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# An Evidence-Based Systematic Review of Chlorophyll by the Natural Standard Research Collaboration

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**ABSTRACT.** An evidence-based systematic review of chlorophyll by the Natural Standard Research Collaboration consolidates the safety and efficacy data available in the scientific literature using a validated, reproducible grading rationale. This article includes written and statistical analysis of clinical trials, plus a compilation of expert opinion, folkloric precedent, history, pharmacology, kinetics/dynamics, interactions, adverse effects, toxicology, and dosing.

**KEYWORDS.** adverse effects, chlorophyll, dosing, evidence-based, interactions, pharmacodynamics, pharmacokinetics, pharmacology, systematic review

## SYSTEMATIC AGGREGATION, ANALYSIS, AND REVIEW OF THE LITERATURE

### Search Strategy

To prepare this Natural Standard review, electronic searches were conducted in several databases (including AMED, CANCERLIT, CINAHL, CISCOP, the Cochrane Library, EMBASE, HerbMed, International Pharmaceutical Abstracts, Medline, and NAPRALERT) from inception to May 2013. Search terms included the common name(s), scientific name(s), and all listed synonyms. Hand searches

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were conducted of 20 additional journals (not indexed in common databases), and of bibliographies from 50 selected secondary references. No restrictions were placed on language or quality of publications. Researchers in the field of complementary and alternative medicine (CAM) were consulted for access to additional references or ongoing research.

### **Selection Criteria**

All literature was collected pertaining to efficacy in humans (regardless of study design, quality, or language), dosing, precautions, adverse effects, use in pregnancy/lactation, interactions, alteration of laboratory assays, and mechanism of action (in vitro, animal research, human data). Standardized inclusion/exclusion criteria were utilized for selection.

### **Data Analysis**

Data extraction and analysis were performed by healthcare professionals conducting clinical work and/or research at academic centers, using standardized instruments that pertained to each review section (defining inclusion/exclusion criteria and analytic techniques, including validated measures of study quality). Data were verified by a second reviewer.

### **Review Process**

A blinded review was conducted by multidisciplinary research-clinical faculty at major academic centers with expertise in epidemiology and biostatistics, pharmacology, toxicology, complementary and alternative medicine (CAM) research, and clinical practice. In cases of editorial disagreement, a three-member panel of the Editorial Board addressed conflicts, and consulted experts when applicable. Authors of studies were contacted when clarification was required.

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#### *Synonyms/Common Names/Related Substances*

- 2-1[Hexyloxyethyl]-2-devinylpyropheophorbide-a (HPPH), ABCG2 substrates, Bn-NCC-1, CD45-peridinin chlorophyll protein, CHL, Chl(a), CHLN, chlorin e6, chlorin p6, chlorophyll *a*, chlorophyll *b*, chlorophyll *c*, chlorophyll *d*, chlorophyll lipiodol, chlorophyll phytol, chlorophyll-a, chlorophyllin, chlorophyllin copper (Cu(II)-chlorophyllin), chlorophyllin iron (Fe(II)-chlorophyllin), chlorophyllin zinc, Chlorophyllipt<sup>®</sup>, chlorophyllpt, copper chlorophyll, CpD-A, CpD-B, CpD-C, CpD-D, E121, fluo-chlorophyllin, hydroxy pheophorbide, *Laminaria*, metallochlorophyllin, microalgae, Nullo<sup>®</sup>, peridinin chlorophyll-alpha protein, pheophorbide, pheophorbide a, pheophorbide-a, pheophytin a, photodynamic antimicrobial therapy (PACT), phytanic acid, phytochemicals, porphobilinogen, porphyrin, PPBa, pristanic acid, protochlorophyllide a, protoporphyrin IX, purpurin-18, Radachlorin<sup>®</sup>, retinoid X receptor (RXR) agonist, sodium copper chlorophyllin, sodium iron chlorophyllin, Sonoflora 1, tetrapyrroles, uroporphyrinogen-III, Yebaike<sup>™</sup> tablet (YBK).

- **Select combination products:** Chlorofresh (sodium copper chlorophyllin, oil of mint), Derifil<sup>®</sup> (chlorophyllin copper complex), FRBA (chlorophyll- and fiber-rich health food), mamoclam (omega-3 polyunsaturated fatty acids, iodine, chlorophyll derivatives), talaporfin sodium (chlorin e6, L-aspartic acid).

## ***CLINICAL BOTTOMLINE/EFFECTIVENESS***

### ***Brief Background***

- Chlorophyll is a chemoprotein commonly known for its contribution to the green pigmentation in plants, and it is related to protoheme, the red pigment of blood (Battersby, 1988). It may be obtained from green leafy vegetables (broccoli, brussels sprouts, cabbage, lettuce, and spinach), algae (*Chlorella* and *Spirulina*), wheatgrass, potatoes (Friedman, 2006), green tea particles (Li et al., 2008), and numerous herbs (alfalfa (Gawel, 2012), damiana, nettle, and parsley).
- Chlorophyll has been used traditionally to improve bad breath and other forms of body odor, including odors of the urine, feces, and infected wounds. In Asia, metabolites of chlorophyll from silkworm excreta have been used for centuries as an internal deodorant (Dai et al., 1992). More recently, chlorophyll has been used to aid in the removal of various toxins via the liver, and it remains a key compound for improving the function of essential detoxification pathways (Fahy et al., 2005). Supportive evidence suggests that it may be used as an anti-inflammatory for conditions such as pancreatitis, as well as a potent antioxidant and chemoprotective agent (Manabe & Steer, 1979). Scientific research has demonstrated that it may be an effective therapeutic agent in the treatment of herpes simplex, benign breast disease, tuberculosis, and rheumatoid arthritis, and as chemoprevention (Belenkii & Krikun, 1971; Bezpалov et al., (2005); Egner et al., (2001); Lozovskaia, 2005; Nenonen, Helve, Rauma, & Hanninen, 1998). Type 2 diabetes and obesity are also being explored as areas where chlorophyll may be used (McCarty, 2001; Schluter, Yubero, Iglesias, Giralt, & Villarroya, 2002).

### ***Scientific Evidence***

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|   |   |
|---|---|
| Protection from aflatoxins                                  | B |
| Cancer prevention   | C |
| Cancer treatment  | C |
| Fibrocystic breast disease                                  | C |
| Herpes  | C |
| Leukopenia  | C |
| Metabolic disorders   | C |
| Pancreatitis  | C |
| Pneumonia   | C |
| Poisoning   | C |
| Reduction of odor from incontinence/bladder catheterization | C |
| Rheumatoid arthritis  | C |
| Sepsis  | C |
| Tuberculosis  | C |

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**Natural Standard Evidence-Based Validated Grading Rationale™**

- Grades reflect the level of available scientific evidence in support of the efficacy of a given therapy for a specific indication.
- Expert opinion and historic/folkloric precedent are not included in this assessment, and are reflected in a separate section of each review (“Expert Opinion and Historic/Folkloric Precedent”).
- Evidence of harm is considered separately; the below grades apply only to evidence of benefit.

| Level of Evidence Grade                        | Criteria  |
|--|---|
| A (strong scientific evidence)                 | Statistically significant evidence of benefit from >2 properly randomized trials (RCTs), OR evidence from one properly conducted RCT AND one properly conducted meta-analysis, OR evidence from multiple RCTs with a clear majority of the properly conducted trials showing statistically significant evidence of benefit AND with supporting evidence in basic science, animal studies, or theory.  |
| B (good scientific evidence)                   | Statistically significant evidence of benefit from 1–2 properly randomized trials, OR evidence of benefit from >1 properly conducted meta-analysis OR evidence of benefit from >1 cohort/case-control/nonrandomized trials AND with supporting evidence in basic science, animal studies, or theory.  |
| C (unclear or conflicting scientific evidence) | Evidence of benefit from >1 small RCT(s) without adequate size, power, statistical significance, or quality of design by objective criteria,* OR conflicting evidence from multiple RCTs without a clear majority of the properly conducted trials showing evidence of benefit or ineffectiveness, OR evidence of benefit from >1 cohort/case-control/nonrandomized trials AND without supporting evidence in basic science, animal studies, or theory, OR evidence of efficacy only from basic science, animal studies, or theory. |
| D (fair negative scientific evidence)          | Statistically significant negative evidence (i.e., lack of evidence of benefit) from cohort/case-control/nonrandomized trials, AND evidence in basic science, animal studies, or theory suggesting a lack of benefit.   |
| F (strong negative scientific evidence)        | Statistically significant negative evidence (i.e., lack of evidence of benefit) from >1 properly randomized adequately powered trial(s) of high-quality design by objective criteria.*  |
| Lack of evidence†                              | Unable to evaluate efficacy due to lack of adequate available human data.   |

\*Objective criteria are derived from validated instruments for evaluating study quality, including the 5-point scale developed by Jadad et al., in which a score below 4 is considered to indicate lesser quality methodologically (Jadad AR, Moore RA, Carroll D, Jenkinson C, Reynolds DJ, Gavaghan DJ, McQuay HJ. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996; 17[1]:1–12).

†Listed separately in the “Historical or Theoretical Uses That Lack Sufficient Evidence” section.

**Historical or Theoretical Uses That Lack Sufficient Evidence**

- Anemia, antioxidant (Atroschi, Rizzo, Westermarck, & Ali-Vehmas, 2002; Galvano, Piva, Ritieni, & Galvano, 2001; Sakagami et al., (2012)), anti-inflammatory, antiviral (Lim et al., (2002); Sakagami et al., (2012)), atherosclerosis, bad breath, blood disorders (porphyria) (Tamura et al., (2006); Warren, Cooper, Wood, & Shoolingin-Jordan, 1998), body odor, constipation, detoxification, diabetes (McCarty, 2001; Schluter, Yubero, Iglesias, Giralt, & Villarroya, 2002), food uses (coloring), gastrointestinal conditions, hyperlipidemia (Adida & Spener, 2002),

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obesity (Schluter et al., 2002), ultraviolet light skin damage protection (Sakagami et al., (2012)), wound healing (Weir & Farley, 2006).

### ***Expert Opinion and Historic/Folkloric Precedent***

- Ecologically, chlorophyll has been investigated as a phytotoxic marker of contaminant exposure in soil–plant systems (Chung, Hu, Wong, & Cheung, 2007; Moreno-Jimenez, Esteban, & Penalosa, 2012) and as an assessment parameter of lake eutrophication (Almroth & Skogen, 2010; Liu, Li, Bu, Zhang, & Liu, 2012), water quality (Kucuksezgin, 2011), and vegetal biochemical content (Cotano & Villate, 2006; He & Mui, 2010).
- Chlorophyll has also been used as a substrate to explore heme A biosynthesis (Hederstedt, 2012), physiological nanomechanics (Chekman, 2010), extranuclear genetics (Hagemann, 2010), forensic methodologies to diagnose drowning (Wang, Yu, & Wang, 2008), the cellular biology of tetrapyrrole metabolism (Mochizuki et al., (2010)), the fluorescence and photoinhibition of various compounds (Ruban & Johnson, 2010; Ryazanova, Voloshin, Dubey, Dubey, & Zozulya, 2008; Zhang, Shen, & Ru, 2006), the genetic identification of expressed sequence tags of kiwifruits (Crowhurst et al., (2008)), and the use of monoclonal antibodies and polymerase chain reaction for prenatal diagnosis of hemoglobinopathies (DSouza et al., (2008)), as well as to compare the efficiency and convenience of spray vs. ointment formulations for wound therapy (Weir & Farley, 2006).
- Clinically, chlorophyll has been used to treat gastrointestinal problems and anemia in the past. Its use in cancer prevention has been suggested (Gruskin, 1940; Hayatsu, Negishi, Arimoto, & Hayatsu, 1993).
- Chlorophyll is not on the U.S. Food and Drug Administration (FDA) Generally Recognized as Safe (GRAS) list.

### ***Brief Safety Summary***

- **Likely safe:** When consumed orally at recommended doses (Egner et al., (2001)).
- **Possibly unsafe:** When used in patients with diabetes or in those taking hypoglycemic agents, due to animal and human research suggesting that chlorophyll metabolites may exert theoretically plausible antidiabetic effects (Hellgren, 2010; McCarty, 2001; Schluter et al., 2002). When used in patients with cardiovascular conditions, due to reported incidences of chest pain following photosensitization with chlorophyll derivatives and subsequent photodynamic therapy (Nava et al., (2011)). When used in patients with gastrointestinal conditions or obstructions, due to case reports of nausea, diarrhea, dry mouth, abdominal cramping, and stool discoloration (Gao & Hu, 2005; Nenonen et al., 1998). When used in patients with compromised liver function, due to a case report of pseudojaundice (Gutierrez Fuentes et al., 1976). When used in combination with agents metabolized by the CYP3A enzyme system, due to in vitro research suggesting that chlorophyllin inhibits CYP3A activity (Sakagami et al., (2010)). When used in combination with immunosuppressant agents, due to human research suggesting that chlorophyll normalizes T lymphocyte and IgA counts (Simvolokov, Nikitin, & Iakovleva, 1989). When used in patients who show signs of photosensitivity to

chlorophyll or any of its metabolites, such as a rash, as cases of dermatitis have been reported (Ebermann, Alth, Kreitner, & Kubin, 1996; Fiedor et al., (1993); Hooper, Sery, & Yamamoto, 1988; Lee, Park, Kim, Han, & Hahn, 1990; Lim et al., (2002); Mathews-Roth, 1993).

- *Likely unsafe:* When used in children, or pregnant and lactating women, due to a lack of available information. When used in patients with known allergy or hypersensitivity to chlorophyll or any of its metabolites, as allergic photosensitive rash has been observed (Mathews-Roth, 1993) and as copper chlorophyll (E141) has been identified as a pseudoallergen (Bohm, Bunselmeyer, Luger, & Brehler, 2001).

## ***DOSING/TOXICOLOGY***

### ***General***

- Doses may be based on those most commonly used in available trials, or on historical practice. However, with natural products it is often not clear what the optimal doses are to balance efficacy and safety. Preparation of products may vary from manufacturer to manufacturer, and from batch to batch within one manufacturer. Because it is often not clear what the active component(s) of a product is, standardization may not be possible, and the clinical effects of different brands may not be comparable.

### ***Standardization***

- Standardization of chlorophyll has not been established and cannot be used to determine efficacy.
- In clinical research, intravenous Radachlorin<sup>®</sup> solution containing 6.50/7.50g of sodium salts of chlorins dissolved in 100 mL of purified water with N-methyl-D-glucamine, and topical Radachlorin<sup>®</sup> gel containing 1.43 g of sodium salts of chlorins, purified water, dimethyl sulfoxide, and carbopol, have been used during photodynamic therapy in cancer patients (Kochneva et al., (2010)). Ampules containing 5 mg of chlorophyll *a* in 1 mL 5% glucose solution have been mixed with 200–500 mL of saline or 5% glucose and used intravenously for the treatment of chronic pancreatitis (Yoshida, Yokono, & Oda, 1980).

### ***Dosing***

*Adult (age ≥18)*

*Oral*

- **Bad breath:** Anecdotally, 100 mg of chlorophyll has been taken two or three times daily.
- **Leukopenia:** 40 mg of sodium copper chlorophyllin (Ye Baike<sup>™</sup> tablet) has been taken three times daily for 1 month (Gao & Hu, 2005).
- **Protection from aflatoxins:** 100 mg of chlorophyllin has been taken three times daily for 4 months (Egner et al., (2001)).

- **Reduction of odor from incontinence/bladder catheterization:** 100 mg of chlorophyllin (Derifil<sup>®</sup>) has been taken daily for 2 weeks (Nahata, Slencsak, & Kamp, 1983). 75 mg of chlorophyll has been used three times daily (Christiansen, Byel, Stromsted, Stenderup, & Eickhoff, 1989). According to secondary sources, 300 mg of chlorophyll has been used daily if odor was still not controlled and 1–2 tablets of 100 mg chlorophyll each have been placed in the empty pouch each time it is reused or changed in a patient who has had an ostomy.

### Topical

- **Burns and wounds:** Theoretical evidence suggests that chlorophyll aids in the growth of new tissue when applied topically; however, reliable scientific evidence is lacking to suggest dosage application and/or form.
- **Cancer treatment:** 0.1 g/cm<sup>2</sup> of Radachlorin<sup>®</sup> gel has been applied topically during 1–3 hr of exposure to 400–800 J/cm<sup>2</sup> of light therapy in two sessions over 4 weeks, three sessions over 1 week, or four sessions over 1 week, for up to 18 months (Kochneva et al., (2010)). 3–6 mg/m<sup>2</sup> of 2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a (HPPH) has been administered 24–48 hr prior to exposure to 150, 175, or 200 J/cm of 665 nm light (Nava et al., (2011)). In breast cancer patients, SonoFlora 1 has been given sublingually 24 hr prior to sonodynamic and photodynamic therapy, although information on treatment dose and duration is unclear (Wang et al., (2009)).
- **Herpes:** 2–5 mg of chlorophyll per 1 g of cream or per 1 mL of saline solution has been applied topically to herpes affected areas 3–6 times daily for an indeterminate duration of time (Belenkii & Krikun, 1971).
- **Sepsis:** 1% Chlorophyllipt<sup>®</sup> ethanol solution has been applied via bandage as a prophylactic treatment to mitigate purulent-septic soft tissue complications; however, information on dose and duration of treatment is unclear (Biliaieva, Korzhyk, & Myronov, 2011).

### Intravenous/Intramuscular

- **Cancer treatment:** 0.5–1.2 mg/kg of Radachlorin<sup>®</sup> has been administered intravenously in combination with 200–300 J/cm<sup>2</sup> of laser irradiation in two sessions over 4 weeks, three sessions over 1 week, or four sessions over 1 week, for up to 18 months (Kochneva et al., (2010)).
- **Pancreatitis:** Infusion of 5–20 mg of water-soluble chlorophyll *a* has been taken daily in 1–2 divided doses for periods of 3 days to 3 years, for a total chlorophyll *a* intake of 30–1,960 mg (Yoshida et al., 1980).

### Children (age <18)

#### Insufficient Available Evidence

#### Toxicology

- Chronic toxicity in dogs receiving intralymphatic injections of Ethiodol, Ethiodol with chlorophyll, and sterile noniodinized poppy seed oil has been reported (Viamonte, Soto, & Recher, 1966).

**ADVERSE EFFECTS/PRECAUTIONS/CONTRAINDICATIONS****Allergy**

- Avoid with known allergy or hypersensitivity to chlorophyll or any of its metabolites. Incidences of allergic photosensitive rash have been observed (Mathews-Roth, 1993). Copper chlorophyll (E141) has been identified as a pseudoallergen (Bohm et al., 2001).

**Adverse Effects**

- **General:** According to available research, it appears that chlorophyll is generally safe and without many side effects or toxicities in nonsensitive people (Egner, Munoz, & Kensler, 2003; Egner et al., (2001); Yoshida et al., 1980). Adverse effects are usually gastrointestinal or dermatologic in nature. In clinical research, grade 3 and 4 adverse events have been reported following photosensitization with chlorin-based HPPH (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a) and subsequent exposure to light therapy, although further details regarding the nature of these events and their relatedness to HPPH therapy are lacking (Nava et al., (2011)).
- **Cardiovascular:** In clinical research, cases of mild-to-moderately severe chest pain necessitating symptomatic treatment have been reported following photosensitization with chlorin-based HPPH and subsequent exposure to light therapy (Nava et al., (2011)).
- **Dermatologic:** Allergic patients exposed to chlorophyll have experienced a photosensitive rash (Mathews-Roth, 1993). It appears that chlorophyll may cause photosensitization when it is taken internally. Cases of dermatitis have been reported following topical administration of chlorophyll cream (Belenkii & Krikun, 1971). Certain carotenoids, such as beta-carotene and canthaxanthin, have been shown to prevent or lessen the photosensitivity that results from taking chlorophyll (Mathews-Roth, 1993).
- **Gastrointestinal:** In a clinical study, half of the patients reported nausea and diarrhea from a combination of chlorophyll and lactobacilli-rich drinks along with a high-fiber diet (Nenonen et al., 1998). Changes in stool color have also been reported following supplementation with sodium copper chlorophyllin (Ye baike™ tablet) (Gao & Hu, 2005). According to secondary sources and human research, other reported gastrointestinal complaints include dry mouth and abdominal cramping (Gao & Hu, 2005).
- **Genitourinary:** When taken orally, chlorophyllin may cause green discoloration of the urine, according to secondary sources.
- **Hematologic:** In animals and yeast, chlorophyll building blocks in combination with iron caused a form of pseudoporphyria (Warren et al., 1998). Also, in animals, lack of the breast cancer-resistant protein BCRP/ABCG2 increased sensitivity to chlorophyll-breakdown metabolites, resulting in phototoxic lesions (Jonker et al., (2002)). These results indicate that humans or animals with low or absent BCRP activity may be at increased risk for developing protoporphyria and diet-dependent phototoxicity.
- **Renal:** When taken orally, chlorophyllin may cause green discoloration of the urine, according to secondary sources.



- **Other:** Food intolerance due to the pseudoallergenic properties of copper chlorophyll has been reported (Bohm et al., 2001). Pseudojaundice is rare, but it has also been reported (Gutierrez Fuentes et al., 1976). Another study showed a diagnostic delay due to chlorophyll in oral rehydration solution (Acheson & Flegg, 1987).

### ***Precautions/Warnings/Contraindications***

- Use cautiously in patients with diabetes or in those taking hypoglycemic agents, due to animal and human research suggesting that chlorophyll metabolites may exert theoretically plausible antidiabetic effects (Hellgren, 2010; McCarty, 2001; Schluter et al., 2002).
- Use cautiously in patients with cardiovascular conditions, due to reported incidences of chest pain following photosensitization with chlorophyll derivatives and subsequent photodynamic therapy (Nava et al., (2011)).
- Use cautiously in patients with gastrointestinal conditions or obstructions, due to case reports of nausea, diarrhea, dry mouth, abdominal cramping, and stool discoloration (Gao & Hu, 2005; Nenonen et al., 1998).
- Use cautiously in patients with compromised liver function, due to case report of pseudojaundice (Gutierrez Fuentes et al., 1976).
- Use cautiously in combination with agents metabolized by the CYP3A enzyme system, due to in vitro research suggesting that chlorophyllin inhibits CYP3A activity (Sakagami et al., (2010)).
- Use cautiously in combination with immunosuppressant agents, due to human research suggesting that chlorophyll normalizes T lymphocyte and IgA counts (Simvolokov et al., 1989).
- Use cautiously in patients who show signs of photosensitivity to chlorophyll or any of its metabolites, such as a rash, as cases of dermatitis have been reported (Ebermann et al., 1996; Fiedor et al., (1993); Hooper et al., 1988; Lee et al., 1990; Lim et al., (2002); Mathews-Roth, 1993).
- Avoid in children due to a lack of available information.
- Avoid in pregnant and lactating women due to a lack of available information.
- Avoid in patients with known allergy or hypersensitivity to chlorophyll or any of its metabolites, as allergic photosensitive rash has been reported (Mathews-Roth, 1993) and copper chlorophyll (E141) has been identified as a pseudoallergen (Bohm et al., 2001).

### ***Pregnancy & Lactation***

- The use of supplemental doses of chlorophyll in pregnant and lactating women is not suggested due to a lack of sufficient available data.
- Information on chlorophyll's effects on lactation is lacking in the National Institute of Health's Lactation and Toxicology Database (LactMed).

## ***INTERACTIONS***

### ***Chlorophyll/Drug Interactions***

- **Antidiabetics:** In animal and human research, the chlorophyll metabolite phytanic acid has been shown to be a natural ligand for retinoid X receptor (RXR)

and is therefore purported to have antidiabetic activity (Hellgren, 2010; McCarty, 2001; Schluter et al., 2002).

- **Antilipemics:** In vitro, the chlorophyll metabolites phytanic and pristanic acids signaled the peroxisome proliferator-activated receptors (PPARs), which belong to the family of ligand-activated nuclear receptors to lipid metabolism, and are therefore purported to affect catabolic lipid metabolism (Adida & Spener, 2002).
- **Antimutagenic agents:** In cellular and human research, chlorophyll and chlorophyllin demonstrated antimutagenic and anticlastogenic effects (Grossi et al., (2012); Hayatsu, 1995; Hayatsu et al., 1993; John, Keshava, Richardson, Weston, & Nath, 2008; Shaughnessy et al., (2011)).
- **Antineoplastics:** In laboratory, animal, and human research, chlorophyll and its metabolites have demonstrated antineoplastic effects (Bui-Xuan, Tang, Wong, & Fung, 2010; Chee, Lee, Ong, & Ho, 2005; Egner et al., 2003; Egner et al., (2001); Gomaa, Ali, El-Tayeb, & Abdel-kader, 2012; Hibasami et al., (2000); Parihar, Dube, & Gupta, 2011; Sarkar, Sharma, & Talukder, 1994; Tajmir-Riahi, Neault, & Diamantoglou, 2004; Tsai, Wu, & Chen, 2010; Unger, 1999; Waladkhani & Clemens, 1998).
- **Antiobesity agents:** In laboratory research, the chlorophyll metabolites phytanic and pristanic acids demonstrated antiobesity properties, including induction of adipocyte differentiation and stimulation of energy dissipation in skeletal muscle (Adida & Spener, 2002; Hellgren, 2010; Schluter et al., 2002).
- **Antiseptics:** In human research, topical 1% Chlorophyllipt<sup>®</sup> solution has been investigated as a possible prophylactic treatment in lieu of systemic antibiotics to mitigate purulent-septic soft tissue complications in ambulatory outpatients; however, additional information is lacking (Biliaieva et al., 2011).
- **Antivirals:** In laboratory and human research, chlorophyll, chlorophyll derivatives from silkworm excreta, and a *Sasa senanensis* Rehder leaf extract containing Fe(II)-chlorophyllin, demonstrated antiviral properties against herpes virus, vesicular stomatitis virus, and human immunodeficiency virus (HIV), respectively (Belenkii & Krikun, 1971; Lim et al., (2002); Sakagami et al., (2012)).
- **Cardiovascular agents:** In clinical research, cases of mild-to-moderately severe chest pain necessitating symptomatic treatment have been reported following photosensitization with chlorin-based HPPH (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a) and subsequent exposure to light therapy (Nava et al., (2011)).
- **CYP450-modifying agents:** In vitro, chlorophyllin inhibited CYP3A activity to a greater extent than *Sasa senanensis* Rehder leaf extract (Sakagami et al., (2010)).
- **Dermatologic agents:** In human research, cases of photosensitive rash and dermatitis have been reported following topical administration of chlorophyll (Belenkii & Krikun, 1971; Mathews-Roth, 1993).
- **Detoxifying agents:** In animal and human research, chlorophyll and chlorophyll-rich diets promoted the excretion of dioxins, polychlorinated dibenzofurans (PCDFs), and polychlorinated dibenzo-p-dioxins (PCDDs) (Nagayama et al., (2007); Nagayama, Takasuga, Tsuji, & Iwasaki, 2005; Nagayama et al., (2003)).
- **Gastrointestinal agents:** In human research, chlorophyll *a* normalized pancreatitis-induced elevations in amylase levels (Yoshida, Yokono, & Oda,

1980). Cases of nausea, diarrhea, dry mouth, abdominal cramping, and stool discoloration have been reported following chlorophyllin supplementation (e.g., Yebaik<sup>TM</sup> tablet) or dietary consumption of chlorophyll-rich products (Gao & Hu, 2005; Nenonen et al., 1998).

- **Hematologics:** In human research, sodium copper chlorophyllin (Yebaik<sup>TM</sup> tablet) and Radachlorin<sup>®</sup> increased peripheral blood leukocyte count (Gao & Hu, 2005; Kochneva et al., (2010)). Increased risk for developing protoporphyria and diet-dependent phototoxicity in humans or animals with low or absent breast cancer-resistant protein (BCRP) activity has been proposed, due to preclinical research demonstrating formation of pseudoporphyria with coadministration of chlorophyll building blocks and iron (Warren, Cooper, Wood, & Shoolingin-Jordan, 1998) and increased sensitivity to chlorophyll-breakdown metabolites in animals lacking the BCRPABCG2 protein (Jonker et al., (2002)).
- **Immunosuppressants:** In human research, Chlorophyllipt<sup>®</sup> coadministered with a standard therapy of sulfonamides, desensitizing drugs, adaptogens, vitamins B and C, and heparin increased levels of T lymphocytes and IgA compared to standard therapy plus broad-spectrum antibiotics (Simvolokov, Nikitin, & Iakovleva, 1989).
- **Photosensitizing agents:** In laboratory and human research, chlorophyll and some of its synthetically produced derivatives demonstrated photosensitizing effects as part of photodynamic therapy (PDT) (Ebermann, Alth, Kreitner, & Kubin, 1996; Fiedor et al., (1993); Hooper, Sery, & Yamamoto, 1988; Kochneva et al., (2010); Lee, Park, Kim, Han, & Hahn, 1990; Lim et al., (2002); Nava et al., (2011); Wang et al., (2009)). Chlorophyll may cause hyperpigmentation or dermatitis, or it may make a patient more sensitive to laser treatment.

#### *Chlorophyll/Herb/Supplement Interactions*

- **Antilipemics:** In vitro, the chlorophyll metabolites phytanic and pristanic acids signaled the PPARs, which belong to the family of ligand-activated nuclear receptors to lipid metabolism, and are therefore purported to affect catabolic lipid metabolism (Adida & Spener, 2002).
- **Antimutagenic agents:** In cellular and human research, chlorophyll and chlorophyllin demonstrated antimutagenic and anticlastogenic effects (Grossi et al., (2012); Hayatsu, 1995; Hayatsu, Negishi, Arimoto, & Hayatsu, 1993; John, Keshava, Richardson, Weston, & Nath, 2008; Shaughnessy et al., (2011)).
- **Antineoplastics:** In laboratory, animal, and human research, chlorophyll and its metabolites demonstrated antineoplastic effects (Bui-Xuan et al., 2010; Chee et al., 2005; Egner et al., 2003; Egner et al., (2001); Gomaa et al., 2012; Hibasami et al., (2000); Parihar, Dube, & Gupta, 2011; Sarkar et al., 1994; Tajmir-Riahi et al., 2004; Tsai et al., 2010; Unger, 1999; Waladkhani & Clemens, 1998).
- **Antioxidants:** In cellular research, chlorophyll and a *Sasa senanensis* Rehder leaf extract containing Fe(II)-chlorophyllin demonstrated superoxide anion and hydroxyl radical-scavenging activity, respectively (Atroschi et al., 2002; Galvano et al., 2001; Sakagami et al., (2012)).
- **Antivirals:** In laboratory and human research, chlorophyll, chlorophyll derivatives from silkworm excreta (CpD), and a *Sasa senanensis* Rehder leaf extract

containing Fe(II)-chlorophyllin demonstrated antiviral properties against herpes virus, vesicular stomatitis virus, and HIV, respectively (Belenkii & Krikun, 1971; Lim et al., (2002); Sakagami et al., (2012)).

- **Cardiovascular agents:** In clinical research, cases of mild-to-moderately severe chest pain necessitating symptomatic treatment only have been reported following photosensitization with chlorin-based HPPH and subsequent exposure to light therapy (Nava et al., (2011)).
- **Carotenoids:** According to a review, beta-carotene or canthaxanthin prevented or lessened chlorophyll-induced photosensitivity (Mathews-Roth, 1993).
- **CYP450-modifying agents:** In vitro, chlorophyllin inhibited CYP3A activity to a greater extent than *Sasa senanensis* Rehder leaf extract (Sakagami et al., (2010)).
- **Detoxifying agents:** In animal and human research, chlorophyll and chlorophyll-rich diets promoted the excretion of dioxins, PCDFs, and PCDDs (Nagayama et al., (2007); Nagayama et al., 2005; Nagayama et al., (2003)).
- **Gastrointestinal agents:** In human research, chlorophyll *a* normalized pancreatitis-induced elevations in amylase levels (Yoshida et al., 1980). Cases of nausea, diarrhea, dry mouth, abdominal cramping, and stool discoloration have been reported following chlorophyllin supplementation (e.g., Yebaiké™ tablet) or dietary consumption of chlorophyll-rich products (Gao & Hu, 2005; Nenonen et al., 1998).
- **Hematologics:** In human research, sodium copper chlorophyllin (Yebaiké™ tablet) and Radachlorin® increased peripheral blood leukocyte count (Gao & Hu, 2005; Kochneva et al., (2010)). An increased risk for developing protoporphyria and diet-dependent phototoxicity in humans or animals with low or absent BCRP activity has been proposed, due to preclinical research demonstrating formation of pseudoporphyria with coadministration of chlorophyll building blocks and iron (Warren et al., 1998) and increased sensitivity to chlorophyll-breakdown metabolites in animals lacking the BCRPABCG2 protein (Jonker et al., (2002)).
- **Hypoglycemics:** In animal and human research, the chlorophyll metabolite phytanic acid has been shown to be a natural ligand for retinoid X receptor (RXR), and it is therefore purported to have antidiabetic activity (Hellgren, 2010; McCarty, 2001; Schluter et al., 2002).
- **Immunosuppressants:** In human research, Chlorophyllipt® coadministered with a standard therapy of sulfonamides, desensitizing drugs, adaptogens, vitamins B and C, and heparin increased levels of T lymphocytes and IgA compared to standard therapy plus broad-spectrum antibiotics (Simvolokov et al., 1989).
- **Pantothenic acid:** In animal research, vitamin C (ascorbic acid) and pantothenic acid exerted preventive effects against photosensitized hemolysis (Kimura & Takahashi, 1981).
- **Photosensitizers:** In laboratory and human research, chlorophyll and some of its synthetically produced derivatives demonstrated photosensitizing effects as part of photodynamic therapy (PDT) (Ebermann et al., 1996; Fiedor et al., (1993); Hooper et al., 1988; Kochneva et al., (2010); Lee et al., 1990; Lim et al., (2002); Nava et al., (2011); Wang et al., (2009)). Chlorophyll may cause hyperpigmentation or dermatitis, or it may make a patient more sensitive to laser treatment.

- **Radioprotective agents:** In vitro, a commercial product of *Sasa senanensis* Rehder leaf extract containing Fe(II)-chlorophyllin demonstrated antiultraviolet (UV) activity (Sakagami et al., (2012)).
- **Vitamin C:** In animal research, vitamin C (ascorbic acid) and pantothenic acid exerted preventive effects against photosensitized hemolysis (Kimura & Takahashi, 1981).
- **Weight loss agents:** In laboratory research, the chlorophyll metabolites phytanic and pristanic acids demonstrated antiobesity properties, including induction of adipocyte differentiation and stimulation of energy dissipation in skeletal muscle (Adida & Spener, 2002; Hellgren, 2010; Schluter, Yubero, Iglesias, Giralt, & Villarroja, 2002).

#### *Chlorophyll/Food Interactions*

- **Protein-rich foods:** According to laboratory research, chlorophyll molecules that adsorb on protein lead to the deaggregation of aqueous pigment, causing an increase in the photosensitizing activity with chlorophyll (Semichaevskii, 1975).

#### *Chlorophyll/Lab Interactions*

- **Diagnostic tests:** According to a study, chlorophyll in oral rehydration solution caused a diagnostic delay (Acheson & Flegg, 1987).
- **Immunoglobulins:** In human research, Chlorophyllipt<sup>®</sup> coadministered with a standard therapy of sulfonamides, desensitizing drugs, adaptogens, vitamins B and C, and heparin increased levels of lymphocytes and IgA compared to standard therapy plus broad-spectrum antibiotics (Simvolokov et al., 1989).
- **Serum polychlorinated dibenzofuran (PCDF) levels:** In animal and human research, chlorophyll and chlorophyll-rich diets promoted the excretion of dioxins, PCDFs, and PCDDs (Nagayama et al., (2007); Nagayama et al., 2005; Nagayama et al., (2003)).
- **Serum polychlorinated dibenzo-p-dioxin (PCDD) levels:** In animal and human research, chlorophyll and chlorophyll-rich diets promoted the excretion of dioxins, PCDFs, and PCDDs (Nagayama et al., (2007); Nagayama et al., 2005; Nagayama et al., (2003)).
- **Urine aflatoxin-N(Atroshi et al., 2002)guanine levels:** In animal and human research, chlorophyllin reduced urinary levels of aflatoxin biomarkers (aflatoxin-N(Atroshi et al., 2002)guanine) and inhibited aflatoxin hepatocarcinogenesis by blocking carcinogen bioavailability (Egner et al., 2003; Egner et al., (2001)).
- **White blood cell count:** In human research, sodium copper chlorophyllin (Yebaike<sup>™</sup> tablet) and Radachlorin<sup>®</sup> increased peripheral blood leukocyte count (Gao & Hu, 2005; Kochneva et al., (2010)).

#### *Chlorophyll/Nutrient Depletion*

- **Carotenoids:** According to a review, beta-carotene or canthaxanthin have prevented or lessened chlorophyll-induced photosensitivity (Mathews-Roth, 1993).
- **Glucose:** According to animal research, the chlorophyll metabolite phytanic acid may have hypoglycemic activity (McCarty, 2001; Schluter et al., 2002).

- **Lipids:** Phytanic and pristanic acids are thought to affect catabolic lipid metabolism (Adida & Spener, 2002).
- **Pantothenic acid:** In animal research, vitamin C (ascorbic acid) and pantothenic acid exerted preventive effects against photosensitized hemolysis (Kimura & Takahashi, 1981).
- **Vitamin C:** In animal research, vitamin C (ascorbic acid) and pantothenic acid exerted preventive effects against photosensitized hemolysis (Kimura & Takahashi, 1981).

## MECHANISM OF ACTION

### Pharmacology

- **Constituents:** Chlorophyll is a molecule found in the green parts of plants. It has many metabolites, including pheophorbide, hydroxy pheophorbide, protoporphyrin IX, phytanic acid, pristanic acid, purpurin-18, and chlorin p6 (Abbott, 2003; Adida & Spener, 2002; Chee et al., 2005; Hooper et al., 1988; Parihar et al., 2011; Xodo, Rapozzi, Zacchigna, Drioli, & Zorzet, 2012). Other known derivatives of chlorophyll include chlorophyllin, chlorophyllin copper (Cu(II)-chlorophyllin), chlorophyllin iron (Fe(II)-chlorophyllin), chlorophyllin zinc, fluo-chlorophyllin, metallochlorophyllin, sodium copper chlorophyllin, and sodium iron chlorophyllin (Gao et al., (2011); Sakagami et al., (2012); Zhang et al., (2012)).
- **Anticarcinogenic effects:** The specific mechanism of the phytochemicals in cancer prevention is not completely clear (Waladkhani & Clemens, 1998). In vitro, 50% MCF-7 tumor cell death was achieved from a chlorophyll derivative concentration 1/138 that of methotrexate (Gomaa et al., 2012). The chlorophyll fraction isolated from *Gynostemma pentaphyllum* dose-dependently inhibited the proliferation of Hep3B cells via cycle arrest in the G<sub>0</sub>/G<sub>1</sub> phase and subsequent cellular necrosis or apoptosis (Tsai et al., 2010). Conjugation of chlorin p6 and histamine increased cellular uptake of chlorin p6 tenfold and induced a four-times-higher phototoxic effect in 4451 and NT8e cancer cell lines vs. chlorin p6 alone (Parihar et al., 2011). Chlorophyllin, a mixture of semisynthetic, water-soluble derivatives of chlorophyll, has been purported to form molecular complexes with carcinogens, thereby blocking their bioavailability (Egner et al., 2003; Tajmir-Riahi et al., 2004). In both animal and human research, chlorophyllin reduced urinary levels of aflatoxin biomarkers and inhibited aflatoxin hepatocarcinogenesis by blocking carcinogen bioavailability (Egner et al., (2001)). However, in animal research, chlorophyllin demonstrated an inconsistent chemoprotective effect on the formation of benzo[a]pyrene (BP) DNA adducts in wild-type and cancer-susceptible mice (John et al., (2012)). The exposure of human lymphoid leukemia Molt 4B cells to pheophorbide-a, a moiety of chlorophyll *a*, led both to growth inhibition and induction of programmed cell death (apoptosis) (Hibasami et al., (2000)). The growth inhibition by pheophorbide-a was much stronger than that by chlorophyll *a*. Pheophorbide-a has also demonstrated antitumor effects in MDA-MB-231 human breast adenocarcinoma cells via activation of mitochondria-mediated apoptosis and extracellular signal-regulated kinase (ERK)-mediated autophagy

(Bui-Xuan et al., 2010). Moreover, pheophorbide-related compounds isolated from *Aglaonema simplex* exhibited moderately strong photocytotoxic activity against human leukemia (HL60) and oral squamous cell carcinoma (HSC-2 and HSC-3) lines, albeit to a lesser extent than that of parent pheophorbide-a (Chee et al., 2005). Purportedly, the inverse relationship between the consumption of fresh vegetables and human gastrointestinal cancer is due to the modification the genotoxic effects of various known toxicants by chlorophyll and chlorophyllin (Sarkar et al., 1994; Unger, 1999).

- **Antidiabetic effects:** The chlorophyll metabolite phytanic acid has been shown to be a natural ligand for retinoid X receptor (RXR) (Hellgren, 2010; McCarty, 2001; Schluter et al., 2002). Synthetic ligands of RXR have shown antidiabetic activity in mice, most likely by stimulating the transcriptional activity of peroxisome proliferator-activated receptor (PPAR)-gamma/RXR heterodimers, much like thiazolidinedione drugs (McCarty, 2001; Schluter et al., 2002). Phytanic acid has also been purported as a PPAR-alpha agonist, although some research has suggested that this particular effect is likely attributable more so to the metabolite pristanic acid, rather than phytanic acid itself (Hellgren, 2010). Although antidiabetic effects are therefore theoretically plausible with chlorophyll metabolites, in human research, dietary consumption of dairy products enriched with phytanic acid lacked evidence of effect on markers of metabolic syndrome risk (Werner et al., (2011)).
- **Antilipemic effects:** Phytanic and pristanic acids are thought to affect catabolic lipid metabolism (Adida & Spener, 2002). In vitro evidence suggests that these chlorophyll metabolites signal the PPARs, which belong to the family of ligand-activated nuclear receptors to lipid metabolism. Moreover, comparative research between humans and apes has identified physiological differences in phytanic acid levels, which, according to investigators, purportedly contributes to cross-species transcriptome differences, possibly related to the expression of genes related to lipid metabolism (Watkins et al., (2010)). Although antilipemic effects are therefore theoretically plausible with chlorophyll metabolites, in human research, dietary consumption of dairy products enriched with phytanic acid lacked evidence of effect on markers of metabolic syndrome risk (Werner et al., (2011)).
- **Antimutagenic effects:** In laboratory research, chlorophyll and chlorophyllin have been found to act like hemin and were antimutagenic in *Salmonella* and in *Drosophila* (Hayatsu et al., 1993). Complex formation between chlorophyllin and heterocyclic amines was also effective in diminishing the cooked beef-derived urinary mutagenicity in humans (Hayatsu, 1995). Chlorophyllin has also demonstrated a protective anticlastogenic effect against N-methyl-N'-nitro-N-nitrosoguanidine (MNNG) and 7,12-dimethylbenz(alpha)anthracene (DMBA) on human HepG2 cells in vitro, but not on mice bone marrow in vivo unless the initial exposure to DMBA was highly toxic (Grossi et al., (2012)). In normal human mammary epithelial cells (NHMECs), chlorophyllin normalized benzo(a)pyrene-induced alterations in gene expression in genes with known functional capacity in apoptosis, cell cycle control, cell motility, cell proliferation, cell signaling, cellular transcription, DNA repair, metabolism, and xenobiotic metabolism (John et al., 2008). In human research, dietary consumption of combination mutagen inhibitors, specifically chlorophyllin tablets, cruciferous

vegetables, and yogurt, selectively decreased DNA damage in target colorectal cells to nearly half, but not in nontarget white blood cells (Shaughnessy et al., (2011)).

- **Antiobesity effects:** In laboratory research, phytanic acid derived from chlorophyll induced the adipocyte differentiation of 3T3-L1 cells in culture as assessed by accumulation of lipid droplets and induction of the aP2 mRNA marker (Schluter, Yubero, Iglesias, Giralt, & Villarroya, 2002). In human preadipocytes in primary culture, phytanic acid also induced adipocyte differentiation. These findings indicate that phytanic acid may act as a natural rexinoid in adipose cells (Hellgren, 2010). Phytanic acid has also been purported to stimulate the dissipation of energy in skeletal muscles via induction of uncoupler protein-1 (UCP1) expression (Hellgren, 2010). Although antidiabetic and antilipemic effects are therefore theoretically plausible with chlorophyll metabolites, in human research, dietary consumption of dairy products enriched with phytanic acid lacked evidence of effect on markers of metabolic syndrome risk (Werner et al., (2011)).
- **Antiodor effects:** In human research with colostomy patients, chlorophyll and chlorophyllin (Derifil<sup>®</sup>) lacked evidence of benefit for reducing the subjective intensity of urinary odor vs. placebo (Christiansen, Byel, Stromsted, Stenderup, & Eickhoff, 1989; Nahata et al., 1983).
- **Antioxidant effects:** In laboratory research, chlorophyll demonstrated protective effects against mycotoxins, most likely as a superoxide anion scavenger protecting cell membranes from mycotoxin-induced damage (Atroshi et al., 2002; Galvano et al., 2001). In vitro, a commercial product of *Sasa senanensis* Rehder leaf extract containing Fe(II)-chlorophyllin demonstrated hydroxyl radical scavenging activity that was five times higher than a similar product containing Cu(II)-chlorophyllin, and comparable to a product containing Cu(II)-chlorophyllin, ginseng, and pine leaf extracts (Sakagami et al., (2012)).
- **Antiseptic effects:** In human research, topical 1% Chlorophyllipt<sup>®</sup> solution has been investigated as a possible prophylactic treatment in lieu of systemic antibiotics to mitigate purulent-septic soft tissue complications in ambulatory outpatients; however, additional information is lacking (Biliaieva, Korzhyk, & Myronov, 2011).
- **Antiviral properties:** In laboratory research, CpD, a photodynamic antiviral agent, caused inactivation of the matrix protein, as well as transcription mechanisms involved in vesicular stomatitis virus replication (Lim et al., (2002)). In vitro, a commercial product of *Sasa senanensis* Rehder leaf extract containing Fe(II)-chlorophyllin demonstrated antihuman immunodeficiency virus (HIV) activity that was five times higher than similar products containing Cu(II)-chlorophyllin, both with or without additional supplementation with ginseng and pine leaf extracts (Sakagami et al., (2012)). However, the anti-HIV activity of *Sasa senanensis* Rehder leaf extract was greater than that of its extracted chlorophyllin fraction (Sakagami et al., (2010)). In human research, topical chlorophyll stopped viral multiplication and lesion development of herpes simplex infections and reduced the frequency of lesion development of herpes zoster (Belenkii & Krikun, 1971).
- **CYP450-modifying effects:** In vitro, chlorophyllin demonstrated increased CYP3A inhibition compared to *Sasa senanensis* Rehder leaf extract (Sakagami



et al., (2010)). In particular, a commercial product of *Sasa senanensis* Rehder leaf extract containing Fe(II)-chlorophyllin demonstrated CYP3A4 inhibitory activity that was one-third that of a similar product containing Cu(II)-chlorophyllin, and one-seventh that of a product containing Cu(II)-chlorophyllin, ginseng, and pine leaf extracts (Sakagami et al., (2012)).

- **Detoxifying effects:** In rats, dietary fiber and chlorophyll have been shown to promote the fecal excretion and reduce liver levels of dioxins, polychlorinated dibenzofurans (PCDFs), and polychlorinated dibenzo-p-dioxins (PCDDs), the causative agents of Yushu, a poisoning by toxins found in rice wine (Nagayama et al., 2005; Nagayama et al., (2003)). These results are supported by human research in which patients consuming chlorophyll-rich diets or combination fiber and chlorophyll-rich health foods (e.g., FBRA) increased excretion of Yusho toxins, according to the author's calculations (Nagayama et al., (2007); Nagayama et al., 2005; Nagayama et al., (2003)).
- **Gastrointestinal effects:** In human research, chlorophyll *a* normalized pancreatitis-induced elevations in amylase levels and ameliorated symptoms of abdominal pain, loss of appetite, fullness, fever, and weakness (Yoshida et al., 1980).
- **Hematologic effects:** In human research, sodium copper chlorophyllin (Yebaiké™ tablet) demonstrated increased treatment efficacy vs. placebo and comparable treatment efficacy vs. Leucogen for increasing peripheral leukocyte count and improving symptoms of dizziness and fatigue in individuals with leukopenia (Gao & Hu, 2005). Topical and intravenous administration of Radachlorin® has also increased peripheral blood leukocyte count and facilitated disease stabilization and regression in cancer patients undergoing photodynamic therapy (PDT) (Kochneva et al., (2010)).
- **Immunomodulatory effects:** In individuals with acute destructive pneumonia, adjunct Chlorophyllipt® coadministered with a standard therapy of sulfonamides, desensitizing drugs, adaptogens, vitamins B and C, and heparin increased levels of lymphocytes and IgA compared to standard therapy plus broad-spectrum antibiotics (Simvolokov et al., 1989).
- **Photodynamic therapy (PDT) properties:** Porphyrin compounds, including chlorophyll and some of its synthetically produced derivatives, are important sensitizers in photodynamic cancer therapy (Ebermann et al., 1996; Ethirajan, Chen, Joshi, & Pandey, 2011; Ficheux, 2009). Chlorophyll derivatives, (CpD-A) produced by use of silkworm excreta could be used as a photosensitizer for PDT of tumors by the use of lights of near 650 nm (Lee et al., 1990). CpD, a photodynamic antiviral agent, caused inactivation of the matrix protein as well as transcription mechanisms involved in vesicular stomatitis virus replication (Lim et al., (2002)). The photosensitizing drugs purpurin-18 and chlorin p6 are also thought to be active in PDT (Hoover, Sery, & Yamamoto, 1988). In addition, two amphiphilic derivatives of chlorophyll, which have high potential as photodynamic therapy sensitizers for malignant melanoma, have been investigated by a combination of laser flash photolysis and pulse radiolysis (Fiedor et al., (1993)). Other chlorophyll-based photosensitizing agents used in PDT include pheophorbide-a (Schlothauer et al., (2012); Xodo, Rapozzi, Zacchigna, Drioli, & Zorzet, 2012) and HPPH (2-1[hexyloxyethyl]-2-devinylpyropheophorbide-a)

(Sunar et al., (2010)) In human research, topical and intravenous administration of Radachlorin<sup>®</sup> increased peripheral blood leukocyte count and facilitated disease stabilization and regression in cancer patients undergoing PDT (Kochneva et al., (2010)). Similar benefits in cancer treatment response have been observed following photosensitization with HPPH (Nava et al., (2011)) and Sonoflora 1 (Wang et al., (2009)).

- **Porphyrin effects:** In mammals and yeast, 5-aminolaevulinic acid dehydratase is a zinc-dependent enzyme that catalyzes the synthesis of porphobilinogen, the pyrrole building block that is incorporated into chlorophyll. The X-ray structure of this enzyme revealed how substitution of the catalytically important zinc ion by lead inactivates the enzyme and causes a form of pseudoporphyria (Warren, Cooper, Wood, & Shoolingin-Jordan, 1998).
- **Radioprotective effects:** In vitro, a commercial product of *Sasa senanensis* Rehder leaf extract containing Fe(II)-chlorophyllin demonstrated antiultraviolet (UV) activity that was four times higher than a similar product containing Cu(II)-chlorophyllin, and one and a half times higher than a product containing Cu(II)-chlorophyllin, ginseng, and pine leaf extracts (Sakagami et al., (2012)).

### Pharmacodynamics/Kinetics

- **Absorption:** According to a clinical study in both normal patients and patients with Refsum's disease, no more than about 5% of the ingested chlorophyll phytol is absorbed by humans (Baxter, 1968).
- **Distribution:** Following the ex vivo topical application of pheophorbide-a to pig ear skin, fluorescence microscopy revealed exclusive pheophorbide-a accumulation in the stratum corneum (Schlothauer et al., (2012)).
- **Excretion:** According to a clinical study in both normal patients and patients with Refsum's disease, 95% of the ingested chlorophyll phytol is excreted in the feces (Baxter, 1968).
- **Metabolism:** Chlorophyll is converted to Mg-free pheophytin derivatives during digestion (Ferruzzi, Failla, & Schwartz, 2001). Other chlorophyll derivatives include phytanic and pristanic acids, which are metabolized within peroxisomes (Mukherji et al., (2003); Schofield & McDonough, 2007). The beta-oxidation pathway cannot degrade phytanic acid until it has been changed to pristanic acid via phytanoyl-CoA 2-hydroxylase (PhyH)-mediated alpha-oxidation (Schofield & McDonough, 2007). However, if the alpha-oxidation pathway has defects, phytanic acid builds up and may cause neurological distress, deterioration of vision, deafness, loss of coordination, and eventual death.
- Chlorophyll may be affected by pH in systems with serum albumin (Semichaevskii & Lozovaya, 1974).
- In vitro, chlorophyllin demonstrated increased CYP3A inhibition compared to *Sasa senanensis* Rehder leaf extract (Sakagami et al., (2010)). In particular, a commercial product of *Sasa senanensis* Rehder leaf extract containing Fe(II)-chlorophyllin demonstrated CYP3A4 inhibitory activity that was one-third that of a similar product containing Cu(II)-chlorophyllin, and one-seventh that of a product containing Cu(II)-chlorophyllin, ginseng, and pine leaf extracts (Sakagami et al., (2012)).

- **Protein binding:** In cellular research, the stability of chlorophyll and chlorophyllin drug–protein complexes with human serum albumin was in the order of  $2.9 \times 10^4/\text{M}$  and  $7.0 \times 10^3/\text{M}$ , respectively (Ahmed-Ouameur et al., (2006)).
- **Transport:** The human ATP-binding cassette (ABC) transporter ABCG2 functions in the removal of toxic metabolites from the body, and has been identified as an efflux transporter of porphyrin and chlorophyll metabolites, including pheophorbide-a and protoporphyrin IX (Asashima et al., (2006); Wakabayashi, Tamura, Saito, Onishi, & Ishikawa, 2006). Inhibition of ABCG2 with fumitremorgin C (FTC), an ABCG2-specific agonist, increased cellular accumulation of pheophorbide-a 5.6-fold (Henrich et al., (2006)). Research on genetic polymorphisms of ABCG2 has identified three alleles, Q126stop, S441N, and F489L, associated with impaired porphyrin transport and possibly related to increased risk of porphyria (Tamura et al., (2006)).

### HISTORY

- In plants, the porphobilinogen synthase family of enzymes catalyzes the first common step in the biosynthesis of the essential tetrapyrroles, such as chlorophyll and porphyrin (Jaffe, 2000). In the leaves and other green parts, chlorophyll in the plant's organelles and cells efficiently absorbs visible radiation, especially red and blue wavelengths (Cilento, 1989). Chlorophyll does not absorb green wavelengths well, which is why this color is reflected and plants appear green to the eye. In fact, the name “chlorophyll” is based on the Greek word *chloros*, which means yellow-green. When, during the process of senescence, chlorophyll-based photosynthesis stops during autumn in temperate climates, the leaves on certain plants lose their green color, revealing yellow and red pigments that also reside in the leaves. Chlorophyll is then degraded via a metabolic pathway specifically activated during senescence (Ougham, Morris, & Thomas, 2005), whereby the colorless, nonfluorescent catabolites of chlorophyll breakdown accumulate in the vacuoles of senescent, nongreen leaves and also in some ripening fruit (Krautler, 2008).
- In the 18th Century, Jan Ingenhousz determined that light is essential for photosynthesis. Two other scientists, Jean Senebier and Theodore de Saussure, discovered that carbon dioxide and water, respectively, were needed. Chlorophyll-containing plants capture radiant energy from the sun and use it to produce oxygen and carbohydrate from carbon dioxide, water, and mineral elements such as nitrogen (Nunes-Nesi, Fernie, & Stitt, 2010; Shimada, 2011).

## EVIDENCE TABLE

| Condition Treated   | Study Type   | Author, Year       | N          | Statistically Significant Results?     | Quality of Study:<br>0-2 = poor<br>3-4 = good<br>5 = excellent | Magnitude of Benefit (how strong is the effect?) | Absolute Risk Reduction | # of Patients Needed to Treat for One Outcome | Comments  |
|---|--|--------------------|------------|--|--|--|-------------------------|---|---|
| Protection from aflatoxins                                  | Randomized controlled trial, double-blind            | Egner, 2001        | 180        | Yes                                    | 5  | Medium   | NA                      | NA  | 100 mg of chlorophyllin vs. placebo three times daily for 4 months.   |
| Cancer treatment  | Before-and-after comparison                          | Kochneva, 2010     | 112        | Unclear                                | NA   | Unclear  | NA                      | NA  | 0.5-1.2 mg/kg of intravenous Radachlorin® followed by laser irradiation at 200-300 J/cm <sup>2</sup> or 0.1 g/cm <sup>2</sup> of topical Radachlorin® gel during 1-3 hours of exposure to laser irradiation at 400-800 J/cm <sup>2</sup> . Control group lacking. |
| Cancer treatment  | Before-and-after comparison                          | Tsukagoshi, 2004   | 42 lesions | P                                      | NA   | P  | NA                      | NA  | 40 mg/m <sup>2</sup> of topical talaporfin sodium, derived from chlorophyll, followed 4-6 hours later by laser irradiation at 100 J/cm <sup>2</sup> .   |
| Leukopenia  | Equivalence trial, randomized                        | Gao, 2005          | 105        | Yes (vs. placebo but not vs. Leucogen) | 2  | Large (vs. placebo, but not vs. Leucogen)        | 58.3%                   | 2   | 40 mg of sodium copper chlorophyllin (YBK) vs. 20 mg of Leucogen vs. 100 mg of vitamin C (placebo) three times daily for 1 month.   |
| Reduction of odor from incontinence/bladder catheterization | Randomized controlled trial, double-blind, crossover | Nahata, 1983       | 47         | No                                     | 3  | NA   | NA                      | NA  | 100 mg of chlorophyllin vs. placebo daily for 2 weeks. Each treatment separated by a washout period of 1 week.  |
| Reduction of odor from incontinence/bladder catheterization | Randomized controlled trial, double-blind, crossover | Christiansen, 1989 | 28         | No                                     | P  | NA   | NA                      | NA  | 75 mg of chlorophyll tablets vs. placebo three times daily.   |

**Explanation of Columns in Natural Standard Evidence Table**

| 1         | 2            | 3            | 4        | 5                          | 6   | 7                    | 8                       | 9                      | 10       |
|-----------|--------------|--------------|----------|----------------------------|---|----------------------|-------------------------|------------------------|----------|
| Condition | Study design | Author, year | <i>N</i> | Statistically significant? | Quality of study<br>0-2 = poor<br>3-4 = good<br>5 = excellent | Magnitude of benefit | Absolute risk reduction | Number needed to treat | Comments |

**Condition**

- Refers to the medical condition or disease targeted by a therapy.

**Study Design**

Common types include:

- **Randomized controlled trial (RCT):** An experimental trial in which participants are assigned randomly to receive either an intervention being tested or placebo. Note that Natural Standard defines RCTs as being placebo-controlled, while studies using active controls are classified as equivalence trials (see below). In RCTs, participants and researchers are often blinded (i.e., unaware of group assignments), although unblinded and quasi-blinded RCTs are also often performed. True random allocation to trial arms, proper blinding, and sufficient sample size are the basis for an adequate RCT.
- **Equivalence trial:** An RCT which compares two active agents. Equivalence trials often compare new treatments to usual (standard) care, and may not include a placebo arm.
- **Before and after comparison:** A study that reports only the change in outcome in each group of a study, and does not report between-group comparisons. This is a common error in studies that claim to be RCTs.
- **Case series:** A description of a group of patients with a condition, treatment, or outcome (e.g., 20 patients with migraine headache underwent acupuncture and 17 reported feeling better afterward). Case series are considered weak evidence of efficacy.
- **Case-control study:** A study in which patients with a certain outcome are selected and compared to similar patients (without the outcome) to see if certain risk factors/predictors are more common in patients with that outcome. This study design is not common in the complementary & alternative medicine literature.
- **Cohort study:** A study which assembles a group of patients with certain baseline characteristics (for example, use of a drug), and follows them forward in time for outcomes. This study design is not common in the complementary & alternative medicine literature.
- **Meta-analysis:** A pooling of multiple trials to increase statistical power (often used to pool data from a number of RCTs with small sample sizes, none which demonstrates significance alone but in aggregate can achieve significance).

Multiple difficulties are encountered when designing/reviewing these analyses; in particular, outcomes measures or therapies may differ from study to study, hindering direct comparison.

- Review: An author's description of his or her opinion based on personal, nonsystematic review of the evidence.
- Systematic review: A review conducted according to prespecified criteria in an attempt to limit bias from the investigators. Systematic reviews often include a meta-analysis of data from the included studies.

### ***Author, Year***

- Identifies the study being described in a row of the table.

### ***N***

- The total number of subjects included in a study (treatment group plus placebo group). Some studies recruit a larger number of subjects initially, but do not use them all because they do not meet the study's entry criteria. In this case, it is the second, smaller number that qualifies as *N*, which includes all subjects that are part of a study at the start date, even if they drop out, are lost to follow-up, or are deemed unsuitable for analysis by the authors. Trials with a large number of dropouts that are not included in the analysis are considered to be weaker evidence for efficacy. For systematic reviews, the number of studies included is reported. For meta-analyses, the number of total subjects included in the analysis or the number of studies may be reported.

### ***Statistically Significant?***

- Results are noted as being statistically significant if a study's authors report statistical significance, or if quantitative evidence of significance is present (such as *p* values). P = pending verification.

### ***Quality of Study***

- A numerical score between 0 and 5 is assigned as a rough measure of study design/reporting quality (0 being weakest and 5 being strongest). This number is based on a well-established, validated scale developed by Jadad et al. (Jadad AR, Moore RA, Carroll D, et al. Assessing the quality of reports of randomized clinical trials: is blinding necessary? *Controlled Clinical Trials* 1996;17[1]:1–12). This calculation does not account for all study elements that may be used to assess quality (other aspects of study design/reporting are addressed in the "Evidence Discussion" sections of reviews).
- A Jadad score is calculated using the seven items in the table given next. The first five items are indications of good quality, and each counts as one point toward an overall quality score. The final two items indicate poor quality, and a point is subtracted for each if its criteria are met. The range of possible scores is 0–5.

### Jadad Score Calculation

| Item  | Score |
|---|-------|
| Was the study described as randomized (this includes words such as randomly, random, and randomization)?  | 0/1   |
| Was the method used to generate the sequence of randomization described and appropriate (table of random numbers, computer-generated, etc.)?  | 0/1   |
| Was the study described as double blind?  | 0/1   |
| Was the method of double blinding described and appropriate (identical placebo, active placebo, dummy, etc.)?   | 0/1   |
| Was there a description of withdrawals and dropouts?  | 0/1   |
| Deduct one point if the method used to generate the sequence of randomization was described and it was inappropriate (patients were allocated alternately, or according to date of birth, hospital number, etc.). | 0/−1  |
| Deduct one point if the study was described as double blind but the method of blinding was inappropriate (e.g., comparison of tablet vs. injection with no double dummy).   | 0/−1  |

### Magnitude of Benefit

- This summarizes how strong a benefit is: small, medium, large, or none. If results are not statistically significant “NA” for “not applicable” is entered. In order to be consistent in defining small, medium, and large benefits across different studies and reviews, Natural Standard defines the magnitude of benefit in terms of the standard deviation (SD) of the outcome measure. Specifically, the benefit is considered:
  - Large: if >1 SD
  - Medium: if 0.5–0.9 SD
  - Small: if 0.2–0.4 SD
- In many cases, studies do not report the standard deviation of change of the outcome measure. However, the change in the standard deviation of the outcome measure (also known as effect size) can be calculated, and is derived by subtracting the mean (or mean difference) in the placebo/control group from the mean (or mean difference) in the treatment group, and dividing that quantity by the pooled standard deviation (Effect size = [Mean Treatment – Mean Placebo]/SDp).

### Absolute Risk Reduction

- This describes the difference between the percent of people in the control/placebo group experiencing a specific outcome (control event rate), and the percent of people in the experimental/therapy group experiencing that same outcome (experimental event rate). Mathematically, Absolute risk reduction (ARR) equals experimental event rate minus control event rate. ARR is better able to discriminate between large and small treatment effects than relative risk reduction (RRR), a calculation that is often cited in studies ([control event rate – experimental event rate]/control event rate). Many studies do not include adequate

data to calculate the ARR, in which cases “NA” is entered into this column. P = pending verification.

### ***Number Needed to Treat***

- This is the number of patients who would need to use the therapy under investigation, for the period of time described in the study, in order for one person to experience the specified benefit. It is calculated by dividing the Absolute Risk Reduction into 1 (1/ARR). P = pending verification.

### ***Comments***

- When appropriate, this brief section may comment on design flaws (inadequately described subjects, lack of blinding, brief follow-up, not intention-to treat, etc.), notable study design elements (crossover, etc.), dosing, and/or specifics of study group/subgroups (age, gender, etc). More detailed description of studies is found in the “Evidence Discussion” section that follows the “Evidence Table” in Natural Standard reviews.

## ***EVIDENCE DISCUSSION***

### ***Protection from Aflatoxins***

- **Summary:** In vitro evidence suggests that chlorophyll may be of use as a chemopreventive agent due to its ability to inhibit the tumor-promoting effects of carcinogens (Egner et al., 2003) and improve the detoxification of toxins involved in cancer promotion. In animal research, chlorophyllin inhibited the absorption of dietary heterocyclic aromatic amines, which may act as potential carcinogens (Sugiyama, Nakandakari, Hayatsu, & Arimoto-Kobayashi, 2002). In one methodologically strong clinical trial, chlorophyllin reduced levels of aflatoxin biomarkers in the urine compared to placebo (Egner et al., (2001)). Although this is promising, further research in this area is warranted to substantiate preliminary findings.
- **Evidence:** Egner et al. conducted a randomized, double-blind, placebo-controlled chemoprevention trial to assess if chlorophyllin could diminish the level of aflatoxin biomarkers in patients at risk for developing hepatocellular carcinoma ( $N = 180$ ) (Egner et al., (2001)). Participants were adults in good general health without history of major chronic illnesses. The sample included men and women aged 25–65 years. The authors used a variety of measures to screen individuals, such as medical history, physical examination, liver ultrasound, electrocardiogram, and routine hematological, hepatic, and renal function tests. To be included in the study, participants were required to have detectable levels of the serum aflatoxin biomarker. Subjects were randomly assigned to receive 100 mg of chlorophyllin or placebo tablets by mouth, three times daily for 4 months. The authors stated that reports of adverse events were lacking. Only one subject in the placebo arm dropped out. Information on standardization, toxic effects, and interactions was lacking. The authors used chem-strip urinalysis, sequential immunoaffinity chromatography, and liquid chromatography-electrospray mass spectrometry to assess levels of aflatoxin-N7-guanine adducts in urine 3 months



after the start of the trial. One hundred sixty-nine samples were viable for laboratory analysis. Chlorophyllin consumption led to an overall 55% reduction ( $p = 0.036$ ) in median urinary levels of aflatoxin biomarkers compared with placebo. Although methodologically strong in general, this study was limited by a short duration of therapy and lack of information regarding maintenance therapy. This trial was included in a literature review by Wogan et al. (2011) (Wogan, Kensler, & Groopman, 2012).

### **Cancer Prevention**

- **Summary:** Epidemiological research examining the association between diet and cancer risk has suggested that various phytochemicals, including chlorophyll, play a protective role in cancer-preventive diets (Divisi, Di, Salvemini, Garramone, & Crisci, 2006). However, compared to phytoestrogens and carotenoids, the two most commonly investigated class of phytochemicals, the association between chlorophyll and cancer risk has been far less frequently studied (Miller & Snyder, 2012). Investigators of a systematic review acknowledged that most studies in this area have been largely inconsistent, and that most associations between individual phytochemicals and cancer risk have either been lacking or were relatively modest in magnitude (Miller & Snyder, 2012). One controlled feeding study has shown that dietary intake of chlorophyllin tablets, cruciferous vegetables, and yogurt exerts DNA-protective effects against fried meat-induced carcinogenesis (Shaughnessy et al., (2011)); however, the effects of chlorophyllin supplementation alone are unclear. Further research investigating the effects of chlorophyll monotherapies is needed.
- **Select combination study (not included in the Evidence Table):** Shaughnessy et al. conducted two controlled feeding studies to examine the combined effects of chlorophyllin, cruciferous vegetables, and yogurt for the prevention of fried meat-induced DNA damage and genotoxicity ( $N = 16$ ) (Shaughnessy et al., (2011)). Eligible participants were at least 18 years old, nonsmoking, not currently taking any prescription medications or antibiotics, and generally in good overall health. In the first study, eight participants were randomly assigned to a dietary regimen of meat cooked at a low (100°C) or high (250°C) temperature for 2 weeks, after which they were crossed over to the other respective regimen for an additional 2 weeks. In the second study, the remaining eight participants were randomly assigned to a dietary regimen of either high-temperature cooked meat alone or in combination with various mutagen inhibitors (chlorophyllin tablets, cruciferous vegetables, and yogurt), after which they were crossed over to the other regimen. Investigated outcomes included mutagenicity and DNA damage, as assessed by *Salmonella* assay and comet assay, respectively. Compared to low-temperature cooked meat, high-temperature cooked meat was highly mutagenic and demonstrated high levels of heterocyclic amines. The urine and feces of participants consuming the high-temperature meat diet also demonstrated increased mutagenicity compared to those consuming the low-temperature meat diet. However, the incorporation of mutagen inhibitors increased the mutagenicity of hydrolyzed urine nearly twofold, suggesting enhanced conjugation, and significantly reduced the mutagenicity of unhydrolyzed

and hydrolyzed feces. Moreover, dietary incorporation of mutagen inhibitors decreased DNA damage in target colorectal cells nearly twofold, in spite of a lack of change in nontarget white blood cells. Investigators concluded that dietary factors, including chlorophyllin, cruciferous vegetables, and yogurt, may reduce procarcinogenic DNA damage induced by fried meat.

### **Cancer Treatment**

- **Summary:** Several studies have investigated the use of photosensitizing agents as an adjunct to photodynamic therapy (PDT) in cancer patients (Moore, Pendse, & Emberton, 2009; Pandey et al., (2006)). Chlorophyll has been suggested to aid in the reduction of side effects associated with PDT, such as those used in management of malignant tumors. Preliminary research has demonstrated reductions in skin photosensitivity in early lung cancer patients who have undergone laser irradiation (Tsukagoshi, 2004) and improvements in overall clinical status, as indicated by partial tumor regression (Kochneva et al., (2010)). Further high-quality research employing rigorous study controls to minimize the effects of bias is required to support the use of chlorophyll derivatives for reducing photosensitivity symptoms.
- **Evidence:** Kochneva et al. conducted an uncontrolled phase II clinical trial to assess the effects of Radachlorin<sup>®</sup> in optimizing the effect of PDT ( $N = 112$ ) (Kochneva et al., (2010)). All included participants presented with basal carcinoma that was scheduled for treatment with PDT. Participants excluded from the study were those with antitumor therapy within 4 weeks of the study, Eastern Cooperative Oncology Group (ECOG) performance status  $\geq 2$ , and a lack of verification of skin cancer diagnosis. Of the participants included in the study, 84 received 0.5–1.2 mg/kg of intravenous Radachlorin<sup>®</sup> (a composition of three derivatives of chlorophyll *a* in solution) in combination with 200–300 J/cm<sup>2</sup> of laser irradiation. The remaining 28 participants received 0.1 g/cm<sup>2</sup> of topical Radachlorin<sup>®</sup> gel during 1–3 hr of exposure to light therapy (400–800 J/cm<sup>2</sup>). These light sessions occurred at the following frequencies: two sessions at an interval of 4 weeks, three sessions at an interval of 1 week, or four sessions at an interval of 1 week. Participants were observed for up to 18 months. The Radachlorin<sup>®</sup> solution contained 6.50/7.50 g of sodium salts of chlorins dissolved in 100 mL of purified water with N-methyl-D-glucamine. The Radachlorin<sup>®</sup> topical gel consisted of 1.43 g of sodium salts of chlorins, purified water, dimethyl sulfoxide, and carbopol. The authors reported a lack of adverse reactions in participants during the course of the treatment or 3 hr after administration of Radachlorin<sup>®</sup>. Although the authors also reported the presence of pain with varied duration (up to 24 hr) in participants receiving the PDT treatment, reports of normal skin damage or subdermal tissue damage after laser and sun exposure were lacking. A lack of treatment-related toxic effects (specifically hematotoxic, nephrotoxic, or hepatotoxic effects) was also reported. Information on dropouts and interactions was lacking from this study. Outcome measures included complete remission, partial remission, partial remission with stabilization, and disease progression in participants. The authors reported that most participants treated with Radachlorin<sup>®</sup> solution ( $N = 67, 80\%$ ) had an increase in

the absolute count of peripheral blood leukocytes. After the 18-month follow-up period, 15.5% of participants treated with Radachlorin<sup>®</sup> solution and 17.6% of participants treated with Radachlorin<sup>®</sup> gel showed partial regression and stabilization. Of the participants who achieved complete remission after 2 months, 92.8% showed preserved remission after 18 months. In patients with multiple lesions, investigators reported that complete remission could be achieved in approximately 70% of cases. This study was limited by lack of control groups, which limited the ability to assess the effects of Radachlorin<sup>®</sup>.

- Tsukagoshi et al. conducted a study to assess the effect of the chlorophyll-based drug talaporfin on diode laser in lung cancer patients (Tsukagoshi, 2004). The treatment used talaporfin sodium, a photosensitizer that has been developed for PDT of various diseases, including malignant tumors, and the Panalas 6405, a diode laser device. The skin photosensitivity caused by talaporfin disappeared faster than the existing photosensitizer. The authors observed clinical benefits in the patients with early lung cancer, with a complete response being obtained in 85.7% of the lesions (36/42 lesions) by the administration of 40 mg/m<sup>2</sup> of talaporfin followed by laser irradiation at 100 J/cm<sup>2</sup>, 4–6 hr later. The sensitivity disappeared mostly within 2 weeks after treatment. Although the results are promising, further clinical studies of photosensitizer kinetics are needed.
- **Select studies of lower methodological quality (not included in the Evidence Table):** Nava et al. conducted two nonrandomized dose escalation studies to determine the safety, efficacy, and optimal dose of light therapy and HPPH (2-[1-hexyloxyethyl]-2-devinyl pyropheophorbide-a) drug therapy for the treatment of precancerous lesions in patients with Barrett's esophagus ( $N = 18$  for each study) (Nava et al., (2011)). Participants had high-grade dysplasia or early intramucosal esophageal adenocarcinoma, as confirmed by biopsy. Administered doses of HPPH, a chlorin-based photosensitizer, were 3–6 mg/m<sup>2</sup>, 24–48 hr after which lesions were exposed to 150, 175, or 200 J/cm of 665 nm light. In total, six participants (16.6%) reported grade 3 and 4 adverse events, while most other participants reported mild-to-moderately severe chest pain necessitating symptomatic treatment only. Dilation was used to treat three esophageal strictures. However, a clear pattern of dose-dependent toxicity was lacking. At light doses of 150 J/cm (48 hr), the optimal effective doses of HPPH were 3 and 4 mg/m<sup>2</sup>. After 1 year of treatment, a 72% complete response rate, defined as the amelioration of high-grade dysplasia and early carcinoma, was seen with 3 mg/m<sup>2</sup> of HPPH plus 175 J/cm of light and 4 mg/m<sup>2</sup> HPPH plus 150 J/cm light. Investigators concluded that HPPH-PDT demonstrates promise as a safe and efficacious treatment for Barrett's esophagus-associated precancerous lesions.
- Wang et al. reported three cases of combination sonodynamic and photodynamic therapy (SPDT) in patients with advanced breast cancer ( $N = 3$ ) (Wang et al., (2009)). All patients had pathologically confirmed evidence of metastatic breast carcinoma previously unresponsive to conventional therapies. Twenty-four hours after sublingual administration of Sonoflora 1, a chlorophyll analog photosensitizer, patients were exposed to SPDT. Following SPDT exposure, all patients demonstrated either a complete or partial treatment response.

### **Fibrocystic Breast Disease**

- **Summary:** The benefits of chlorophyll in benign breast disease may be attributed to its ability to alter liver enzyme pathways involved in estrogen metabolism. These include the CYP1A1 and CYP3A4 pathways that govern hydroxylation and methylation of estrogens, which play a role in the development of hormone-dependent tumors and conditions. One low-quality study has demonstrated positive results in patients with benign breast disease with mamoclam, a combination product containing chlorophyll, omega-3 polyunsaturated fatty acids, and iodine (Bezpalov et al., (2005)). However, more research is needed to confirm preliminary results and elucidate the effects of chlorophyll alone.
- **Select combination study (not included in the Evidence Table):** Bezpalov et al. conducted a clinical trial to assess the effects of a new drug “mamoclam” in patients with benign breast disease ( $N = 33$ ) (Bezpalov et al., (2005)). The drug contains omega-3 polyunsaturated fatty acids, iodine, and chlorophyll derivatives and is produced from the brown sea alga *Laminaria*. Patients (mean age:  $42.5 \pm 1.1$  years) were given two tablets of the drug three times daily for 3 months. Examination included clinical evaluation of symptoms of mastopathy and dysalgomenorrhea, breast sonography, and mammography. Therapeutic response was presented as reduced mastalgia, premenopausal syndrome, dysmenorrhea and algomenorrhea, breast cyst regression, and attenuated pain associated with benign breast disease and palpation. Positive response was reported in 94% of patients. The authors concluded that the drug should be indicated for benign breast disease treatment. Limitations of this study included a lack of a placebo group. Also, due to the coadministration of other compounds, the effects of chlorophyll alone are unable to be determined from this trial.

### **Herpes**

- **Summary:** One case series has been performed to determine the effects of chlorophyll in the treatment of herpes simplex and herpes zoster (Belenkii & Krikun, 1971). Although preliminary results demonstrated some beneficial effects with regard to viral replication, symptomatic pain, and the manifestation of lesions, more high-quality research is needed in this area.
- **Select study of lower methodological quality (not included in the Evidence Table):** Belen’kii and Krikun conducted a case series to assess the effects of topical chlorophyll preparations on herpes zoster and herpes simplex viral infections on the skin ( $N = 91$ ) (Belenkii & Krikun, 1971). Participants had cutaneous herpes zoster ( $N = 57$ ) or herpes simplex ( $N = 34$ ), but further information on inclusion and exclusion criteria was lacking. Chlorophyll cream or solution (produced at the Forestry University in St. Petersburg, Russia) was applied topically on affected areas three to six times daily. Information on treatment duration was lacking. The treatment contained 2–5 mg of chlorophyll per 1 g of cream or per 1 mL of saline solution. The chlorophyll cream was well tolerated, but a few people developed dermatitis. Information on toxic effects, dropouts, and interactions was lacking. Outcome measures included resolution of symptoms and pain. In 50 participants with herpes zoster, eight participants recovered after 2–4 days, 38 participants recovered after 5–7 days, and two participants recovered after > 12 days. In

20 participants with herpes simplex virus, 18 participants recovered after 2–4 days, and two recovered after 5–7 days of treatment. The authors mentioned that using preparations of chlorophyll during the infiltration stages of herpes simplex stopped virus multiplication and development of lesions, while if the participants had already developed lesions, the preparation was less effective but probably quickened the healing process. In herpes zoster infections, chlorophyll was unable to stop viral replication and appearance of symptoms; however, the symptoms were less frequent. The authors stated that participants noticed a decrease in pain after the first day of using the chlorophyll preparation. Limitations of this study included a lack of blinding, randomization, and description of dropouts. Other limitations included a lack of objective outcome measures and statistical calculations, and inconsistent reporting of results.

### **Leukopenia**

- **Summary:** Early evidence has suggested that supplementation with sodium copper chlorophyllin (Yebaiké™ tablet; YBK) is equally effective as Leucogen with regard to increasing leukocyte count and reducing symptoms of dizziness and fatigue in patients with leukopenia (Gao & Hu, 2005). Although this is promising, further high-quality research in this area is needed to confirm or refute preliminary findings.
- **Evidence:** Gao and Hu conducted a randomized equivalence trial to assess the benefits and safety of YBK in the treatment of leukopenia ( $N = 105$ ) (Gao & Hu, 2005). Participants included in the study were observed from November 2003 to March 2005. Those with a white blood cell count (WBC) of  $<4.0 \times 10^9/L$  were included if they presented with neurosis symptoms (dizziness, fatigue, anorexia, and insomnia). Participants were randomized to receive YBK treatment, Leucogen treatment, or vitamin C treatment. Participants in the YBK group orally received 40 mg of YBK (Hangzhou Qianjing Pharmaceutical, China) three times daily. Participants in the Leucogen group orally received 20 mg of Leucogen three times daily. The group considered the placebo group received 100 mg of vitamin C three times daily. The study lasted for a period of 1 month. Information on standardization, toxic effects, and interactions was lacking. The authors reported that a lack of treatment-related adverse effects was observed. However, it was also reported that 53 patients in the YBK group reported a change in stool color during treatment, one patient reported complaints of dry mouth, and another patient reported symptoms of mild abdominal cramps. All participants completed the study. Outcome measures included changes in the peripheral leukocyte count, therapeutic efficacy, and improvements in dizziness, fatigue, anorexia, and insomnia. Compared to the placebo group, participants treated with YBK showed a significant increase in leukocyte count (from  $3.5 \pm 0.4$  to  $3.6 \pm 0.8$  vs. from  $3.5 \pm 0.3$  to  $5.6 \pm 1.1$ ;  $p < 0.01$ ). The therapeutic efficacy of YBK treatment was significantly greater than placebo treatment (85.0% vs. 26.7%;  $p < 0.01$ ). However, statistically significant between-group differences were lacking compared to Leucogen treatment. Compared to the placebo group, participants treated with YBK showed a significant improvement in dizziness (from 13/15 to 11/15 vs. from 52/60 to 18/60,  $p < 0.01$ ) and fatigue (from 14/15 to 13/15 vs.

from 56/60 to 11/60,  $p < 0.01$ ). Significant between-group differences in anorexia and insomnia were lacking. The investigators concluded that treatment with YBK demonstrated some beneficial effects when used to treat leukopenia, similar to that of Leucogen. The study was limited by a lack of blinding and adequate description of randomization, which may have allowed the introduction of bias.

### **Metabolic Disorders**

- **Summary:** Phytanic acid is a chlorophyll product produced in ruminant animals. In healthy individuals, dietary intake of phytanic acid from dairy products of cows fed differing amounts of chlorophyll-rich plant material lacked evidence of effect on markers of metabolic syndrome risk (Werner et al., (2011)). However, the direct effects of chlorophyll supplementation on metabolic syndrome risk factors are unclear. Further research in this area is required.
- **Select study of lower methodological quality (not included in the Evidence Table):** Werner et al. conducted a randomized, double-blind, controlled dietary intervention trial to examine the effect of dairy fat intake on the plasma concentration of phytanic acid and markers of metabolic syndrome in healthy individuals ( $N = 14$ ) (Werner et al., (2011)). Phytanic acid is produced from chlorophyll in ruminant animals, and its levels in cow milk differ based on the amount of green plant material consumed by the animal. In this study, dairy products with differing levels of phytanic acid were obtained from cows fed roughage with low or high chlorophyll contents. Specifically, participants consumed a test diet of 45 g of milk fat daily from butter and cheese containing 0.24wt% phytanic acid (phytanic diet), or a control diet containing 0.13wt% phytanic acid (control diet). Compared to baseline, an increasing trend in plasma phytanic acid concentration was seen in both groups, with a maximum 15% increase in the phytanic diet group and a 24% increase in the control diet group. However, significant effects on markers of metabolic syndrome risk were lacking for either group. Investigators concluded that increased intake of dairy fat modifies the plasma concentration of phytanic acid, irrespective of cow feeding regime and dietary phytanic acid intake, but that the effects of phytanic acid on metabolic syndrome risk markers are unclear. Also, the effects of chlorophyll supplementation directly are unable to be determined from this trial.

### **Pancreatitis**

- **Summary:** Animal studies have concluded that chlorophyll *a* reduces the mortality rate of experimental pancreatitis (Yoshida et al., 1980). In case series research, normalization of serum amylase levels and improvements in adverse abdominal symptoms were seen in patients with chronic pancreatitis following supplementation with chlorophyll *a* (Yoshida et al., 1980). Although this is promising, further high-quality research is required in this area before any firm conclusions may be made.
- **Select study of lower methodological quality (not included in the Evidence Table):** Yoshida et al. conducted a case series to assess the efficacy of chlorophyll *a* in the treatment of chronic pancreatitis ( $N = 34$ ) (Yoshida et al., 1980). Individuals aged 27–64 years who presented with chronic pancreatitis were included in

the study. All included participants were recruited from the University Hospital of the University of Tokyo. All participants were treated with 5–20 mg of intravenous chlorophyll *a* (Nampo Pharmaceutical Company, Tokyo) in one to two divided doses daily for periods ranging from 3 days to 3 years. The total doses of chlorophyll *a* treatment were 30–1,960 mg. The ampules of treatment contained 5 mg of chlorophyll *a* in 1 mL of 5% glucose solution. Prior to intravenous infusion, the ampule solutions were mixed with 200–500 mL of saline or 5% glucose. The authors stated that reports of adverse effects or allergic reactions were lacking. Information on toxic effects, dropouts, and interactions was also lacking. Outcome measures included improvements in abdominal signs and clinical tests, such as serum and urine amylase levels, as well as on X-ray examination to assess the efficacy on chronic pancreatitis. After completion of therapy with chlorophyll *a*, individual serum amylase levels returned to normal range. It was also shown that while serum amylase levels increased with pancreatitis attacks, those levels returned to normal after chlorophyll *a* treatment. Abdominal signs such as pain, loss of appetite, fullness, fever, and weakness were eliminated in a majority of the cases. Abdominal pain was relieved at a rapid rate of 20–30 min after chlorophyll *a* infusion, but most patients reported a rebound in abdominal pain 4–5 hr after the infusion. This study was limited by a lack of a control group, which limits the ability to objectively assess the effects of chlorophyll *a* treatment.

### **Pneumonia**

- **Summary:** In preliminary research, inclusion of Chlorophyllipt® (a eucalyptus-derived extract of chlorophyll *a* and *b*) as part of a complex, multicomponent therapy significantly speeded up the normalization of immune system function in patients with acute destructive pneumonia and regulated T lymphocyte counts (Simvolokov et al., 1989). Additional research is required to further elaborate on the immune-modifying effects of chlorophyll.
- **Select combination study (not included in the Evidence Table):** Simvolokov et al. conducted a controlled study to assess the effects of Chlorophyllipt® for acute destructive pneumonia ( $N = 41$ ) (Simvolokov et al., 1989). Adults aged 21–68 years with acute destructive pneumonia were included. Further information on inclusion and exclusion criteria was lacking. Participants randomized into the active control group ( $N = 19$ ) received standard therapy with broad-spectrum antibiotics, sulfonamides, desensitizing drugs, adaptogens, and vitamins B and C, and 10,000 units of heparin daily for 15 days. The treatment group ( $N = 22$ ) received the same standard treatments, except in place of antibiotics, they were intravenously administered 150 mL of chlorophyll solution (Chlorophyllipt® composed of chlorophyll *a* and *b* extracts from eucalyptus leaves) with an extra 5,000 units of heparin twice daily for 14–15 days. The trial duration was 30 days. Each treatment dose of 150 mL of normal saline was mixed with 8–10 mL of 0.25% chlorophyll solution. The authors stated that Chlorophyllipt® was well tolerated. Information on toxic effects, dropouts, and interactions was lacking. Outcome measures included clinical symptoms, X-ray results, immune system function (T lymphocytes; immunoglobulins [Ig] A, M, and G; leukocytes; band cells), serum albumin, total protein, and the erythrocyte sedimentation rate (ESR). Statistical

comparisons of baseline group characteristics were lacking. In the chlorophyll group, there was a significant decrease from baseline in leukocytes (from  $11.4 \pm 1.1$  to  $7.4 \pm 0.8 \times 10^9/L$ ;  $p < 0.01$ ), band cells (from  $11.6 \pm 1.2$  to  $5.1 \pm 0.7\%$ ;  $p < 0.001$ ), and ESR (from  $45.9 \pm 3.5$  vs.  $23.8 \pm 2.1$  mm/hr;  $p < 0.001$ ), while significant changes were lacking in the active control group. Total protein lacked significant changes for both groups when compared to baseline. Compared to baseline, albumin significantly increased (from  $40.3 \pm 3.0$  to  $48.1 \pm 2.1\%$ ;  $p < 0.05$ ) in the chlorophyll group and lacked a significant difference in the active control group. When the chlorophyll group was compared to the control group, participants had significantly more lymphocytes (from  $31.3 \pm 2.2$  vs.  $16.7 \pm 1.2\%$ , respectively;  $p < 0.001$ ) and IgA (from  $2.1 \pm 0.13$  vs.  $1.7 \pm 0.1$  g/L, respectively;  $p < 0.05$ ) at the end of the study. Significant between-group differences in IgM and IgG levels were lacking. The authors stated that in the first few days of treatment with Chlorophyllipt<sup>®</sup>, temperature decreased, patients felt better, phlegm production decreased, and bad breath disappeared. Three participants developed chronic lung abscesses and had to be sent for surgical treatment; however, it was unreported to which treatment group these participants belonged. The authors concluded that including Chlorophyllipt<sup>®</sup> in complex therapy significantly speeds up the normalization of laboratory- and X-ray-assessed immune system function in individuals with acute destructive pneumonia. Limitations of this study included a lack of blinding, randomization, description of dropouts, and between-group characteristic comparisons at baseline. Other limitations included a lack of complete result reporting, information on the cure rate of acute destructive pneumonia, and information as to which broad-spectrum antibiotics were replaced by the Chlorophyllipt<sup>®</sup> treatment. Moreover, due to the coadministration of various other immune-modulating agents, the effects of chlorophyll alone are unable to be determined.

### Poisoning

- Summary:** The accumulation of organic pollutants in the body, such as dioxins and polychlorinated biphenyls (PCBs), has been implicated in the etiology of various adverse health effects. Yusho is a poisoning caused by ingestion of rice oil contaminated with PCBs, specifically polychlorinated dibenzofurans (PCDFs) and polychlorinated dibenzo-p-dioxins (PCDDs). Foods containing dietary fiber and chlorophyll, lipids (squalane), and anion exchange resins have been investigated for their ability to minimize the body's accumulation of PCBs and dioxins (Mochida, Fukata, Matsuno, & Mori, 2007). In rats, dietary fiber and chlorophyll have been shown to promote the fecal excretion of dioxins and to reduce their levels in rat liver (Nagayama et al., 2005). The benefits may be due to activation of phase II liver enzymes, resulting in increased toxin elimination. Preliminary research in individuals with Yusho poisoning has indicated that a chlorophyll-rich diet may increase PCDF and PCB elimination (Nagayama et al., (2007); Nagayama et al., 2005); however, further high-quality research is needed.
- Select combination studies (not included in the Evidence Table):** Nagayama et al. conducted a clinical trial to examine the effects of FBFA intake on the excretion of PCDFs and PCDDs in individuals with Yusho poisoning ( $N = 18$ ) (Nagayama



et al., (2007)). Male and female participants were divided into one of two groups and administered varying levels of FBRA, a health food rich in dietary fiber and chlorophyll. Baseline levels of the PCDF congeners 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF, and 1,2,3,6,7,8-HxCDF were two to three times higher in group A participants (1.36, 0.491, 0.150 pg/g, respectively) vs. group B participants (0.571, 0.159, 0.064 pg/g, respectively). Participants in group A were given 7–10.5 g of FBRA three times daily after each meal during year 1 but no supplementation during year 2. Participants in group B were given a similar regimen of FBRA but only during year 2. Outcomes investigated were serum PCDF concentration after year 1 and year 2, as well as the calculated average net excretion of PCDF congeners due to FBRA intake. Following supplementation in group A, 120, 372, and 96 ng/patient of 2,3,4,7,8-PeCDF, 1,2,3,4,7,8-HxCDF and 1,2,3,6,7,8-HxCDF, respectively, were excreted from the body. In group B, 36 ng/patient of 2,3,4,7,8-PeCDF was excreted, while excretion of the other two PCDF congeners was lacking. Investigators concluded that FBFA promoted the excretion of PCDF congeners more effectively in Yusho patients with a higher baseline concentration of PCDFs in the blood. However, due to the coadministration of high levels of fiber in FBRA, the effects of chlorophyll alone are unable to be determined.

- Nagayama et al. conducted a clinical trial to assess the effects of a chlorophyll-rich diet on the active elimination of causative PCDFs and PCDDs in Japanese patients (Nagayama et al., 2005). This study revealed concentrations of PCDFs and PCDDs of those in the chlorophyll group decreased by 30.5 and 33.9%, respectively, with decreases of 22.0 and 24.5%, respectively, in the nonintake group. Their total body burdens just before and 1 year after the study were calculated on the assumptions that the body fat was also contaminated with these congeners at their blood levels on the lipid weight basis and the content of body fat was 20% of the body weight. The authors computed the average amounts in excretion of pentachlorodibenzofuran (PeCDF) and hexachlorodibenzo-p-dioxin (HxCDD) from the body in both the chlorophyll-intake and nonintake groups. Consequently, the amounts of excretion of PeCDF and HxCDD in the chlorophyll-intake group were 2.1 and 1.9 times greater, respectively, than those in the nonintake group. Therefore, chlorophyll seemed to promote the fecal excretion of PeCDF and HxCDD, the main causative PCDFs/DDs congeners of Yusho. The authors also expected chlorophyll to reduce their body burdens of patients with Yusho and to improve some objective and subjective symptoms in Yusho patients. However, the effects of chlorophyll supplementation alone, rather than as a part of a dietary intervention, are unclear from this trial.

### ***Reduction of Odor from Incontinence/Bladder Catheterization***

- **Summary:** According to historical use, chlorophyll has been suggested to improve body odor in colostomy patients (Blake, 1968). Despite empirical use, results from available clinical research do not support the use of chlorophyll for this indication (Christiansen et al., 1989; Nahata et al., 1983). Further, high-quality research is needed in this area before any firm conclusions may be made.
- **Evidence:** Nahata et al. conducted a randomized, double-blind, placebo-controlled crossover trial to assess the efficacy of chlorophyllin for reducing

urinary odor in incontinent patients ( $N = 47$ ) (Nahata et al., 1983). Participants with an average age of 72.4 years, who were identified to have incontinence and urinary odor and who had Foley catheters, were included. Further information on inclusion and exclusion criteria was lacking. Participants received 100 mg of chlorophyllin (Derifil<sup>®</sup>) or placebo daily for 2 weeks, followed by a 1-week washout period. Both the chlorophyllin and placebo treatments were provisioned from Rystan Company, Inc., New York. After the washout period, participants received 2 weeks of the alternate regimen. Discussion of standardization, allergies, interactions, and toxic effects was lacking. Investigators noted that adverse events were lacking in all participants. A total of 47 participants entered the trial, but the results from 27 participants were excluded from analysis because they left the nursing home before finishing the study. The outcome measure was the average intensity of urinary odor on a visual analog scale (VAS) of 0–10. Statistically significant between-group differences were lacking, according to the VAS scale. Limitations of this study included the small study population, use of a subject outcome measure, and a short duration of therapy, which may have led to a lack of statistical significance. There was also a lack of description of randomization and blinding procedures, which may have introduced bias.

- Christiansen et al. conducted a randomized, double-blind, crossover study to investigate the use of chlorophyll in the reduction of fecal odor in colostomy patients ( $N = 28$ ) (Christiansen et al., 1989). Colostomy patients were given 75 mg of chlorophyll tablets or placebo three times daily. The authors found that the effect of chlorophyll did not differ from that of a placebo in the patients' subjective assessment of the unpleasant odor. A weakness of this study was the lack of objective odor assessment by a third party.

### **Rheumatoid Arthritis**

- **Summary:** Diets high in chlorophyll have been hypothesized to modify intestinal flora, resulting in improved management of immune disorders, including rheumatoid arthritis. However, evidence indicating a direct link between disease parameters associated with rheumatoid arthritis and consumption of an uncooked, lactobacilli-rich vegan diet is lacking (Nenonen et al., 1998). More evidence is needed to support the use of chlorophyll in autoimmune diseases.
- **Select combination study (not included in the Evidence Table):** Nenonen et al. conducted a randomized controlled trial to assess the effects of an uncooked vegan diet, rich in lactobacilli, on rheumatic symptoms in rheumatoid arthritis patients (Nenonen et al., 1998). The intervention group experienced subjective relief of rheumatic symptoms during treatment, but a benefit was lacking for objective parameters, including C-reactive protein (CRP), ESR, and joint counts (Nenonen et al., 1998). The authors reported that a return to an omnivorous diet aggravated symptoms, but this was not specified as being significant. Half of the patients experienced adverse effects (nausea, diarrhea) during the diet and stopped the experiment prematurely. The positive subjective effect experienced by the patients was not discernible in the more objective measures of disease activity (Health Assessment Questionnaire, duration of morning stiffness, pain at rest, and pain on movement). Indicators of rheumatic disease activity lacked a

statistically significant difference between groups. However, a composite index showed a higher number of patients with a three- to five-point improvement in disease activity measures in the intervention group. Stepwise regression analysis associated a decrease in the disease activity (measured as change in the Disease Activity Score, DAS) with lactobacilli-rich and chlorophyll-rich drinks, increased fiber intake, and a lack of need for gold, methotrexate, or steroid medication ( $R^2 = 0.48, p = 0.02$ ). The authors concluded that an uncooked vegan diet, rich in lactobacilli, may decrease subjective symptoms of rheumatoid arthritis. The study also concluded that large amounts of living lactobacilli consumed daily may have positive effects on objective measures of rheumatoid arthritis. Weaknesses of this study included improper randomization and an improper control. Higher-quality trials are necessary to determine the direct effects of chlorophyll in patients with rheumatoid arthritis.

### **Sepsis**

- **Summary:** Information from one uncontrolled clinical trial suggested that topical application of 1% Chlorophyllipt<sup>®</sup> solution may be used as a prophylactic treatment in lieu of systemic antibiotics to mitigate purulent-septic soft tissue complications in ambulatory outpatients (Biliaieva et al., 2011). Although this is promising, further high-quality research is needed in this area before any firm conclusions may be made.
- **Select study of lower methodological quality (not included in the Evidence Table):** Biliaieva et al. examined the prophylactic effects of topically applied 1% Chlorophyllipt<sup>®</sup> ethanol solution on purulent-septic soft tissue complications in ambulatory outpatients ( $N = 56$ ) (Biliaieva et al., 2011). Chlorophyllipt<sup>®</sup> was applied via bandage in conjunction with ultraviolet irradiation and ultrahigh-frequency electric fields. Investigators concluded that prophylactic treatment with Chlorophyllipt<sup>®</sup> may exclude systemic application of antibiotics; however, further details are lacking.

### **Tuberculosis**

- **Summary:** In patients with tuberculosis, dietary intake of chlorophyll during chemotherapy treatment improved immune parameters and free radical indices, such as malonic dialdehyde (Lozovskaia, 2005). However, other supportive evidence publicized for this indication is lacking. Further clinical trials incorporating chlorophyll monotherapies are required to support its use in tuberculosis patients.
- **Select combination study (not included in the Evidence Table):** Lozovskaia et al. conducted a study to assess the effects of dietary supplementation with chlorophyll from *Laminaria* on the complex treatment of pulmonary tuberculosis in adolescents ( $N = 78$ ) (Lozovskaia, 2005). Forty-eight patients receiving chemotherapy were administered chlorophyll, while 30 patients in the comparison group were receiving chemotherapy alone. The author established that

diets high in *Laminaria* promote favorable radiological dynamics and improve the functional activity of T lymphocytes and plasma malonic dialdehyde levels. However, the effects of chlorophyll supplementation alone, rather than as a part of a dietary intervention, are unclear from this trial.

### **BRANDS USED IN CLINICAL TRIALS/THIRD-PARTY TESTING**

- Chlorophyllipt<sup>®</sup> (Arterirum Co., Kiev, Ukraine) (Biliaieva et al., 2011; Simvolokov et al., 1989).
- Derifil<sup>®</sup> chlorophyllin copper complex (Rystan, Little Falls, NJ) (Egner et al., 2001; Nahata et al., 1983).
- Radachlorin<sup>®</sup> (RADA-PHARMA Co. Ltd., Moscow, Russia) (Tsukagoshi, 2004).
- Yebaike<sup>™</sup> tablet (Hangzhou Qianjing Pharmaceutical, China) (Gao & Hu, 2005).

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