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## **Complementary and Alternative Medicine and Pediatrics: focus on Herbal Products and Nutritional Therapy**

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### **I - Introduction**

The use of complementary and alternative medicine (CAM) in both children and adults has been increasing dramatically.<sup>1,2,3</sup> Pediatric health care providers must inquire about its use, as parents may already be integrating CAM in the treatment of their children, without necessarily disclosing such use.<sup>3,4,5,6,7</sup> To promote communication, it is important that health care providers are knowledgeable about the various types and the most commonly used CAM therapies.

The definition of CAM is commonly accepted as a "broad domain of healing resources that encompass all health systems, modalities, and practices and their accompanying theories and beliefs, other than those intrinsic to the politically dominant health system of a particular society or culture in a given historical period."<sup>8</sup> The World Health Organization estimates most of the world's population regularly uses traditional medicine as first line therapy (as opposed to conventional Western medicine)<sup>9</sup>. The National Center for Complementary and Alternative Medicine (NCCAM), a branch of the National Institutes of Health in the United States, classifies CAM into 5 main categories or domains: 1) alternative medical systems, which are built on complete systems of theory and practice (e.g. Traditional Chinese medicine and Ayurvedic Medicine); 2) mind-body interventions, which aim to enhance the mind's capacity to affect bodily function and symptoms (e.g. meditation, prayer, etc.); 3) biologically based therapies, such as herbs, foods, and vitamins; 4) manipulative and body-based methods, such as chiropractic or osteopathic manipulation; and 5) energy therapies, such as biofield therapies (intended to affect the energy fields that surround the human body e.g. qi

gong, Reiki, and therapeutic touch) or bioelectromagnetic-based therapies, which involve the unconventional use of electromagnetic fields (e.g. pulsed fields, magnetic fields, etc.)<sup>10</sup>. The majority of this paper will focus on biologically based therapies, also known as natural health products.

### **Natural health products (NHPs)**

Generally speaking, NHPs are used in the diagnosis, treatment, or prevention of disease, or maintaining and/or promoting health. It is important to note that the majority of CAM use is without the guidance of a health care provider (i.e. "self-help"). According to the Natural Health Products Directorate of Health Canada (2), NHPs encompass:

- a. homeopathic preparation;
- b. substance or substances used as traditional medicine, including, but not limited to, a substance used as a traditional Chinese medicine, a traditional Ayurvedic (East Indian) medicine or a North American aboriginal medicine;
- c. mineral or a trace element, a vitamin, an amino acid, an essential fatty acid or other botanical, animal or microorganism derived substances. The most commonly used natural health products include herbal and dietary supplements (e.g. vitamins).

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## Incidence and frequency of usage

Herbal supplements are part of a growing trend of patient-directed care in the United States. Herbal supplement use in the United States is a multibillion-dollar industry with sales of over 3.87 billion dollars in 1998<sup>11</sup>. Although sales in 2000 declined by 6.5% due to negative publicity regarding safety concerns, industry projections call for a 5-6% growth in the upcoming years<sup>12</sup>. In the United States, 60 % of the population uses some form of dietary supplement on a daily basis<sup>13</sup>. Surveys by Eisenberg indicate that over 70% of those taking supplements do not tell their primary care provider of their supplement use, leaving both the practitioner and client in a precarious position<sup>14</sup>. This survey also indicated that 12% of adults used herbal medicines and 5.5% used megavitamins. Additionally, 20% of those taking herbal medications also take a prescription medication placing them at risk for a drug/herb interaction<sup>15</sup>. *As with the adult population, there is an increased use in CAM by children and adolescents. Motivating factors for CAM use vary by age group and extent of parental involvement.* In young infants and children, CAM use by parents is predictive of use in young children<sup>16</sup>. In this group of younger children, the most common illness for which CAM was used was upper respiratory illness. Children with chronic or incurable illnesses have higher usage rates of CAM than their healthy counterparts. CAM use has been reported in 46% of children with cancer, 55% of children with asthma, 66% of children with Cystic Fibrosis, 70% of children with Juvenile Rheumatoid Arthritis and 41% of children and young adults with Inflammatory Bowel Disease, 20% of children with Attention Deficit Hyperactivity Disorder or depression, more than 30% of children with Autistic Spectrum Disorder and 56 % of children with Cerebral Palsy<sup>17-23</sup>. Although adolescents may use CAM for illnesses, there is also an increasing reported use of herbal preparations for a legal "high". The Internet is a source of nutrition and health information for teens, and information on how to procure and utilize biologically active compounds abounds.

### Note from Alliance Representative:

The Paediatric Session at International Congress of Dietetics, May/2004 in Chicago was a joint venture across the borders between Dietitians of Canada Paediatric Nutrition Network (DCPNN) and ADA Paediatric Nutrition Practice Group (PNPG) and from the inception of the topic through to the planning and sponsorship of the event. The topic had international appeal with the growing popularity of complementary alternative medicine (CAM) worldwide. By using speakers from US and Canada we were able to cover the impact of regulations from each country and some of the key issues concerning safety and efficacy of complementary care in pediatrics. CAM is a very broad topic thus the presentation focused on Herbal Products and Nutritional Therapy. This CAM feature article which is being published in both network newsletters this summer, provides the opportunity to share the information with the members of DCPNN and PNPG.

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Herbal preparations abused for this purpose include wormwood, nutmeg, valerian, catnip, ginseng, and "herbal ecstasy", which is a combination of caffeine and ephedrine/pseudo ephedrine. Additionally, goldenseal is purported to be a masking agent for drug tests<sup>24</sup>. The FDA recently released a list of supplements that consumers should not purchase because they contain harmful ingredients, yet are currently being promoted as safe and legal alternatives of illicit drugs. Included in the list are products such as Trip2Night, Invigorate II, Snuffadelic, Liquid Speed, Solar Water, Orange Butterfly, Smooz and Green Hornet Liquid (<http://www.fda.gov/bbs/topics/news/2004/NEW01049.html>. Accessed May 4, 2004). In addition to plant-based biologically active compounds, other ingredients include high levels of diphenhydramine and dextromethorphan which are found in over the counter cold preparations and gammahydroxybutrate (GHB) commonly known as the "date-rape" drug. *Dietitians and health-care providers should routinely assess for the use of CAM in children and adolescents.*

The herbal medicines listed in **Table 1** represent the top 12 selling herbs accounting for 95% of sales in the United States in 1999 although little data exists on the frequency of use in the pediatric

population.

See **Appendix 1 - Herbal Products** which illustrates the typical use, dosing, side effects, known drug interactions and contraindications of the top selling herbal medicines. The herbal preparations listed represent research studies using purported active ingredients and may not represent the actual products available to consumers.

**Table 1 - Top Selling Herbs in the US Market** ( from Information Resources, Inc. January 1, 1999)

Herb	\$ Millions	% of growth
Ginkgo	153	140
St. John's Wort	140	2801
Ginseng	95	26
Garlic	83	27
Echinacea	33	151
Saw Palmetto	20	138
Grape seed	11	38
Kava	8	73
Evening Primrose	8	104
Echinacea/ Golden-seal	8	80
Cranberry	8	75
Valerian	8	35

## **II - Issues related to product quality, regulatory standards, and adverse events**

### **Standardization**

Lack of standardization is a major difference between NHPs and pharmaceuticals. NHP heterogeneity can be attributed to a number of sources: (i) species that are collected in error (i.e. misidentification); (ii) different collection methods (i.e. aerial vs. root of plant); (iii) different extraction techniques (e.g. aqueous vs. alcoholic); and (iv) product impurity (e.g. contamination, adulteration, etc.). As a result, there can be considerable batch to batch variation in purity and potency, and contamination is a major concern (e.g. heavy metal poisoning from traditional Chinese medicines has been reported several times).<sup>25,26,27</sup> Other studies examining the quantity of active ingredient across brands found from 0-200% of the label claim.<sup>28</sup> Frequent surveillance by consumer groups show significant issues regarding standards and labeling issues. Consumer Labs routinely analyzes popular dietary supplements and often-over 50% of the supplements tested fail to meet their own labeling standards.

Regulatory standards to deal with these issues vary between countries; we will explore the regulatory standards adopted in Canada and the United States.

### **Canadian Regulation of NHPs**

In June 2003, Canada approved new regulatory standards for NHPs, which encompass guidelines for issuing product licenses, site licenses, and good manufacturing practices (GMP). The GMP for NHPs describes government standards for premises, equipment, personnel, sanitation, operations, quality assurance, stability and record keeping of NHPs. The regulations also discuss clinical trials of NHPs with human subjects, with specific requirements for NHP clinical trials to be pre-approved by the regulatory agency, the sponsor's obligations, and guidelines for reporting adverse events. NHP manufacturers have until December 31 2009 to adhere to these regulatory standards. There is a

concern that Canadian researchers do not yet know they need to seek regulatory approval prior to NHP research and that Canadian health care providers do not know that they can (and should) report adverse events related to natural health products.<sup>29</sup> The standards adopted by Canadian regulators were set to distinguish NHPs from foods and from conventional pharmaceuticals, both of which are regulated differently than NHPs. As stated in the regulatory document, "these Regulations are intended to provide Canadians with ready access to products that are safe, effective, and of high quality, while respecting freedom of choice and philosophical and cultural diversity."<sup>30</sup> The burden to regulate is not eased by the exponential growth in the number of CAM products or practices available.

### **American Regulations and Herbal and Dietary Supplement Guidelines**

The passage of the Dietary Supplement Health and Education Act (DSHEA) in 1994 significantly changed the way herbal and dietary supplements are regulated in the United States, and have overriding affects for practitioners wishing to integrate these products into their pediatric practice. Prior to 1994, the FDA regulated herbs as food additives and over 250 herbs were classified as "generally regarded as safe" (GRAS). In the early 1990's, the FDA threatened to remove herbal based medicines from the GRAS list, and stated that when food additives are used as pharmacotherapy, they should be classified and regulated as drugs. The passage of DSHEA, was in part, was the public's response to this impending removal. As a consequence, the burden of purity, safety and efficacy has shifted from the manufacturer, as with conventional pharmaceuticals, to the FDA, such that the FDA must prove a product is dangerous or poses an unreasonable health risk before it can be removed from the market. Despite this added

responsibility, the FDA was not allocated additional budget or staff to address these concerns. As a consequence, at the present time, the FDA can only react to safety issues rather than proactively address and prevent them.

### **Drug-NHP interactions**

Three factors combine to increase the likelihood of drug-NHP interactions. First, patients with serious, chronic or recurrent illness are the most likely to use CAM<sup>31,32</sup> – these are also the patients most likely to be on prescription medications. Second, most patients using CAM use it to complement their health care, not replace it<sup>31,32</sup>. Third, research confirms that a substantial proportion of individuals who use NHPs, use more than one simultaneously.<sup>3,33</sup> Lessons learned from experience with drug interactions, whereby the likelihood of an adverse event increases exponentially as the number of medications increases<sup>34</sup>, would predict that this scenario makes such patients likely to experience an adverse event<sup>35,36</sup>.

### **Adverse events and NHPs**

The recent ban on ephedra highlights some of these issues. Ephedra, or ma huang, has been used in traditional medicines for thousands of years, focusing primarily on the treatment of asthmatic or upper respiratory conditions with few reported safety issues possibly due to the traditional preparation of this herb. However, analysis of commercial ma huang products have shown lot to lot variations, labeling inconsistencies and one product having no detectable active ingredient.<sup>37,38</sup> Side effects were rarely listed on the label and can be considerable for those using ma huang based products. Side effects include insomnia, dry mouth, headache, and hypertensive episodes leading to seizures or strokes.<sup>39</sup> Dosing recommendations may be listed on the label but rarely are given for the pediatric population. Drug-herb interactions can be a signifi-

**Ephedra, or ma huang,**



cant problem and often these contraindications are not listed on the label for consumers to make informed choices for their children. In a recent survey of herbal therapy use in a pediatric emergency room setting, 5% of those reporting herbal therapy use reported given ephedra to their child with the most dangerous drug-herb interactions being ephedra and albuterol.<sup>40</sup>

While the lack of regulatory oversight is a significant factor in the adverse reactions reported, consumer belief that “natural” equates to safe or harmless must be viewed as a contributing factor. In 1996, 400,000 cases of herbal or homeopathic poisonings were reported to poison

control centers.<sup>41</sup> Although data is lacking on the frequency of poisonings in pediatrics, herbal medicines are rarely packaged in child resistant packaging.<sup>42</sup> Some herbal medications, albeit “natural”, are inherently dangerous and should be avoided based on their pharmacological actions and adverse consequences. Of the toxicities reported, hepatotoxicity was the most common.<sup>43</sup> An example of a commonly used naturally occurring hepatotoxin is German-der. Often recommended as an antipyretic and as a weight reduction aid, German-der contains hepatotoxic alkaloids, which can cause hepatocyte necrosis and cell death.<sup>44</sup> Another popular herb, which is a known liver toxin, is chaparral. Chaparral, used by Native Americans for centuries as a “blood purifier”, has been linked with at least 18 adverse effects reported to the FDA with hepatotoxicity evident in 13 cases. The pattern of liver injury was consistent with drug induced hepatitis with two patients experiencing acute fulminant liver failure requiring liver transplantation.<sup>45</sup> The issues are pervasive throughout the industry and present the real challenges for pediatric practitioners attempting to integrate CAM into their practice.

### **III-Usage of Vitamin / Mineral supplements and Special Diets**

Dietary supplements can cause problems related to nutrient excesses, nutrient imbalances, or adverse interactions with medical care<sup>46</sup>. It is critical to determine the safety of the supplements for use in children. The usage of multivitamin-mineral supplements has been growing in popularity. There is little scientific evidence of benefit or harm to the average person using low

“.....there is limited support for the use of specialized diets like the casein-and or gluten-free diet.....”

dose multivitamin-mineral supplements in amounts that do not exceed 100 % of recommended intake levels (Recommended Dietary Allowance – RDA and Adequate Intake). People consuming both highly fortified foods and multivitamins can easily consume 300% of the RDA/AI for many known nutrients. Dietitians should provide guidance to consumers concerning the intake of nutrients from both fortified and unfortified foods and supplements.<sup>47</sup> The Dietary Reference Intakes (DRIs) also include Tolerable Upper Intake Levels (ULs) for many nutrients; intakes above the UL are not safe.

There is the ongoing challenge for parents of children with chronic illness or special needs to decode the conflicting information and claims from many anecdotal stories and communications on the Internet and glitz-buying clubs.

Vitamin and mineral supplements are popular for usage in children with Down syndrome e.g. NuTriVene-D® (International Nutrition Maryland),<sup>48, 49, 50</sup> Autism Spectrum Disorder (ASD) e.g. vitamin B6 and magnesium supplements,<sup>51,52</sup> Attention Deficit Disorder (ADHD) e.g. megavitamin or fatty acid supplementation,<sup>53, 54</sup> Cystic fibrosis e.g. usage of supplements like Manna-tech® Optimal Health Products,<sup>55,56</sup> Diabetes e.g. usage of vitamin/trace elements for glycemic control<sup>57</sup> and mega dose supplements for treatment of Cancer<sup>58</sup> e.g. as part of program from Centre for Integrated Healing (<http://www.healing.bcc.ca/>

[programs\\_intro.shtml](#) - accessed May 2004). Unfortunately conclusive, well designed studies to determine whether particular nutritional supplements can achieve the goals claimed by its manufacturers are rare. Research of vitamin and mineral supplements has also been hindered by a lack of accurate and meaningful assays that detect functional micronutrient deficiencies.

The identification of specific “target” behaviors that the parent wants to change should be objectively quantified in order to evaluate the effectiveness of an alternative nutritional therapy. It is important to target the challenging behaviors, set up a controlled trial, and have several observers evaluate the changes in different settings.<sup>59</sup> N of 1 trials (i.e. multiple crossover trials in a single patient) may be one way to achieve this objective assessment.

Dietary restrictions for treatment of ASD have been reported to reduce the behavioral symptoms of autism, but there is limited support for the use of specialized diets like the casein-and or gluten-free diet, which is based on the “excess opioid peptide theory.”<sup>60</sup> Also there is the risk of amino acid deficiencies<sup>61</sup> The theory backing the therapy remains unproven and controversial, and further research is needed to determine the type of child that might benefit from these interventions.<sup>62</sup>

Over the years, various dietary therapies have been proposed as causes and /or treatment for ADHD.<sup>53</sup> There were conflicting and puzzling results from studies using the restrictive diets like the Feingold Diet. Restrictive diets may limit a child’s food selections leading to deficiencies. But the usage of foods in less processed forms along with reduction in sugar and sweets may be positive for not only the child with ADHD but also for the whole family. Children with food allergies may exhibit behaviors such as irritability and decreased attention. Food allergies have not been determined to be a factor in ADHD.

Parents of children with chronic illness or special needs should be encouraged to consult with their primary

care physician before introducing any new treatment, medication or dietary supplement into their child's regimen or before removing a prescribed therapy from their treatment plan. See *Appendix 2- Alternative Nutritional Therapies*

#### **IV - Reliable Sources of Information**

Fortunately, for those seeking pediatric specific information, recent work has identified hundreds of published randomized controlled trials (RCTs) that investigate NHPs in children.<sup>63</sup> The four journals that published the largest number of paediatric NHP RCTs were American Journal of Clinical Nutrition, Pediatrics, Journal of Pediatrics and Lancet. Medline indexed 93.2% of these RCTs, suggesting that the RCT-level evidence is easily accessed, if you look for it.<sup>64</sup>

Although some RCTs demonstrated the effectiveness of certain aspects of NHPs in the pediatric population, many of these studies suffer from inadequate methodological rigor.<sup>65</sup> Although some of these methodological issues are shared with RCTs in conventional medicine, their persistence promotes ongoing skepticism of NHPs. - *Table 2.*

#### **V- How to discuss CAM with parents**

The American Academy of Pediatrics Committee on Children with Disabilities has developed a statement regarding "Counseling Families Who Choose Complementary and Alternative Medicine for Their Child with Chronic Illness or Disability".<sup>66</sup> It can be used as a guide to follow when discussing CAM with patients and their families:

1. Ask about use: inquiring does not

- equal endorsing use
2. A non-judgmental attitude is preferred
3. Seek information for yourself and be prepared to share it with families
4. Evaluate scientific merits of specific therapeutic approaches
5. Identify risks or potential harmful effects (including opportunity costs, whereby known effective therapies are not pursued, and financial burden
6. Provide families with information on a range of therapeutic options (avoid therapeutic nihilism)
7. Educate families to evaluate information about all treatment approaches
8. Avoid dismissal of alternative therapies in a way that communicates a lack of sensitivity or concern for the family's perspective.
9. Recognize feeling threatened and guard against becoming defensive
10. Offer to assist in monitoring and evaluating the patients in ongoing follow-up

#### **VI - Future research in pediatrics and CAM**

There is an urgent need to collect safety and efficacy data about CAM in children. Frequently quoted obstacles to CAM research include: limited clinical data, lack of standardized products, complex interventions that are highly dependent on the individual, and concerns about the applicability of traditional research methodology.<sup>67,68,69</sup> Issues related to safety, including dosing, are critical in pediatric research. Whereas research in conventional pharmaceuticals has typically occurred in a sequence of animal and then adult human studies before exposing children, the research agenda in children should reflect the fact that children are already exposed to NHPs. NCCAM supports rigorous research on CAM, trains researchers in CAM, and disseminates information to the public and professionals on which CAM modalities work, which do not, and why.<sup>1</sup> Criteria used by NCCAM to prioritize research opportunities include: quantity and quality of preliminary data, extent

**Table 2- Where to find the evidence - Reliable Sources**

Resources	Criteria	Comments	Access
National Center for Complementary and Alternative Medicine (NCCAM)	<a href="http://nccam.nih.gov/htdig/search.html">http://nccam.nih.gov/htdig/search.html</a>	Informational website, part of US National Institutes of Health. Specific treatment information can be found at: <a href="http://nccam.nih.gov/health/bytreatment.htm">http://nccam.nih.gov/health/bytreatment.htm</a>	Free.
AMED (Allied and Complementary Medicine Database) 1985-present	Includes peer reviewed journals & others significant to the field.	Database includes English-language and European sources, journals, newspapers and books. Produced by the British Library. About 50% of the journals in AMED are indexed in MEDLINE.	Subscription Required.
Natural Standard	Systematic, peer-reviewed analyses of complementary and alternative therapies. <a href="http://www.naturalstandard.com/">http://www.naturalstandard.com/</a>	Evidence-based, individual studies are quality assessed with a validated scale and graded. Includes observational and experimental evidence.	Subscription Required.
The Health Professional's Guide to Popular Dietary Supplements. 2 <sup>nd</sup> edition, A. Fragakis, American Dietetic Association (ADA) 2003		Excellent review of dietary supplements including: media claims, research, key points and references.	Book for purchase from ADA <a href="http://www.eatright.org/Public/ProductCatalog/104.cfm">http://www.eatright.org/Public/ProductCatalog/104.cfm</a>
Institute of Medicine of the National Academy of Science. Framework for Evaluating the Safety of Dietary Supplements	<a href="http://www.iom.edu/project.asp?id=4605">http://www.iom.edu/project.asp?id=4605</a>	Informational website with a recently published framework for evaluating issues regarding ingredient safety in dietary supplements in the United States	Free
United States Food and Drug Administration. Center for Food Safety and Applied Nutrition	<a href="http://vm.cfsan.fda.gov/~dms/supplemnt.html">http://vm.cfsan.fda.gov/~dms/supplemnt.html</a>	Informational website providing background information regarding U.S. regulatory issues surrounding dietary supplements	Free

of public use, public health importance of disease being treated, feasibility, and cost.<sup>70</sup> Pediatric CAM research priorities have been identified as those: already widely used by children and families; already researched to some extent in animal models and adults; and having a potentially significant risk of substantial costs or side effects.<sup>71</sup> To this one could add therapies of potentially significant benefit or interaction with conventional therapeutic approaches. Since it is often not known what CAM therapies are being taken by sub-populations of children, there are renewed efforts by some funders to identify utilization data.<sup>72</sup> Since CAM is a patient-led phenomenon, it is appropriate to guide research priorities accordingly.

## VII- Where to go from here

The work to be done to improve pediatric CAM is enormous and varied in scope. Educational initiatives are needed at every level: consumers need to be informed about issues related to product heterogeneity and quality, and variations in practitioner educational backgrounds that are exacerbated when their field is not regulated. Trainees, both conventional and complementary, need an opportunity for cross-training, so they may learn about issues critical to shared patient care. Health care providers must be encouraged to ask about CAM use and to be aware of potential interaction and/or synergy between natural health products and conventional medications. Policy-makers need to continue to refine regulations of both CAM practitioners and products, so the public has access to safe CAM therapies. Research opportunities are many and varied, and in recent years, additional funding has become available. Improved dissemination of research results would promote consumer and health care provider knowledge. Fortunately, pediatric CAM research and education is garnering more attention across North America, and will help

promote the safe and informed use of CAM in children.

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## Appendix 1—Herbal Products

Herb	Typical Usage	Dosing	Side Effects	Drug Interactions	Contraindications	Research
<b>Cranberry</b>	<ul style="list-style-type: none"> <li>Prevent and treat Urinary tract infections</li> </ul>	<ul style="list-style-type: none"> <li>7.5 g concentrate in 50 ml</li> </ul>	<ul style="list-style-type: none"> <li>None known</li> </ul>	<ul style="list-style-type: none"> <li>None known</li> </ul>	<ul style="list-style-type: none"> <li>Allergies</li> </ul>	<ul style="list-style-type: none"> <li>No effectiveness noted in catheterized children</li> </ul>
<b>Echinacea</b>	<ul style="list-style-type: none"> <li>Supportive therapy for colds and chronic infections of the respiratory tract and lower urinary tract</li> <li>Wound healing</li> <li>Immune stimulation</li> <li>Antimicrobial</li> </ul>	<ul style="list-style-type: none"> <li>Not standardized</li> <li>Dried extract: 300-400 mg tid</li> <li>Tincture: 30-50 drops (1 drop = 20 µL) tid</li> </ul>	<ul style="list-style-type: none"> <li>Parenteral: short-term fever reactions, nausea and vomiting</li> <li>Anaphylaxis (rare)</li> </ul>	<ul style="list-style-type: none"> <li>May decrease effectiveness of immunosuppressant medication</li> </ul>	<ul style="list-style-type: none"> <li>Progressive systemic diseases, such as HIV, tuberculosis, leukosis, and multiple sclerosis</li> <li>Allergies</li> </ul>	<ul style="list-style-type: none"> <li>Although Echinacea may be efficacious, trial data is weak and inconclusive</li> <li>Species of Echinacea determines effectiveness</li> </ul>
<b>Ephedra</b>	<ul style="list-style-type: none"> <li>Weight loss</li> <li>Performance Enhancement</li> <li>Energy</li> <li>Asthma</li> </ul>	<ul style="list-style-type: none"> <li>Adults: Herb preparations corresponding to 15-30 mg total alkaloid</li> <li>Children: Herb preparations corresponding to 0.5 mg total alkaloid per kg of body weight</li> </ul>	<ul style="list-style-type: none"> <li>Insomnia</li> <li>Motor restlessness</li> <li>Irritability</li> <li>Headaches</li> <li>Nausea &amp; vomiting</li> <li>Disturbances of urination</li> <li>Tachycardia</li> </ul>	<ul style="list-style-type: none"> <li>Do not use with MAO inhibitors or cardiac glycosides</li> </ul>	<ul style="list-style-type: none"> <li>Associated with deaths related to MI and CVA</li> </ul>	<ul style="list-style-type: none"> <li>Combination of ephedra and caffeine containing herbs can cause dry mouth, heart palpitations, changes in blood pressure, and insomnia in some subjects.</li> <li>Recently banned by FDA however, available through internet sites</li> </ul>
<b>Garlic</b>	<ul style="list-style-type: none"> <li>Lowering elevated levels of lipids in the blood</li> <li>Preventative measure for age-dependent vascular changes</li> <li>Mild antihypertensive</li> <li>Ant platelet</li> <li>Antioxidant</li> <li>Antimicrobial</li> <li>Cancer prevention</li> </ul>	<ul style="list-style-type: none"> <li>Fresh cloves: 0.5- 1 qd</li> <li>Pills: 600-900 mg qd, standardized to 0.6%-1.3% allicin</li> <li>Powder: 0.4 to 1.2 g</li> </ul>	<ul style="list-style-type: none"> <li>Gastrointestinal symptoms</li> <li>Mild side effects: halitosis, body odor, topical irritations</li> <li>Allergy (rare)</li> </ul>	<ul style="list-style-type: none"> <li>Changes pharmacokinetic variables of paracetamol,</li> <li>Decreases blood concentrations of warfarin</li> <li>Produces hypoglycemia when taken with chlorpromide</li> <li>May increase bleeding time with aspirin</li> </ul>	<ul style="list-style-type: none"> <li>Garlic should not be consumed prior to surgery</li> <li>Increases the anticoagulant effect of warfarin</li> </ul>	<ul style="list-style-type: none"> <li>Dozens of trials suggest, but have not adequately proven, that garlic can decrease the risk factors for atherosclerosis, particularly hypercholesterolemia.</li> <li>Garlic is considered safe by the FDA, based on the lack of known serious adverse outcomes.</li> </ul>

## Appendix 1—Herbal Products - continued

Herb	Typical Usage	Dosing	Side Effects	Drug Interactions	Contraindications	Research
<b>Ginkgo</b>	<ul style="list-style-type: none"> <li>Memory deficits, disturbances in concentration, dizziness, headaches</li> <li>Antioxidant</li> </ul>	<ul style="list-style-type: none"> <li>Use extract standardized to 6% terpenoids, 24% flavonoids 40-80 mg bid-tid</li> </ul>	<ul style="list-style-type: none"> <li>Stomach or intestinal upset</li> <li>Headaches</li> <li>Allergic skin reaction</li> </ul>	<ul style="list-style-type: none"> <li>Bleeding when combined with warfarin and aspirin Do not use with NSAIDS</li> <li>Raised blood pressure when combined trazodone.</li> </ul>	<ul style="list-style-type: none"> <li>May enhance the action of platelet-aggregation inhibitors</li> <li>Contraindicated in patients with bleeding disorders</li> </ul>	<ul style="list-style-type: none"> <li>Encouraging data, but currently no compelling evidence shows that ginkgo enhances normal cognitive function</li> <li>Has been shown to be beneficial in treating dementia</li> </ul>
<b>Ginseng</b>	<ul style="list-style-type: none"> <li>Endurance/adaptation enhancer</li> <li>Enhances "quality of life"</li> <li>Immune/endocrine stimulant</li> </ul>	<ul style="list-style-type: none"> <li>Root: 1-3 g qd</li> <li>Pills: 100-300 mg tid, extract standardized to &gt; 7% ginsenosides</li> </ul>	<ul style="list-style-type: none"> <li>Diarrhea</li> <li>Euphoria</li> <li>Headache</li> <li>Hypertension</li> <li>Hypotension</li> <li>Insomnia</li> <li>Mastalgia</li> <li>Nausea</li> <li>Vaginal bleeding</li> </ul>	<ul style="list-style-type: none"> <li>Lowers blood concentrations of alcohol and warfarin</li> <li>Induces mania if used concomitantly with phenelzine</li> <li>May decrease effectiveness of antihypertensive and anti-estrogens</li> <li>May potentate effects of CNS stimulants and hypoglycemic</li> <li>May also decrease the effectiveness of immunosuppressant and potentate the effectiveness of sildenafil.</li> </ul>	<ul style="list-style-type: none"> <li>Hypertension, cardiovascular disease</li> <li>Hypotension</li> <li>Diabetes mellitus</li> </ul>	<ul style="list-style-type: none"> <li>Poor evidence to support the usage of Ginseng as an ergogenic aid or as an energy enhancer.</li> <li>Ginseng abuse syndrome often reported as a side effect but quality of original research was limited</li> </ul>
<b>Kava</b>	<ul style="list-style-type: none"> <li>Euphoric effect</li> <li>Stress</li> </ul>	<ul style="list-style-type: none"> <li>Wide therapeutic window</li> <li>70-240 mg of dried root extract qd</li> </ul>	<ul style="list-style-type: none"> <li>Reversible yellowish discoloring of skin, nails, and hair (chronic abuse)</li> <li>Visual disturbances</li> <li>Dizziness</li> <li>Gastrointestinal discomfort</li> <li>Extrapyramidal effects (rare)</li> <li>Hepatitis</li> </ul>	<ul style="list-style-type: none"> <li>Increases "off" periods in Parkinson patients taking levodopa and can cause a semi comatose state when given concomitantly with alprazolam.</li> </ul>	<ul style="list-style-type: none"> <li>Children &lt; 12 year, renal disease, thrombocytopenia, neutropenia</li> <li>Becoming an herb that is abused by adolescents seeking a legal high</li> </ul>	<ul style="list-style-type: none"> <li>In two small trials, results suggested that short-term administration of kava is effective in reducing anxiety</li> </ul>
<b>Goldenseal</b>	<ul style="list-style-type: none"> <li>Antibacterial, antiviral, ineffective</li> <li>Often combined with Echinacea which drives sales data</li> <li>Topical antibiotic</li> <li>Mouth sores and sore throats</li> </ul>	<ul style="list-style-type: none"> <li>As a topical preparation, apply cream adequate to cover wound</li> <li>For sore throats and mouth sores .5-1.0 gram in a cup of water</li> </ul>	<ul style="list-style-type: none"> <li>Photosensitivity</li> </ul>	<ul style="list-style-type: none"> <li>No serious drug interactions known</li> </ul>	<ul style="list-style-type: none"> <li>May cause jaundice and should be avoided by those with elevated bilirubin levels</li> <li>Women of childbearing age</li> </ul>	<ul style="list-style-type: none"> <li>No evidence showing goldenseal stimulates the immune system. Systemic absorption of this herb is poor</li> </ul>

## Appendix 1—Herbal Products - continued

Herb	Typical Usage	Dosing	Side Effects	Drug Interactions	Contraindications	Research
<b>St. John's Wort</b>	<ul style="list-style-type: none"> <li>—Mild to moderate depressive states, restlessness, anxiety, and irritability</li> <li>—Antimicrobial</li> <li>—Wound healing</li> <li>—Treatment of alcoholism</li> </ul>	<ul style="list-style-type: none"> <li>—Tablets: 320 mg tid of extract standardized to 0.3% hypericin</li> <li>—Topical</li> </ul>	<ul style="list-style-type: none"> <li>—photosensitization especially in fair skinned individuals</li> <li>—Cataracts may be a long term consequence</li> </ul>	<ul style="list-style-type: none"> <li>—Lowers blood concentrations of cyclosporine, amityline, digoxin, indinavir, warfarin, phenprocoumon and theophylline.</li> <li>—May cause inter-menstrual bleeding, delirium or mild serotonin syndrome, respectively, when used concomitantly with oral contraceptives, loperamide or serotonin-reuptake inhibitors. List of drug interactions is substantial</li> </ul>	<ul style="list-style-type: none"> <li>—Caution when taking serotonin uptake inhibitors.</li> <li>—Known photosensitivity</li> <li>—Do not give to children</li> </ul>	<ul style="list-style-type: none"> <li>—Several studies support St. John's Wort as an effective treatment for mild to moderate depression.</li> </ul>
<b>Valerian</b>	<ul style="list-style-type: none"> <li>—Sleep aid</li> <li>—Spasmodic</li> </ul>	<ul style="list-style-type: none"> <li>—Capsules: 400 mg qhs as necessary (&gt;12 years)</li> <li>—Tea: 2-3 g = 1 tsp tid</li> <li>—Tincture: 3-5 ml tid</li> </ul>	<ul style="list-style-type: none"> <li>—Headache</li> <li>—Palpitations</li> <li>—Insomnia</li> </ul>	<ul style="list-style-type: none"> <li>—Should not be taken with other sedatives or before driving or in situations where alertness is required</li> <li>—May take up to 4 weeks to be effective</li> </ul>	<ul style="list-style-type: none"> <li>—Pregnant women due to a cytotoxic and mutagenic activity in vitro</li> </ul>	<ul style="list-style-type: none"> <li>—In 2 randomized, blind, and placebo-controlled trials, valerian resulted in significantly improved sleep quality and decreased sleep latency, with no residual sedation in the morning.</li> <li>—Independent testing has shown valerian preparations may be contaminated with cadmium and lead</li> </ul>
<b>Evening primrose oil</b>	<ul style="list-style-type: none"> <li>—PMS</li> <li>—Cyclical breast pain</li> <li>—Diabetic neuropathy</li> <li>—Rheumatoid arthritis (RA)</li> <li>—Atopic dermatitis</li> </ul>	<ul style="list-style-type: none"> <li>—2-4 grams/day</li> <li>—Active ingredient is Gamma Linolenic acid</li> </ul>	<ul style="list-style-type: none"> <li>—nausea, best taken with food</li> <li>—Belching, bloating</li> </ul>	<ul style="list-style-type: none"> <li>—May lower seizure threshold in patients taking anticonvulsants or tricyclic antidepressants</li> </ul>	<ul style="list-style-type: none"> <li>—May effect platelet aggregation and should be used with caution with NSAIDS and anticoagulants</li> </ul>	<ul style="list-style-type: none"> <li>—Little solid data to support use in PMS</li> <li>—Conflicting data on use in RA</li> </ul>
<b>Grape seed</b>	<ul style="list-style-type: none"> <li>—Antioxidant</li> <li>—Bruising</li> <li>—Edema</li> <li>—Venous insufficiency</li> </ul>	<ul style="list-style-type: none"> <li>—Active ingredient proanthocyanidin</li> <li>—150-300 mg</li> <li>—Food sources of active ingredients include, red wine, tea, cranberries, blueberries</li> </ul>	<ul style="list-style-type: none"> <li>—Mild GI distress</li> <li>—Generally considered safe</li> </ul>	<ul style="list-style-type: none"> <li>—Caution with anticoagulant therapies</li> </ul>	<ul style="list-style-type: none"> <li>—Strong evidence for use in venous insufficiency</li> <li>—Recent RCT showed no efficacy in treating allergic symptoms</li> </ul>	

## Appendix 2 - Alternative Nutritional Therapy (special diets or vitamin/mineral supplements)

Condition	Diet or Vitamin/Mineral Supplements	Reason for Usage or Claims	Contraindications or concerns	Research/Comments
Down Syndrome (DS) <sup>48,49,50</sup>	Targeted Nutrition Intervention (TNI) Example - NuTriVene-D® (International Nutrition Maryland)	Improved health, growth, and immune function, cognitive enhancement, prevention of amelioration of long term degeneration and disability	A typical TNI s A typical TNI supplement contains about 56 nutrients including vitamins, mineral, enzymes, amino acids, electrolytes etc. Some of the vitamin/minerals contents exceed the recommended intake levels and other compounds do not have any established recommended intakes.	There has been no consistent or rigorous proof that any form of nutritional supplementation improves the outcome in DS. There is increasing evidence to suggest that increased oxidative stress may be involved in the pathology of DS. Therefore clinical trials are needed to evaluate the hypothesis that antioxidant supplementation may improve the outcome in DS.
Cystic Fibrosis (CF) <sup>55,56</sup>	Mannatech® Optimal Health Products (OHP), "neutraceuticals and "glyconutrients" products are based on the aloe vera plant. The key ingredient in the product is Ambertose, "a patent pending blend of specific plant-based complex carbohydrates that contain sugars necessary for the proper glycosylation of cellular proteins."	Carbohydrate Metabolism: when adequate glucose is not available (as in fasting or high-level energy expenditure), amino acids are converted to glucose through the process of gluconeogenesis. Marketing Claims: Acknowledgement that we can synthesize the carbohydrate in Ambertose, but indicates many elements (toxins, stress, drugs, virus and other "invaders") can interfere in the conversion process and "may leave the body without all the necessary carbohydrate to form proper cell-to-cell words".	Aloe Vera is unstable and inactivated when processed.	Cystic Fibrosis (CF) Foundation response in 2003 was that "Mannatech® Optimal Health Products (OHP), have been promoted as a possible treatment or cure for CF. Whereas these products may have health benefits for some people with CF, there is very little scientific evidence to corroborate these claims. In addition, there is no data as to the safety of these supplements when taken in high doses for a period of time.
Autism Spectrum Disorder (ASD) <sup>60, 61, 62</sup>	Gluten-and Casein-free Diets	Gluten – and Casein-free diet is based on the "excess opioid peptide theory" In theory, autistic symptoms are thought to be due to opioid peptides (gluten and casein can become opioid peptides) entering the blood stream through the "leaky gut" and reaching the brain or there could be lack of enzymes to break down the proteins properly. Too much opioid may have an undesirable effect in the brain and contribute to autistic-like symptoms.	Elimination diets can be potentially harmful in young children, there is concern that such treatment without appropriate guidance, may result in compromised nutritional status and impaired growth. Additionally, given that children with ASD tend to be more selective eaters due to behavioural issues than other children, nutritional concerns should remain a priority in this population.	The theory backing the therapy remains unproven and controversial, further research is needed to determine the type of child that might benefit from these interventions. Recent research suggests that restricted diets may exacerbate the essential amino acid deficiencies identified in children with ASD.
	Vitamin B6 – Magnesium used in treatment of ASD .	To diminish undesirable behaviours and to improve attention, speech, sleep patterns, eye contact, eye contact, reduce hyperactivity and self-stimulation and improve health.	The vitamin B6 is given along with magnesium to counterbalance the deficiency of magnesium that mega-dose B6 can induce. Overall toxicity of the B6 has been rare but acute doses have been known to cause ataxia, loss of fine-motor control, changes in gait and peripheral neuropathy in humans.	Recent Cochrane review concluded that there is no evidence of an acceptable high level to state that a combination of Vitamin B6 and magnesium improves the behaviour or social and communication skills of children and adults with autism.

**Appendix 2 - Alternative Nutritional Therapy (special diets or vitamin/mineral supplements) - continued**

Condition	Diet or Vitamin/Mineral Supplements	Reason for Usage or Claims	Contraindications or concerns	Research
Attention Deficit Hyperactivity Disorder (ADHD) <small>53, 54</small>	Restrictive Diets - Feingold Diet or Food Additives and Salicylates free diets. Later other restrictions were added like preservatives, sugar, milk and any other food that the child could not tolerate.	To reduce hyperactivity behaviour.	The restrictive diets are being used for a variety of problems leading to possible deficiencies from limiting selections of foods. Families should work with a dietitian and other health professionals if the child's diet is being altered or restricted for behavioural management.	Earlier results appeared positive but the studies were not controlled and the positive results reported were believed to be a placebo effect.
	Fatty Acid Supplementation - DHA (docosahexaenoic acid)	Proposed that altered fatty acid metabolism may occur in some children with ADHD. Some children with ADHD may have essential fatty acid deficiency.		A recent, randomized, double blind, placebo controlled study trial was conducted in 63 children where children were given DHA (docosahexaenoic acid) or placebo for 4 months. However, there was no statistically significant improvement in any objective (attention tests) or subjective measures (parent evaluations of behaviour) of ADHD symptoms.
	Megavitamin Therapy (especially Vitamin B6, thiamine, magnesium, zinc and iron)	Claim that the children with ADHD and learning problems have biochemical imbalances and that these disturbances can be eliminated by mega-vitamin therapy.	The use megavitamins can be dangerous leading to liver toxicity. In addition families may spend a lot of money on vitamins without addressing the basic problems related to the behaviour issues.	Additional controlled studies have not indicated any benefit from megavitamin therapy for ADHD.
Diabetes <sup>51</sup>	Vitamin/trace elements including - Chromium most studied, L-Carnitine and Vanadium less conclusive	For glycemic control in Diabetes Chromium's action is linked with glucose tolerance factor (GTF) and has been shown to increase the number of insulin receptors, to enhance receptor binding, and to potentiate insulin action.	No reported adverse effects from the chromium used in the trials.	Chromium has been studied the most - but without reliable assays to check for deficiencies, these theories have been difficult to test. L-Carnitine and Vanadium preliminary studies have been promising but warrant further study.
Cancer <sup>38</sup>	Centre for Integrated Healing "Holistic healing" program." Diet is one part of the program. They prescribe vitamins and minerals and guidelines for a "healthy diet." Part of the guidelines stress minimal dairy and minimal animal fat consumption.	Their literature stresses that spontaneous healing of advanced, untreatable cancer can happen and they outline the criteria for this. Their philosophy is to eat "whole foods that nature provides - avoid refined, processed and adulterated foods".	The supplements they prescribe are at very high levels - for example up to 12 grams Vitamin C daily and 50,000 IU of beta-carotene and up to 1600 IU of Vitamin D, etc. There is concern with recommendations for usage of mega vitamins, minerals for a child who needs extra calories, mega-doses should be avoided.	The program advocates for individualization but the recommendations made are often based on anecdotal information without the scientific research to back them up. There is concern that a patient will be compromising their care from standard therapy when they are on this program. <i>(As per communication with Marlene Wardle RD, April 21, 2004, Oncology Dietitian at British Columbia Childrens Hospital, Vancouver, BC, Canada)</i>