Assessment of the Pharmacology, Toxicology, Safety and Efficacy of Echinacea Species

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1.0 Introduction

1.1 Background

A literature search was conducted to examine and evaluate Echinacea for purposes of determining its biochemical actions, pharmacology, regulatory status, safety, and therapeutic uses. The findings are presented in this review.

1.2 Historical Perspective

Extracts from plants have been used for their therapeutic properties since before recorded time. Many drugs used today were originally isolated from plants, e.g. morphine from poppy, digoxin from foxglove and salicylic acid from willow.

Echinacea is a therapeutic plant indigenous to the United States (U.S.) It has been found throughout the U.S. but mainly in the area from the mid-west to the prairie regions of Pennsylvania. Echinacea has been described as the most important plant used by Native Americans for the treatment of diseases. The name Echinacea is derived from the Greek echinos for sea urchin or hedgehog due to its spiny appearance. It is a perennial member of the daisy or asteraceae family and grows 1 to 2 feet tall. The taste is slightly sweet, then bitter. Echinacea leaves a tingling sensation on the tongue after oral administration. The odor is faintly aromatic.

There are nine different Echinacea species. Three species predominately used in herbal medications are Echinacea angustifolia (narrow leaved coneflower), Echinacea pallida (pale purple coneflower) and Echinacea purpurea (purple coneflower). Two species used on a more limited basis are Echinacea paradoxa and Echinacea simulata. Synonyms for Echinacea are Black Sampson, Coneflower, Niggerhead, Rudbeckia, Brauneria pallida (Nutt.) Sampson Root, Sonnenhutwurzel, Igelkopfwurzel (German), Racine d'Echinacea (French), Scurvy Root and Hedgehog.

Historically, Echinacea has been credited for playing a role in the cure of many conditions and diseases. In fact, Echinacea was one of the most popular natural treatments in the U.S. in 1898, but by the early 1900's it fell out of favor. At that time, medical care focus changed to the germ theory, newly discovered antibiotics and available synthetic drugs. An article published in the 1909 Journal of the American Medical Association stated, “Echinacea was unworthy of future consideration”. Echinacea's use in the U.S. almost ground to a halt in the 1930's with the introduction of the Food and Drug Administration's (FDA) stricter requirement for drug testing.

Echinacea was introduced to the European homeopathic practitioner in the late 1800's. As Echinacea's popularity grew, a supply shortage in Europe developed. To overcome the shortage, Dr. Gerhard Madaus of Madaus & Company, Cologne, Germany, purchased seeds from the U.S. and started cultivating Echinacea.
purpurea in Germany.\(^2\) With their own readily available supply of Echinacea, Europeans, particularly Germans, continued to use Echinacea, and its popularity maintained a steady growth.\(^{15,17}\)

1.3 Echinacea Use In Modern Times

Germany uses the greatest amount of herbal medications/herbal medications mixtures. “Today in Germany most of the herbal drugs, even mixtures of herbal drugs, are registered as conventional drugs. This means that they meet the same stringent criteria of quality, efficacy and safety as synthetic drugs.”\(^{18}\) Currently, in France, Italy, Austria, Switzerland and Germany, herbs and herb-based medicines are an integral part of conventional medicine.\(^{1,14}\)

1.4 European Regulatory Status

Commission E was established by the German government (German Federal Institute for Drugs and Medical Devices) in 1978 to evaluate herbal remedies for safety and efficacy.\(^{19}\) Since 1978, Commission E has published over 300 monographs detailing herbal extracts and mixtures of herbal extracts, their safety, effectiveness, adverse events, contraindications and dose ranges. The monographs were recently translated into English.\(^{20}\) Unfortunately, the monographs do not site the references used in the printed conclusions, which makes it difficult to evaluate the monograph’s statements and recommendations from a scientific perspective. Commission E recognized and approved for use Echinacea purpurea herb in 1989 and Echinacea pallida herb, Echinacea purpurea root and Echinacea angustifolia herb and root in 1992.\(^{20}\) More than three million herbal prescriptions are written each year in Germany and in 1996, 500 different Echinacea containing products were reported on the market.\(^{3,15}\)

1.5 Uses Among the U.S. Population

Echinacea was reintroduced to the U.S. from European manufacturers in the 1970’s and its popularity continues to grow.\(^{13}\) In 1990, 3 in 10 U.S. adults were found to use some form of non-conventional treatment. In 1997, the number was 4 in 10.\(^{9,21,22}\) Use of herbal remedies is more common among the well educated, the affluent and women.\(^{23}\) Older persons of both sexes are also more likely to use herbal remedies.\(^{9}\)

In the U.S., herbal remedies are classified as phytoceuticals, medicinal herbs, botanicals or dietary supplements.\(^{24,25}\) Use of herbal remedies is considered by some as integrative, unproven, unconventional, complementary or alternative medicine. Herbal remedies do not conform to the standards of the mainstream medical community, receive relatively little attention in U.S. medical schools and are not commonly reimbursed by health insurance plans.\(^{26}\)
1.6 U.S. Regulatory Status

In 1994 the U.S. Dietary Supplement Health and Education Act (DSHEA) was established. By passing this act, Congress intended to allow consumers the opportunity to decide for themselves about supplement use. Under the DSHEA, herbal products do not have to prove they are safe before marketing. Health claims cannot be made indicating that the herb will prevent a disease but claims can be made in relation to maintenance of health.

In contrast to herbal remedies, prescription and over-the-counter medications have stringent examination before they are presented to the public. To date, there is no legal requirement for testing herbal products before or after marketing. Once marketed the burden of proof is on the U.S. Food and Drug Administration (FDA) to prove that a dietary supplement is unsafe and must be removed from shelves. Two working groups under the Botanical Subcommittee of FDA's Center for Drug Evaluation and Research (CDER) have been established to develop regulatory guidelines for the approval of botanicals as pharmaceuticals.

Herbal remedies often report effectiveness based on anecdotal reports and testimonials. There are more than 400 herbal studies that have been published dealing with 324 different plants and plant substances used as medicinals. Many of these studies are published in German and have not been translated into English. Additionally, most of the studies have not been evaluated by U.S. regulatory agencies. Various authors have reviewed the studies in German and reported a lack of study design, conduct, randomization and serious concerns about the quality of methodology. In 1997, a National Institutes of Health expert panel reviewed studies published in German and English. The conclusion of the panel was that current evidence is inadequate for development of practice guidelines for alternative therapies largely because of the lack of relevant outcome data from high-quality clinical trials. Some advocates of herbal remedies respond to the lack of clinical data by saying that alternative therapies cannot be subjected to the standard scientific method but instead must rely on anecdotes, beliefs, theories, testimonials and opinions to support effectiveness and justify continued use.

Herbal studies carried out in the U.S. are limited. This is most likely due to the fact that manufacturers of herbal remedies are not required to conduct clinical studies. Further, under DSHEA the manufacturers cannot be required to conduct clinical studies unless they plan to market products as drugs rather than as dietary supplement.

There is a financial disincentive for the herbal industry to support clinical efficacy research. Companies often state that lack of patent protection prevents them from conducting clinical trials because there is little potential to gain a competitive
advantage. The plants themselves cannot be patented; the process to extract the active component of the plant may be.

In 1992, The National Institutes of Health established the Office of Alternative Medicine (OAH) which has as its purpose to sponsor: research; grant writing workshops; clinical investigations; conferences; international liaison; liaison with the National Institute of Health Institutes and other governmental agencies (e.g. HCFA, AHCPR and FDA); and the development and oversight of ten federally funded centers for alternative medicine research. In addition, the federal government’s National Toxicology Program (NTP) has recognized the need to study herbal remedies. In December 1999, it was reported that NTP will design and initiate studies to identify adverse effects of prolonged use or high doses of herbal remedies. Studies will focus on the most popular herbals including Echinacea.
2.0 Echinacea Plants

2.1 Characteristics

2.1.1 Parts Of The Plant Utilized

Phytochemicals vary among the many Echinacea species and occur at various concentrations in different parts of the plant.\(^{15,30}\) The parts of the plants utilized for their medicinal purposes are as follows:

- **Echinacea purpurea** herb - fresh above ground parts harvested at flowering time and freshly processed above ground parts harvested during the flowering season
- **Echinacea purpurea** root - underground parts harvested mechanically
- **Echinacea pallida** - fresh or dried above ground parts collected at the time of flowering
- **Echinacea pallida** root - fresh or dried root cultivated using a plow, air-dried.
- **Echinacea angustifolia** - fresh or dried roots or the fresh or dried above ground parts collected at the time of flowering.\(^6,20\)

The uniqueness of each species is clearly demonstrated by specific parts of the species used, how it is harvested and prepared.

2.1.2 Growing Conditions and Environmental Influences

Plant maturity, soil, climate and harvest schedule can also cause phytochemical variations. Additionally, poor record keeping by gatherers and importers of herbs and nonstandardized identification techniques influence phytochemical content.\(^{19}\) Herbal industry experts appear to recognize some of these problems and have developed a mandate to become responsible, proactive and to self-regulate products. Experts have publicly stated “We have seen that there is the need to assure the quality of herbal products, beginning with their collection and harvesting to handling and processing, along with appropriate good manufacturing practices.”\(^{14}\) To maintain the integrity of the Echinacea it has been suggested that the harvest date be included on Echinacea product labels.\(^{31}\)

2.3 Storage

Most monographs specify that Echinacea products should be stored at room temperature i.e., between 59° F and 86° F or 15° C to 30° C.\(^{32}\) The monographs further specify that the raw herb, tinctures or infusions should be stored in airtight, dry and light resistant containers.\(^{16,32}\)
2.4 Need For Standardization

The many influences on phytochemical composition and activity, added to the fact that Echinacea is often found in combination with other potentially active herbs leads to a confusing mix of products offering different dosages and dosing formats. This confusion is further compounded by a lack of adequate regulation among herbal plant manufacturers. Standardization would establish levels of an active ingredient or ingredients in a final product.

Standardization was named as one of the most important research needs for herbal medicines at the National Institute of Environmental Health Sciences International Workshop to "Evaluate Research Needs on the Use and Safety of Medicinal Herbs" in 1996. Organizations working towards standardization include: The International Federation of Pharmaceutical Manufacturers Association and the WHO Program on International Drug Monitoring. The International Federation of Pharmaceutical Manufacturers Association represents the global research-based pharmaceutical industry and aims to ensure the same standards of safety, quality and efficacy for new medications and more efficient registration for use worldwide. The WHO Program on International Drug Monitoring has established a project based at the Uppsala Sweden Monitoring Center. The project has as its mission attainment of "global standardization of herbal medicines".

Research has also been done to differentiate the Echinacea seed prior to planting. Each species seed has its own unique structure (e.g. shape, anatomy) and phytochemical property (components, essential oil, alkamides).
3.0 Biochemical Actions and Pharmacology

It is important to identify the biologically active component(s) of Echinacea. In many cases the overall pharmacologic effects and therapeutic actions may not be derived from a single compound but from a combination of several compounds, each contributing to the effect.

Many studies have been done to isolate the active ingredient(s) in Echinacea. Some biochemical constituents that Echinacea purpurea, Echinacea pallida and Echinacea angustifolia have in common are: polysaccharides, glycoproteins, echiacoside, caffeoyl conjugates and lipid components.4

3.1 Polysaccharides

3.1.1 Echinacea purpurea

Purified polysaccharide fractions from Echinacea purpurea have been shown to stimulate macrophages independent of T-cells.37-40 The immunostimulating fraction of Echinacea purpurea herb are two heteroglycans with molecular weight of 35,000 and 450,000 Dalton with 4-O-methylglucurononoarabinoxylan being identified as the most active heteroglycan.31 4'7 42

Acidic arabinogalactan was shown in one study to be effective in activating macrophages to cause cytotoxicity against tumor cells and microorganisms (Leishmania enriettii). Acidic arabinogalactan induced macrophages to produce tumor necrosis factor, interleukin 1 and interferon-beta 2. It did not activate B cells nor did it induce T cells to produce interleukin 2, interferon-beta 2 or interferon-gamma. A slight increase in T cell proliferation was observed.37

The isolated polysaccharide neutral fucogalactoxyloglucan from Echinacea purpurea has no mutagenic effect on human lymphocytes.2

Polysaccharides also act as anti-inflammatory agents. Echinacea purpurea root polysaccharides have been shown to inhibit edema in both mouse ear and hind paw of the rat.39

Purified polysaccharides from Echinacea purpurea in vitro stimulated macrophages to high toxicity against tumor cells. The polysaccharides caused the macrophages to produce and secrete oxygen radicals and interleukin 1. The therapeutic action appeared to be independent of lymphocytes. The polysaccharides were unable to stimulate T-lymphocytes but B-lymphocytes did proliferate. In tissue culture, the polysaccharides were found to be completely nontoxic. The author concluded that
purified polysaccharides from Echinacea purpurea might have therapeutic value with tumors and infectious diseases.\textsuperscript{5}

3.1.2 Echinacea pallida

Echinacea pallida root contains the water-soluble immunostimulating polysaccharides acidic arabinorhamnogalactans.\textsuperscript{6}

3.1.3 Echinacea angustifolia

Echinacea angustifolia also has an anti-inflammatory fraction. The Echinacea angustifolia fraction has a molecular weight between 30,000 and 100,000 Dalton.\textsuperscript{42}

3.2 Glycoproteins

Echinacea purpurea root is known to contain immunostimulating glycoproteins.\textsuperscript{6} The glycoproteins, arabinogalactan proteins, have their own unique antigenic regions. This uniqueness was determined when the arabinogalactan proteins extracted from Baptisia tinctoria, an immunostimulating herb, were compared with the arabinogalactan proteins found in Echinacea purpurea.\textsuperscript{43}

3.3 Alkamides

The alkamide fraction of Echinacea has been suggested as the component most relevant for Echinacea standardization.\textsuperscript{31} Alkamides are mainly found in the roots and each species is unique.\textsuperscript{12} While above ground parts of the three species have very similar alkamide patterns, the roots have very different patterns. The roots of Echinacea purpurea and Echinacea angustifolia contain alkamides while the roots of Echinacea pallida have relatively small amounts of alkamides but contain larger amounts of ketoalkenes.\textsuperscript{7,44} Two additional Echinacea species are being researched. They are Echinacea simulata and Echinacea paradoxa. Echinacea simulata contains the same alkamides found in Echinacea angustifolia and ketoalkenes like those found in Echinacea pallida\textsuperscript{10} Echinacea paradoxa contained ketoalkenynes that were almost identical to those found in Echinacea pallida\textsuperscript{10}

However, the alkamide fraction may not be the best fraction for standardization. Perry tested Echinacea purpurea to determine if chopping, drying and temperature variations have any impact on alkamide levels. Alkamide levels are slightly reduced by chopping; drying had no effect but temperature had a significant impact. It has been reported that storing Echinacea at the temperature of 24°C for 64 weeks resulted in >80% decrease in alkamide level. Deep-freezing (-18°C) also resulted in a significant decrease in alkamide level falling to 60% of the highest level in 64 week samples.\textsuperscript{31}
The *n*-hexane alkamide extract of *Echinacea angustifolia* has been shown to working as an anti-inflammatory agent.\(^{45}\)

### 3.4 Echinacoside and Caffeoyl Conjugates

Echinacoside present in *Echinacea* does not provide antibacterial or immunologic activity, but stimulates phagocytosis.\(^{37}\) Along with choric acid, echinacoside has also been shown to protect native collagen from free radical damage through a scavenging effect on reactive oxygen species, and/or C-, N-, S-centered secondary radicals.\(^{46}\)

The enzyme hyaluronidase is produced by some pathogens and is used to penetrate tissues and thereby causes infection. Caffeoyl conjugates, chicoric acid and caftaric acids found in *Echinacea angustifolia* roots demonstrate a high anti-hyaluronidase activity thereby creating activity in the immune system. The anti-hyaluronidase action participates in connective tissue regeneration and elimination of pathogenic organisms.\(^{37}\)

### 3.5 Lipid Components

*Echinacea* also contains lipid and lipid soluble components. The anti-tumor activity is thought to be attributable to Echinacin, a polysaccharide, and an oncolytic lipid-soluble hydrocarbon in *Echinacea*’s essential oil. USDA researchers have discovered a tumor-inhibiting oncolytic lipid soluble hydrocarbon for the essential oil of *Echinacea* that may be tumor inhibiting.\(^{39}\) (A list of the volatile oils found in *Echinacea* species can be found in reference 6).

The lipophilic fractions of *Echinacea purpurea*, *Echinacea pallida* and *Echinacea angustifolia* roots (ethanolic extracts) appear to be more active than the polar fractions.\(^{37}\)
4.0 Safety

4.1 Background

There is little doubt that many medicinal herbs have preventive and/or therapeutic effects. Like any therapeutic agent, adverse events can occur if overdosed or used incorrectly. The adverse events may be due to consumer and/or health care provider lack of knowledge of the toxic potential of some herbal remedies. Consumers and health care providers alike may also be unaware of the herb-to-herb interactions and herb-to-drug interactions.\textsuperscript{1,47} Many consumers incorrectly believe that herbal remedies are safe because they are "natural", they pose no risk and do not cause side effects.\textsuperscript{1,23,28,47-49} In addition, because they are natural products, many consumers fail to tell their health care providers that they are taking herbal remedies.\textsuperscript{1,29} It has been reported that as many as 70 percent of subjects taking alternative medications do not communicate this to their physicians.\textsuperscript{26,50}

The increasing use of herbal remedies in the U.S. has resulted in the need to assess the safety of these products. One recent market survey reported that Americans spend close to $4 billion a year on herbal supplements and that Echinacea preparations are the leading botanical medicine with close to 10% of the herbal product market.

4.2 Contraindications

4.2.1 Allergic Reactions

Individuals with atopy could be at risk for developing life-threatening allergic reactions and anaphylaxis if they are allergic to members of the sunflower family asteraceae or other structurally similar allergens.\textsuperscript{9,32,33,51}

4.2.3 Disease Conditions

Because of conceivable activation of autoimmune aggression and other overactive immune responses, Echinacea is not recommended in progressive systemic and autoimmune disorders such as AIDS, or AIDS related illnesses, any autoimmune disorder, tuberculosis, multiple sclerosis, leucosis, collagen disorders and diabetes mellitus.\textsuperscript{6,9,30,32,51,52}

(NOTE: reference 6 and 20 only caution use in diabetics if used parenterally)

4.2.4 Drug Interactions

Echinacea-drug interactions were cited in the literature but no explanations were provided. Echinacea should be avoided when taking anabolic steroids, amiodarone, methotrexate or ketoconazole.\textsuperscript{32,51}
4.2.5 Pregnancy, Labor and Delivery and Nursing Pregnancy

Information regarding the safety of Echinacea in pregnant women is sparse. The Commission E monograph addresses the pharmacologic effects of Echinacea angustifolia herb and root and Echinacea pallida herb and root by stating "do not use during pregnancy". Other literature states "Do not use if pregnant-Safety for use in pregnancy has not been established. Some contraindications are thought to exist." The Physician's Desk Reference states, "Parental administration should be avoided during pregnancy."  

In animal models, Echinacea has not been found to be mutagenic in bacterial or mammalian cell assays. In experimental situations Echinacea has been found to exhibit a weak oxytocic effect. Echinacea purpurea did not produce malignant cell transformation in a hamster embryo model for an in vitro carcinogenicity study.

Currently, a study on Echinacea use during pregnancy is being conducted at the Hospital for Sick Children, Toronto Canada. The objective of this study is to determine the safety of Echinacea in pregnancy as well as patient perception of risk in comparison to pharmaceutical drugs. Studies have not been conducted to determine Echinacea's effects on labor and delivery or in nursing animals.

4.2.6 Adverse Events

In early 1993, the FDA Center for Food Safety and Applied Nutrition Office of Special Nutritionals began to maintain a voluntary reporting system for consumers and health care professionals.

As of October 20, 1998, there were 2,621 adverse events reported related to herbal use from a total of 3,451 products. Of these adverse events, there were 52 matches for Echinacea with 47 adverse event reports. Of the 52 matches, 22 (42%) were reported with Echinacea use alone and 30 (58%) were combined with one or more herbal products. It should be noted that the information submitted to the FDA provides no certainty that a reported adverse event can be attributed to Echinacea, as the information collected is insufficient to make this determination. This data cannot be used to estimate the incidence rate of occurrence in the general population. Appendix A provides descriptions of adverse event reported to the U.S. Food and Drug Administration Center for Food Safety and Applied Nutrition Office of Special Nutritionals for Echinacea and products with Echinacea as one of the ingredients.

Adverse events from correctly administered Echinacea preparations are thought to be rare. Only at concentrations 1000-times higher than the lower concentration at which beneficial enhancement of proliferation observed, was inhibition of human lymphocyte proliferation to phytohemagglutinin observed in vitro.
reported lack of adverse events in healthy subjects, infants and children as well as subjects receiving Echinacea preparations orally for periods of 10 to 12 weeks. Echinacea has been found not to alter total and LDL cholesterol, triglycerides or glucose levels.

Echinacin® has been shown to be non-toxic in rats and mice at doses far in excess of those used in human therapy: in vitro mutagenicity and carcinogenicity tests are also negative.

In human studies, the most common reactions were:

1. Symptoms of immunostimulation such as shivering, fever and muscle weakness in adults and children are often associated with parenteral and intramuscular administration but not generally observed following oral administration. In some cases, the symptoms can be attributed to the stimulation of cytokinase, a therapeutic goal.

2. Dislike of Echinacea's taste was the major complaint from 21 subjects (1.07%) out of a total of 1,231 subjects being treated for relapsing respiratory and urinary infections treated for 4-6 weeks with Echinacin® lozenges, 1 lozenge, 3 times daily.

3. In a study in 108 subjects, 4 (7%) of the subjects receiving Echinacea reported, central nervous system symptoms (tiredness, somnolence, dizziness, headache, aggressiveness). Gastrointestinal symptoms (nausea or heartburn after intake, mild epigastric pain, constipation) were reported equally by 4 subjects in the treatment and placebo groups (7%, 7%, respectively); and

4. Allergic skin reactions in 4 cases casually related to Echinacin® treatment from 1989 to 1995 were reported.

4.2.7 Duration of Echinacea Use and Safety

The duration of Echinacea use is controversial. The literature often states that Echinacea can be used for up to and including 8 weeks. Tachyphylaxis is said to occur if Echinacea is used for more than 8 weeks although mechanisms, which could explain this phenomenon, have not been identified. It has been stated that if used beyond 8 weeks, Echinacea could cause hepatotoxicity and therefore it should not be used with other known hepatotoxic drugs. The magnitude of this hepatotoxicity has been questioned since Echinacea lacks the 1, 2 unsaturated necrine ring system associated with hepatotoxicity of pyrrolizidine alkaloids.

Thus, there is no clear evidence that use should be restricted to less than 8 weeks. Echinacea has been administered up to 12 weeks with no adverse events reported.
4.2.8 Duration of Echinacea Use and Safety in Animal Models

Single oral or intravenous doses of Echinacea purpurea were found to be non-toxic in rats and mice. When rats received Echinacea purpurea for 4 weeks, at levels up to 60 times higher than recommended in the Commission E monograph, toxicity was not found. Microorganisms and mammalian cells in vitro and in mice gave negative tests results for mutagenicity.
5.0 Efficacy

Throughout the literature Echinacea has been credited with playing a role in the cure of many conditions and diseases including "colds, tonsillitis, toothache, boils, carbuncles, abscesses, typhoid fever, puerperal fever, diphtheria, bed sores, phlebitis, bowel pain, snake bites, rabies, seizures, wound infection, bad blood and cancer". Many of these claims are based on wives' tales, anecdotal reports and personal testimony and cannot be verified. Scientific studies on Echinacea reported in the literature are summarized below:

It is important to note that many of the scientific studies used Echinacin®, a lyophilized expressed juice from Echinacea purpurea available from Madaus & Company Cologne, Germany, as the study drug. Echinacin® is available for parenteral use, as Echinacin® Liquidum (2.5:1 dilution) and as lozenges® (88.5 mg per lozenge). The main active component in Echinacin® is the 75,000 Dalton polysaccharide acidic arabinogalactan.

Equally as important in the therapeutic use review is the fact that many Echinacea studies are available only in German and the original published studies could not be translated. Instead, review articles, of the original published studies, written in English were relied upon.

5.1 Specific Therapeutic Relationships

5.1.1 Skin

Topical extracts from Echinacea species have been found to be effective in a variety of skin disorders. Extracts may be used for the prevention and treatment of photo damage of the skin by UVA/UVB radiation in which oxidative stress plays a critical role.

Echinacea extracts were used in a study of 4500 subjects with inflammatory skin conditions including psoriasis. Eighty-five percent of the subjects were cured with topical applications of Echinacea.

In animal models, partially purified aqueous extracts of Echinacea angustifolia inhibited edema, when applied topically and intravenously. In mice, topically applied extract inhibited croton oil induced edema. In rats Echinacea angustifolia extract administered intravenously inhibited carrageen induced edema in the hind paw.

5.1.2 Respiratory Infection

5.1.2.2 Upper Respiratory Infections in Children and Adults
In an uncontrolled study involving 170 children with whooping cough, 77 were treated with antibiotics alone, 30 with a combination of antibiotics and Echinacin® and 63 with Echinacin® alone. Improvement was more rapid in children treated with Echinacin® alone and infection reoccurred more frequently when Echinacin® was administered with the antibiotic.²

In an uncontrolled study involving 257 children, ranging in age from infants to 14 years of age, suffering from severe cough with vomiting 1-2 week duration, Echinacin® was administered (0.1g/2ml intramuscularly) twice daily for 3-21 days. Study subjects experienced recovery within 5-14 days.⁵

In adults, eight out of nine respiratory infection studies reported a positive response as a result of Echinacea administration. In the eight studies reporting positive responses, six studies showed a statistically significant benefit and two showed a trend. The six displaying significance were divided into two groups. Four of the six focused on subjects with upper respiratory symptoms and two focused on subjects with flu-like symptoms (fever, chills and muscle ache). The species and parts of the Echinacea plant differed in the six studies. Echinacea angustifolia herb and root and Echinacea purpurea root were administered in two studies and Echinacea purpurea herb and root, Echinacea purpurea (part not specified) were each administered in one study. Lack of objective validated measures was identified as a weakness in these adult respiratory studies.¹⁵

The ninth study failed to show a benefit and is unpublished. The lack of efficacy was reportedly related to insufficient dose of Echinacea angustifolia. The dose used in this study was not reported however.¹⁵ The amount of Echinacea used therapeutically was reviewed by Melchart et al. He found that 900 mg per day of an ethanolic extract of Echinacea purpurea had a positive effect on the symptoms of upper respiratory infection whereas 450 mg per day did not.¹⁸

Henneicke-von Zepelin found a significant improvement in cold symptoms (p<0.05) when studying 259 patients receiving either Esberitox® N (containing 7.5 mg of Echinacea purpurea root and Echinacea pallida root, 1:1 plus other ingredients) or placebo.⁵⁸

5.1.2.3 Prophylactic for Upper Respiratory Infections

Evidence to support prophylactic use of Echinacea to reduce the incidence of upper respiratory infections is inconclusive. One hundred nine subjects, having had more than 3 colds the previous winter, took part in an 8-week double-blind placebo controlled study comparing treatment of oral Echinacin® Liquidum (n=54) with placebo twice daily (n=54) (one subject dropped from study). Blood samples were taken at three intervals: prior to taking study drug, after 4 and after 8 weeks. The study concluded that subjects receiving Echinacin® were somewhat healthier than
the placebo-treated subjects.\textsuperscript{2} Subjects receiving Echinacin\textregistered{} had less numbers of colds (incidence), the colds were rated as less harsh (severity), and lasted for a shorter number of days (duration).

<table>
<thead>
<tr>
<th></th>
<th>Study Drug</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Incidence</td>
<td>19%</td>
<td>32%</td>
</tr>
<tr>
<td>Severity</td>
<td>17%</td>
<td>37%</td>
</tr>
<tr>
<td>Duration</td>
<td>5.34 days</td>
<td>7.54 days</td>
</tr>
</tbody>
</table>

A review of 4 upper respiratory infections prevention studies in adults published from January 1997 to February 1999 revealed that three of the prevention studies reported marginal benefits while the fourth study did not.\textsuperscript{15}

In contrast, 47 healthy marathon runners receiving 12 weeks of either Echinacin\textregistered{} lozenges (n=23) or placebo (n=24) were studied. The incidence of the common cold was not significantly different between the groups. Subjects were found to be equally insensitive to colds.\textsuperscript{2}

One hundred and eight subjects, having had 3 or more colds the previous year, were given either 4 mL fluid extract of Echinacea purpurea or 4 mL placebo-juice twice a day for 8 weeks. There were no significant differences in the incidence, duration, or severity of colds and respiratory infection in the two groups.\textsuperscript{3,9}

5.1.3 Immunotherapy/Infection

One of the most interesting activities of Echinacea is its ability to enhance the immune response. A number of in vivo, in vitro and animal studies have documented the activation of immunologic activity. A suggested mechanism to explain the immunostimulating effects of Echinacea extracts is the enhancement of neutrophils, phagocytes and cytokine secretion by macrophages.\textsuperscript{2,18,37}

5.1.3.1 In Vivo Studies

In an open-labeled study, 12 healthy subjects receiving Echinacin \textregistered{} Liquidum drops for 5 days had significantly higher phagocytic activity of isolated neutrophils when compared to 12 health subjects receiving placebo.\textsuperscript{2}

One hundred thirty-four healthy subjects were involved in five placebo controlled randomized studies. Two studies tested intravenous homeopathic mixtures of Echinacea angustifolia, two studies tested oral alcoholic extracts of Echinacea purpurea and one study tested both extracts of Echinacea pallida and Echinacea purpurea. Only in two of the studies (Study 1- Echinacea angustifolia: 2 mL
intravenous per day and Study 2- Echinacea purpurea root: 30 drops 3 times per day) was phagocytic activity significant. The remaining three studies showed no significant effects. The remaining three studies showed no significant effects.18

Melchart et al stated that phytotherapeutic immunomodulators aim to normalize and optimize immunologic responses. He added that they may have little to no impact when taken by healthy, young subjects.16 Parnham suggested that Echinacin® has little effect, stimulatory or adverse on normal immune response but is most effective as an oral immunostimulant, in subjects slightly to moderately compromised.2

In a study involving 500 children with tuberculosis Echinacin® was administered intravenously at doses starting at 0.5 mL to 5 mLs, for a period of 2 days, then repeated up to 15 times over several weeks. Some children showed signs of general condition improvement associated with acute signs of immunostimulation such as shivering, headache, vomiting and fever within 2-4 hours of receiving the injection. The symptoms disappeared within 2-4 hours. A 40-100% increase in blood leucocyte count was observed which returned to normal with 6-8 hours.2

A study involving 91 children, including 2 infants and 67 small children, reported that 94% (n=88) of the subjects showed an increase of more than 29% in lymphocyte counts.2

In an open-labeled study, subjects were treated for 7 days with intramuscular or subcutaneous preparations of the squeezed sap of Echinacea purpurea. A marked increase in mean total lymphocyte count in the peripheral blood was observed after 7 days of treatment. 2

5.1.3.2 In Vitro Studies

In another study, 12 healthy males received 4 consecutive days of intramuscular administration of Echinacin®. Significant increases of neutrophils to cause phagocytosis of Candida albicans ex vivo were reported.2

Echinacin® had a stimulating effect on the production of lymphokines by lymphocytes and in the transformation test. Toxicity was only produced with very high concentrations not used clinically.40

Human white blood cells increased phagocytosis of yeast cells by 20-40% when stimulated by Echinacea compared to controls.37

Another study found that when Echinacea extract was given as a single dose, cell-mediated immunity was stimulated. If a higher dose was taken on a daily basis, the immune response was inhibited.40
5.1.3.3 Animal Models

Ethanolic extracts of Echinacea purpurea, Echinacea pallida and Echinacea angustifolia roots enhanced phagocytosis significantly in mice.\(^{37}\)

Echinacea purpurea extracts stimulated phagocytosis by stimulating the production of cytokines (interferon, tumor necrosis factor, interleukin-1 and interleukin) in mice.\(^{37,59}\)

5.14 Anti-Viral/Bacterial Activity/Immune System Diseases

Echinacea has long been associated with anti-viral, anti-bacterial properties. The anti-viral, anti-bacterial property may be due to the immunostimulant activity, anti-infective quality or both.

5.1.4.1 In Vivo

In one study, Echinacea purpurea extract enhanced cellular immune formation of peripheral blood mononuclear cells in subjects with either chronic fatigue syndrome or AIDS.\(^{37}\)

5.1.4.2 In Vitro

In one study, Viracea\(^{®}\), a topical microbicide blend of benzalkonium chloride and phyto-chemicals derived from Echinacea purpurea, was tested against 40 strains of herpes simplex virus. Study results showed the extract had good antiviral activity to resistant acyclovir and acyclovir susceptible strains.\(^{8}\)

Another study reported that Echinacea angustifolia D1 along with other components of the complex Oligoplex displayed results comparable to vancomycin at concentrations of 0.063-2mg/l for S. pyogenes, S. agalactiae, S. pneumonia, S. aureas and E. faecalis but not for H. influenza or Bacteroides sp.\(^{37}\)

Purified polysaccharide cells from Echinacea purpurea were used to activate macrophages (M phi) from different organs in mice to produce interleukin-1, Tumor necrosis factor alpha and interleukin-6. Elevated amounts of reactive oxygen intermediates were shown to inhibit the growth of Candida albicans in vitro.\(^{37}\)

5.1.4.3 Animal Models

In mice, purified polysaccharide cells from Echinacea purpurea stimulated phagocytes in the spleen, bone marrow and migration of granulocytes to the peripheral blood. These polysaccharides were credited with protecting the mice against the lethal infections of Listeria and Candida albicans. Sheep red blood cells
showed no antibody protection after exposure to Echinacea purpurea polysaccharide cells.\textsuperscript{37}

5.1.5 Tumor Activity

5.1.5.1 In Vivo

A study was conducted in 15 subjects with advanced colorectal cancers. The subjects received immunotherapy consisting of low-dose intravenous cyclophosphamide, every 28 days, 33 mg/m\textsuperscript{2}, thymostimulin intramuscularly, 30 mg/m\textsuperscript{2}, and Echinacin\textsuperscript{B} 60 mg/m\textsuperscript{2} together with thymostimulin intramuscularly following the low-dose cyclophosphamide (on days 3-20 after once daily than twice a week). Two months after the start of the therapy, 1 subject displayed partial tumor regression, and 6 subjects displayed stable disease condition. Therapy was well tolerated by all subjects. No adverse events were reported.\textsuperscript{60}

In another study, serum levels of properdin, tumor necrosis factor alpha, interleukins 1, 6 and 10 and several other cytokines increased after Echinacea administration.\textsuperscript{5}

5.1.6 Gynecological Infections

Parnham reviewed studies of women with gynecological infections.\textsuperscript{2} Two groups, (n=226 and n=129), following the same protocol with periuteral infections received intravenous Echinacin\textsuperscript{B} treatment. Recovery rates were reported as 55-70\% and 50-85\% respectively. In another study, 60 women treated for postpartal mastitis with intravenous Echinacin\textsuperscript{B} demonstrated a response rate of greater than 90\%.

An open labeled study of 283 women diagnosed as having relapsing vaginal candidiasis was also reviewed. All subjects received 6 days of antymycotic therapy. At the conclusion of the antymycotic therapy 123 subjects received no additional treatment. The remaining subjects received 10 weeks of Echinacea treatment. Twenty 20 subjects received Echinacin\textsuperscript{B} subcutaneously, 60 received Echinacin\textsuperscript{B} intramuscularly, 20 received Echinacin\textsuperscript{B} intravenously and 60 were treated with Echinacin\textsuperscript{B} Liquidum for 10 weeks. The recurrence rate for antymycotic therapy alone and subcutaneous, intramuscular, intravenous and oral therapy administration was: 60.5\%, 15.0\%, 5.0\%, 15.0\% and 17.0\%, respectively. There were no adverse events reported for the oral group and response was similar to the responses achieved by parenteral treatment. Adverse events were reported as mild to moderate in 8-10\% of the subcutaneous or intramuscular treatment groups or general and mild, 3-5\% in the subcutaneous, intramuscular and intravenous groups.

5.2 Extraction Methods
There are several different extraction methods, which influence phytochemical content, and therapeutic response. The extraction methods include: fluid, alcoholic, lipophilic and pressed juice. It was reported that extracting the polysaccharide by differential solubility leads to a polysaccharide several times more active than the aqueous extract.

Fluid extracts are most often used as immunostimulating agents for treatment and prevention of infectious disorders including colds and respiratory infections.3 Alcoholic extracts increase phagocytosis by human neutrophils in vitro,2 exhibit a positive effect on the symptoms of upper respiratory infection18 and have the longest shelf life.32 The lipophilic extracts appear to be more active than the polar fractions.37 Expressed juice is used as a non-specific agent to strengthen the intrinsic defense capacity of the body, exerting a non-specific immunostimulant action.60 The squeezed sap inhibits human lymphocyte proliferation to phytohemagglutinin40 and reduces the risk of infection 14% when compared to placebo.18 Echinacea purpurea flower is squeezed releasing an important polysaccharide credited with macrophage stimulation.

5.3 Dosage Form

The potency of the phytochemicals is dependent on route of administration. Echinacea is available in the following dosage forms:

   Oral: liquid extract powder, freeze-dried, capsules, tablets, pills, tinctures, teas;
   Topical: cream, salve, lotion, gels, ointment; and
   Injectable: intramuscular, subcutaneous and Intravenous.13, 18, 20, 32

Oral administration is simple, results in slower absorption, lower peak plasma levels and makes it possible to continue treatment for longer periods of time than with parenteral administration.1

Intravenous administration correlates to the highest peak plasma levels.2, 40 Intramuscular, subcutaneous and intravenous Echinacea preparations are not available in the U.S.
6.0 Conclusion

Extracts of Echinacea species are used for a variety of therapeutic purposes. Review of the literature reveals that many questions about Echinacea remain to be answered: the species that has the most therapeutic benefit, the part of the plant with the most active ingredients, the ingredient or ingredients that are the most active, the best way to extract the active ingredient and how to assure a standard amount of active ingredient.

What is evident in the literature is the safety of Echinacea. Echinacea is considered a safe herb. In controlled studies and in anecdotal reports, Echinacea appears to be very well tolerated in infants, children and adults. Echinacea had little to no impact on healthy subjects but impacted positively in subjects with mild to moderate respiratory infection. Incidents of adverse events are rare and there is no known toxicity. The most common reactions reported by study subjects were unpleasant taste, tiredness, somnolence, dizziness, headache, aggressiveness and allergic reactions.
Appendix A
Appendix A

Summary of the SN/AEMS Web Report Search Results for echinacea from the U.S. Food and Drug Administration Center for Food Safety and Applied Nutrition Office of Special Nutritionals

<table>
<thead>
<tr>
<th>Adverse Event as Reported</th>
<th>Name of Product</th>
<th>Manufacturer</th>
<th>Ingredient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anorexia paresthesia, psychological, systemic symptoms*</td>
<td>Echinacea</td>
<td>Rainbow Light Nutritional Systems</td>
<td>echinacea</td>
</tr>
<tr>
<td>Selenium poisoning*</td>
<td>Echinaceapc</td>
<td>Douglas Labs</td>
<td>echinacea</td>
</tr>
<tr>
<td>Arsenic poisoning*</td>
<td>Echinacea Pills</td>
<td>Unknown</td>
<td>echinacea</td>
</tr>
<tr>
<td>Constipation, &amp; lumps in gluteus maximus*</td>
<td>Echinacea with Goldenseal</td>
<td>Unknown</td>
<td>echinacea</td>
</tr>
<tr>
<td>Child with high level of lead in blood*</td>
<td>Echinacea</td>
<td>Unknown</td>
<td>echinacea</td>
</tr>
<tr>
<td>Acute back and abdominal pain, and toxic hepatitis</td>
<td>Nature's Resource Echinacea Herb</td>
<td>Mudock Health Care</td>
<td>echinacea</td>
</tr>
<tr>
<td>Severe and prolonged anticoagulation, bleeding into skin and soft tissues*</td>
<td>Echinacea</td>
<td>Unknown</td>
<td>echinacea</td>
</tr>
<tr>
<td>Lymph nodes swollen and puffy: back of neck, groin, and underarm; symptoms subsided after product use stopped</td>
<td>Echinacea drops</td>
<td>Unknown</td>
<td>echinacea</td>
</tr>
<tr>
<td>Nausea, diarrhea, sweating</td>
<td>Echinacea Capsules</td>
<td>Sundown vitamins</td>
<td>echinacea</td>
</tr>
<tr>
<td>Elevated blood pressure, flushing welts*</td>
<td>Echinacea</td>
<td>Unknown</td>
<td>echinacea</td>
</tr>
<tr>
<td>Increasing anxiety, anger, and stress*</td>
<td>Echinacea</td>
<td>Nature's sunshine Products</td>
<td>echinacea</td>
</tr>
<tr>
<td>Death, non-viral hepatitis*</td>
<td>Echinacea</td>
<td>Unknown</td>
<td>echinacea</td>
</tr>
<tr>
<td>Toxic hepatitis*</td>
<td>Echinacea</td>
<td>Unknown</td>
<td>echinacea</td>
</tr>
<tr>
<td>Diarrhea</td>
<td>Sundown Herbal Echinacea</td>
<td>Douglas Labs</td>
<td>echinacea</td>
</tr>
<tr>
<td>Fainted</td>
<td>Echinacea</td>
<td>Unknown</td>
<td>echinacea</td>
</tr>
<tr>
<td>Vomiting, diarrhea, chills</td>
<td>Purple Cone Flower Echinacea Herb</td>
<td>Sundown Vitamins</td>
<td>echinacea</td>
</tr>
<tr>
<td>Swelling/pain on right the head, right eye, al with visual field defect</td>
<td>Freeze Dried Echinacea</td>
<td>Eclectic Institute</td>
<td>echinacea</td>
</tr>
<tr>
<td>Adverse Event as Reported</td>
<td>Name of Product</td>
<td>Manufacturer</td>
<td>Ingredient</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------------</td>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>Vomiting, diarrhea, and bloody stools</td>
<td>Echinacea 400 mg</td>
<td>Herbal Authority</td>
<td>echinacea</td>
</tr>
<tr>
<td>Severe vomiting</td>
<td>Echinacea Herbal Dietary Supplement</td>
<td>Avon Products</td>
<td>echinacea</td>
</tr>
<tr>
<td>Tongue swelling and difficulty swallowing</td>
<td>Echinacea</td>
<td>Unknown</td>
<td>echinacea</td>
</tr>
<tr>
<td>Sores on buccal mucosa and gums on left side of mouth</td>
<td>Echinacea</td>
<td>Nature's Way Products, Inc</td>
<td>echinacea</td>
</tr>
<tr>
<td>Puritis, rash, erythema multiforme</td>
<td>Echinacea</td>
<td>Unknown</td>
<td>echinacea</td>
</tr>
<tr>
<td>Hives, diarrhea*</td>
<td>Herbal Extract Drops</td>
<td>Nature's Way Products, Inc</td>
<td>echinacea, vegetable glycerin</td>
</tr>
<tr>
<td>Vomited while sleeping, also went into a deep sleep</td>
<td>Echinacea tincture</td>
<td>Becca's Herbs</td>
<td>echinacea angustifolia, grain alcohol</td>
</tr>
<tr>
<td>Anorexia paresthesia, psychological, systemic symptoms*</td>
<td>Zand Insure Herbal</td>
<td>McZand Herbal, Inc</td>
<td>echinacea, goldenseal</td>
</tr>
<tr>
<td>Dermatomyositis*</td>
<td>Health-Gard with Echinacea</td>
<td>Twin Labs, Inc</td>
<td>echinacea, others</td>
</tr>
<tr>
<td>Death*</td>
<td>Echinacea with Goldenseal</td>
<td>Nature's Way Products, Inc</td>
<td>echinacea goldenseal</td>
</tr>
<tr>
<td>Death*</td>
<td>Echinacea with Mushrooms</td>
<td>Nature's Way Products, Inc</td>
<td>echinacea, mushrooms</td>
</tr>
<tr>
<td>Severe gastroenteritis resulting in diarrhea, dehydration and hospitalization</td>
<td>Echinacea angustifolia, Echinacea purpurea, Pure Biochelated Herbal Extract</td>
<td>Nature's Answer, Inc</td>
<td>echinacea, vegetable glycerin, grain alcohol</td>
</tr>
<tr>
<td>High blood pressure*</td>
<td>Goldenseal Capsules</td>
<td>Herbs 'n' Essence by Suzanne</td>
<td>Goldenseal, echinacea, myrrh, slippery elm, cayenne</td>
</tr>
<tr>
<td>High blood pressure*</td>
<td>Allergy-Ease Extract</td>
<td>Herbs 'n' Essence by Suzanne</td>
<td>ephedra, elder flower, echinacea, goldenseal, eyebright, red clover, peppermint, alcohol</td>
</tr>
<tr>
<td>Puritic whole-body rash, eosinophilia, hypotension, pericardial tamponade*</td>
<td>Echinacea and Goldenseal Combination</td>
<td>Insure Herbal</td>
<td>echinacea, goldenseal, red clover, sage, burdock root, peppermint, prairie dock, parsley, fennel, ginger, bayberry, chamomile, skullcap, valerian root, cayenne, ?</td>
</tr>
<tr>
<td>Adverse Event as Reported</td>
<td>Name of Product</td>
<td>Manufacturer</td>
<td>Ingredient</td>
</tr>
<tr>
<td>---------------------------</td>
<td>-------------------------------</td>
<td>----------------------------</td>
<td>------------</td>
</tr>
<tr>
<td>Increasing anxiety, anger and stress*</td>
<td>Insure Herbal</td>
<td>McZand Herbal, Inc</td>
<td>echinacea, goldenseal, red clover, sage, peppermint, prairie dock, parsley, fennel, ginger, bayberry, chamomile, valerian, barberry, cayenne</td>
</tr>
<tr>
<td>Increasing anxiety, anger and stress*</td>
<td>Insure Herbal</td>
<td>McZand Herbal, Inc</td>
<td>echinacea, goldenseal, red clover, sage, peppermint, prairie dock, parsley, fennel, ginger, bayberry, chamomile, valerian, barberry, cayenne</td>
</tr>
<tr>
<td>Lost consciousness, had black diarrhea, severe abdominal cramps*</td>
<td>Internal Detox</td>
<td>American College of Advancement in Medication</td>
<td>echinacea angustifolia, gallium aparine, urtica urens 3X, berberis vulgaris6X, thuja occidentalis 12X, chelidonium majus 6X, nux vomica 6X, natrum hypochlor 6X</td>
</tr>
<tr>
<td>Urticaria and burning rash, severe hair loss, thyroid deficiency, depigmentation of skin, chronic autoimmune syndrome, unable to withstand sun</td>
<td>Deep Defense</td>
<td>Rainbow Light Nutritional Systems</td>
<td>astragalus, reishi mushroom, shiitake mushroom, echinacea, polypore mushroom, grain alcohol</td>
</tr>
<tr>
<td>Experienced a rush, heart sped up, chest pressure near heart, left arm went numb, left hand was tingly, headache, light nausea</td>
<td>Power Time</td>
<td>Laci Le Beau Corp</td>
<td>guarana, ginseng, spirulina, bee pollen, bissy nut, echinacea, gotu kola, wu-chi, mulan, fo-ti</td>
</tr>
<tr>
<td>Constipation followed by bloody stool</td>
<td>Ultra Mega II Multiple Vitamins and Minerals</td>
<td>General Nutrition Products, Inc (GNC)</td>
<td>vitamins, minerals, choline, PABA, inositol, rutin, lecithin, spirulina, bee pollen, Siberian ginseng, echinacea, dong-quai, horsetail, oat bran, alfalfa, parsley, watercress, chromium, others</td>
</tr>
<tr>
<td>Adverse Event as Reported</td>
<td>Name of Product</td>
<td>Manufacturer</td>
<td>Ingredient</td>
</tr>
<tr>
<td>---------------------------</td>
<td>----------------</td>
<td>--------------</td>
<td>------------</td>
</tr>
<tr>
<td>Death*</td>
<td>Ultramega Gold</td>
<td>General Nutrition Corporation (NC)</td>
<td>vitamins, mineral, goldenseal, chlorophyll, echinacea, parsley, peppermint, watercress, ginkgo biloba, bee pollen, green tea, chromium picolinate, vitamin A (17,500 IU), niacinamide, calcium, phosphorus, magnesium, iodine, copper, potassium, others</td>
</tr>
<tr>
<td>Headaches, blurred vision, lightheaded and dizzy</td>
<td>Nature's Secret AM/PM Ultimate cleanse with Multi-Fiber and Multi-Herb</td>
<td>Nature's Secret/Health, Inc</td>
<td>hawthorn berry, red clover, skullcap, black cohosh, slippery elm, echinacea, ginkgo biloba, cascara sagrada, shattered cell wall chlorella, lactobacilli, fenugreek, yarrow, horsetail, others</td>
</tr>
<tr>
<td>Autoimmune hepatitis</td>
<td>Delux Tea</td>
<td>House of Hezekiah</td>
<td>rose hips, red clover, nettle, alfalfa, burdock, dandelion, goldenseal, echinacea, pau d'arco, ginger, cinnamon, clove, stevia</td>
</tr>
<tr>
<td>Seizure and stroke*</td>
<td>Cybergenics Quick Trim Complex 3</td>
<td>LL&amp;S Research Corp</td>
<td>senna leaves, licorice, fennel, buckthorn, cascara sagrada, stearic acid, citrus pectin, psyllium seed, red clover, echinacea, prune powder, Siberian ginseng, ginkgo biloba, fenugreek, acidophilus, aloe vera gel, chlorophyll, others</td>
</tr>
<tr>
<td>Adverse Event as Reported</td>
<td>Name of Product</td>
<td>Manufacturer</td>
<td>Ingredient</td>
</tr>
<tr>
<td>------------------------------------------------------------------------------------------</td>
<td>--------------------------------</td>
<td>------------------------</td>
<td>-----------------------------------------------------------------------------</td>
</tr>
<tr>
<td>Palpitations and migraine headaches*</td>
<td>Cybergenics Quick Trim Complex 3</td>
<td>L&amp;S Research Corp</td>
<td>senna leaves, licorice, fennel, buckthorn, cascara sagrada, stearic acid,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>citrus pectin, psyllium seed, red clover, echinacea, prune powder, Siberian</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ginseng, ginkgo biloba, fenugreek, acidophilus, aloe vera gel, chlorophyll,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>others</td>
</tr>
<tr>
<td>Death</td>
<td>Cybergenics Quick Trim Complex 3</td>
<td>L&amp;S Research Corp</td>
<td>senna leaves, licorice, fennel, buckthorn, cascara sagrada, stearic acid,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>citrus pectin, psyllium seed, red clover, echinacea, prune powder, Siberian</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ginseng, ginkgo biloba, fenugreek, acidophilus, aloe vera gel, chlorophyll,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>others</td>
</tr>
<tr>
<td>Ventricular fibrillation, cardiac arrest and seizure*</td>
<td>Cybergenics Quick Trim Complex 3</td>
<td>L&amp;S Research Corp</td>
<td>senna leaves, licorice, fennel, buckthorn, cascara sagrada, stearic acid,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>citrus pectin, psyllium seed, red clover, echinacea, prune powder, Siberian</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>ginseng, ginkgo biloba, fenugreek, acidophilus, aloe vera gel, chlorophyll,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>others</td>
</tr>
<tr>
<td>Blurred vision, nausea, pounding heart</td>
<td>Ultra Energy Now</td>
<td>Phoenix Health Products</td>
<td>ma-huang, guarana, astragalus, ginseng, fo-ti, gutu kola, kava kava,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>echinacea, ginkgo biloba, panax ginseng, goldenseal, cayenne, niacin,</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>chromium picolinate</td>
</tr>
<tr>
<td>Adverse Event as Reported</td>
<td>Name of Product</td>
<td>Manufacturer</td>
<td>Ingredient</td>
</tr>
<tr>
<td>---------------------------</td>
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</tr>
<tr>
<td>Stomach pain</td>
<td>Natural Herbal Energizer</td>
<td>Advantage Marketing System</td>
<td>ma-huang, guarana extract, gotu kola, Siberian ginseng, fo-ti, ginkgo biloba, willow bark, niggel sativa, cayenne pepper, hawthorn berry extract, green tea extract, selenium, echinacea, bladderwurk, reishi mushroom</td>
</tr>
<tr>
<td>Diarrhea, progressive proximal muscle weakness, nephritic syndrome</td>
<td>Internal Cleansing system Multi-Herb Formula</td>
<td>Harmony Formulas</td>
<td>fenugreek, yarrow flower, cat's claw, hawthorn berry, Australian herb, licorice root, marshmellow, red clover, red raspberry root, skullcap, burdock root, chickweed, mullein, black cohosh, Irish moss, kelp slippery elm bark, echinacea, ginggo, others</td>
</tr>
<tr>
<td>Pancreatitis*</td>
<td>Arthafect with Arthred</td>
<td>Relliv, Inc</td>
<td>arthred, glucosamine sulfate, ginkgo biloba, borage oil, turmeric, boswellian serrata, ashwangandha, cat's claw, sarsaparilla root, licorice root, burdock root, barley grass, echinacea, yucca, devil's claw, bilberry, capsicum, aloe vera, bioperine, others</td>
</tr>
<tr>
<td>Took vitamins instead of insulin and now hospitalized*</td>
<td>Nature's Sunshine Echinacea</td>
<td>Nature's Sunshine Products</td>
<td>Unknown</td>
</tr>
</tbody>
</table>

* More than one special nutritional product was reported in association with the adverse event.