Bioflavonoids in Oncology

Clinical experience with the use of Flavin7 Gold, Pilot Study

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Abstract

Aims: Prevention of' malignant diseases, improvement of the quality of life of patients under cancer treatment regimens, care and rehabilitation. Observation of clinical status, changes in the course ofthe disease with emphasis on the quality of life during the use of the high bioflavonoid content **Flavin7 Gold** dietary supplement.

Methods: Dietary supplement, **Flavin7 Gold** was added to standard treatments, randomized, multi-center, controlled clinical trial on 295 patients in 33 centers.

Results: **Flavin7 Gold** is a dietary supplement containing bioflavonoid, resveratrol, anthocyanidos, vitamins, minerals and traceminerals. lt's oxidative radical scavenging activity is a function of concentration and time, and exceeds the effectiveness of similar products on the market. In this study, the treating physicians found that **Flavin7 Gold** inhibits the growth of tumors, reduces or alleviates the side effects of chemotherapy and radiation therapy. **Flavin7 Gold** displays hepatoprotective properties and protects against cardio toxicity. Reduces pain caused by bone metastases. The treating physicians observed improved quality of life and symptoms of depression.

Conclusions: The review of international scientific literature and epidemiology data suggest that the role of bioflavonoids is more accepted in prevention. Presently, the scientifically proven treatment methods are not successful to reasonably improve quality of life, survival figures, complete and partial remission. **Flavin7 Gold** given as a dietary supplement markedly improved the quality of life and the ratio of complete and partial remission of our patients. Our clinical observations suggest that the introduction of bioflavonoid supplements can effectively reduce the cardiovascular and cancer morbidity, mortality and chemo-prevention could become more successful. We strongly suggest further clinical research that meets the expectations and international standards of the society of oncologysts. In the challenging field of oncology there is a place for complementary modalities of chemo-prevention and symptom-control.

In the last decade the treatment outcome of some malignant diseases was improved, but far below expectations, taking the very high-cost diagnostic and therapeutic procedures in consideration.

Our national cancer morbidity and mortality inevitably requires the introduction of new prophylactic and treatment methods.

Complementary treatment modalities in cancer patients are widely accepted, some of them are supported by health insurance plans in western societies.

Viscum album, thymus extract, cell-, peptide-, enzyme-therapy, physio-, phyto-therapy, kinesiology, guided symbiosis, equilibrium of micro-organisms in the intestines, local and whole body hyperthermia, orthomolecular vitamin and trace-mineral treatment, antioxidant biomedical treatment in the everyday care of cancer patients is essential, based on clinical observations and controlled clinical research.

"Nil nocere" and "salus aegroti suprema lex" are our guiding principles in the prevention, therapy and rehabilitation of cancer patients.

Overview of literature

In the last 5-10 years we experienced substantial growth in the number of articles on oxidative stress, anti-oxidants and free radicals. Anti-oxidant clinical studies were published focused on cardiovascular and malignant diseases.

Substantial amount of knowledge and experience has been gathered on the physiological, pathophysiological, pharmacological effects of the bioflavonoid group of anti-oxidants. More than five thousand types of bioflavonoid have been identified. Our references were taken from studies conducted worldwide 011 the scientifically proven effects of bioflavonoids.

Fisetin. apigenin and lutcolin inhibit carcinogenesis (1).

Quercetin and apigenin inhibit the development of melanoma, the capability of melanoma to metastasize and infiltrate surrounding tissue. (2).

Resveratrol inhibits the mitosis of malignant cells, ability to metastasize, neo-vascularisation and angiogenesis (3).

Silymarin was observed to have anti-angiogenetic, anti-peroxidative and free radical scavenger properties, therefore, reduces degeneration of cell membranes through its inhibitor effects on lipid peroxidation. It increases the ribosomal RNA synthesis through the activity of RNA polymerase in the nucleus (4).

Hungarian authors' published results showing that resveratrol induces apoptosis 011 human malignant cell lines and decreases mitotic activity (5), inhibits Cox-2 transcription on human breast cancer cell lines and promotes its anti-inflammatory effect (6). Resveratrol is a co-factor in anti-inflammatory and chemo-protective activity (7). Flavonoid baieain induces apoptosis on prostate cancer cell lines (8).

Quercetin showed promising results in treating cancer in combination with hyperthermia (9).

A recently conducted clinical epidemiological study concluded that the higher the flavonoid (especially quercetin) intake, the lower the risk of developing lung cancer (10).

We found a study published in 1984 found that certain flavonoids inhibit aromatase (11). Lately, the thyrosine kinase inhibitor activity of genistein, luteolin and quercetin was described in the literature (12).

Flavin7 Gold contains all the mentioned flavonoids with the exception of baicain.

Physiological effects of flavonoid, anthocyanidines established with different testing systems in the scientific literature

1. **inhibit oxidative stress, free radical scavenger, anti-oxidant**
(through the inhibition of lipid peroxidation in the phospholipids layer of bio-membranes, decrease the oxidised LDL ratio and triglyceride level)
2. **modify the enzyme activity, usually inhibition**
(inhibits xantin-oxidase and monoamino-oxidase. lipoxigenase dependent peroxidation inhibitor, aromatase inhibitor)
3. **anti-viral, anti-bacterial, anti-mycotic effects**
4. **hepato-protective, neuro-protective effects**
5. **increase vascular permeability, anti-arteriosclerotic effect**
6. **inhibit platelet aggregation**

7. **facilitate the regeneration of vitamin E, increase vitamin C and P-earotene levels.**
8. **reduce the long-term complications of diabetes**

The above properties inter-relate in certain ways: hepato-protection relates to free radical scavenger activity, anti-oxidant effect to the xantin-oxidase inhibitor properties, anti-allergenic, anti-asthma effects to 5-lipoxigenasc inhibitor properties. Flavonids have so called "structure-specific activity" that is responsible for the multi-focal effects.

Free Radicals

Scientifically sound research in the field of free radicals has been done by Albert S/.ent-Gyorgyi, the Hungarian-bom Nobel Price winner. He focused his work on the pathological changes caused by free radicals and the biological treatment of these conditions. His pioneer work is a statement that basic research brings us closer to answers to the great questions of Life and Health.

At the beginning, the free radicals attack the cell membrane and the membrane of the nucleus, then they attack the DNA molecule, and too the proteins and lipids. Free radicals have an important role in the process of carcinogenesis, myocardial ischemia, the development of sclerotic plaques in the arteries, certain neurological diseases, the process of aging, and other degenerative conditions.

The degree of anti-oxidant effects of flavonoids is based on the structure of the given molecule, and shows close positive correlation with the degree of hydroxylation. Flavonoides are able to neutralize highly reactive hydroxyl radicals (metal chelating agents too), therefore they inhibit Fenton- and Haber-Weiss reactions that generate very highly reactive, aggressive free radicals. Furthermore, they retain their anti-oxidant properties after the formation of metal ions and flavonoid complexes.

The product

Flavin7 Gold is a concentrate of flavonoids and other plant-derived anti-oxidants that is manufactured by molecule separation process from seven different fruits.

Main components are: miricetin, quercetin, caemferol. isohamnetin. morin, catechin, epicatechin, malvidin. caftaric acid, trans-resveratrol. cis-resveratrol. krisin. galangin. apigenin, fisetin, luteolin. pelargonidin, cyanidin, delfinidin. petinidin. peonidin.

Flavin7 Gold trace-mineral contents (nig 1): boron 6.00. cuprum 0.97, iron 2.00, potassium 2100.00. manganese 2.00, sodium 17.00, phosphorus 245.00. and zinc 1.20. The product contains no arsenic, cadmium, cobalt, chromium, mercury, nickel, lead, vanadium in detectable amounts.

In vitro studies

Prof. S. Sipka (University of Medical Sciences, Debrecen, Faculty of Internal Medicine) found in vitro, that the ability of generating free radicals by peripheral phagocytes was inhibited 50% by adding 25 umol l **Flavin7 Gold** to the cell culture. When the concentration was increased to 50 ¿iniol 1, the degree of inhibition was 70%. Further increase of concentration did not increase the inhibition higher than 70%.

Animal studies

Prof. A. Szentmiklosi (University of Medical Sciences, Debrecen, Faculty of Pharmacology) studied the effects of **Flavin7 Gold** on rabbit and Guinea-pig isolated atrial and trachea smooth muscle. He also studied the vaso-

contractibility and the protective effect of **Flavin7 Gold**on the endothelium of the aorta and carotid arteries. He concluded that **Flavin7 Gold** is a very promising product in the treatment of cardiovascular and cardiorespiratory diseases. He suggests further in vivo studies with **Flavin7 Gold**.

Patients and methods

Flavin7 Gold is a registered dietary supplement in Hungary. Public Foundation organized a multi-center clinical study with 55 volunteer physicians (family physicians, specialists working in hospitals) to observe the clinically significant changes in the courses of the diseases during the administration of **Flavin7 Gold**.

The **Flavin7 Gold** was added to the personalized institutional standard treatment: therefore it was complementary, not alternative to the treatment. Between November 1, 2002 and October 31, 2003, 500 volunteer patients were enrolled that received the **Flavin7 Gold** product free of charge for 6 months. The participants were followed for 6 months: the treating physicians performed physical examinations, routine lab tests and performance assessments.

Disease groups:

1. Cardio-vascular, cerebro-vascular and peripheral vascular diseases. CAD verified by ECK. Echo, history of angina pectoris, myocardial infarction. Peripheral vascular diseases, Raynaud syndrome, etc. (150 patients, 30%)

2. Malignant diseases: also, in some cases benign tumours. Malignancies were verified by histo-pathology. Localisations included breast, stomach, lung, prostate, obstetrical. CNS, head and neck, malignant haematology. (250 patients. 50%)

In this group exclusion criteria were:

a. Iviing cancer occupying > 50% of the chest cavity
b. Liver tumour occupying > 50% of the organ
c. Metastasis to the CNS and/or vertebrae
d. Life expectancy < 6 months

3. Other conditions: liver diseases, allergies, menopause, osteoporosis, sclerosis multiplex, chronic inflammation. Alzheimer disease, autoimmune diseases, etc. (100 patients. 20%)

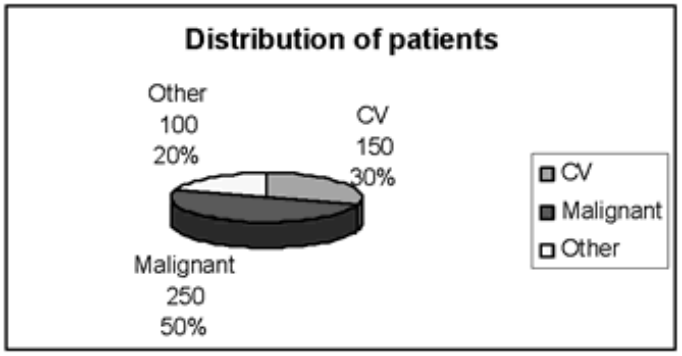

Figure 1

All 500 volunteer subjects signed consents. The clinical status was followed at 6 weeks. 12 weeks and 24 weeks of the **Flavin7 Gold** treatment.

The treating physicians followed the study patients according to standard diagnostic and treatment protocols, also using hospital reports for the interpretation of their clinical status.

After completing the 6 months treatment and follow up period, the physicians summarized the changes in the disease status, physical and psychological status of the patients and gave their opinion on the effects of **Flavin7 Gold** in that particular patient.

The data sent in by 32 physicians were suitable for further analysis. (19 family physicians, 7 oncologists, 2 internists, 1 ENT specialist, 1 pulmonologist. and 1 research fellow)

Results

We received data suitable for analysis on 295 patients (100%).

1. **Vascular disease group: 31 patients (10.5%)**
2. **Malignant disease group: 232 patients (78.2%)**
3. **Other conditions: 32 patients (11.3%)**

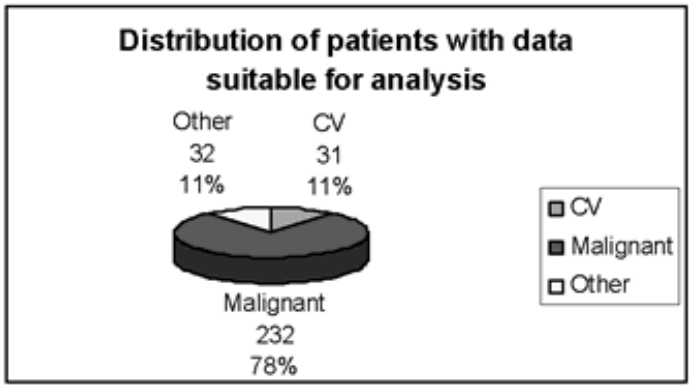

Figure 2

I. In the vascular disease group 2 patients progressed (6%), 8 not changed (26%) and 21 patients' cardio-respiratory status improved significantly (68%).

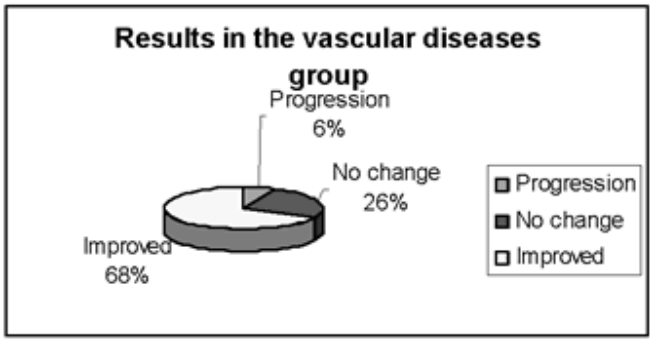

Figure 3

2. In the malignant disease group 65 patients progressed (30%), 66 patients' status were stabile with good quality of life (30%). and 89 patients showed significant clinical remission (40%).

The 30% progression rate includes the patients died during follow up.

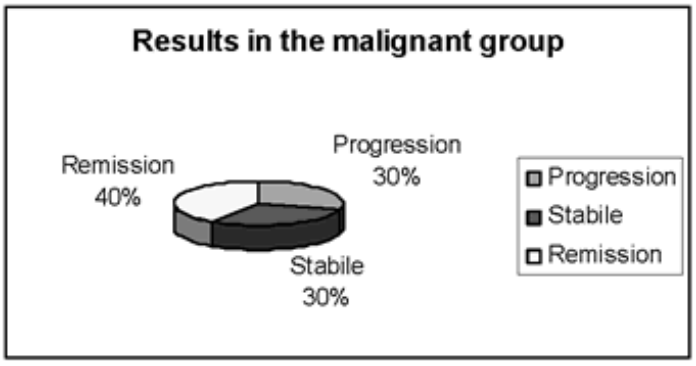

Figure 4

The clinical assessments in the malignant diseases group convinced us that the introduction of **Flavin7 Gold** as a complement to the standard treatment markedly improved the quality of life of our patients, decreased or eliminated the side effects of chemo-. radiotherapy, and showed hepato-protective and protected them from cardio-toxicity, and decreased the pain in patients with bone metastases. After chemotherapy in patients treated with **Flavin7 Gold** the platelet and white cell counts returned to normal sooner. To our surprise, a number of patients reported that their depression was significantly improved during the treatment with **Flavin7 Gold**.

In the malignant disease group 30 deaths were reported during the follow up period. Review ing these cases. 12 of them did not meet the inclusion exclusion criteria; they entered to the study with end-stage diseases. These 30 patients* physicians and family members agreed that the patients' pain and quality of life had been tolerable until almost the last days of their lives.

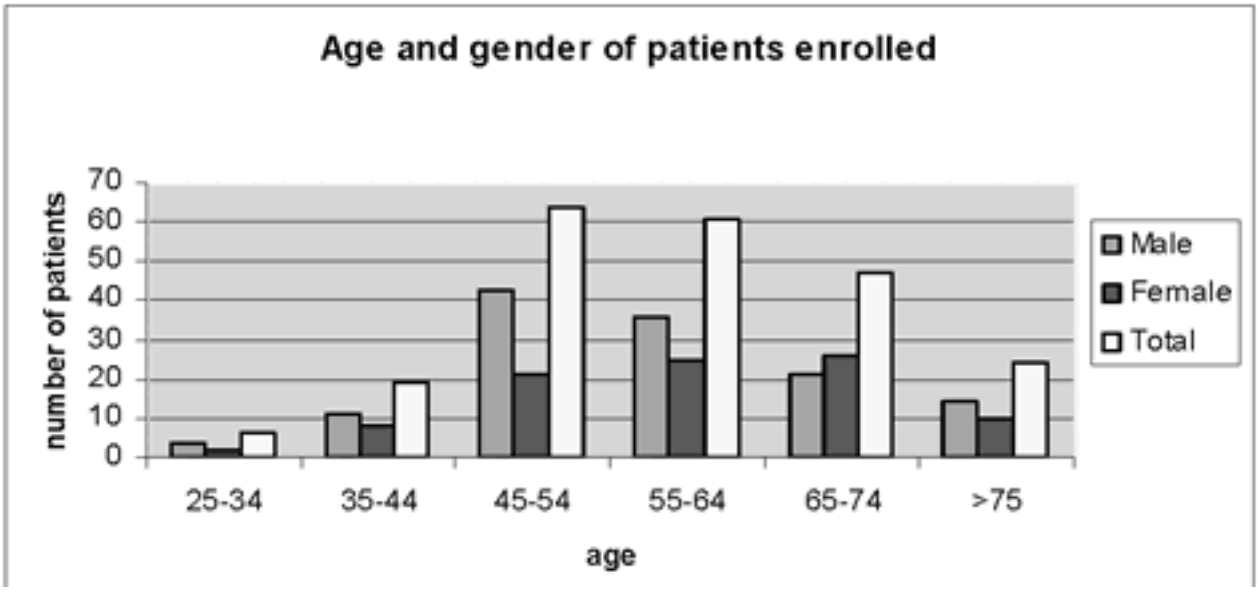

Figure 5

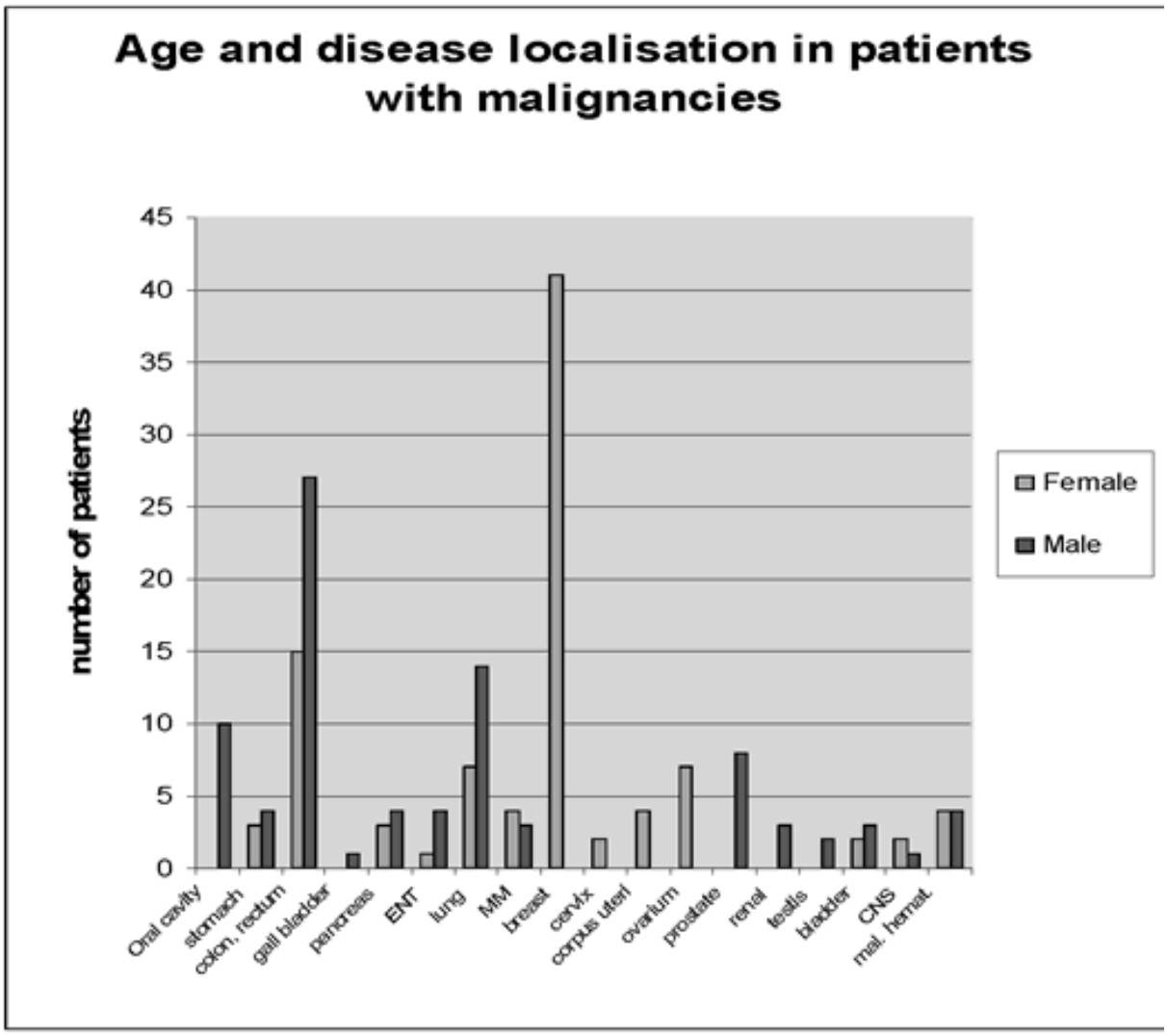

Figure 6

It worth mentioning that I. Fias. M.D.. chief radiation oncologist of the Gyor County Oncology Center, who followed 34 patients with malignant diseases for 30 months, observed that **Flavin7 Gold** decreases the side effects of chemotherapy. All the patients reported improvement with quality of life, appetite, energy and pain. Particularly interesting the follow ups of a group of 8 high risk patients: they received combination treatment of surgery, chemo- and radiation therapy and were defined as high risk patients for relapse or second malignancy. All these 8 patients reported improved quality of life, and show no signs of relapse or secondary malignancies for a period of 2.5 years.

Another interesting group of patients are physicians who are suffering from malignant diseases and observed themselves and confirmed the above results.

3. Other conditions group: liver cirrhosis, chronic hepatitis, diabetes, COPD (chronic obstructive pulmonary diseases), asthma, allergic conditions. Hie hepato-protective effect of **Flavin7 Gold** was plausible when the liver function tests of a patient with de-compensated liver cirrhosis returned to normal during the treatment. In the case of diabetes mellitus. serum glucose levels gradually decreased and returned to the normal range. In the case of COPD. the exhaled nitrous-oxide level significantly decreased, that implicates the decreased inflammation in the respiratory tract. (M. Balasko, MD et al. University of Medical Sciences, Pecs, Faculty of Patho-physiology.)

Another very interesting patient who suffered serious obstructive peripheral vascular disease as a complication of diabetes mellitus and had a pain-free walking distance of 10 meters only, which improved 200-250 meters during the 6 months **Flavin7 Gold** treatment. Naturally, it resulted in tremendous improvement in the psychological status and the overall quality of life of this patient.

Discussion

Based on this pilot study, **Flavin7 Gold** dietary supplement markedly improved the quality of life and the ratio of complete and partial remission of our patients. Bioflavonoid supplements can effectively improve the cardiovascular and cancer morbidity, mortality and chemo-prevention could become more successful. We strongly suggest further clinical research that meets the expectations and international standards of the society of oncologists.

In the challenging field of oncology there is a place for complementary modalities of chemo-prevention and symptom-control.

Acknowledgements

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