INTRODUCTION

The fact that fruits play an important role in human health is not new. What is new is that numerous bioactive compounds in vegetables and fruit, most notably berries, are being identified, quantified, and characterized. The rationale for the use of berries as a chemopreventive agent originates from epidemiological studies in which fruit and vegetable consumption has been shown to be inversely related to cancer mortality.1 One of the major Guidelines for Cancer Prevention promulgated by the American Institute for Cancer Research (AICR) is to eat a diet rich in a variety of plant-based foods, especially dark green leafy vegetables and fruits. Among the fruits, berries are of interest due to their large content of compounds with demonstrated chemopreventive activity, including vitamins A, C, and E, folic acid, calcium, selenium, ß-sitosterol, ellagic and ferulic acids, flavonols such as kaempferol, myricetin, and quercetin, and multiple anthocyanins. What is also new is that evidence-based research is being generated through experimental studies and human clinical trials to show that berries are chemopreventive and how they function on a molecular level; specifically how they influence the modulation of certain genes associated with cancer progression. Berries exhibit pharmacologic effects on a number of physiologic parameters such as cell proliferation, new blood vessel formation (angiogenesis), programmed cell death (apoptosis), inflammation, tumor invasion/metastasis, and cell signaling. Certainly, the antioxidant and free radical scavenging properties of berries are also important mechanisms to consider. As a result, numerous biomarkers have been and will continue to be identified that are associated with modulation of these cellular functions.

Concomitantly, there is a renewed interest in chemoprevention by whole foods, rather than purified compounds, to maximize health benefits while preventing risk of disease and minimizing toxicity. It has been proposed that the disease fighting and chemopreventive potential of whole foods may be due to a synergistic activity among different phytochemicals contained in fruits and vegetables.2 This combined activity of different phytochemicals represents another important reason to investigate food-based approaches to cancer prevention. Berries are just one of the many foodstuffs being studied to better understand the important role of diet in the prevention of cancer. Other chemopreventive foods and beverages include tomatoes, cruciferous vegetables, dark chocolate, olives, red wine, and tea. With an estimated 564,830 Americans expected to die of cancer in 2005, emerging research in chemoprevention lends itself to significant health benefits and a promising approach to the control of cancer.3 With berries, a fruitaceutical versus pharmaceutical, or prevention versus treatment approach to cancer control and survivorship, is being heavily investigated. This review provides an overview of cancer chemoprevention, the role of berries in modifying the carcinogenic process, and details the most recent scientific literature highlighting the results of experimental studies pertaining to berries and cancer research.

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Chemoprevention with Berries

Christine L. Sardo, MPH RD LD

Christine L. Sardo, MPH, RD, LD

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Dear NCC Members,

It is with great pleasure that I write you this note. We had a very successful FNCE meeting and the NCC Executive Board has made some great advances for the DPG to obtain more member benefits, greater recognition and acceptance as the leaders in complementary care. At FNCE we were able to attract new members (thank you for joining!), reconnect with past members and best of all, enjoy the beautiful island.

For those of you who are interested in or already have a practice which incorporates functional medicine (in our case, nutrition), we are encouraged that the hard work of Rita Batheja and Laura Lagano along with Kathy Swift have engendered our select population with great learning and educational opportunities in the near and distant future. To learn more about where you get further your complementary education please see the NCC Website as it often is ahead of the curve in relation to continuing education opportunities. Additionally, we remind you that the Natural Medicines Comprehensive Database is here for our use. Do not be afraid to jump on the NCC-listserv, network with other RDs and of course be yourself.

The winter brings a time to reflect on what you wish to accomplish in the New Year (new due to the rise of new flowers and a warmer sun). I ask that we as a collective DPG think about growing NCC so that we are the force to be revered and inquired about as it relates to dispelling the term “unconventional” but rather usher in integrative medicine to its rightful place at the table of 21st century medicine. Be an active part of NCC and watch us all soar!

Douglas S. Kalman PhD-candidate, RD, FACN

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We invite you to submit articles, news and comments. Contact us for author guidelines.

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In 2003, while developing the University of Michigan Integrative Medicine Clinical Services, nutrition was considered a priority. Evaluation of existing nutrition tools revealed none that reflected current evidence-based nutrition recommendations suitable to an integrative approach. Monica Myklebust, MD and Jenna Wunder, MPH, RD decided to create such a tool.

Released in March 2005, the Healing Foods Pyramid (HFP) is an alternative to the USDA pyramid. The HFP emphasizes:

- **Healing Foods**: Only foods known to have healing benefits or essential nutrients are included.
- **Plant-based choices**: Plant foods create the base of the pyramid and may be accented by animal foods.
- **Variety and Balance**: Balance and variety of color, nutrients, and portion size celebrate abundance.
- **Support of a Healthful Environment**: The foods we choose and our health reflect the health of our earth.
- **Mindful Eating**: Truly savor, enjoy, and focus on what you are eating in an environment that is not accented by the television or other distracting events.

**Thirteen Unique Categories**

- **Water**: forms the pyramid’s base and is the recommended beverage of choice. A rainbow of organic Fruits and Vegetables offers the greatest variety of antioxidants. Whole Grains are emphasized and include starchy vegetables, which are metabolized like grains by the body. Legumes, including soy, are excellent sources of non-animal protein. The Healthy Fats category emphasizes consumption of plant sources, such as olive oil and nuts, while strictly avoiding trans-fats and hydrogenated oils. Seasonings include herbs and roots that offer culinary and medicinal benefits. Eggs are an inexpensive high quality protein source and Dairy includes foods rich in calcium. In Fish & Seafood, sources high in omega-3 fatty acids are prioritized, while Lean Meats complement rather than dominate a meal. Accompaniments include: dark chocolate as a source of antioxidants; alcohol which may offer health benefits when used in moderation; and tea: black, green, or white. Personal Space at the top of the pyramid is reserved for treats consumed occasionally.

The HFP offers daily, weekly, and optional choices to accommodate people with a variety of dietary needs and preferences, including vegetarians. The recommendations support optimal health as well as the prevention and treatment of many conditions, such as diabetes, heart disease, obesity, high blood pressure, inflammation, mood disorders, and pain.

**Using the Healing Foods Pyramid**

Enclosed in this newsletter is your own copy of the HFP. Laminated handouts for use with patients, and posters suitable for the office include pyramid highlights and serving size information. They are available for purchase at [www.med.umich.edu/umim](http://www.med.umich.edu/umim). This site also offers extensive supporting information about each category, including scientific references. By simply clicking on a category, the user is directed to Facts About guidelines. Here, specific health benefits and concerns, recommended frequency of consumption, and other helpful details are outlined. Questions about farm-raised fish, organic produce, antioxidants, and many other contemporary topics are answered.

We encourage celebration of abundance and variety in nourishment. Please share how you have integrated the Healing Foods Pyramid into your practice, into your life, and the lives of your clients.

Monica Myklebust, MD is a board-certified family physician and Director of the University of Michigan Integrative Medicine Clinical Services. Dana Poindexter Schaad is a graduate student in the dietetics program at the University of Michigan School of Public Health and completed a summer internship as part of the HFP team.

**The Healing Foods Pyramid supports healthy choices, teaching people that it feels good to eat well.**

**Member Benefit**

Do you know someone who practices in the area of complementary nutrition and contributed significantly to the advancement of the NCC-DPG and its mission? Then consider nominating them for an Excellence in Service Award. NCC will be accepting nominations for Excellence in Service Awards for 2006-2007 in early 2007. Look for more details in the Winter NCC newsletter or email June Gnass, Nominating Committee Chair, 2006-2007 at Junegnass@hotmail.com.
Supplements Commonly Used by Persons with Diabetes
Katherine Stephens-Bogard MS RD CDE

NCC’s continuing professional education editor, Katherine Stephens-Bogard, MS, RD, CDE, presented at the 2006 American Association of Diabetes Educator’s annual meeting held in Los Angeles, CA. Below is a brief summary of her presentation titled Pills-n-Potions: Supplements Commonly Used in Diabetes Management and a table that summarizes supplements most commonly used by patients with diabetes.

Supplement use is a multibillion dollar industry. Use of supplements is not merely limited to vitamin/mineral preparations but includes herbs, botanicals, and nutraceuticals. Available without a prescription, supplements are “unregulated.” Indiscriminate use of supplements has resulted in injury and death. However, just because supplements are unregulated it does not mean that they are unsafe or unproven. There is a growing body of scientific evidence of the efficacy of certain supplements. As the evidence mounts, formulations and dosages, indications and contraindications are continually being elucidated. As such, there is potential for safe incorporation of supplements in diabetes management. Healthcare practitioners providing diabetes care and education need to be cognizant of the common supplements and their utility if not to recommend them but, at the minimum, to promote dialogue between patient and provider. Too often, patients do not disclose utilization for fear of reprimand.

A study published in Diabetes Care in 2006 revealed that approximately 50% of patients surveyed reported using some form of complementary alternative medicine (CAM)—supplements, mind/body therapies, chiropractic—concomitant to traditional/conventional care. It is estimated that the person with diabetes is 1.5 times more likely to use CAM than a person without. Furthermore, as indicated, such inclusion is not readily divulged to the healthcare provider.

The chart (right) lists supplements most commonly used by persons with diabetes for glycemic management as well as management or attenuation of the microvascular and macrovascular complications of diabetes.

Katherine Stephens-Bogard, MS, RD, CDE, is a certified diabetes educator, dietitian, and exercise physiologist at The Washington Hospital Diabetes Education & Management Program. She can be contacted at 724-250-6262 (phone); 724-250-6263 (fax) or kstephensbogard@washingtonhospital.org

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**Nutraceutical** | **Disease/Indication** | **Dose** | **Notations**
---|---|---|---
Alpha-lipoic acid | DM—† | +insulin sensitivity*, †glucose disposal ⊂TZD**, †symptom of peripheral neuropathy** | Oral dose: 600-1800 mg/day (4 weeks for efficacy) | Lower doses were not as effective, and too long to show improvement
B-Complex | CAD—‡ | +homocysteinemia, +atherosclerosis, increase arterial blood flow | Folic Acid: 0-4.5 mg/day B₁₂: 50-200 mg/day B₆: —0.5 mg/day (most common 2.5 mg Folic Acid, 2.5 mg B₁₂, 0.5 mg B₆) | Greatest benefit was in combination
Cinnamon | DM—‡ | +BG (FES & pp)* | 1-6 g/day (1 tsp-4.75 g) | Cassia Cinnamon (Chinese/ American-Cinnamon) * monitor BG’s - DM mods may need adjusted
Bilberry | DM—‡ | improve retinal lesion | whole fruit or 100 mg bid as a tea/extract | Leaf is utilized in tea/extracts
CoQ10 | CAD—‡ | +HTN | 50-200 mg/day in divided doses with meals | Soft gel or oil-based (emulsified) formulation
Forugreek | DM—‡ | post prandial BG; | +15 g/kg ground seeds (or 5 g per meal) | 1 tsp/g Standardize to soybeans, peanuts, peanuts (members of the Fabucaeous family) might be allergies to forugreek seeds
Garlic | CAD—‡ | +LDL | 300-500 mg/day | Atlantic is the bioactive compound
Ginseng | DM—‡ | +carbohydrate absorption, +glucose transport & uptake, +insulin secretion | American Ginseng 3 g/day Asian Ginseng 200 mg/day | Efficient is questionable, and not without deleterious side effects (TBP) & numerous drug interactions
Gymnema | DM—‡ | +insulin sensitivity | 400 mg/day | Leaf is the applicable plant part; GS is the officious extract, *monitor BG’s—mods may need dosedness
Magnesium | CAD—‡ | +LDL, +HDL | 400-1000 mg/day | Magnesium oxide or magnesium chloride
Omega 3 fatty acids | CAD—‡ (supplement) | -risk of MI, stroke (food) | 1-3 g/day (supplement) 6-9 oz. fish/week (food) | Ultra-processed
Poeosarol | DM—‡ | +LDL | 5-20 mg/day (10 mg most studied) | In tandem with diet/exercise Source: sugarcane. Caution with anti-platelet Rx
Pickle pear (Nopal) | DM—‡ | +carbohydrate absorption, +insulin sensitivity | 100-500 g/day of broiled stems | Glen, stem (pulp, flowers, leaves have all been used; it is considered a vegetable in southwestern/Mexican cuisine.
Psyllium Fiber | DM—‡ | +pp BGs by 14-20% | > 15 g/day, total soluble & insoluble fiber > 25 g/day, best benefits @ dosages double this | If as supplement best if 5 g 1 hour before meal
Quercetin | DM—‡ | +management of retinopathy | 500 mg bid | Best source is whole foods—red wine, apples, onions, garlic
Stanislosterol Esters | CAD—‡ | +fats & cholesterol | 2 g/day (stand) 3.4 g/day (stand) | Bionutri® (stand) or Take Control® (stand) 4 Thu-Sat
Vandurin | DM—‡ | +stimulate glycogen synthesis | 100 mg/day (31 mg elemental vanadium) | Vandurin sulfate preferred form; processed with caution as the US is 1.8 mg/day
Chemoprevention with Berries – continued from page 21

WHAT IS CHEMOPREVENTION?

The term chemoprevention was coined by Michael Sporn et al. in 1976 to define the use of specific natural or synthetic chemical agents to reverse, suppress, or prevent induction and progression to invasive cancer.6 This definition is contrasted with the term chemotherapy used by Professor Paul Ehrlich in the early 20th century to describe a synthetic agent employed to treat disease.5

The early studies in chemoprevention did not emphasize whole foods but rather focused on the effect of specific isolated compounds. Common chemopreventive compounds such as lycopene (in tomatoes), sulforaphane (in broccoli), indoles (in cabbage), and genistein (in soy) have been well studied over the years to better understand their chemopreventive effects. In many of these studies, the isolated compounds did not elicit a more favorable outcome than feeding the whole food and in many cases, these compounds at high doses were either cancer promoters, cancer inducers, or were found to be toxic.6,7 Emerging research is now indicating that chronic, low level doses of these compounds administered intact in whole foods elicit a better chemopreventive outcome than administering high doses of a single agent. Consequently, the term chemoprevention has evolved to include the administration of naturally occurring entities in the diet, including whole foods.5 According to the American Cancer Society and numerous epidemiologic studies, approximately 85% of human cancer is caused by exposure to external factors such as chemical carcinogens in tobacco smoke, chemical pollutants in air, water, food, drugs, radiation, dietary constituents, and infectious agents.3,9-14 Interestingly, family history of cancer accounts for only 5% to 8% of all cancers in the United States.3 Cancer risk from the aforementioned environmental carcinogens is strongly influenced by many factors, including genetics, age, ethnicity, sex, immune function, pre-existing disease, and level of nutrition.15 Chemoprevention has been successfully achieved in numerous animal experiments over the past 25 years, and has been validated in several major clinical trials.16-18 As Sporn et al. indicate, the logical approach to controlling cancer is to prevent the complex series of events before the cells have become committed to form invasive and metastatic malignancies.17

WHY BERRIES?

Over 20 years ago, Palmer and Bakshi demonstrated that ellagic acid inhibited chemical carcinogenesis.19 Shortly thereafter, Dixit et al. demonstrated inhibition of DNA adducts and benzo(a)pyrene metabolism, and Chang et al. demonstrated inhibition of tumors in mouse skin by ellagic acid.20,21 Subsequently, Daniel, Stoner, and colleagues searched for foods containing high concentrations of ellagic acid in hopes of finding foods with chemopreventive activity.22 During this investigation, Daniel and Stoner found that a number of nuts and fruits had high concentrations of ellagic acid, with the highest concentrations in black raspberries, strawberries, cranberries, walnuts, and pecans. Consequently, numerous studies with ellagic acid ensued.21-23-27 After the finding that berries contained high concentrations of ellagic acid, Stoner and colleagues conducted numerous studies with black raspberries and strawberries for prevention of aerodigestive tract cancers.6,8,20,22,27,29,41,59-64 In addition to the ellagic acid content, there are numerous reasons why berries are attractive chemopreventive agents.

1) Berries are a rich source of polyphenolic compounds: Berries contain a number of highly active phytochemicals, most notably, the polyphenols (bioflavonoids, phenolic acids), as well as carotenoids (b-carotene, zeaxanthin, lutein), and phytosterols (b-sitosterol, campesterol).28 Berries are also abundant sources of known nutrients and micronutrients such as vitamins A, C, E, iron, zinc and magnesium; and fiber in the form of lignin and cellulose. The pharmacologic effects of these nutrients are well documented.29 For example, calcium and adequate folic acid supplementation are protective against colon cancer in humans.30,31 Additional epidemiologic studies have shown strong associations between selenium uptake and reductions in liver, esophageal, colon, skin, and prostate cancers.32-33

2) Berries demonstrate anticarcinogenic activity: Numerous experimental studies in animals have shown that polyphenols in general, and berries specifically, exhibit antimutagenic and anticarcinogenic effects.29 The anti-inflammatory, anti-proliferative, and anti-oxidant properties of berries illustrate just three of the potentially numerous mechanisms of action whereby berries exert their effects. Other than the mechanisms discussed previously,
berries prevent DNA damage and modulate Phase I and Phase II enzymes. Together, these mechanisms are involved in the prevention of the initiation and promotion/progression stages of carcinogenesis.

3) Berries provide a food-based approach to cancer prevention and health maintenance and promotion: As Potter and Liu describe, berries provide a natural ‘polypharmacy’ whereby several bioactive compounds are ingested at once. This is beneficial not only for anti-cancer benefits, but also for chronic diseases in general.

BIOACTIVE COMPONENTS IN BERRIES

The most abundant bioactive components of berries belong to one of the most widely studied classes of phytochemicals – the polyphenols. Polyphenols are ubiquitous in nature and undoubtedly plentiful in a fruit-based diet. From a plant physiology standpoint, polyphenols are of great interest since they contribute to the morphology of the plant (i.e., colored pigments) and are involved in plant growth and reproduction. They also protect crops from bacterial and fungal infections and provide plants with a defense mechanism to protect against insect infestation. To do this, polyphenols can act as phytoalexins (where they create physical and chemical barriers to protect the plant) or increase food astringency, making the food unpalatable. Polyphenols can be divided into several different subclasses (i.e., simple phenols, benzoquinones, stilbenes, lignins, flavonoids) depending on their basic chemical structure. While epidemiological evidence suggests a protective effect of polyphenols from fruits and vegetables on human cancer, the majority of human evidence for an inverse association with vegetable and fruit consumption comes from case-control studies.

Polyphenols are not only found in fruits, but also in roots, stems and leaves (i.e., tea polyphenols, soy isoflavones) and are found in common foods including dark chocolate, olives, whole grains, legumes, and red wine. The three major classes of polyphenols are the phenolic acids (ellagic acid, gallic acid, chlorogenic acid), bioflavonoids (isoflavones, catechins, quercetin, kaempferol), and the complex polyphenols. Other large classes of polyphenols are categorized as stilbenes (resveratrol) and coumarins.

Phenolic Acids are derived from benzoic (i.e., gallic) and cinnamic (i.e., p-coumaric, ferulic, chlorogenic) acids. Berries contain high concentrations of ellagic acid at 2 mg/g dry weight of the berry. Most (70%) of the ellagic acid is found in the seed of the berry (only 0.1 mg/g in the pulp) in the form of ellagitannins that yield ellagic acid when hydrolyzed.

Flavonoids represent the most abundant group of polyphenols, which are divided into 13 classes containing more than 5000 compounds; large majorities are still unknown and new compounds are constantly being identified. The functionality of flavonoids in plants is broad – they serve as antioxidants, protect against UV damage, and have been shown to alter the metabolic activation of carcinogens and to have preventive effects in vivo.

It has been estimated that two thirds of the polyphenols in our diet are derived from the flavonoids and only one third from the phenolic acids. An important subgroup of flavonoids are the anthocyanins. Black raspberries contain approx 15 - 20 mg/g of flavonoids in the form of anthocyanins, which give the berries their intense purple/blue color. Overall, the anthocyanins appear in relatively high concentrations in the U.S. diet, with estimates of daily intake at 180 - 215 mg/day. When contrasted with other dietary flavonoids such as genistein, quercetin, and apigenin, an estimated intake of 20 - 25 mg/day was reported.

The composition of plant polyphenols is influenced by a number of factors – from growth and development, to stage of maturation (i.e., ripe fruits have higher anthocyanin concentrations, and phenolic acid concentrations are highest when fruits are green), to genetics/type of cultivar, and effect of storage. Because the polyphenolic profile is dependent on so many factors, standardization is extremely complex and difficult, resulting in different determinations in various experimental studies. This may be the reason why there are large differences in composition of active compounds in herbal and fruit preparations that are available on the market today. One of the bioassays developed to determine the level of antioxidant capacity in a variety of fruits and vegetables is the Oxygen Radical Absorption Capacity (ORAC). The ORAC assay is utilized to evaluate the antioxidant activity of different fruits, vegetables, extracts, and tea.

Complex polyphenols can be grouped into hydrolysable and nonhydrolysable (condensed) tannins. Black raspberries contain hydrolysable tannins with only small amounts of condensed tannins, whereas other fruits (i.e., strawberries) may contain equal portions of both. Grapes and Japanese persimmons primarily contain condensed tannins in the form of proanthocyanidins.

CHEMOPREVENTION OF THE CARCINOGENESIS PROCESS BY BERRIES

Cancer is an extremely complex biologic process. The development of a malignant tumor begins with one or more normal healthy cells that are altered and begin the cascade to an abnormal growth, eventually leading to a malignant tumor. Successful implementation of chemoprevention hinges on an in-depth understanding of the many exogenous (environmental) and endogenous (genetic, hormonal, and immunological) factors, as well as the complex cellular, genetic, and biochemical mechanisms that comprise the carcinogenesis process.
The multi-step process of carcinogenesis has been detailed in numerous articles and demonstrates a biologic phenomenon that cancer progression proceeds through a series of distinct stages, which may be reversed or suppressed at any of the various points.\textsuperscript{17,18,55,56} This multistage process consists of 1) initiation 2) promotion and 3) progression.

\textit{Initiation} begins when the DNA in a cell or population of cells is damaged by exposure to chemicals and/or oxidative stress.\textsuperscript{57,58} If this damage is not repaired, it can lead to genetic mutations and genomic instability. It is estimated that most adults have initiated cells. Once a cell is initiated it, it may or may not result in the formation of a tumor (this stage is reversible) and the tissue appears normal.

\textit{Promotion} is the stage in between initiation and the development of a premalignant lesion and is also generally reversible. The promotion stage is defined by a condition whereby initiated cells begin to proliferate out of control. Inflammation frequently increases cell proliferation and is involved in the promotion stage. Both intra and inter cell signaling are also affected causing cells to lose their ability to communicate with one another and with themselves. As a result, damaged cells do not die as they are supposed to do (programmed cell death or apoptosis) and a benign tumor or cluster of abnormal cells (i.e., colon polyp, oral leukoplakia) develops.

\textit{Progression} is characterized first by dysplasia and ultimately by invasion and metastasis due to additional genetic or epigenetic alterations (such as loss of tumor suppressor function or activation of oncogenes) and progressive genomic instability. The population of initiated and promoted cells ultimately becomes a malignant tumor. Rather than occurring in these three distinct stages in a predictable order, human tumors are best characterized as an accumulation of cells in various stages that participate in the formation of a tumor. As Sporn et al. indicated, this complex process will probably require the action of multiple pharmacological agents to prevent end-stage disease and it is unlikely that a single ‘magic bullet’ will ever be found that can prevent malignancy.\textsuperscript{17}

Progress to date in the carcinogenesis field has revealed several points of intervention that may be amenable to mechanism-based prevention strategies.\textsuperscript{56} Initiation of tumor cells may occur between birth and the time that a precancerous lesion is detected. This is the best place for intervention, i.e., prevent the premalignant lesion from ever developing. As Hursting et al. indicate, possible ways of interfering with tumor initiation include the following: 1) modifying carcinogen activation 2) enhancing the detoxification process 3) enhancing the DNA repair processes.\textsuperscript{56}

Possible ways of blocking promotion/progression include: 1) scavenging of ROS 2) altering the expression of genes involved in cell signaling – particularly those regulating cell proliferation, apoptosis, and differentiation 3) decreasing inflammation.\textsuperscript{56}

Studies conducted by Stoner et al., at the Ohio State University Comprehensive Cancer Center and School of Public Health, demonstrate that berries prevent specific steps in the carcinogenesis process (initiation, promotion, progression).\textsuperscript{59-63} The main objective of these preclinical studies was simply to learn if berries could intervene in the steps associated with the carcinogenic process by either slowing down or inhibiting cancer development. In these studies, a standardized preparation of freeze-dried berries was used. Each berry preparation was of the same cultivar, grown in the same soil conditions each year, harvested at the same degree of ripeness, washed and frozen within two to four hours of picking, and freeze-dried under conditions that preserve the components in the berries.\textsuperscript{41}

\textbf{Colon studies:} In studies using freeze-dried black raspberries and strawberries, esophageal tumors were initiated using n-nitrosomethylbenzylamine (NMBA). When berries were fed at 5% and 10% in the diet for two weeks prior to NMBA treatment, and throughout a 30 week period (a complete chemoprevention study), they significantly inhibited tumor numbers by up to 56\%\textsuperscript{,60,61} This study demonstrated that berries inhibit events associated with cell initiation and promotion/progression. In a “post-initiation” scheme, whereby the berries were fed after the tumor was initiated, berries inhibited tumor progression as evidenced by the reduction in the number of tumors and precancerous lesions that developed. Specifically, the freeze dried berries significantly reduced tumor incidence, tumor multiplicity and pre-neoplastic lesion development, as well as reducing cell proliferation.\textsuperscript{60,61} Studies were simultaneously conducted to determine the effect of berries on molecular events involved in the carcinogenic process. A significant reduction in O\textsuperscript{-}methyl guanine levels (a common DNA adduct) was found, suggesting that one or more components in black raspberries and strawberries influence the metabolism or the binding of the carcinogen to DNA.\textsuperscript{60,61}

In addition to the above parameters, other molecular mechanisms have been identified that are modulated by berries including...
reductions in cyclooxygenase-2 (COX-2), nuclear factor kappa beta (NFKb), activating protein-1 (AP-1), Caspase 3, vascular endothelial growth factor (VEGF), c-jun, and inducible nitric oxide (iNOS).63,64

TAKE HOME MESSAGE

One of the biggest obstacles to cancer prevention is the common misconception that people consider themselves healthy until they have an invasive cancer or sign of overt disease. Failure to detect the earliest stages of disease results in a failure to use sensible preventive measures.16,18,65 These failures often stem from inaccessibility to medical care, lack of education, and economic conditions. Ultimately, prevention produces an increased quality of life whereas treatment of end-stage disease results in the opposite effect.17 When considering chemopreventive strategies for the general population, a range of options exist. At one end of the spectrum a reductionist approach is used, in which high levels of isolated compounds – either synthetic or natural (i.e., vitamins, minerals, b-carotene) - are administered. At the other end of the spectrum, an intent to treat (i.e., pharmacologic or herbal supplements with unspecified activity) approach is used. It is the opinion of its author that the void in the middle of this spectrum can and should be filled with a whole food-based approach. As research progresses and more is learned about the role of polyphenols, carotenoids, and other promising bioactive agents, a food-based approach to cancer prevention is a viable and extremely valuable prevention strategy. Over the years, the National Cancer Institute (NCI) has recognized the importance of chemoprevention and has since made it a top priority with more than 400 potential agents currently under investigation. While it may be premature to formulate public health guidelines regarding specific fruits, it may be reasonable to suggest that one to two of the recommended five to nine daily servings of fruits and vegetables come from berries. While the research reviewed in this article indicates that the amount of fresh berries required to achieve adequate concentrations for significant chemopreventive outcomes would be one to two cups per day, the use of freeze-dried berries provides a simple and safe alternative.61 Additionally, the use of freeze-dried berries creates numerous novel delivery methods (i.e., sprinkle on yogurt, bake in muffins, blend in smoothies) that achieve the same concentrations with less volume. It is also important to encourage patients and clients to think outside the box when attempting to include berries in their diet. Some examples include: 1) Adding strawberries to salad or salad dressings (roasted asparagus with raspberry vinaigrette) 2) Pairing berries with meat or fish (curried halibut with strawberry relish) 3) Including berries in sauces and salsas (blackberry barbeque sauce, raspberry chipotle sauce) 4) Using berries in beverages (homemade strawberry lemonade, agua fresca). Freeze dried berries are commercially available through several retailers and on-line catalogs.
The chances that you have known someone with cancer are high. Cancer of all kinds is the #2 cause of death in the US. Chances are also high that each person you’ve known with cancer has undertaken a conventional course of treatment. Some of those people have, however, also investigated complementary and alternative cancer treatments. Complementary modalities available help to alleviate the toxic effects of chemotherapy (through supplementation for example) and to mitigate the emotional aspects of cancer (through yoga for example), among other modalities. Others have chosen the alternative route as a substitute for the modern course of cancer treatment. Supporters of alternative cancer treatments welcome these options. Modern, or conventional, cancer treatments for specific types of cancer vary little among institutions, neglecting the importance of individual responses to treatment. Complementary and alternative methods do away with protocol and take a fresh look at treating our nation’s #2 killer.

Interest in complementary and alternative cancer treatments has sparked many hospitals to add practitioners or departments that specialize in complementary and alternative medicine. The patient’s access to these options varies on the belief system of the individual’s oncologist’s and the level of communication of the healthcare facility itself. This article highlights several facilities that provide complementary and alternative treatments as primary options by several allopathically trained physicians. Each facility has a different model of care but the goals of these facilities are similar – work with the patient, rather than the disease as a substitute for the modern course of treatment. Supporters of alternative cancer treatments welcome these options. Modern, or conventional, cancer treatments for specific types of cancer vary little among institutions, neglecting the importance of individual responses to treatment. Complementary and alternative methods do away with protocol and take a fresh look at treating our nation’s #2 killer. Complementary modalities available help to alleviate the toxic effects of chemotherapy (through supplementation for example) and to mitigate the emotional aspects of cancer (through yoga for example), among other modalities. Others have chosen the alternative route as a substitute for the modern course of cancer treatment. Supporters of alternative cancer treatments welcome these options. Modern, or conventional, cancer treatments for specific types of cancer vary little among institutions, neglecting the importance of individual responses to treatment. Complementary and alternative methods do away with protocol and take a fresh look at treating our nation’s #2 killer.

### Member Benefit

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### CAM Cancer Facility Options

**Laura W. Lagano, MS, RD**

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immune system, and help conventional cancer treatments work more effectively.

The center of a second facility’s model is patient care based on the philosophy of disciplined gradualism. After diagnosis the practitioners begin with the least invasive, least damaging approaches to care. Encouraging a partnership, the patient is empowered with knowledge to make decisions about treatment progression. According to the center’s researchers, “The best cancer care strives not only to increase tumor-killing potential with prudent use of anticancer agents like chemotherapy, but also to prevent damage to healthy tissue through nutritional intervention, complementary mind-body therapies, and the use of specific supplements as directed by our physicians and registered dietitians.”

The model used by a third facility is sound therapy, which has its basis in vibrational medicine. Think of the ultrasound procedures used in physical therapy. In addition to sound therapy, nutritional interventions including dietary changes, supplementation, mushroom extracts, omega-3 fatty acids, and botanicals are incorporated. Every level of the body’s healing processes – physiological, genetic, psychosocial, and spiritual – is the focus used to create an optimal state of well-being. For more information about vibrational medicine, also known as energy healing with its basis in Chinese medicine, consult Vibrational Medicine by Richard Gerber.

The fourth facility to be reviewed is a network of treatment hospitals and facilities located across the United States

Patient Empowerment Medicine (PEM) is at the buzzword at these facilities. PEM is a philosophy that puts patients first and in the center of their care. Patients partner with doctors and other professionals who teach, guide, and encourage them to participate at the patient’s comfort zone. The cancer treatment experience, it is believed, comprises much more than the treatments themselves. Variables including the expertise of the healthcare provider, the method of treatment administration, and the surroundings in which the treatments play a critical role in patient outcomes. These facilities focus on the whole person impact of cancer and how the cancer experience affects people physically, emotionally, and spiritually.

For up-to-the-minute information about alternative cancer treatments consult the Moss Report (www.cancerdecisions.com). A former science writer and director of public affairs at Memorial Sloan-Kettering Cancer Center, Ralph Moss is considered one of the most knowledgeable writers on alternative cancer treatments. Moss has a scientific advisory board of several well-respected cancer practitioners including Keith Block and Mitchell Gaynor. Also on his board is someone familiar to NCC members – James Duke, noted botanist and author of The Green Pharmacy.
Herb Clips

Once again we are pleased to present the following HerbClip™ as a courtesy of the American botanical Council’s (ABC) special relationship with Nutrition In Complementary Care (NCC), a dietetic practice group of American Dietetic Association. A benefit of ABC membership, HerbClip is a publication of summaries and critical reviews of seminal articles culled from scientific and medical journals, newsletters, government documents, special reports, and mainstream media. Through this service, ABC provides valuable information about compelling issues that influence the research, marketing, and responsible use of medicinal plants. This and more than 2,700 other HerbClips are available in online and print editions as a benefit of ABC membership at the Academic Member level and higher. As an NCC member you can now receive a 33% discount off a Professional Membership to ABC for one year (a $150 value for $100) plus a free copy of The ABC Clinical Guide to Herbs (a $69.95 value, which provides 12 hours of continuing education credit for Registered Dietitians). Join the 3,000 other individuals, companies, agencies, and organizations around the globe and become a member of ABC today by calling 800-373-7105 and mention your membership in NCC.

Wayne Silverman, PhD, Chief Administrative Officer, American Botanical Council
Laura W. Lagano, MS RD, Publications Chair, Nutrition in Complementary Care

Effects of Ginkgo Use on Metformin Pharmacokinetics in Diabetic and Non-Diabetic Subjects

Kudolo GB, Wang W, Javors M, Blodgett J.


One of the most popular herbal supplements is ginkgo (Ginkgo biloba) extract. Ginkgo is usually ingested for its beneficial cognitive effects to enhance mental acuity and to help enhance memory, and, secondarily, for its peripheral circulatory effects. However, the focus of this trial was to evaluate the effect of ginkgo ingestion on metformin in diabetic and nondiabetic patients.

In a previous study, the authors showed that the ingestion of a single dose (120 mg) of a generic ginkgo extract for 3 months resulted in an increase in pancreatic β-cell function and a decrease in collagen- and arachidonic acid–mediated platelet aggregation and thromboxane B2 synthesis. [Twenty volunteers at the University of Texas Health Science Center in San Antonio took 120 mg of a 50:1 standardized ginkgo extract, with guaranteed chemical standardization of 24% ginkgo flavone glycosides and 6% terpenes (Walgreens Co., Deerfield, IL). The volunteers took ginkgo at bedtime each day for three months, and each served as his or her own control. See HC 010919-196] Type-2 diabetic patients usually have hyperactive platelets which lead to a high tendency to form blood clots (thrombi) in the tiny blood vessels. Thus diabetic subjects are prone to the development of heart attacks and stroke. Low-dose aspirin is now recommended for the prevention of platelet hyperactivity, which leads to inhibition of thromboxane B2 formation, makes the blood more fluid and free-flowing to prevent both first and secondary heart attacks. They also showed that ingestion of the ginkgo extract might improve platelet function in patients with type-2 diabetes mellitus (T2DM). Because of the increasing popularity of ginkgo and the increasing prevalence of T2DM, a strong possibility exists that ginkgo extracts and diabetes medications will be co-ingested. Thus, the objective of this study was to determine whether the ingestion of a ginkgo extract [described as containing 24.7% flavone glycosides (12.6% quercetin, 10.1% kaempferol, and 2.0% isorhamnetin) and 6% terpenes (4.3% ginkgolide A, 3.3% ginkgolide B, 0.09% ginkgolide C, and 2.4% bilobalide)] in conjunction with metformin—a drug used to treat type-2 diabetes—would alter the pharmacokinetics and efficacy of metformin (Glucophage®, Merck, licensed in US to Bristol-Meyers Squibb).

Twenty subjects (n = 12 women and 8 men), 10 with normal glucose tolerance (NGT) and 10 with T2DM, were enrolled in this randomized, double-blind, placebo-controlled crossover study, which was conducted at the Frederic C. Barter General Clinical Research Center of the South Texas Veterans Health Care System (San Antonio, TX). The subjects ingested either an alfalfa (Medicago sativa)-based placebo or a single dose (120 mg) of ginkgo extract daily for 3 months in each arm of the study. The subjects returned to the research center monthly to provide blood samples and to complete questionnaires. At the end of each 3-month treatment period, the subjects returned to the research center to undergo the pharmacokinetic studies. The subjects fasted overnight and then the NGT subjects ingested a single dose of 500 mg metformin, and the T2DM subjects ingested their prescribed dose of metformin (250–850 mg per day) plus 120 mg ginkgo extract. Blood and urine samples were collected over 8 hours from both the NGT and T2DM subjects and for the first 2 hours of the next 3 days from the T2DM subjects. Hematologic, lipid, glucose, and insulin concentrations were measured, and renal function was tested.

The ingestion of ginkgo extract for 3 months had no significant effect on renal function or lipid, glucose, insulin, or hematologic concentrations in either group, except for a significant decrease (from 7.7 ± 1.2% to 7.2 ± 0.9%; P < 0.05) in glycated hemoglobin concentrations in the T2DM subjects. The ingestion of ginkgo extract did not significantly affect the urinary excretion rate of metformin in either group; however, metformin excretion decreased significantly with ginkgo extract ingestion in those subjects who consumed 850 mg metformin. The ingestion of ginkgo extract did not significantly affect any of the pharmacokinetic variables of metformin measured in either the NGT or T2DM group, except for a significant increase (from 0.117 ±
0.085 to 0.141 ± 0.100; P < 0.05) in the elimination rate in the T2DM group.

The results indicate that the ingestion of 120 mg of ginkgo extract did not significantly affect the clinical variables measured, and co-ingestion of this extract and metformin had no significant effect on the pharmacokinetic variables measured at a metformin dose of 500 mg or less. The authors conclude that ginkgo extract does not produce insulin resistance in NGT subjects or exacerbate the condition in those with impaired glucose tolerance or T2DM. Thus, “it appears that it is probably safe to co-ingest ginkgo extract with metformin.” However, the authors note that it cannot be predicted how doses larger than 120 mg per day will interact with the doses of metformin evaluated in this study (i.e., 250–850 mg per day).

It bears emphasis that the authors used the term “EGB 761,” a registered trademark of Willmar Schwabe Pharmaceutical Co., Karlsruhe, Germany), in the title of and throughout this article to describe the preparation studied in this trial. The true EGB 761® is the world’s first and leading standardized extract made from the ginkgo leaves and is the subject of over 100 published clinical trials covering mainly the effects of EGB 761 on cognitive functions in normal and cognitively-impaired adults as well as effects on peripheral circulation, e.g. peripheral arterial occlusive disease (a.k.a. intermittent claudication). This patented ginkgo extract is licensed as a medicine and/or sold as a dietary supplement in many countries. In a personal communication with the primary author (GB Kudolo, 2006), Mark Blumenthal (Founder & Executive Director of the American Botanical Council) confirmed that a generic extract of ginkgo provided by Whole Health Nutrition (Edmonds, WA) was actually employed in this trial; thus, the term “EGB 761” should not have been used in this article. Kudolo stated that the extract in this study “contained constituents which compare favorably with the famed standardized 50:1 EGB 761 (of approx. 24% flavonol glycosides and 6% terpenes).” This is however not achieved by the product tested according to the analysis of the product, which was provided by the authors. The extract used contained 10% of the pharmacologically active terpene lactones, which may result in a very different efficacy than achieved by EGb 761. Also the interaction potential might be changed, which means that the results described are valid only for this specific extract, but not for ginkgo extracts in general. In addition, as Blumenthal responded in a letter to the editor of the journal: “such chemical and biological equivalence is not technically possible” because simply relying on attempts to concentrate a ginkgo extract to a 50:1 concentration and to standardize the terpenes (ginkgolides A and B and bilobalides) to 6% and the flavonoids (rutin, quercetin, and kaempferol) to 24% accounts for only approximately 30% of the extract. This obviously leaves 70% of the extract uncharacterized, and no publications in the literature have provided the chemical characterization of this fraction. Thus, it is inaccurate and potentially misleading (obviously not the intent of the authors) to claim that the ginkgo extract used in this study compared favorably with EGB 761, i.e., based solely on these chemical standardization parameters.

Furthermore, Blumenthal asserts in his letter that the alfalfa-based placebo used in this study may have been inappropriate since alfalfa contains nutrients and other phytochemicals that cannot be considered inert; thus, these active ingredients may have produced clinically observable results that may have confounded the statistical comparisons between groups. Kudolo defends the use of the alfalfa-based placebo on the basis that this was a crossover study (i.e., both groups ingested the placebo in different cycles) and that “any change in the outcome could be ascribed to the active ingredient of the Ginkgo extract, rather than to a non-specific plant constituent.”

—Brenda Milot, ELS

Green Tea and Mortality Due to Cardiovascular Disease, Cancer, and All Causes.

Little Association with Reduced Cancer Deaths was Found Kuriyama S, Shimazu T, Ohmori K, et al. Green tea consumption and mortality due to cardiovascular disease, cancer, and all causes in Japan: the Ohsaki study. JAMA. September 13, 2006;296(10):1255-1265.

Tea ranks second to water as the most consumed beverage worldwide. Forms of tea include green, oolong, and black, which originate from the leaves of the plant Camellia sinensis. Green tea polyphenols have been studied in vitro and in animals as a protectant against cardiovascular disease (CVD) and cancer. However, say the authors, the effects of green tea consumption in humans remains unclear. They examined the association between green tea consumption and mortality due to all causes, to CVD, and to cancer within a large population-based cohort study in northeastern Japan.

In the Ohsaki National Health Insurance Cohort Study, the authors delivered a self-administered questionnaire, including items on dietary intake, between October and December 1994 to all national health insurance beneficiaries aged 40 to 79 years living in the catchment area of Ohsaki Public Health Center, Miyagi Prefecture.

The questionnaire included items about the frequency of recent average consumption of 4 beverages (green tea, oolong tea, black tea, and coffee), and 36 items about food, as well as items regarding the consumption of alcohol and tobacco, personal and family history of disease, job status, level of education, body weight, height, amount of time participating in sports or exercise, and time spent walking every day. The frequency of green tea consumption was divided into 5 categories.

Of 54,996 eligible persons, 52,029 (95%) responded. Of those, 40,530 were included in the study analysis. The participants were
followed for as many as 11 years for all-cause mortality and for as many as 7 years for cause-specific mortality.

At baseline, participants who consumed green tea more often tended to be older and were more likely to be unemployed, to engage in sports or exercise, or to have a history of hypertension and diabetes mellitus, and were less likely to spend time walking. Men were more likely to have a history of gastric ulcer and women to be obese. No apparent associations between smoking status or alcohol drinking and green tea consumption were noted.

The participants were followed for mortality and migration. For those who died, the authors investigated cause of death by reviewing the death certificates filed at Ohsaki Public Health Center. Cause of death was coded according to the International Statistical Classification of Diseases and Related Health Problems, Tenth Revision (ICD-10).

During 11 years of follow-up (1995-2005), 4,209 participants died. The authors found that green tea consumption was inversely associated with mortality due to all causes and that the inverse association was more pronounced in women (P=0.03 for interaction with sex).

The multivariate hazard ratios of mortality due to all causes associated with different frequencies of green tea consumptions were reported as follows:-

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 cup/day</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>1-2 cups/day</td>
<td>0.96 (0.87-1.05)</td>
</tr>
<tr>
<td>3-4 cups/day</td>
<td>0.90 (0.82-0.98)</td>
</tr>
<tr>
<td>5 or more cups/day</td>
<td>0.84 (0.77-0.92)</td>
</tr>
</tbody>
</table>

During 7 years of follow-up (1995-2001), the authors report that 892 participants died of CVD and 1,134 died of cancer. The inverse association with CVD mortality was stronger than that with allcause mortality (with the strongest inverse association observed for stroke mortality). The association appeared to be more pronounced in participants who had never smoked. Again, the inverse association was stronger in women (P=0.004 for trend).

The authors reported the following hazard ratios for CVD mortality:

<table>
<thead>
<tr>
<th>Frequency</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Less than 1 cup/day</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>1-2 cups/day</td>
<td>0.87 (0.72-1.06)</td>
</tr>
<tr>
<td>3-4 cups/day</td>
<td>0.77 (0.63-0.93)</td>
</tr>
<tr>
<td>5 or more cups/day</td>
<td>0.74 (0.62-0.89)</td>
</tr>
</tbody>
</table>

The participants who consumed 5 or more cups per day of green tea had a risk of all-cause mortality that was 16% lower (during 11 years of follow-up) and a CVD mortality that was 26% lower (during 7 years of follow-up) than those who consumed less than 1 cup per day.

The authors report that the hazard ratios of cancer mortality were not significantly different from 1.00 in all green tea consumption categories compared with the lowest-consumption category.

Thus, the authors conclude that "green tea consumption is associated with reduced mortality due to all causes and due to cardiovascular disease but not with reduced mortality due to cancer."

—Shari Henson

An independent, nonprofit, international organization, the American Botanical Council (ABC) disseminates information about the responsible use of herbal medicine. ABC serves the public, researchers, educators, industry, and media, as well as healthcare professionals including dietitians. Since its establishment in 1988, ABC has been a highly-respected resource and an innovative force. In addition to HerbClip and The ABC Clinical Guide to Herbs, ABC circulates its journal HerbalGram and several other publications; provides continuing education materials for healthcare professionals; produces its extensive website www.herbalgram.org; offers internships for health professionals; provides herbal safety information for use on product labels; and conducts seminars, presentations, and workshops by ABC founder Mark Blumenthal, and other staff members. ABC membership and support for individual programs provide the resources to keep serving the needs of the complementary and alternative medicine field.
Chemoprevention with Berries

Objectives for the NCC CPE Newsletter Article: Chemoprevention with Berries

After reading this review article, the nutrition professional will be able to:

1. Define chemoprevention.
2. Compare/contrast chemoprevention and chemotherapy.
3. Identify the three stages of cancer progression.
4. Identify the bioactive components in berries.
5. State the benefit of ‘whole-food’ versus ‘isolated compound’ approach to chemoprevention and health promotion.
6. State the proposed number of berry servings recommended daily.
7. List the ways to include berries in the diet.

Approved for 1 CPE credit.

Questions:

Questions 1 and 2 are based on the following scenario: A client with a strong family history of colon cancer and a personal history of polyps presents to the office for MNT. This client travels for a living, does not cook, and really is not interested in learning.

1. As part of a low-fat, high fiber diet, it is reasonable to recommend the inclusion of how many berry servings daily?
   A. 3-4  B. 0-1  C. 1-2  D. 5-9

2. What are practical ways of including berries into the meal plan?
   1. Carry freeze-dried strawberries and add to the yogurt served at the hotel breakfast buffet.
   2. Carry dried cranberries and blueberries, and have with the peanuts on the airplane.
   3. Grill salmon flavored with blackberry BBQ sauce.
   4. Make a berry smoothie for breakfast.
   A. All of the above  B. 1, 2, 4  C. 1, 2, 3  D. 1, 2

3. True/False: Chemoprevention is the utilization of synthetic agents alone or in combination with isolated compounds, such as β-carotene, to treat disease.

4. Berries are high in which phytochemicals?
   A. phytoalexins, indoles, genistein
   B. polyphenols, phenolic acids, indoles, ellagic acids
   C. polyphenols—phenolic acids, bioflavonoids, complex polyphenols

5. True/False: The intact berry shows more favorable anti-mutagenic and anti-carcinogenic effect than the isolated ellagic acid.

6. The three stages of carcinogenesis are:
   A. inflammation, oxidation, proliferation
   B. insult, invasion, metastasis
   C. initiation, promotion, progression

Answer Key


PLEASE CIRCLE THE CORRECT ANSWERS:


CPE Reporting Form • FALL 2006 - Nutrigenomics
EXPIRATION DATE: 09/08
Please Print or type

Name: ____________________________
Address: __________________________
ADA Membership #: __________________________
Phone: __________________________
Email address: __________________________
NCC Member  Yes ____  No ____
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This activity has been approved for one hour of CPE credit. You will be notified if hour is not approved.

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