007).

## 32.2.3 Effects on the immune system

### 32.2.3.1 Restoration of the damaged immune response

Avemar can repair damaged immune systems and improve the functioning of the cellular immune response, an effect derived from its stimulatory effect on the maturation and differentiation of bone marrow lymphocytes. Avemar's stimulatory effect on cellular immune response plays a vital role in its clinical effectiveness, acting as an autoimmune cancer treatment (http://www.avemar-alternativetherapy.com/aboutAvemar.ews).

## 32.2.4 Increase of blastic transformation

Avemar's immunomodulatory activities were originally discovered in a study on the compound's effect on immunological function in mice. Avemar considerably improved the blastic transformation of peripheral blood T cells activated by concanavalin A in this investigation. In other studies, C57B1 mice were given skin transplants from the coisogenic mouse strain B10LP, which could be tolerated for 16–25 days before rejection. Thymectomized control (untreated) mice rejected the transplant after 52 days (male) or 41 days (female). Thymectomized mice given Avemar rejected the grafts after 29 days (male) or 33 days (female) (female). Control (nonthymectomized) mice rejected the transplants after 21 or 29 days. These data reveal the considerable impact of Avemar treatment on these animals, with the immunological function of mice severely weakened by thymectomy restored to near that of nonthymectomized mice (untreated) (Mate et al., 1999).

Interestingly, subsequent investigations conducted as part of this group to determine if Avemar's immunostimulatory actions could be attributed to a single active molecule, 2,6-dimethoxy-*p*-benzoquinone, revealed that they could not. Avemar's immunomodulatory and immunological restorative actions may be used therapeutically in a variety of clinical indications of a compromised immune response. The effect of Avemar therapy on characteristics of experimental systemic lupus erythematosus in naive mice was also investigated (Ehrenfeld et al., 2001).

## 32.2.5 Effects on the metabolism of cancer cells

### 32.2.5.1 Alters glucose/nucleic acid metabolism

The researchers looked at how Avemar affected Jurkat leukemia cell viability, proliferation, cell cycle distribution, apoptosis, and the activity of glycolytic/pentose cycle enzymes that control carbon flow for nucleic acid synthesis. Avemar has a cytotoxic IC50 value of 0.2 mg/mL for Jurkat tumor cells and higher dosages of the crude powder limit Jurkat cell proliferation in a dose-dependent manner. Avemar suppresses cell growth by more than 50% at concentrations greater than 0.2 mg/mL (72 hours incubation), which is anticipated by the emergence of a sub-G1 peak on flow histograms at 48 hours. Avemar's growth-inhibiting activity was associated with substantial induction of apoptosis, according to laser scanning cytometry of propidium iodide- and annexin V-stained cells. The inhibition of apoptosis by benzyloxycarbonyl-Val-Ala-Asp fluoromethyl ketone but enhanced proteolysis of poly(ADP-ribose) suggests that caspases mediate Avemar's cellular actions. Glucose-6-phosphate dehydrogenase and transketolase activity were dose-dependent and linked with lower 13C incorporation and pentose cycle substrate flow into RNA ribose. This decrease in pentose cycle enzyme activity and carbon flow toward nucleic acid precursor synthesis provides a mechanistic insight into the cell growth-controlling and apoptosis-inducing effects of fermented wheat germ. Avemar has a 50-fold greater IC50 (10.02 mg/mL) for inducing a biological response in the peripheral blood lymphocytes, providing a broad therapeutic window for this additional cancer treatment method with minimal adverse consequences (Boros et al., 2001).

## 32.2.6 Inhibits the synthesis of MHC-I

T cell and B cell tumor lymphocytic cell lines were used in in vitro model research. Tyrosine phosphorylation of intracellular proteins and intracellular $Ca^{2+}$ increase was investigated using immunoblotting with an antiphosphotyrosine antibody and cytofluorimetry using $Ca^{2+}$-sensitive fluorescent dyes, Fluo-3 AM and FuraRed-AM,

respectively. Cytofluorimetry was used to identify apoptosis by staining the DNA with propidium iodide and detecting the "sub-G1" cell population. The cell surface MHC class I molecules were examined by indirect immunofluorescence on a cytofluorimeter using a monoclonal antibody to the human MHC class I polymorphism region. The increase in intracellular $Ca^{2+}$ concentration was caused by MSC-stimulated tyrosine phosphorylation of intracellular proteins and the input of extracellular $Ca^{2+}$. Apoptosis of 20%–40% was seen in the cell lines after 24 hours of MSC therapy. MSC therapy reduced the number of cell surface MHC class I proteins by 70%–85% as compared with the nonstimulated control. In healthy peripheral blood mononuclear cells, MSC did not trigger the same level of apoptosis. Inhibiting cellular tyrosine phosphatase activity or $Ca^{2+}$ influx had the opposite impact, increasing or decreasing Avemar-induced apoptosis and MHC class I downregulation. A benzoquinone component (2,6-dimethoxy-pbenzoquinone) in MSC caused apoptosis and downregulation of MHC class I molecules in tumor T and B cell lines. These findings imply that MSC works on lymphoid tumor cells by lowering MHC class I expression and specifically driving tumor cell death via tyrosine phosphorylation and $Ca^{2+}$ influx. 2,6-dimethoxy-pbenzoquinone, one of the components of MSC, has been proven to be an important factor in MSC-mediated cell response (Fajka-boja et al., 2002).

#### 32.2.6.1 Enhances tumor necrosis factor-alpha production

TNF-Alpha (tumor necrosis factor-alpha) is one of the significant cytokines capable of killing tumor cells. By increasing its production, tumor angiogenesis (growth of new blood vessels) is ameliorated, and apoptosis (programmed cell death) of the cancer cells is directly stimulated (Telekes et al., 2005).

### 32.2.7 Increase in ICAM-1 level

The intracellular adhesion molecule ICAM-1 (CD54) ensures that immuno-competent cells can pass through vessel walls to approach cancer cells and kill them. As a result, malignant tumors cannot grow beyond a diameter of 1 mm without developing their vessel system (tumor angiogenesis). However, as newly developed tumor vessels contain deficient levels of ICAM*I, immuno-competent cells do not invade the tumor via its vessels.

Avemar has a significant stimulatory effect on ICAM-1 protein synthesis, thus enhancing the cellular anticancer immune response. Avemar achieves this directly and indirectly by increasing the TNF-Alpha production of macrophages, which helps leukocytes and lymphocytes reach the tumor cells (Telekes et al., 2009).

### 32.2.8 Stimulation of apoptosis (programmed cell death) of tumor cells

Avemar's influence on apoptosis is one of the most critical aspects of its effect mechanism. The balance between apoptosis (programmed cell death) and cell proliferation is of primary importance in the histological integrity of tissues. A decreased ratio of apoptosis is a typical feature of malignant transformation. Avemar increases the apoptosis of tumor cells, resulting in their death, yet, at the same time, does not influence the life cycle of normal cells.

Cell cycle studies revealed an increased ratio of sub-G1/S phase cells at the detriment of S phase cells (an indirect marker of apoptosis); this was also demonstrated through FACS analysis (flow cytometry). Caspase-3 protease-mediated cleavage of PARP (poly-(ADP-ribose)polymerase), a process leading to apoptosis, is enhanced by the use of Avemar, something attributable to Avemar's impairment of DNA repair (http://www.avemar-alternativetherapy.com/aboutAvemar.ews).

### 32.2.9 Inhibition of carcinogenesis

Avemar has been shown in animal studies to be capable of suppressing the growth of rat colon cancer. Four-week-old inbred male F-344 rats were employed in this investigation. Azoxymethane has been shown to cause colon cancer (AOM). Ten untreated rats were used as controls (Group-1). AOM was dissolved in physiologic saline for the treatment of the animals in group 2, and the animals received three subcutaneous injections, 1 week apart, of 15 mg/kg body weight (b/w) each. Avemar, a FWGE standardized to 2,6-dimethoxy-*p*-benzoquinone, was provided as a possible chemopreventive drug in two further groups. MSC was dissolved in water and administered once daily via gavage at a dose of 3 g/kg b/w. In group 3, animals got MSC 2 weeks before the first AOM injection and every day thereafter until they were killed 32 weeks later. In group 4, only the basal diet and MSC were given.

After the experiment, all of the rats were exsanguinated, the big abdominal arteries were cut under light ether anesthesia, and an autopsy was done. The percentage of mice developing colon tumors and the number of tumors per animal were as follows: groups 1—0 and 0; groups 2—83.0 and 2.3; groups 3—44.8 ($P$ .001) and 1.3 ($P$ .004); and groups 4—0 and 0. Histologically, all of the tumors were malignant. The quantity of ACF (abnormal crypt foci) per region ($cm^2$) in group 2 was 4.85, but it was only 2.03 in group 3 ($P$ .0001) (Zalatnai et al., 2001).

### 32.2.10 *Reduces chemotherapy-induced febrile neutropenia*

In pediatric cancer patients, FWGE decreases chemotherapy-induced febrile neutropenia.

An open-label, matched-pair (by diagnosis, stage of disease, age, and gender) pilot clinical trial was conducted to see if combining the medical nutrient MSC (Avemar) with cytotoxic drugs and continuing MSC administration on its own helped to reduce the incidence of treatment-related febrile neutropenia in children with solid cancers when compared with the same treatments without MSC. This study enrolled 22 patients (11 pairs) between December 1998 and May 2002. The tumor staging was the same in each pair at the start (mainly pTNM = T2N0M0), except in two cases when patients in the MSC group had a worse prognosis (metastasis at baseline). Between the two groups, there were no discernible differences in terms of average age, length of treatment time (MSC), follow-up, number of patients with central venous catheters, number of chemotherapy cycles, frequency of preventive counter neutropenic interventions, or type and dosage of antibiotic and antipyretic therapy. There was no progression of the malignant condition during the therapy (follow-up) period. At the end of the study, however, there was a significant difference in the number and frequency of febrile neutropenic events between the two groups: 30 febrile neutropenic episodes (24.8%) in the MSC group versus 46 (43.4%) in the control group (Wilcoxon signed rank test, $P$ .05). Continuous supplementing of anticancer medications with the medicinal nutrient, MSC reduces the risk of treatment-related febrile neutropenia in children with solid tumors (Garami et al., 2004).

## 32.3 Proven properties

AVEMAR has been proven to

- Prevent the development of cancerous and precancerous lesions.
- Improve overall survival, metastases-free survival, and progression-free survival of cancer sufferers
- Lengthen and even cease the time to cancer recurrence following surgery, radiation, and chemotherapy
- Improve tolerance for surgeries, chemotherapy, and radiotherapy
- Enhance and not interfere with the anticancer effects of chemotherapies.
- Decrease the severity of the immune suppressive effects of surgery, radiation, and chemotherapy
- Expand the applicability of anticancer therapies by preventing immunosuppressive side effects
- Reduce the side effects of chemotherapy and works synergistically with all cytotoxic agents without compromising their efficacy. It also reduces chemotherapy-induced febrile neutropenia
- Enhance the quality of life and physical condition of early and late-stage cancer patients—less fatigue, pain, depression, and increased appetite, which helps patients gain lost weight.
- Speed up the recovery of normal immune functions following immuno-suppressive therapies.
- Act as an Autoimmune Treatment, Be an Immune Regulator. In autoimmune diseases, it is immunosuppressive; in malignancies, it stimulates the immune system.
- Can benefit patients with all types of cancer—it is not specific
- Prevent opportunistic infection and sepsis
- Prevent cancer-related cachexia
- Prevent cancer cell proliferation
- Inhibit cancer cell motility
- Enhance the ability of NK cells to identify and kill cancerous and other target cells by downregulating the presentation of MHC-I molecules on infected cells.
- Restore the bone marrow's ability to produce red blood cells (https://www.AVEMAR.co/).

## 32.4 Safety

Many pieces of evidence are available to show that Avemar is safe when used as intended. Avemar has been the subject of various animal and human effectiveness research, but none of these investigations have found any evidence of unfavorable consequences. Avemar has been sold for years in many nations with no side effects reported. Last but not least, Avemar has undergone screening tests for genotoxicity, mutagenicity, and carcinogenicity, acute toxicity studies in rats and mice, subacute toxicity studies in rats, and subchronic toxicity studies in rats and mice. It has also been examined for hematologic effects in multiyear studies of human cancer patients (Boros et al., 2005).

## 32.5 Adverse effect

AVEMAR has been given the designation of "Generally Recognized As Safe." There haven't been any significant adverse effects of its ingestion to date. The rare reports of health hazards must nonetheless be taken into consideration. Use of AVEMAR is not advised following organ transplantation, radiation therapy, or while pregnant (Demidov et al., 2008). Several people with colorectal cancer have reported experiencing mild gastrointestinal side effects (Elek, 2005).

## 32.6 Future aspects

Avemar includes 2,6-dimethoxy-*p*-benzoquinon, a potential antioxidant source. The potential for sourdough lactic acid bacteria fermentation to produce 2-methoxy benzoquinone and 2,6-dimethoxy-*p*-benzoquinone has been investigated. When tested for antiproliferative ability, sourdough fermented wheat significantly reduced the growth of ovarian cancer, colon cancer, and human germ cell cancers (Rizzello et al., 2013). There is always room for development, even if Avemar has previously demonstrated that it is a powerful cytotoxic agent. Its effectiveness may be increased if new probiotic microbe strains ferment wheat germ and other germs. Comparative analysis of commercial wheat germ extract and other plant germ extract against diverse cell lines is necessary to uncover hidden efficacies and confirm the lack of toxicity. Controlled clinical trials are also necessary to investigate potential side effects.

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