Oncology Nutrition Connection

Oncology Nutrition
a dietetic practice group of the
Academy of Nutrition and Dietetics

A publication of the ON DPG
ON DPG Website
www.oncologynutrition.org

Volume 23, Number 2, 2016
ISSN 1545-9896

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ON DPG Message from the Chair

For this issue of *Oncology Nutrition Connection*'s Message from the Chair, we are highlighting a letter from the Chair of a different DPG, the Clinical Nutrition Management (CNM) DPG. This all began at the ON DPG Breakfast at FNCE 2014, where Elaine Trujillo, MS, RDN, Past Chair of ON DPG and Ann Yaktine, PhD, RD, Director of the Food and Nutrition Board at the Institute of Medicine (IOM), presented ON DPG's plan to hold an IOM workshop to address *Access to Nutrition Care in Outpatient Oncology*. One of our active ON DPG members, Terese Scollard, MBA, RD, LD, also is an active member of CNM DPG. Terese had the tremendous vision to see how our workshop could lay the foundation for improved access to RDs in many settings, not just in outpatient oncology. She had the foresight to invite CNM DPG to support our workshop, and ON DPG was amazed and grateful when CNM pledged some of their hard-earned budget to support *our* workshop. We say "Kudos!" to CNM DPG, and are pleased to share this letter from CNM DPG with you!

To members of CNM DPG and ON DPG,

The quality of operational practices and level of service integration can vary widely among cancer programs. Cancer programs strive for quality; however, there remain inconsistencies within and between programs related to nutritional practices and access. Operational practices can negatively or positively impact patients' nutritional status and outcomes.

Common concerns to both Clinical Nutrition Management and the Oncology Nutrition Practice Group are improving patient access to nutrition care, improving the quality of and timing of nutrition intervention, support for team nutrition care planning for patients, and improvement of access to nutritional services for all cancer patients.

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A publication of Oncology Nutrition (ON), a dietetic practice group of the Academy of Nutrition and Dietetics. ISSN 1545-9896.

Visit the ON DPG website at www.oncologynutrition.org

Editor:
Suzanne Dixon, MPH, MS, RDN
sdixon@umich.edu

Associate Editor:
Jodie Greear, MS, RD, LDN
jodie.greear@gmail.com

Oncology Nutrition Connection (ONC) ISSN 1545-9896, is the official newsletter of the Oncology Nutrition Dietetic Practice Group (ON DPG), a practice group of the Academy of Nutrition and Dietetics, and is published quarterly. All issues of ONC are distributed to members in electronic format only.

Articles published in ONC highlight specific diseases or areas of practice in oncology nutrition. Viewpoints and statements in each newsletter do not necessarily reflect the policies and/or positions of the Academy of Nutrition and Dietetics or ON DPG.

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National standards for cancer nutrition services do not include quality metrics with which to evaluate success or identify improvement activities within cancer nutrition programs. Reports in the literature on practices, staffing levels, and training of professionals are inconclusive, and therefore, challenging for program leadership to identify the best workflows or program practices. Few programs include periodic nutrition risk screening with a validated and reliable screening tool to identify patients who are struggling with nutrition before, during or after treatment. Therefore, patients' nutritional problems and needs may be missed or inadvertently delayed until they result in treatment dose reductions, serious side effects, and inability to heal and recover.

The Oncology DPG has taken the major step to plan for a collaborative workshop with the Institute of Medicine to review the topic of nutrition care in cancer. The CNM DPG, with a common concern for this topic, has allocated $4,000 of member resources to support the IOM Workshop.

Every cancer patient deserves access to quality nutrition care provided by a registered dietitian, embedded in cancer treatment programs. We must be advocates for our patients, and strive for the provision of quality nutrition care within our organizations and our own clinical practice. Attention to the basics of nutrition and hydration lessens suffering, readmissions, delays in treatment, and gives hope to patients and families. For these reasons, the CNM DPG is happy to support this important first step of helping to finance the Nutrition and Cancer IOM Workshop.

We encourage our members to consider donating individually at: https://www.oncologynutrition.org/get-involved/register-to-become-a-member/iom-workshop/

Sincerely,
The Board of the Clinical Nutrition Management Dietetic Practice Group
Caroline Steele, MS, RD, CSP, IBCLC
Chair, CNM DPG 2015-2016

Brief Report: Fluoride Toxicity in Hematopoietic Cell Transplantation

By Kerry McMillen, MS, RD, CSO

Many hematopoietic cell transplant (HCT) patients are treated for invasive fungal infections. First line therapy for fungal pneumonia is voriconazole, which is a fluorinated triazole compound (1). At standard voriconazole dosing, daily fluoride intake may be as high as 62.6 mg. The WHO guidelines document that fluoride intake of >6 mg/day increases risk of skeletal events, such as increased fracture risk, tingling and numbness in extremities, and joint pain (2,3). Because fluoride toxicity symptoms include bone pain and weakness, which also are common in many post-HCT patients, fluoride toxicity may be overlooked.

In an article by Gerber and colleagues, contributors to fluoride-related, clinically relevant skeletal disease in patients on voriconazole treatment include (1):

- Impaired renal function. Gerber et al. noted fluoride levels are inversely correlated to glomerular filtration rate (GFR) (1). Impaired renal function, common with immunosuppressive medications such as tacrolimus, cyclosporine and sirolimus, is associated with higher circulating fluoride levels.

- Prolonged intake. Patients in the Gerber study developed toxicity symptoms between 3 and 7.5 months.
- Individual differences in pharmacogenetics and drug-drug interactions.
- Inflammatory processes, the symptoms of which may be masked when patients are on systemic corticosteroids, commonly used for Graft vs. Host Disease treatment.

Patients complaining of bone pain and weakness on voriconazole should be evaluated for fluoride toxicity. If fluoride levels are high, patients should be counseled to limit dietary and other fluoride sources; choosing fluoride-free toothpaste, avoiding fluoridated water and avoiding eating the bones of fish such as sardines are examples of steps a patient can take to lower fluoride intake. For the majority of patients, symptoms of fluoride toxicity resolve after discontinuing voriconazole. Bone pain resolves rapidly and skeletal disease resolves over time (1).

It is important to include fluoride toxicity in the differential of post-HCT patients on voriconazole presenting with bone pain and/or weakness, especially with concomitant renal insufficiency. Identifying fluoride toxicity early will allow the dietitian to adequately counsel the patient regarding appropriate medical nutrition therapy to limit fluoride exposure.

Kerry McMillen, MS, RD, CSO is a Clinical Dietitian with the Seattle Cancer Care Alliance in Seattle, Washington.

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Pediatric Oncology Nutrition Corner: Critical Differences in Pediatric and Adult Cancers

By Nancy Sacks, MS, RD, LD and Chelsea Schulman, MS, RD, LDN

Introduction

Cancer is the leading cause of death by disease among children in the United States (1). Leukemia, brain, and other central nervous system (CNS) tumors account for more than half of new diagnoses of major childhood cancers. Advances in treatment for childhood cancer, along with supportive care and participation in clinical trials, have improved survival. The combined five-year survival rate for all childhood cancers has improved from less than fifty percent prior to the 1970s to eighty percent currently (2-4). As of 2010, an estimated 379,112 survivors of childhood cancer were living in the United States (5). Approximately 24 percent of these childhood cancer survivors are living more than thirty years after their diagnosis, thus contributing to the growing number of long-term survivors (6).

Current therapies for pediatric cancer include surgery, radiation, chemotherapy, and hematopoietic cell transplantation, all of which may result in side effects that adversely impact nutritional status (7-10). Cancer and the associated treatment can affect growth and development (weight loss/gain and attainment of appropriate linear growth) and contribute to altered body composition. The childhood cancer survivorship population is unique, and interpretation of indices used to assess nutritional status in healthy children and adults may not accurately reflect nutritional status because of abnormal growth secondary to treatment.

Childhood Cancer Compared to Adult Cancer

The classification of childhood cancers differs from adult cancers. Unlike adult cancers, which are usually tabulated by primary site, childhood cancers are classified by histologic type and primary site based on the International Classification of Childhood Cancer (ICCC) criteria (Fig 1) (11). The predominant types of pediatric cancers (0-19 years old) are leukemia (26%), cancers of the brain and central nervous system (CNS) (18%), and lymphoma (14%) (12), which together comprise roughly 60% of childhood cancer cases. Less common histologic types and sites make up the remaining 40% of childhood cancer cases; it is important to note exact percentages for disease types differ when cases are separated by age for children (0-14 years old) and adolescents (15-19 years old) (Fig 2) (12).

Figure 1. International Classification of Childhood Cancer (11)

Leukemia
Lymphomas and Reticuloendothelial Neoplasms
Central Nervous System (CNS)
Sympathetic Nervous System Tumors
Retinoblastoma
Renal Tumors
Hepatic Tumors
Malignant Bone Tumors
Soft-Tissue Sarcomas
Germ-Cell, Trophoblastic and other Gonadal Neoplasms
Carcinomas and other Malignant Epithelial Neoplasms
Other and Unspecified Malignant Neoplasms

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Among adults, the leading new cancer cases are prostate cancer (27%) for males and breast cancer (29%) for females. Lung and bronchus cancer (14%) is the second leading cancer type and colon and rectum is the third (12).

The etiology of most pediatric cancers currently is unknown, but is hypothesized to be related to genetic mutations, similar to adult cancers (13). These mutations lead to rapid and uncontrolled cell growth, eventually resulting in cancerous cells. Increased cancer risk is associated with familial syndromes and genetic abnormalities including Li-Fraumeni syndrome, Beckwith-Wiedemann syndrome, Fanconi anemia syndrome, Noonan syndrome, von Hippel-Lindau syndrome, and Down syndrome (14). Children with Down syndrome are 10-20 times more likely to develop leukemia than children without Down syndrome; however, only a very small proportion of childhood leukemia is linked to Down syndrome (15). In childhood cancers, about five percent are due to gene mutations that are inherited. One example is the inherited mutation of the RB1 gene, which causes 25-30% of the retinoblastoma cases in children (12). However, retinoblastoma only accounts for three percent of childhood cancers overall. Much more research on the genetic and environmental causes of childhood cancers is needed.

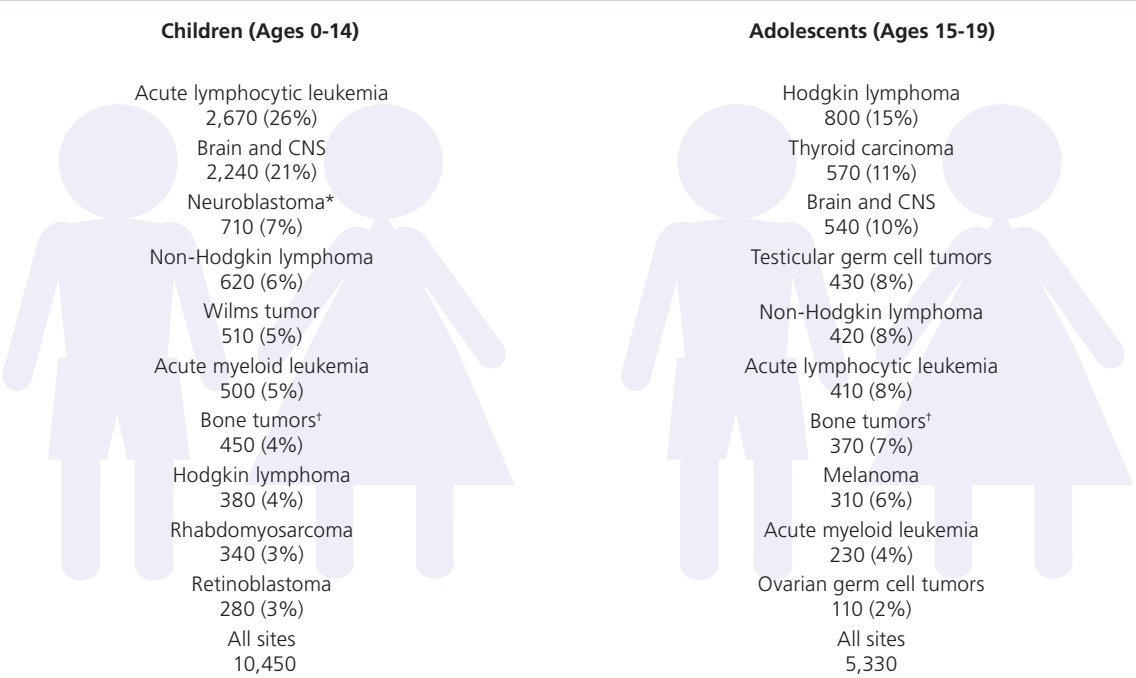
Genetic mutations that cause cancer also can arise during the development of a fetus in the womb. For example, one in every 100 children is born with a genetic abnormality that increases the risk for leukemia, although only one child in 8,000 with that abnormality actually develops leukemia (16). Given these statistics, it is clear that genetic risk factors may be necessary, but not sufficient to cause any case of childhood cancer. Furthermore, environmental factors are difficult to identify due to the rarity of childhood cancer. It is difficult to accurately assess environmental exposures occurring during early prenatal and fetal time periods, and into childhood as well (17).

Compared with children, the incidence rate of adult cancer is much higher. According to the National Cancer Institute's Surveillance, Epidemiology, and End Results, 2,053 out of 100,000 adults over forty years of age living in the United States were diagnosed with cancer each year from 2001-2007 (4). In that same timespan, only 32 out of 100,000 American children (0-14 years of age) developed cancer. In adults, environmental causes of cancer are better understood compared with childhood cancer, because childhood cancers are rare and the environmental exposures from prenatal to post-birth are difficult to ascertain accurately (18). In adults, risk factors such as tobacco use and secondhand smoke exposures, asbestos, and ultraviolet radiation are commonly known to cause cancer. This type of causal pathway has not been defined for most childhood cancers.

Incidence and Mortality Trends

The overall incidence for childhood cancer among all sites increased by 0.6% per year between 1975 and 1990 (12,19). However, incidence varies by cancer site and is

Figure 2. Estimated New Cases of Childhood and Adolescent Cancer, United States, 2014



Estimates are for malignant cancers only and are rounded to the nearest 10. In addition, 730 children and 630 adolescents will be diagnosed with benign and borderline brain tumors in 2014.
CNS = central nervous system
* Includes ganglioneuroblastoma.
†Bone tumors include osteosarcoma and Ewing sarcoma.

highest for acute lymphocytic leukemia (ALL) and brain/CNS cancers (Fig 3). Also of note is the increasing incidence of acute myeloid leukemia (AML), non-Hodgkin's lymphoma (NHL), and testicular germ cell tumors. More positively, the overall mortality rate for all childhood cancers has continued to decline annually from 1975-2010, with the most dramatic decrease in mortality rates seen for ALL and brain/CNS cancers (12). The improvement in survival rates for children and adolescents with cancer is shown in Figure 2.

Advances in treatment for childhood cancer, supportive care, and the high proportion of patients participating in clinical trials have resulted in improvements in survival (20). Although survival rates vary by cancer type, overall, more than eighty percent of pediatric oncology patients diagnosed with cancer live at least five years after their initial diagnosis, with an estimated 363,000 survivors of childhood cancer living in the United States as of 2009 (4,18). Important differences in survival exist between pediatric and adult cases of certain cancer types that occur more commonly in children. The 5-year survival rate for ALL in children, for example, is greater than 85% (21). For adults with ALL, survival is strongly associated with specific molecular and genetic factors, though the overall 5-yearsurvival rate for the group as a whole is much lower, at around 40% (22).

Approximately 24% of these childhood cancer survivors have survived more than thirty years since their diagnosis, joining the growing number of long-term survivors of childhood and adult onset cancer in the United States (6).

Nutrition Status in Cancer Patients and Survivors

At diagnosis, the incidence of malnutrition, also called undernutrition, in children with cancer ranges from 8-60%, depending on cancer type, stage of disease, and the criteria used to determine nutritional status (8). The nutrition indices used to document malnutrition are based on age and specific criteria related to expected growth rates: for ≤2 years (<10th percentile in weight for length) (23) and for >2 and ≤20 years (<5th percentile of BMI for age and sex) (24). The incidence of malnutrition increases during treatment and is related to the multi-modal nature of therapy (25,26). Malnutrition has been associated with increased risk of infection, treatment toxicity, higher incidence of relapse, decreased rate of survival and poor tumor response to therapy (8, 27-29). Suboptimal nutritional status, particularly when a child is very young, can affect a child's ability to reach maximal cognitive and physical growth even after therapy is completed (8).

The Childhood Cancer Survivor Study (CCSF) is a retrospective cohort study that tracks the health status of adults who were diagnosed with childhood cancer between 1970 and 1986 and compares the results with those of their siblings. Findings from the CCSS reported that two out of three survivors (at least five years post-diagnosis) develop a chronic health condition, and more than one-third develop a condition that is severe or life-threatening (30). Nutritional status and growth can be affected by many factors in children with cancer. It is well known that multi-modal cancer treatment can have acute effects and chronic late effects in childhood cancer survivors. Cancer and its treatment can impact hormones, growth rates, and contribute to altered body composition (31). The survivorship population is unique, and interpretation of indices used to assess normal growth in children and nutritional status in adults can be challenging. These population norms may not provide an accurate assessment of nutritional status for childhood cancer survivors. The late effects of treatment can progress into adulthood, therefore requiring multi-disciplinary teams to monitor and manage medical conditions long term (32).

Available Resources

The Pediatric Subgroup of the Oncology Nutrition Dietetic Practice Group (ONDPG) is dedicated to providing direction and leadership for quality pediatric oncology nutrition practice through education, research, and identification of reputable resources, some of which are identified here. The Academy of Nutrition and Dietetics Pediatric Nutrition Care Manual offers specific oncology-related guidance for practitioners (33). Topics covered include nutritional management of nausea and vomiting, nutrition therapy and support, survivorship, and other key areas. The Children's Oncology Group (COG), a National Cancer Institute supported clinical trials group, is the world's largest organization devoted exclusively to childhood and adolescent cancer research (34). The COG encompasses more than 9,000 childhood cancer experts from treatment and research facilities all over the world. More than 90% of children diagnosed with cancer annually are treated at a COG institution. With a growing number of childhood cancer survivors living into adulthood, it is important for oncology practitioners to have the available resources necessary to care for these children and best manage the late effects related to cancer treatment.

We have recently formed the Pediatric Subunit group within the ONDPG, which will focus on the pediatric oncology population and childhood cancer survivors. The Subunit has identified projects that may help best meet the needs of Registered Dietitians Nutritionists (RDNs) working in this area. In the near future, the Pediatric Subunit will be reaching out to you for your support and ideas. A webinar on Nutrition and the Pediatric Oncology Population, sponsored by the Academy and ONDPG, was presented on May 12, 2015, and is available on the ON DPG website for members to review. This webinar provides an excellent overview and a wealth of resources and references. The next resource that the Pediatric Subgroup will release is a list of references and resources including websites, books and additional information for RDs working in this field. The Pediatric subunit will update this resource list quarterly. We are interested in hearing about topics of interest to you, the ON DPG membership and any RDN working with pediatric cancer survivors.

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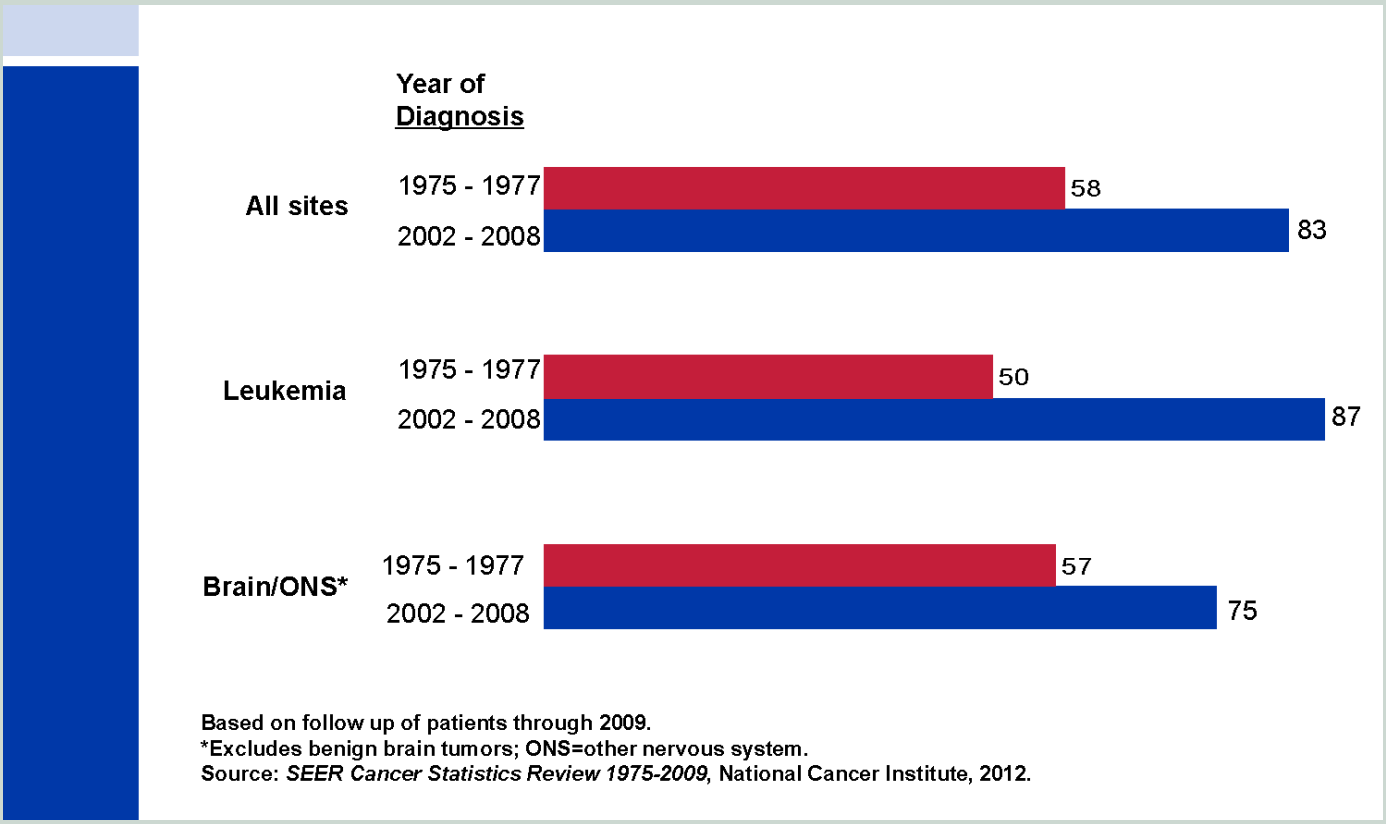
Figure 3. Trends in 5 year Relative Survival Rates for Cancer in Children and Adolescents (0-19 years), 1975-2010



Nancy Sacks, MS, RD, LD is a Pediatric Oncology Dietitian, and Chelsea Schulman, MS, RD, LDN is a Pediatric Dietitian, both at the Children's Hospital of Philadelphia (CHOP) in Philadelphia, Pennsylvania.

To join the Pediatric Subunit of the Oncology Nutrition Dietetic Practice Group, and to receive the latest group notifications, please email Katie.Badgett@STJUDE.ORG. For more information on the Pediatric Subunit, contact Pediatric Subunit Chair Rachel Hill at: Rachel.Hill@cookchildrens.org, or Pediatric Subunit Chair-elect Nancy Sacks at: sacks@email.chop.edu.

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CPE Article: Miraculin and The Miracle Berry: An Option for Dysguesia?

By Doreen Renee Cudnik, MS, RD, LD

Purpose – This literature review provides an overview of the miracle berry and its unique taste-modifying glycoprotein, miraculin, with particular reference to its history, function, proposed mechanisms of action, limitations, and current and potential uses, including potential applications in oncology nutrition practice.
Design/methodology/approach – Database queries utilizing PubMed, the Web of Knowledge, Google Scholar, and Science Direct were conducted with combinations of the following keywords: miraculin, miracle berry, miracle fruit, *Synsepalum dulcificum*, and taste-modifier.
Findings – The miracle berry's glycoprotein, miraculin, has a unique ability to sweeten sour tastes. Its applications are intriguing, particularly as an alternative sweetener and antioxidant, its expression in transgenic plants, and for improving the dysgeusia of chemotherapy patients.
Originality/value – To the author's knowledge there is a deficiency of current literature reviews on the miracle berry and miraculin. Its mechanism of action and applications need to be researched to a further degree.
Keywords: Miracle berry, Miraculin, *Synsepalum dulcificum*, Miracle Fruit, Taste-modifier, Glycoprotein, Chemotherapy, Antioxidants, Alternative sweetener, Transgenics

Introduction

The fruit of *Synsepalum dulcificum*—the miracle berry—is indigenous to the tropical rainforests of West Africa from Ghana to the Congo, and transforms the taste of sour food and drink into one of remarkable sweetness (1,2). This taste-modifying sensation is due to a glycoprotein, fittingly named miraculin, found in the pulp of the miracle berry (3). Chewing a miracle berry coats the tongue with miraculin. The combination of an acidic/sour food or drink of less than a pH of 7 along with miraculin activates the sweet taste receptors for an approximate period of thirty minutes to two hours and lasting up to three hours in some cases (4,5).

History of the Miracle Berry

The English physician and botanist William Freeman Daniell provided the first thorough description of the tropical miracle berry in 1852 (6). While stationed as an army surgeon in the Gold Coast (now the country of Ghana), Daniell encountered the "miraculous berry" and the West African natives who consumed it. The berry was well known to the indigenous people as assarbah, tanté, or agbayun and was sold in local markets (1,7). Daniell explained that in order to make some food more palatable, the natives often chewed the berry before eating strong, "acidulated specialties," such as kankies (sour cornbread), and before drinking intensely sour palm wine and pitto (beer) (1,7,8). More than a century passed before two research teams in Japan and the Netherlands independently isolated and purified the active substance that makes the berry unique: the glycoprotein miraculin (9-11).

Description of the Miracle Berry

The miracle berry is approximately the size (0.75 inch) and shape (ellipsoidal) of a Spanish peanut, and grows on the *Synsepalum dulcificum* bush (12,13). The whole berry is comprised of a thin-layered

(Continued on next page)

pulp over a large seed (1). When ripe, the berry turns red, likely due to anthocyanins present in the berry's flesh (14). The plant grows best in acidic soil (4.5 > pH > 5.8) and frost-free conditions (15). When grown from seedlings, fruiting occurs in approximately three to four years; the bush grows slowly and reaches six to fifteen feet in height when fully mature (16). In 1919 the miracle berry was introduced into the United States by Fairchild (17), founder of the Fairchild Tropical Gardens in Florida.

The miracle berry only has a slight cherry-like flavor and some consider it nearly tasteless. However, the taste of sour (acidic) food or drink is changed to a perception of sweetness, when these foods are consumed after the berry (4,18,19). The berry modifies the overall flavor perception by, for example, changing sour lemon juice into a sweet drink with a subtly altered lemon flavor. The taste-modifying function is due to the active substance found in the berry—miraculin.

Overview of Miraculin

Miraculin is a compound found within the thin-layered pulp of the miracle berry. It is a glycoprotein consisting of 191 amino acid residues with two glycosylated polypeptides, Asn-42 and Asn-186, cross-linked by a disulfide bond (15,20-24). Miraculin is a macromolecule with a molecular mass of 24,600, and is "400,000 times sweeter than sucrose on a molar basis" (20,25). It consists of up to 13.9% sugars, including glucosamine, mannose, galactose, xylose, and fucose (21,26,27).

Once activated by sour food or drink, miraculin displaces a portion of the acidity with sweetness. This dramatically reduces the sour acuity and augments the sweetness acuity, mimicking the effect of adding sugar to the acid (5,28). The natural aroma and taste of the sour food or drink are still present, to some degree (8). The miracle berry does not modify purely bitter, salty, or other sweet tastes, (29-32) and may or may not affect perceptions of metallic flavors commonly documented in individuals in cancer treatment.

Additionally, miraculin is deactivated by heat and high or low pH conditions—below pH 2 and above pH 12 (4,10).

Hellekant *et al.* (33) reported that the potency of the miraculin-induced sweetness effect is contingent upon the concentration of the miraculin along with the type of acid consumed. For example, Igarashi *et al.* (31) found that, in conjunction with miraculin, citric acid is perceived as tasting twice as sweet as acetic acid, if all other factors are equal. Chen *et al.* (34) described that the maximum sweetness intensity produced by miraculin is equivalent to 0.3 M of sucrose. For reference, a 0.3 M sucrose solution has 0.3 moles of sucrose per liter of solution, or 103 grams of sucrose per liter. This is 3.6 ounces of sucrose dissolved into 4.2 cups of water.

The taste-modifying effect of miraculin begins a few seconds after consumption, though several minutes of chewing the berry's pulp may be necessary to sufficiently coat the taste buds. The duration of the taste-modifying effect typically lasts thirty minutes to two hours, or until the miraculin is thoroughly diluted and dissociated by salivary amylase (30,35).

It should be noted that although the taste receptors require less than 0.1 mg of miraculin to induce a sweetening effect, the duration is dose-dependent (36). Kurihara and Beidler (9) demonstrated that the taste-altering effects of a 2.3 µM solution of miraculin held in the mouth for five minutes lasted for more than three hours.

Miraculin's Mechanism of Action

Miraculin's specific mechanism of action remains an enigma (22,37). Typically, macromolecules do not influence taste or smell (4). Anomalies exist, however, and miraculin became the first known (and is still recognized as the most well known) macromolecule able to elicit a shift in taste perception (30,38).

Although speculative mechanisms have been proposed in the literature, what is known is that miraculin binds tightly to the lingual epithelium's microvilli plasma membrane of sweet-taste receptors (hT1R2-hT1R3) without activating them. It is experienced as flavorless (4,35,39,40). Miraculin does not activate these receptors until exposed to an acidic pH, generally between pH 3.0 and 6.0 (30,41,42).

Kurihara and Beidler (43) first proposed the theory that an acidic environment induces a dynamic conformational change to the shape of the miraculin molecule sufficiently to allow the carbohydrate portion of the molecule to stimulate the "sweet site." Thus, only when the pH decreases within the mouth—when acidic food or drink is consumed—miraculin changes its structure and activates the sweet-taste receptors (39,44).

As previously mentioned, the acidity of the food or drink still exists, but it is significantly attenuated by the sweetness perception of the activated miraculin. Food or drink that does not have acidity, therefore, is not affected. One could liken this situation to a key and lock. A key (the miraculin) does not fit all the way into a lock (the sweetness receptors). However, once the key is exposed to acidity, it transforms its shape and fits perfectly. Once unlocked, a person experiences the perception of sweetness.

Misaka (39) postulates that miraculin pivots between its function as a sweetness agonist and an antagonist dependent upon the pH value of the consumed food or drink. When the tongue is exposed to miraculin in an acidic environment, the molecule binds to the sweet-taste receptors and behaves as an agonist for sweet flavor. When the receptors detect a neutral pH, miraculin—as an antagonist—inhibits the activation of the sweetness receptors. For a period of time (typically thirty minutes to two hours), miraculin has the ability to reactivate the sweet-taste receptors whenever an acidic pH is detected.

Another theory, proposed by Dzendolet (45), suggests that miraculin blocks the sour

receptor sites, and allows a sweet taste to be generated by the anionic group of an acid molecule. Also, miraculin could be influencing the taste of acids primarily by causing the excitation of sites that usually mediate sweetness, and not by causing any peripheral suppression of responses to acid (12). Miraculin in the presence of acid adds sweetness, while reducing sourness by mixture suppression (28,46).

Limitations for Practical Applications of Miracle Berry

For a period of time, sour food or drink (acidic pH) is perceived sweetly whether or not a person desires this. As an example, when eating a mixed meal, a grapefruit would be very pleasant, but pickled vegetables, for instance, may not taste particularly appetizing with a sweet overtone. In fact many sour tastes are desirable (47). After application of miraculin, for instance, a sour green apple may no longer taste refreshing; it may taste overly sweet, which some perceive as "artificially sweet," as reported in experiments conducted by Litt and Shiv (19). Essentially, affecting the overall flavor may not always be enjoyable.

One of the largest obstacles to potential applications of miraculin to address taste perception abnormalities lies in the miracle berry's availability. It is not sold within a mass distribution retail chain (e.g., grocery stores) (48). As stated before, the miracle berry only grows well in specific climates. It is not widely found in nature, and not readily available to consumers at this time.

Another issue with access to the miracle berry is that it is highly perishable. Miraculin is thermolabile and is inactivated below pH 3 and above pH 12 (1,30). The protein backbone of miraculin is evidently important as proteolytic modification leads to loss in activity (49). While the deactivation of miraculin from intense pH values would not be an issue under normal conditions, the deactivation from heating can be a problem. For instance, the miracle berry cannot be used in cooking or in processed foods. Moreover, the miracle berry also has limited availability due its short shelf life, and spoils in about two days (50). Despite these limitations to widespread availability, potential preservation techniques are being researched, such as utilizing a coating of the polysaccharide chitosan (51). Currently, the miracle berry can be stored at -20° F for approximately three months before use without significant degradation (13).

Regulatory Issues

Miraculin faces regulatory impedance from the U.S. Food and Drug Administration (FDA) and the European Union where it is not yet legally recognized as an approved food additive. It has been recognized by Japan's Ministry of Health and Welfare (52).

In the late 1960s, a Massachusetts-based company—the Miralin Corporation—was formed and established large-scale plantations of *Synsepalum dulcificum* in the West Indies and Brazil, developing new hybrids and propagation techniques (53). This company began to introduce an extract in tablet form called miracle fruit concentrate (MFC), consisting of a partially purified extract containing hydrolyzed cereal solids and a Miracle Fruit Drop (54,55). Special diets and menus were developed incorporating MFC as an aid to reduce energy intake. Despite fairly extensive toxicological evaluation and considerable investment, of at least $5 million, the extract did not obtain FDA approval. In 1974, the FDA issued a regulatory letter requesting the company to cease "interstate shipments." The company was liquidated in 1976, and in May 1977, all products containing *Synsepalum dulcificum* were denied food additive status (56). Sun *et al.* (57) reports "BioResources International, Inc. (Somerset, NJ, USA) currently is undertaking the commercial development of miraculin for use as a taste masking agent, low-calorie sweetener, and flavor enhancer."

It should be recognized, however, that "there is a fundamental difference between miraculin and food additives, because it is not necessary to add miraculin to the food itself" (8). Unlike the FDA, the U.S. Department of Agriculture (USDA) does not maintain restrictions on the miracle berry. Growing, selling, and eating miracle berries in the United States is legal (57).

Relevance

Science has numerous new avenues for research into the miracle berry's botany, horticulture, and miraculin's biochemistry, physiology, and chemical structure-taste relationships. Nevertheless, the miracle berry and miraculin ultimately will succeed or fail on the criteria of practicality and utility, however academically interesting it may be otherwise (15). Fortunately, there may be a variety of uses for this unusual food. Although it is generally recognized as more of a novelty food item, the miracle berry may provide certain health benefits.

Humans readily crave and ingest sweet-tasting foods, and miraculin may be a healthier alternative to some of the more traditional sweeteners, such as table sugar—sucrose (47). At a calorically negligible quantity of 100 µg of miraculin, a long-lasting sweetening effect can be achieved (39). Miraculin is "400,000 times sweeter than sucrose on a molar basis," and provides many times its own weight in sucrose-equivalent sweetness (20,52). Because miraculin can be used in minute amounts, it is not a contributing factor in tooth decay (3). The sweetening effect of miraculin could be useful in general, but particularly for chewing gums, mouthwashes, and other oral product applications (58).

Miraculin has a similar sweetening effect compared with sucrose in controlled experiments (5,36,59). Participants stated that they could not detect a taste distinction between the two, and, unlike sucrose, miraculin neither induced a subsequent craving for sucrose nor triggered a demand for insulin (37,41,60). Chen *et al.* (61) conducted a prospective

(Continued on next page)

study that demonstrated miraculin improved insulin sensitivity in rats. Consequently, people who suffer from obesity and diabetes may find miraculin very useful for limiting sugar intake (48). In addition to its potential as an alternative to sugar, the miracle berry may be a healthy fruit in its own right, namely for its antioxidant properties.

A study published in 2011 examined the antioxidant properties of the miracle berry (18). In regard to flavonoid and phenolic content, the results suggest that the skin, pulp, and seed of the miracle berry exhibit potent antioxidant activity. A 2014 study presented similar results, but demonstrated that the highest concentrations of antioxidant-rich phytochemicals are found within the miracle berry's flesh. Even more intriguing is that the miracle berry contains substantially larger quantities of ascorbic acid and several significant (and relatively rare) phenolics when compared with other commonly-known, antioxidant-rich berries, such as blueberries, blackberries, cranberries, red raspberries, and strawberries (14). Although the antioxidant properties of the miracle berry are notable, its potential to help patients receiving chemotherapy may be significant.

The miracle berry could benefit individuals receiving cancer chemotherapy and radiation treatment who often experience taste alterations (dysgeusia) or decreases in taste acuity (ageusia). Spielman (62) notes "as a consequence of ionizing radiation, there are changes in the salivary flow rate and in the composition, oral bacterial flora, and turnover rate of taste cells." Serving as a flavor enhancer, miraculin may have the ability to increase the desire of cancer patients to eat. Some chemotherapy treatments leave an unpleasant, noxious taste in the mouth, for which no standard remedy exists (63). Food aversions related to dysgeusia are experienced by more than fifty percent of patients receiving chemotherapy (64). This may lead to decreasing nutrient intakes, decreased treatment tolerance, secondary to malnutrition, and decreases in general well-being (65,66).

Soares *et al.* completed a trial with oncology patients drawn from the Mount Sinai Medical Center in Miami, Florida. The authors led a randomized crossover pilot study of 23 participants in order to determine if the miracle berry improves dysgeusia (67). The miracle berries were obtained from a botanical garden in Miami and stored under controlled temperature conditions prior to use in the study At baseline, 87% of participants reported dysgeusia and 78% experienced no taste at all. After using the miracle berry, 30% reported improvements in taste.

Another pilot study was conducted by Wilken and Satiroff (65) among eight patients from a Nebraska oncology clinic. This crossover study consisted of randomly selected chemotherapy patients, and taste improvements were recorded for all participants after consumption of the miracle berry. Despite the positive results, larger confirmatory research is warranted due to the small sample sizes.

Transgenics

Despite miraculin's relative stability, the miracle berry is limited mainly by its availability and perishability (56). Thus, alternative means to provide a consistent supply would improve access. Research to produce recombinant miraculin protein are underway using transgenic plants in Japan (68-70). Transgenics involves the transfer of genes from one species into a different species.

Genetically modified *Escherichia coli*, *Aspergillus oryzae*, and tobacco plants have been unsuccessful in expressing active miraculin. In 2006 Japanese biotechnologists reported that they had succeeded in expressing recombinant miraculin in transgenic lettuce that exhibited activity (22,72,73). Since that time, recombinant miraculin has also been successfully expressed in transgenic strawberries and transgenic tomatoes (57).

Unlike the miracle berry, these plants are readily harvested in more temperate regions and substantial yields of miraculin can be obtained (72). Transgenic tomatoes appear to be the most promising of the three transgenic options, because transgenic tomatoes yield higher levels of recombinant miraculin when compared with transgenic strawberries. Further, gene silencing from generation to generation was not an issue in tomatoes, as it was with transgenic lettuce (71,74-76). In fact, transgenic tomatoes can produce higher levels of miraculin per gram of fresh weight than the miracle berry itself (26,77). Moreover, miraculin expressed in transgenic tomatoes appears to be more stable due to the acidic environment of the tomato (21,72,78). Further studies will assess "toxicity, allergenicity, digestibility, thermal stability, insertion position in the host genome, and processing status" (15).

Conclusion

The miracle berry, with its glycoprotein miraculin, is very unique. The full mechanism of action of its flavor modifying ability to convert sour to sweet is not completely understood, and small study sample sizes in clinical trials must be addressed with larger trials. Nonetheless, the miracle berry's potential is promising as an alternative sweetener, as an antioxidant-rich food item, and for improving dysgeusia in patients receiving chemotherapy. The miracle berry is limited by availability and perishability, and researchers are producing recombinant miraculin in transgenic plants, notably tomatoes, to address these issues. Further research into the mechanisms of action of miraculin, the miracle berry's potential therapeutic uses, and efficient production and enhanced availability are required for this food to realize its full potential.

Doreen Renee Cudnik, MS, RD, LD completed this review to fulfill a requirement of her graduate program in human nutrition.

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Medical Cannabis Comes Out from Underground

By Donna Shields, MS, RDN

The use of cannabis for various health conditions is becoming a more common topic of discussion in healthcare circles today. The cannabis plant has been used medicinally for thousands of years and is well known to herbalists, naturopathic medicine practitioners, and other non-conventional healthcare providers; however, today medical cannabis has moved into mainstream conversation. Since cannabis has recently emerged as a trending topic in the medicinal arena, it could be considered as a part of comprehensive care plans for certain patients.

The science in this area is continuing to develop, and continued research is needed to fully understand the risks as well as benefits associated with different types, doses, and forms of medical cannabis. The purpose of this article is to give the registered dietitian nutritionist (RDN) an understanding of basic medical marijuana issues and their impact on how to use this information to help educate and guide patients.

State of the Industry

Currently, 23 states and the District of Columbia allow for the use of medical cannabis. Of those 23, only four states and the District of Columbia currently permit adult (21+ years of age) recreational use of cannabis: Colorado, Oregon, Washington, and Alaska (1). There is no uniform federal policy in place governing the legality of medical cannabis use, however, in 2002, the Ninth Circuit Court of Appeals held, in Conant v. Walters, that the federal government could not punish, or threaten to punish, a physician solely for telling a patient that his or her use of marijuana for medical purposes is proper (2). However, it remains illegal for a physician to "aid and abet" a patient to obtain marijuana or conspire with him or her to do so. This means a physician may discuss the pros and cons of medical marijuana with his or her patient, and issue a written or oral recommendation to use marijuana within a bona fide doctor-patient relationship, without fear of legal reprisal (2). The physician may not prescribe or dispense marijuana to a patient, or recommend it with the specific intent that the patient will use the recommendation as a prescription to obtain marijuana (2).

In states that have legalized medical cannabis, a physician, and in some cases a nurse practitioner, can recommend (not prescribe) the use of the cannabis for patients who meet an approved, qualifying medical condition (3). The patchwork of qualifying conditions varies state by state, but will change over time as new conditions are added. However, cancer is currently a qualifying condition in all states and likely will remain on the list (3).

With the passage of California's Proposition 215 in 1996, medically-approved patients in that state began to purchase their cannabis from a dispensary; many could not cultivate their own cannabis, or locate a caregiver to grow it for them (4). Prior to 2002, the Controlled Substance Act (CSA) promised to prosecute any physician who prescribed or recommended cannabis to patients by revoking their licensure. Any patient who used the prescribed cannabis, also could be prosecuted, as could those affiliated with dispensaries (5). In the Conant v. Walters case, previously mentioned, a group of California patients and physicians sued the federal government (2), and due to the outcome of this case, today, health practitioners can be confident their recommendations for medical cannabis will no longer carry the burden of federal prosecution (5).

The Obama Administration and the Department of Justice issued a memorandum on August 29, 2013 to United States attorneys in all fifty states, announcing it would take a "hands off" approach regarding cannabis in those states with legalized use. The memo directed federal prosecutors to focus on eight areas of enforcement rather than spending time targeting individual users (6,7). New bills have been introduced into Congress, which would allow for increased federal acceptance. For instance, H.R. 1940 *Respect State Marijuana Laws Act of 2015*, was sponsored to amend the Controlled Substance Act of 1970 (CSA) to provide provisions related to cannabis to cover any person acting in compliance with state laws (8).

However, even though state legislation has set policy for the legal status of medical cannabis use in many locations, cannabis remains a Schedule I drug under the CSA. This means cannabis is listed alongside drugs such as heroin and LSD, and is defined as being highly addictive and having no accepted medical use (9). With new evidence emerging that cannabis may offer therapeutic value, there is interest in investigating it further. Unfortunately, the Schedule I classification has made it difficult for researchers to adequately test the effects of cannabis on certain illnesses (9). Until and unless the federal classification changes, uncertainty around the legality of medical cannabis will remain. The Obama memorandum was a step forward toward clarifying legal issues around medical cannabis use, but the federal government also made it clear it reserves the right to revisit its position in the future (6,9).

Because of changing state and federal mandates, RDNs will need to familiarize themselves with what is allowed in the states where they practice. It is equally

valuable for practitioners to stay current on national policy regarding tolerance or prosecution of medical marijuana use.

Cannabis as a Healing Tool

One of the more recognized uses for medical cannabis is cancer treatment symptom management. The topic was presented by Donald Abrams, MD and Kelay Trentham, MS, RDN, CSO at the 2015 *Food & Nutrition Conference & Expo,* during an Oncology Nutrition Dietetic Practice Group (ON DPG) Session. An article titled C*annabis in Cancer Care* was published recently in *Clinical Pharmacology & Therapeutics*, discussing the potential benefits of cannabis (10). Cannabinoids are the physiologically active chemical constituents of cannabis that mimic the effects of the body's own endocannabinoid system (ECS) (11). The term endocannabinoid came into use in the 1990s after the discovery of cell membrane receptors to which the exogenous cannabinoid known as delta-9-tetrahydrocannabinol (THC) could bind (12). These findings indicated there likely was an endogenous cannabinoid system (ECS). This system now is known to be comprised of cannabinoid receptors and enzymes for biosynthesis and inactivation of endocannabinoids, and two key endocannabinoids identified to date are anandamide (AEA) and 2-arachidonoylglycerol (2-AG) (10,11,12). Furthermore, endocannabinoids appear to be involved in the control of cell metabolism, differentiation, proliferation, and death (12).

Exogenous cannabinoid action occurs at the receptor level; and cannabis produces its psychotropic and peripheral effects through activation of CB1 and CB2 receptors (11). CB1 receptors are located primarily in the central nervous system (CNS), whereas CB2 receptors are located primarily in blood and/or immune-related cells (12,13). Interestingly, the activation of the CB1 receptors on axon terminals by exogenous cannabinoids (delta-9-tetrahydrocannabinol (THC)) and by endogenous cannabinoids (endocannabinoids) released by postsynaptic neurons leads to inhibition of neurotransmission; this may explain the cognitive and memory deficits elicited by these cannabinoids (14). All endocannabinoids identified so far are derivatives (amides, esters, ethers) of long-chain polyunsaturated fatty acids and exhibit varying selectivity for the two cannabinoid receptors; however, more ECS receptors continue to be identified, and are present in various tissues throughout the body (12). Although research is limited, this endocannabinoid system seems to play an integral role in an ever-increasing number of pathological conditions (12,13). Activation at the receptor level appears to mitigate nausea, vomiting, anorexia, cachexia, chronic pain, and loss of appetite, many of which can accompany chemotherapy (12,13).

Although the use of cannabis currently focuses on managing cancer-treatment symptoms, some research indicates cannabinoids may inhibit tumor growth as well (13,15). The first human clinical study assessing the anti-tumor activity of cannabinoids, a small pilot trial, was published in the *British Journal of Cancer* in 2006 (15). Nine patients with recurrent glioblastoma multiforme were administered THC intratumorally. Legal and ethical concerns dictated that the pilot study be conducted in a cohort of terminal patients who had failed the standard therapies, including surgery and/or radiotherapies (15). Patients underwent physical, neurological, biochemical, and hematological examinations as well as magnetic resonance and CT scans of the brain to measure tumor size changes (15). The plasma and urine concentration of THC was determined daily, and western blot methodology was used on tumor biopsies. This was not only the first clinical study to assess cannabinoid antitumor action but also the first human study in which a cannabinoid was administered intracranially. The study concluded THC has a fair safety profile, and THC does not facilitate tumor growth nor decrease patient survival. Additional trials are needed to determine whether cannabinoids could be used as tumor growth inhibitors, in conjunction with conventional palliative care approaches (13,15). The study was very small and additional research is sorely needed, but unfortunately, because medical cannabis retains schedule 1 status, larger, more long-term studies have yet to be completed (9,15).

However, not all medical cannabis research has ceased. At the Center for Medicinal Cannabis Research at the University of California, San Diego, the analgesic effect of cannabis to manage chronic pain, the most common indication for medical cannabis use, is being investigated (17). While cannabis alone appears to be effective for some types of pain management, it also may provide the added benefit of reducing opioid use for pain relief (18).

Beyond cancer management, cannabis appears to hold promise for conditions that also may respond to nutrition intervention, such as gastrointestinal issues (e.g., GERD, IBS), immune disorders, diabetes, Crohn's disease, ADHD, inflammation, multiple sclerosis, neurodegenerative disorders (Parkinson's disease, Huntington's disease, Tourette's syndrome, Alzheimer's disease), epilepsy, osteoporosis, cardiovascular disorders, obesity, and metabolic syndrome-related disorders (10-14). RDNs interested in offering a holistic approach to disease and condition management need to become more knowledgeable about the mechanisms of action of medical cannabis and how this may be utilized by patients, in conjunction with medical nutrition therapy.

Dosage & Delivery Systems (see Disclosure)

Appropriate dosage recommendations for medical cannabis can be challenging to determine. Numerous variables, including differences in plant strains, strain potency, delivery route, and individual differences

(Continued on next page)

in absorption, tolerance, and response to cannabis can dramatically alter response to the drug. These variables, in turn, will affect the amount and frequency of use an individual will require to obtain optimal symptom relief. For most patients, a very low dose is initiated, and effects are carefully monitored to determine response. Dr. Mary Lynch, a pain researcher and head of the *Canadian Consortium for Investigation of Cannabinoids in Human Therapeutics*, suggests it is best to start out with the lowest dose possible, particularly for the naive, first-time user. Using protocols she and colleagues are developing for research on medical use of smoked cannabis, she recommends naive users begin with 1 puff (or toke) usually before bed, to help with pain, with increasing intake as required for the desired outcome (19).

Experienced users often know what dose is the most effective for them; however, Lynch recommends that a dose of 2 to 4 puffs, 3 times a day is reasonable, depending on response. The dose can be titrated accordingly. Those who prefer non-smoked cannabis may start with a small quantity of an edible product. A common recommendation is to consume one-quarter to one-half of an edible product that is considered to be one dose, or use approximately 0.25 grams of dried cannabis flower in a vaporizer, prior to each meal (19). Regarding edibles, however, it should be noted that different products may list different milligram amounts as equivalent to "one dose"; one quarter of an edible item containing 10 mg of THC per serving would be a higher dose than one quarter of an edible listing 5 mg of THC per serving. Consultation with a knowledgeable medical resource is, therefore, essential. Further, a knowledgeable practitioner must understand a low oral dose for one person may not be low for another individual. Extreme caution is always warranted with ingested cannabis, because individual tolerance of secondary metabolites, such as 11-hydroxy THC (20), varies.

Many delivery options are available for those who prefer not to smoke cannabis. One of the more popular is vaporizing. Vaporizing allows for the release of active chemical compounds in an inhalant form. The vapor form eliminates taking in unwanted particulate matter and potentially toxic compounds which can be generated with combustion (10,21). Additionally, for many people, vaporizing allows for more consistent and accurate dosing than smoking; ultimately, it can result in less cannabis required to achieve the desired therapeutic effects (22).

Tinctures, topical products, and edibles also are common routes for medical cannabis delivery. Tinctures are absorbed rapidly through the oral mucosa, allowing for rapid systemic effects and drug response. Topical cannabis products, in the form of salves, oils, creams, and transdermal patches, can be applied directly on the skin. Topical treatments may be used to relieve inflammatory joint pain, muscle soreness, and conditions such as psoriasis or eczema (23). Topicals tend to have few, if any, psychoactive effects because the active constituents do not reach significant concentration in the bloodstream due the reduced absorption rate (23).

Another delivery option is cannabis-infused edibles. These items are available primarily as baked goods, candies, and beverages. Oral ingestion of THC or cannabis has different pharmacokinetics compared with the inhalation route. The onset of action is delayed, making titration more difficult (19). When consumed through food-related items, cannabinoids are absorbed through the intestinal tract and then undergo first-pass metabolism where the liver intercepts the majority of the cannabinoids consumed; THC and its metabolites are lipophilic compounds and their tissue distribution is governed by their physiochemical properties (10). Because cannabinoids are fat soluble, the processing of these secondary metabolites by the liver can vary from person to person. Like most plants, the phytochemistry of cannabis is complex. More than 480 cannabis compounds have been identified, including amino acids, fatty acids, steroid compounds, cannabinoids, flavonoids, stilbenoids, terpenoids, lignans, and akaloids (10,24). The distribution and concentrations of these compounds vary by plant part used, age of the plant, plant varietal, growth conditions, harvest time, and storage conditions.

Edibles can be a difficult delivery mechanism for patients new to medical cannabis due to the delayed response time; a patient may be inclined to consume more cannabis food product than is needed for a therapeutic effect. Because of varied titration and psychoactive metabolites, a cannabis naive patient may not want to start with edibles; they may want to assess their response from smoking or vaporizing first, before moving forward with oral cannabis options (23).

For more seasoned medical cannabis patients, with proper knowledge, preparing edibles at home may be a less sugared, higher nutritional value alternative to low nutritional value products typically sold at local dispensaries. Tinctures and oral sprays also allow oral delivery without excess sugar and calories.

Why Should RDNs Be Concerned?

Patients are becoming more interested and willing to incorporate various non-conventional modalities into treatment plans, which will require a paradigm shift in healthcare for proper management. Medical cannabis can have a place in the healing toolbox. Being knowledgeable and confident regarding education of patients on the therapeutic effects of cannabis can enhance the registered dietitian nutritionist's practice, and may provide a competitive edge for private practitioners.

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Disclosure: Information provided in "Dosage and Delivery" should not be taken as advice or recommendation on the use of medical cannabis products, nor should it be used in place of consultation with a qualified healthcare professional.

Donna Shields, MS, RDN is a co-founder with Laura Lagano, MS, RDN, CDN of the Holistic Cannabis Network, an online education and training platform for practitioners and their patients who are interested in medical cannabis and its integration with other healing modalities. Donna also is co-founder of the Holistic Cannabis Summit, online April 4-7, 2016, and contributor to the recently published The Cannabis Kitchen Cookbook.

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Email: Dianne.Piepenburg@va.gov (primary) or piepenburgmom@yahoo.com (secondary)

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Email: rhonelevin@gmail.com

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Email: jeannine.b.mills@hitchcock.org

Katrina Claghorn, MS, RD, CSO, LDN
Email: katrina.claghorn@uphs.upenn.edu

Janet Mildrew, RD
Email: janet.mildrew@rivhs.com

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Email: heather.bell_temin@hotmail.com

Jeannine Mills, MS, RD, CSO, LD
Email: jeannine.b.mills@hitchcock.org

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Email: katrina.claghorn@uphs.upenn.edu

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Email: sdixon@umich.edu

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Email: kristen.lange@moffitt.org

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Email: denise.snyder@duke.edu

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Email: kelayt@gmail.com

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Email: rhonelevin@gmail.com

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Email: mpetzel@mdanderson.org

Maureen Huhmann, DCN, RD, CSO
Email: Maureen.huhmann@us.nestle.com

Elaine Trujillo, MS, RDN
Email: trujille@mail.nih.gov

Jeannine Mills, MS, RD, CSO, LD
Email: jeannine.b.mills@hitchcock.org

Andreea Nguyen, MS, RD, CSO, LD, CNSC
Email: andreea.nguyen@baylorhealth.edu

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