Review Article

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Warfarin-chlorophyll products, herb-drug interactions

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Abstract

Warfarin is one of the most commonly prescribed anticoagulants for preventing the formation of blood clots to reduce the risk of heart attack, stroke, deep vein thrombosis, and other serious conditions. Warfarin belongs to a group of vitamin K antagonists that has a narrow therapeutic index, slow onset of action and significant drug-drug, herb-drug interactions. Its unpredictable dose-response relationship can increase risks of bleeding complications or inadequate anticoagulation. Consumption of foods and nutritional supplements rich in vitamin K can interfere with warfarin treatment because vitamin K can reduce the warfarin's effectiveness and potentially increase the risk of blood clots. There are chlorophyll products that are claimed to be beneficial to health when taken as a supplement in solid or liquid forms. Chlorophyll products are now increasingly distributed all over the world. These products make patients and healthcare providers confused about how they affect the effectiveness of warfarin treatment because they are derived from green vegetables, which have been known to cause significant herb-drug interactions. This review provides some information about chlorophylls and chlorophyll products that can potentially interact with warfarin, and some forms, such as chlorophyll drops or chlorophyll water, that can be taken safely because they contain the lowest amount of vitamin K.

Keyword: Warfarin, Herb-drug interaction, Chlorophyll, Chlorophyllin, Vitamin K

Introduction

Warfarin is an oral anticoagulant drug that is clinically used in the treatment and primary or secondary prevention of venous and arterial thromboembolic events. It acts as a vitamin K antagonist by inhibiting the enzyme vitamin K epoxide reductase, which is essential for the functioning of factor VII and IX during anticoagulation[1] Vitamin K antagonists are highly effective in many settings and are now used by millions of patients worldwide[2]. Warfarin is important in preventing the formation of blood clots and extension of clots already formed, while also minimizing the risk of embolization of blood clots to other vital organs, such as the lungs and brain[3].

Inappropriate anticoagulation control can expose patients to the risk of complications. Herb-drug interactions are significant for warfarin that has a narrow therapeutic index. They can lead to either an increase or decrease in the anticoagulant effect. Those that increase the anticoagulant effect will significantly increase the risk of serious bleeding conditions. Interactions that decrease the anticoagulant effect will significantly increase the risk of thromboembolic complications of the condition for which warfarin was prescribed[4].

There is an increase in the consumption of medicinal plants and herbal products globally, especially in developing and developed countries[5]. The use of herbal medicinal products and supplements has increased tremendously over the past three decades with at least 80% of people worldwide relying on them for some part of their primary healthcare[6]. Nearly 40%

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of patients with cardiovascular disease or stroke used concomitant herbs along with their prescribed medications[7].

Herb-drug interactions are often unsuspected by physicians for several reasons, such as 1) most trained physicians lack adequate knowledge on herbal drugs and their potentials for drug interactions[8], 2) inadequate physician-patient communication about the use of herbal products[9], and 3) since the pharmacokinetic and pharmacodynamic characteristics of most herbal supplements are not completely recognized they can vary considerably in composition depending on the source and package, thus, potential interactions are often unpredictable[10].

Chlorophyll is a natural pigment produced by green plants and algae. This molecule can absorb light energy to produce their own food through photosynthesis[11]. Chlorophyll makes plants and algae appear green because it reflects the green wavelengths found in sunlight, while absorbing all other colors[12]. Several reports have demonstrated that plant pigments play important roles in human health in preventing some diseases[13]. Aside of its health benefits, chlorophyll is used as a natural coloring agent in foods and cosmetics[14].

Chlorophyll and its derivatives have a long history in traditional medicine[15]. There is evidence that chlorophyll may exert activities such as wound healing[16], anti-inflammation[17], antioxidant & antimutaginic[18], anticarcinogen[19], and antibacterial activities[20]. It is a photosensitizer in photodynamic therapy[21]. Chlorophyllin has been used in alternative medicine as an aid to reduce the odor of urine or feces[22].

The demand for chlorophyll has dramatically increased due to the recent popularity of using natural instead of artificial additives[23]. Under the current law, chlorophyll is like other herbal products that are defined as dietary supplements and manufacturers can produce, sell, and market them without first demonstrating safety and efficacy, as is required for pharmaceutical drugs[24]. Although chlorophyll, as with other herbal remedies, is perceived as being natural and safe, many might experience adverse effects or herb-drug interactions that are underreported and can sometimes cause life-threatening consequences[25].

As a result of widespread promotion of chlorophyll products in the media, the use of chlorophyll supplements is prevalent among the healthy population and some patients who are taking prescription medications. The current review was therefore aimed at providing an overview of chlorophyll and chlorophyll products with their potential for warfarin drug interactions, based on the available evidence. In addition, recommendations for patients and healthcare providers to minimize these interactions will be highlighted.

Pharmacological activity, uses, and effectiveness of chlorophylls

There are several types of chlorophyll, namely chlorophyll a, b, c, d, and e. Chlorophyll a and b are the two types that are widely distributed in higher plants. Chlorophyll c is present in diatoms, dinoflagellates, and brown algae. Chlorophyll d is found in red algae while chlorophyll e is a rare type found in some golden algae[26]. Chlorophyll derivatives consist of chlorophyllin, chlorophyllin copper, sodium copper chlorophyllin, chlorophyllin iron, sodium iron chlorophyllin, chlorophyllin zinc, fluochlorophyllin and metallochlorophyllin[27–29]. Besides, chlorophyll has many metabolites, such as pheophorbide, protoporphyrin IX, phytanic acid, pristanic acid, purpurin-18, and chlorin p6[30–32].

Chlorophyll a showed antioxidant activity only at high concentrations of about 1 mMol/L, and the mechanism of action involved might not be related to the capacity of the hydrogen donation, but to the protection of linoleic acid against oxidation and/or prevention of the decomposition of hydroperoxides[33]. Sodium copper chlorophyllin, sodium zinc chlorophyllin, and sodium iron chlorophyllin had dose-dependent antioxidant activity responses. In the β-carotene bleaching assay, the antioxidant effects of sodium copper chlorophyllin, sodium zinc chlorophyllin, and sodium iron chlorophyllin (EC50 = 0.04, 0.38 and 0.90 mg/ml, respectively) were better than that of ascorbic acid (EC50 = 4.0 mg/ml)[34].

Chlorophyll a, b, and pheophytin (the Mg-chelated form of chlorophyll) showed significant dose-dependent activity in the 1,1-diphenyl-2-picrylhydrazyl (DPPH) assay. They also had the ability to chelate Fe(II) and the ability to prevent the formation of thiobarbituric acid reactive substances during the Cu-mediated peroxidation of low density lipoprotein, with the pheophytins being the strongest antioxidants[35]. However, in the DPPH assay, the effective dosage of ascorbic acid was more than ten times lower than that of sodium copper chlorophyllin, sodium zinc chlorophyllin, and sodium iron chlorophyllin at the same scavenging rate[34].

Phytol/phytanic acid, a derivative of chlorophyll, has a potential role in the management of insulin resistance and metabolic disorders that accompany diabetes and/or obesity, through activating the retinoid X receptor. It has been suggested that phytol can be administered with lower doses of thiazolidinediones, the insulin sensitizers, to maintain the full therapeutic action, but with lesser side effects[36].

According to historical use, chlorophyll has been suggested to improve body odor in colostomy patients at doses of 100-200 mg/day[37,38]. A double-blind study in 125 incontinent patients received 100 mg twice a day (at 12 hourly intervals) for 3 days, reported a marked reduction in the body odor as compared with that of non-treatment group[39]. However, limitations of this study included the use of subjective outcome measures, a short duration of therapy, and the blinding procedures that may have introduced bias.

In a group of 62 geriatric nursing home patients (32 patients in test group, 30 patients in placebo group), chlorophyllin tablets 100 mg/day three times daily for the first 7 to 10 days, and thereafter one tablet twice daily, the duration of the study was 6 months, were found to be helpful in controlling body and fecal odors and also easing chronic constipation[40].

A randomized, double-blind, cross-over study in 28 colostomy patients, found that 75 mg chlorophyll tablets thrice daily did not differ from that of a placebo in the patients' subjective assessment of the unpleasant odor, but the weakness of this study was the lack of objective odor assessment and the duration of administration[41].

Trimethylaminuria (TMA) is a metabolic hereditary disorder characterized by the inability to excrete trimethylamine, a compound with a fishy or foul odor. It was found that copper chlorophyllin (total 180 mg per day for three weeks) was effective at reducing free urinary TMA concentration and therefore decreased the foul smell[41].

Chemoprevention by chlorophyll was investigated in a rat multi-organ carcinogenesis model. Twenty-one male rats in three gavage groups (N = 7 rats each) received five daily doses of 250 mcg/kg of [(3)H]-aflatoxin-B1 alone, or with 250 mg/kg chlorophyllin, or with 300 mg/kg of chlorophyll. The results suggested that chlorophyll and chlorophyllin provide potent chemoprotection against early biochemical and late pathophysiological biomarkers of aflatoxin-B1 carcinogenesis in the rat liver and colon[42].

In a randomized, double-blind, placebo-controlled chemoprevention trial, tested on 180 healthy adults, randomly assigned to ingest 100 mg of chlorophyllin or a placebo three times a day for 4 months. The results found that chlorophyllin consumption led to an overall 55% reduction (P = 0.036) in urinary levels of aflatoxin biomarkers compared with those taking placebo[43].

However, it might take a long time, as long as 20 years, between aflatoxin-B1 exposure and the development of cancer in humans to determine whether chlorophyllin can reduce the incidence of hepatocellular carcinoma in people exposed to high levels of dietary aflatoxin-B[44]. No research has reached that point and it is not known whether chlorophyllin will be useful in the prevention of cancers in people who were not exposed to significant levels of dietary aflatoxin-B1[45]. Many questions remain unanswered regarding the exact mechanisms of action and the implication for other types of cancer and the potential for natural chlorophylls in the diet to provide cancer protection.

The uses and effectiveness of chlorophyll have been reviewed by the Natural Standard

Evidence-Based Validated Grading Rationale™, based on the available scientific evidence, in support of the efficacy for all the uses of chlorophyll. This was conducted via electronic searches in several databases, from inception to May 2013. In the review, most of the uses of chlorophyll were evaluated individually and given a grade C (unclear or conflicting scientific evidence), except for the use of chlorophyll as protection against aflatoxins, which was given a grade B (good or positive scientific evidence)[46,47], as shown in table 1.

Table 1. Efficacy of uses of chlorophyll based on scientific evidence with brief summary and comments.

Uses	Brief summary/ comments	Grade*
Protection of aflatoxins	In a randomized, double-blind, placebo-controlled chemoprevention trial in 180 healthy adults, 100 mg of chlorophyllin 3 times a day for 4 month, led to an overall 55% reduction (P = 0.036) in median urinary levels of the aflatoxin biomarker compared with those taking placebo[43].	B
Cancer prevention	Pharmacokinetic experiments in rats and trout, found that oral co-treatments of 0–4000 ppm dietary chlorophyll along with 0 – 225 ppm of carcinogens such as aflatoxin B1 (AFB1), dibenzo (*def,p*) chrysene (DBC), and certain heterocyclic amines, for up to 4 weeks, interfere with oral absorption of such carcinogens, thus reducing their systemic bioavailability and potential for genetic damage. However, at DBC doses above the optima, chlorophyll co-treatments failed to inhibit tumor incidence and significantly enhanced multiplicity[48].	C
Cancer (Photodynamic therapy adjunct)	Chlorophyll a is not suitable for using in photodynamic therapy due to its high aggregation tendency and low solubility in physiological liquids but may provide a suitable source for the synthesis of new chlorophyll that comply with the pharmaceutical requirements[21], and was approved in the USA to treat cancer in phase I/II clinical trials (ongoing)[49].	C
Fibrocystic breast disease	The benefits of chlorophyll may be attributed to its ability to alter liver enzyme pathways involved in estrogen metabolism[46]. A clinical trial of the drug containing omega-3, iodine and chlorophylls, 33 patients, taking 2 tablets thrice a day for 3 months, 94% of patients reported positive response50. Therapeutic response presented as reduced mastalgia, premenopausal syndrome, dysmenorrhea and algomenorrhea, breast cyst regression as well as attenuated pain associated with benign breast disease and palpation. However, this study lacks of a placebo group and the amount of each drug. Also, due to the mixture of compounds, the effects of chlorophyll alone are unable to be determined.	C
Herpes (Simplex and Zoster)	Topical chlorophyll (2-5 mg of chlorophyll per 1 g of cream) when applied 3-6 times daily can stop multiplication and lesion development of herpes simplex and reduced the frequency of lesion development of herpes zoster. However, the research is only a case series (N = 91) and the information on the duration, blinding, and randomization were lacking. Moreover, a few people developed dermatitis after use[51].	C

Table 1. Efficacy of uses of chlorophyll based on scientific evidence with brief summary and comments.

Uses	Brief summary/ comments	Grade*
Leukopenia	Sodium copper chlorophyllin 40 mg, 3 times per day for 1 month, can increase peripheral leukocyte count, improve symptoms of dizziness and fatigue when compared with the placebo group (patients received vitamin C tablets 100 mg, 3 times per day). The total effective rate being 85%, similar to that in the leucogen treated group (83.3%, patients orally received 20 mg of Leucogen 3 times daily, for 1 month). No adverse reaction was found in the treatment course[52]. However, the study lacks of information about blinding and randomization.	C
Metabolic disorders	Antidiabetic and antilipemic effects are theoretically plausible with chlorophyll metabolites (phytanic and pristanic acids)[31], but in human research, dietary consumption of dairy products enriched with phytanic acid lacked evidence of effect on markers of metabolic syndrome risk[53]. Also, the effects of chlorophyll supplementation in metabolic disorders are unable to be determined.	C
Pancreatitis (chronic)	In an animal study, chlorophyllin a may reduce mortality rate of experimental pancreatitis. In case series research (N = 34), patients were treated with 5-20 mg of IV chlorophyll a in 1-2 divided doses daily for 3 days to 3 years. It was shown that while serum amylase levels increased with pancreatitis attacks, those levels returned to normal after chlorophyll a treatment. Abdominal pain, loss of appetite, fullness, fever, and weakness were eliminated in a majority of the cases, but most patients reported a rebound in abdominal pain 4–5 hr after the infusion[46]. However, his study was limited by a lack of a control group.	C
Pneumonia	In a human controlled trial, the control group (N = 19) received standard therapy with sulfonamides, 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 with an extra 5,000 units of heparin twice daily for 14–15 days. In the chlorophyll group, there was a significant decrease in leukocytes, band cells and ESR, but increase in albumin, lymphocytes and IgA[47,54]. Limitations of this study were a lack of blinding and randomization.	C
Poisoning	FBRA (a health food rich in dietary fiber and Chlorophyll) 7–10.5 g three times daily after each meal for 1 year promoted the excretion of polychlorinated dibenzofurans (PCDFs) in Yusho patients (a disease caused by ingestion of rice oil contaminated with polychlorinated dibenzofurans and biphenyls) with a higher baseline concentration of PCDFs in the blood55. However, due to the coadministration of high levels of fiber in FBRA, the effects of chlorophyll alone are unable to be determined.	C
Reduction of odor from incontinence/bladder catheterization	In human research, chlorophyll 100-300 mg/day daily for the duration from 3 days to 6 months can improve odor in colostomy patients. However, lacks of evidence of benefit for reducing subjective intensity of urinary odor vs. placebo41. Also most of the studies used subjective outcome measures and lacks of blinding procedures.	C

Table 1. Efficacy of uses of chlorophyll based on scientific evidence with brief summary and comments.

Uses	Brief summary/ comments	Grade*
Rheumatoid arthritis	Diet high in chlorophyll may result in improved immune disorders, such as rheumatoid arthritis[46,56]. However, evidence indicating a direct link between rheumatoid arthritis disease parameters and the consumption of chlorophyll alone is lacking.	C
Sepsis	In an uncontrolled clinical trial ($N = 56$) suggested that topical application of 1% Chlorophyllipt solution via bandage, in conjunction with ultraviolet irradiation and ultra-high frequency electric fields may be useful as a prophylactic treatment of purulent-septic soft tissue complications in ambulatory outpatients[47,57]. However, further details about dose and duration are lacking.	C
Tuberculosis	In 48 patients with tuberculosis, dietary intake of chlorophyll from *Laminaria* during chemotherapy treatment improved the functional activity of T lymphocytes and free radical indices, such as plasma malonic dialdehyde levels[47,58]. However, the effects of chlorophyll alone, rather than as a part of a dietary intervention, are unclear.	C

* Grading system consists of grade A (strong or strong positive scientific evidence), B (good or positive scientific evidence), C (unclear or conflicting scientific evidence), D (negative scientific evidence), F (strong negative scientific evidence), and X (lack of evidence)[46,47].

The natural standard system did not give grades for all indications of chlorophyll[47]. In addition, not all uses of chlorophyllin have been approved by the FDA[22]. Sodium copper chlorophyllin (declared on labels as chlorophyllin or chlorophylline) is only permitted in citrus based dry beverage mixes as a color additive. Besides, the FDA is limiting the sources of chlorophyll used to make sodium copper chlorophyllin to only alfalfa (*Medicago sativa*)[59].

Pharmacodynamics/kinetics of chlorophylls

Absorption:

In a 4-month randomized double-blind, clinical trial, in 90 participants, each group received three pills daily containing a placebo or 100 mg of chlorophyllin. The serum samples were taken and found to appear green in color. After ascertaining the source of the color, serum samples were found to contain copper chlorin e4 ethyl ester as well as copper chlorin e4 which originated in the chlorophyll tablet. This study suggested that chlorophyll can be absorbed into the bloodstream, and finally passed into the blood circulation[60].

In healthy men and patients with Refsum's disease (characterized by progressive neurological dysfunction and accumulation of phytanic acid in fat-containing tissues), pheophytin a (the Mg-free derivative of chlorophyll a) was fed, and feces were collected and analyzed. It was found that no more than 5% of the ingested chlorophyll phytol was absorbed by humans[61]. Chlorophyll was converted to Mg-free pheophytin derivatives during digestion in the Caco-2 human cell model[62].

Metabolism:

The *in vitro* CYP3A4 inhibitory activity of three commercial products of *Sasa senanensis* Rehder extract demonstrated that the extract containing Fe(II)- chlorophyllin could inhibit CYP3A4, and the activity 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[28]. The CYP3A4 inhibitory activity of the product containing Fe(II)- chlorophyllin was significantly lower than the one observed in grapefruit juice and chlorophyllin[63].

Protein binding:

Interactions between bovine serum albumin and chlorophyll in aqueous solution under physiological conditions were conducted and found the binding constants, at different temperatures, indicating the low affinity of bovine serum albumin and chlorophyll[64]. In addition, chlorophyll may be affected by the pH in the systems with serum albumin[65]. It was found that chlorophyll and chlorophyllin were bound to plasma proteins approximately 14% and 15%, respectively[66].

Excretion:

In a clinical trial, pheophytin a (the Mg-free derivative of chlorophyll a), was fed to healthy humans and patients with Refsum's disease, to determine the extent of the absorption of chlorophyll phytol by the intestine. In all subjects, 90-95% of the administered radioactivity was recovered in the feces, still largely in the unchanged form[61].

Chlorophyll/drug interactions

There is a case report of delayed methotrexate clearance following the administration of a complementary medication containing chlorophyll. As no impurities were detected in the chlorophyll sample, it is likely that methotrexate clearance was delayed due to an interaction with the excretion or metabolism[67]. However, interactions between chlorophyll and methotrexate have not been described in the literature before, and the mechanism of the suspected interaction described here is still unknown.

The chlorophyll metabolite, phytanic acid, showed antidiabetic activity in animals, and it was found to be a natural ligand for the retinoid X receptor[68]. By docking simulation and modulation of the biochemical alterations, oral phytol/phytanic acid (250 mg/kg) and/or pioglitazone (5 mg/kg) improved significantly the glucose homeostasis, lipid panel, raised the serum adiponectin level, and lowered the TNF-α, reaching in most cases an effect similar to that of 10 mg/kg pioglitazone[36]. Therefore, patients taking chlorophyll with drugs that may lower the blood sugar (or insulin injections) should be monitored closely.

Chlorophylls showed *in vitro* antioxidant activity. Their derivatives and metabolites also have potent antioxidant activity[33,35,35]. Although the mechanism of action of the antioxidant activity in the human body is unpredictable, and might not relate to the *in vitro* activity; chlorophylls may have synergistic effects with antioxidant drugs. In chemotherapy treatment, the effect of antioxidants during chemotherapy and radiation therapy is controversial. Several randomized clinical trials have demonstrated that co-administration of antioxidants with chemotherapy or radiation therapy reduces the side effects[69–71], but some data indicates that antioxidants may protect tumor cells as well as healthy cells from oxidative damage generated by radiation therapy and some chemotherapeutic agents[72,73]. Therefore, caution should be advised when chlorophyll is used during cancer treatment.

Warfarin/ green vegetables interactions

High vitamin K in leafy green vegetables can decrease the therapeutic effectiveness of warfarin. Very large amounts of vitamin K from a single meal with vegetables (400 g of vegetables with 700 to 1500 micrograms of vitamin K1) can measurably change the INR, but occasional typical servings (<100 g) would probably have little lasting impact on the INR[74]. However, the interactions among various sources of vitamin K, chemical forms of vitamin K, age and genotype of warfarin-treated patients, and other factors that are related to this issue need to be evaluated[74]. Patients who take warfarin should aim to eat a similar amount of vitamin K each week. It is not necessary to avoid these foods, and the use of warfarin should not interfere with a healthy diet. The goal should be to eat a similar amount on a regular basis rather than having large day-to-day variations in intake[75].

Potential for warfarin/chlorophyll interactions

Clinically significant interactions between warfarin-green vegetables containing vitamin K have been recognized through case studies worldwide for many years[25], but isolated

chlorophyll from green vegetables causing interactions with warfarin has not been explained and not yet recorded. Several pieces of research have suggested that interactions of clinical importance were indeed certified by case reports[76]; however, the information about chlorophyll/warfarin interactions is still limited.

Warfarin is well absorbed, highly bound to the plasma proteins (99%), and is metabolized via the cytochrome P450 system. It is an indirect anticoagulant, exerting its effect by preventing the internal recycling of oxidized vitamin K to reduced vitamin K. Reduced vitamin K is necessary to enable carboxylation of the terminal g-glutamic acid residue of the vitamin K–dependent clotting factors (factors II, VII, IX, and X). The metabolism of warfarin allows for both pharmacokinetic and pharmacodynamic mechanisms for drug interactions[77].

Unlike most small-molecule drugs that comprise a single chemical compound, many chlorophyll products are complex mixtures of chemical constituents. Since chlorophylls are found in almost all herb plants, this review attempts to identify the possible corresponding mechanism of interactions between chlorophyll itself and warfarin, not the chlorophyll products that may contain vitamin K.

Induction or inhibition of cytochrome P450 isozymes:

Warfarin has two active isomers: S-isomer and R-isomer. S warfarin is five times more potent an anticoagulant than R warfarin[78], and it is metabolized primarily by the cytochrome P450 2C9 isozyme (CYP2C9), while R warfarin is metabolized by cytochrome P450 1A2 and 3A4 isozymes[77]. Drugs that induce or inhibit these enzyme systems have the ability to alter warfarin metabolism and to decrease or increase the INR, respectively.

Research on the pharmacodynamics/kinetics of chlorophyll found that chlorophyllin inhibited CYP3A activity; especially, a commercial product containing Fe(II)-chlorophyllin demonstrated CYP3A4 inhibitory activity that was one-third that of a product containing Cu(II)-chlorophyllin, and one-seventh that of a product containing Cu(II)-chlorophyllin, ginseng, and pine leaf extracts[28].

Inhibition of CYP3A4 liver enzymes by chlorophyllin may result in increased INR, although the interaction is thought to be of smaller impact than those affecting the CYP P450 2C9 component[77]. However, evidence to support this is lacking. CYP3A4 is mainly responsible for the metabolism of R-warfarin, which is much less potent than S-warfarin. Interactions involving these isoenzymes tend to be delayed for many reasons, including the time required for the process of induction, and the synthesis of new enzymes. The complete effect of the interaction will not be observed until it has reached a steady state, that might take two to three weeks or even longer for plant substances with longer half-lives[79].

Displacement of binding with plasma proteins

As mentioned above, warfarin is highly bound to plasma protein, mainly albumin, and has the potential to interact with other high protein binding substances[77]. *In vitro* interactions between bovine serum albumin and chlorophyll, in aqueous solution under physiological conditions, indicated "low affinity binding" of bovine serum albumin and chlorophyll[64]. Therefore, the interactions involving the plasma protein binding is likely to be minimal.

Alteration in vitamin K status

Chlorophyll itself has no report on the alteration in vitamin K status. However, some chlorophyll products containing vitamin K can affect the INR. A high vitamin K intake can decrease the therapeutic effectiveness of warfarin[74]. For example, increases in the consumption of chlorophyll products containing vitamin K will decrease the INR.

Contribution of hemorrhagic or thrombotic risk

Chlorophyll itself has no reports of impairing the platelets' ability to function. However, there is a claim that the magnesium in fat-soluble chlorophyll acts as an anti-platelet aggregation. Magnesium may inhibit experimental arterial thrombus formation by inhibition of

platelet activity. However, inhibition of platelet aggregation has mainly been shown with high concentrations of magnesium (> 2 mM)[80].

Not only does the chlorophyll complicate the determination of the interactions, but also the manufacturing procedures of chlorophyll products contribute to the overall complexity. In the U.S. (and other countries) chlorophyll products are sold as dietary supplements, which are not regulated by the FDA. Therefore, no product quality and efficacy evaluation is require prior to marketing[81].

Chlorophyll products

Chlorophyll is a plant pigment that is responsible for the absorption of light in the process of photosynthesis. The basic structure of chlorophyll is a porphyrin ring similar to that of heme in hemoglobin (Figure 1), although the central atom in the chlorophyll is magnesium instead of iron[82]. The long hydrocarbon tail attached to the porphyrin ring makes chlorophyll fat-soluble and water-insoluble. Two different types of chlorophyll are found in plants, which are chlorophyll a and chlorophyll b (Figure 2). Chlorophyll b is distinguished from chlorophyll a by a 7-formyl instead of the 7-methyl-substitutent[26]. The small difference in one of the side chains allows each type of chlorophyll to absorb light at slightly different wavelengths[83].

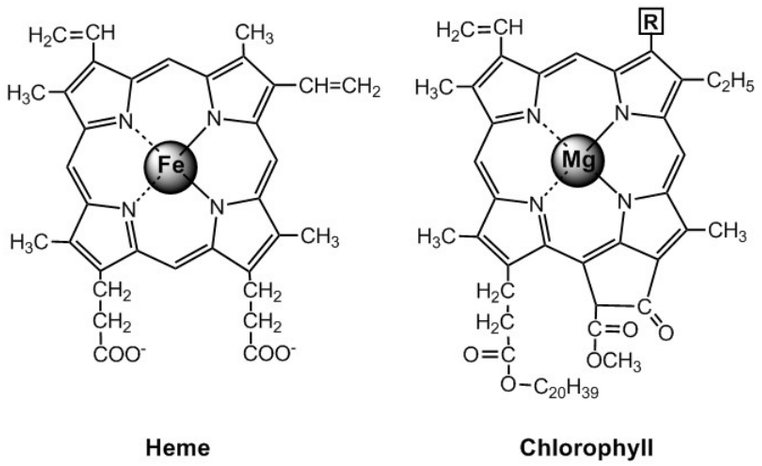


Figure 1. Chemical structures of heme and chlorophyll.

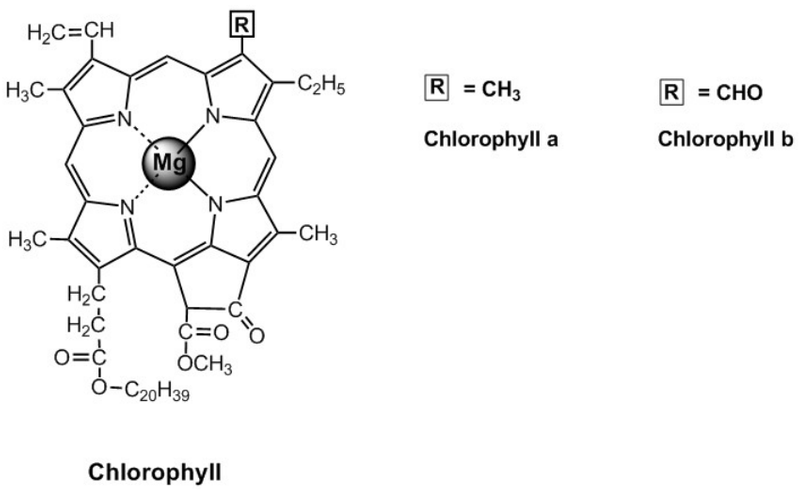


Figure 2. Chemical structures of natural chlorophyll: chlorophyll a and chlorophyll b.

As chlorophylls do not dissolve in water, scientists have made a semi-synthetic mixture of sodium copper salts derived from chlorophyll called chlorophyllin. Natural chlorophyll is not as stable as chlorophyllin and is much more expensive; therefore, most over-the-counter chlorophyll supplements actually contain chlorophyllin[82].

During the synthesis of chlorophyllin, the magnesium atom at the center of the ring is replaced with copper and the phytol tail ($-C_{20}H_{39}$) is lost[84]. Unlike natural chlorophyll, chlorophyllin is water-soluble. Although the content of different chlorophyllin mixtures may vary, two compounds commonly found in commercial chlorophyllin mixtures are trisodium copper chlorin e6 and disodium copper chlorin e4[82] (Figure 3).

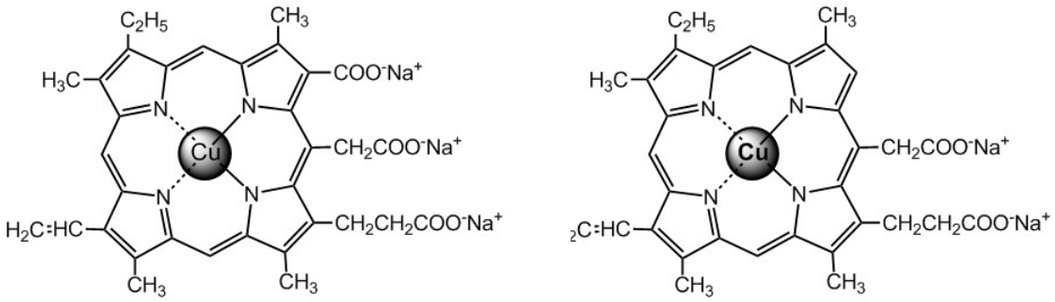


Figure 3. Two commercial chlorophyllin compounds: trisodium copper chlorin e6 and disodium copper chlorin e4.

Chlorophyll liquid forms

Most chlorophyll liquids, either chlorophyll water or chlorophyll drops, which contain chlorophyllin (a water-soluble form), are manufactured by three main steps: (1) extraction of chlorophyll from plant material with an appropriate solvent, (2) preparation of water-soluble derivatives by alkaline hydrolysis of ester groups of chlorophyll (saponification), and (3) replacement of the magnesium ion of the natural chlorophyll with copper[59]. These liquid forms have either the least or are without fat-soluble vitamins, including vitamin K derivatives that can interfere with warfarin treatment.

The product labels should clearly show that they contain sodium copper chlorophyllin, not natural chlorophyll, as shown in Figure 4.

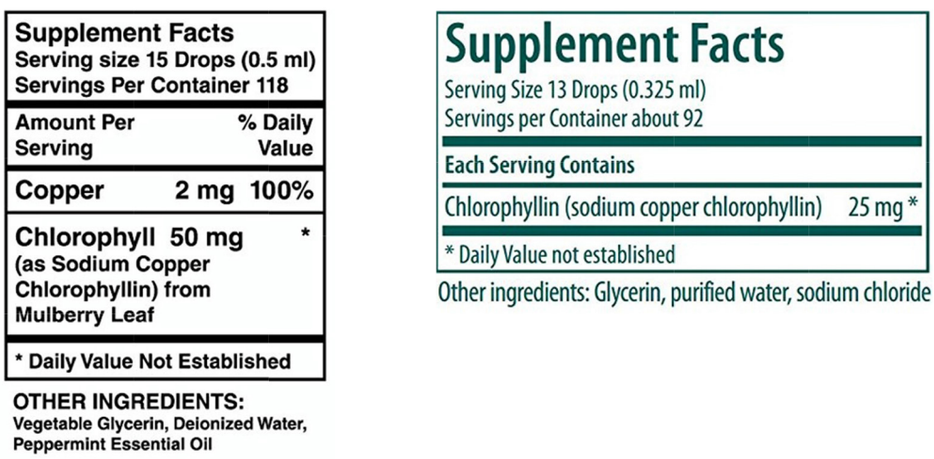
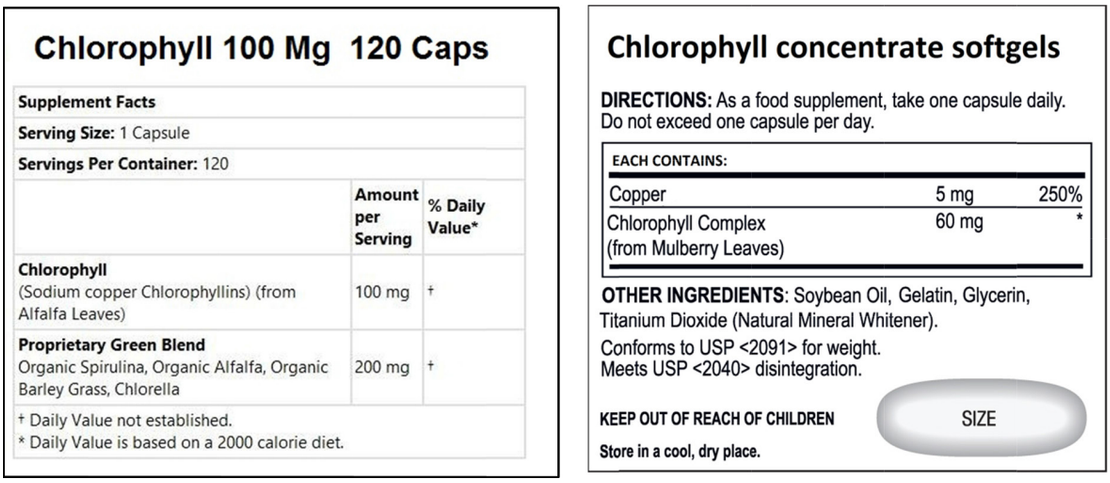


Figure 4. Example of product labels of chlorophyll or chlorophyllin liquid forms (from https://www.amazon.com, accessed on 31st May 2017)

Chlorophyll solid forms

Chlorophyll tablets, capsules, or other solid forms might contain chlorophyllin or natural chlorophyll fat-soluble nutrients and some products might add other green plants, such as spirulina, alfalfa leaves, barley grass, or chlorella. The products that are labeled as containing a chlorophyll complex contain unspecified chlorophyll derivatives that may be soluble or insoluble in water. Examples of product labels are shown in Figure 5.

A chlorophyll gel cap is a different from of chlorophyll liquid, but similar to chlorophyll tablets. This gel cap is fat-soluble containing natural chlorophylls present in plants. While liquid chlorophyll does not contain any fat-soluble vitamins, chlorophyll gel caps, tablets, or capsules contain vitamins A, D, E, and K85.



Chlorophyll 100 Mg 120 Caps

Supplement Facts		
Serving Size: 1 Capsule		
Servings Per Container: 120		
	Amount per Serving	**% Daily Value***
Chlorophyll (Sodium copper Chlorophyllins) (from Alfalfa Leaves)	100 mg	†
Proprietary Green Blend Organic Spirulina, Organic Alfalfa, Organic Barley Grass, Chlorella	200 mg	†
† Daily Value not established. * Daily Value is based on a 2000 calorie diet.		

Chlorophyll concentrate softgels

DIRECTIONS: As a food supplement, take one capsule daily. Do not exceed one capsule per day.

EACH CONTAINS:		
Copper	5 mg	250%
Chlorophyll Complex (from Mulberry Leaves)	60 mg	*

OTHER INGREDIENTS: Soybean Oil, Gelatin, Glycerin, Titanium Dioxide (Natural Mineral Whitener).

Conforms to USP <2091> for weight.
Meets USP <2040> disintegration.

KEEP OUT OF REACH OF CHILDREN

Store in a cool, dry place.

SIZE

Figure 5. Example of product labels of chlorophyll solid forms that contain vitamin K. (from https://www.amazon.com, accessed on 31st May 2017)

Safety of Chlorophyll and its derivatives

Chlorophylls and chlorophyllins have the part of magnesium replaced by copper. Any toxic effects are therefore, in part, due to free ionisable copper present in the complex[86]. A study found that ingested chlorophyll was excreted in the faces as calcium complex. No copper storage occurred in liver, kidney or spleen of rats at dietary levels of 0.1% or 1% of sodium and potassium chlorophyllin copper complex, and there was no effect on iron storage at these levels[86].

In acute toxicity tests, six mice were given 2,500 mg/kg sodium chlorophyllin copper complex orally for 7 days without any adverse effects. Five male and four female rats were fed a diet containing 15% potassium sodium chlorophyllin copper complex for 10 days without any adverse effects except weight loss related to food refusal. Two guinea-pigs, two rabbits, two cats and one dog were given sodium chlorophyllin copper complex 1,000 mg/kg orally daily for seven days without any adverse effects[87].

For long-term toxicity study in rats, groups of 40 rats were fed diets containing 0, 0.1, 1.0 and 3% of potassium sodium chlorophyllin copper complex over their life span. Growth rate, feed efficiency, hematology and urinalysis were comparable to the controls. Reproduction showed no impairment of conception. No gross or histopathological changes attributable to the potassium sodium chlorophyllin copper complex were seen. There was no evidence of copper toxicity or deposition in liver, kidney or spleen[86].

Chlorophyll has been a popular supplement for over a decade, but so far there is no clear evidence about its health benefits. Chlorophyll a and chlorophyll b are natural fat-soluble chlorophylls that are not known to be toxic.

Chlorophyll is likely safe for most people when taken by mouth. However, it can make the fecal matter turn a dark green color. Magnesium in the chlorophyll structure can also cause side effects including diarrhea and gastrointestinal cramping if taken above the recommended dose.

Chlorophyll is the molecule that absorbs sunlight to create energy in the process of photosynthesis. Therefore, taking chlorophyll can cause the skin to become extra-sensitive to sunlight. Furthermore, taking chlorophyll with photosensitizing drugs might increase the risks of sunburn, freckles, dark spots, blistering, or rashes on areas of skin exposed to the light[46]. Patients should be advised to apply sunblock and wear protective clothing when expose to the sun as well as avoiding taking chlorophyll along with drugs that cause photosensitivity[47].

In 2002, in the United States, potassium sodium copper chlorophyllin was listed for use as a color additive in dentifrices that are either drugs or cosmetics. The FDA permits over the counter use of a chlorophyllin copper complex as an internal deodorant in doses up to 300 mg daily[59]. Estimate of acceptable daily intake for human is 0-15 mg/kg of potassium sodium chlorophyllin copper complex[86].

Contraindication

Patients with severe renal insufficiency are at higher risk of adverse effects from magnesium supplementation. Although magnesium in the center of chlorophyll and chlorophyllin molecules have replaced by copper, there is still some magnesium remaining that maybe passed through blood circulation and excreted by the kidney. Hypermagnesaemia may develop in patients with creatinine clearances <10 mL/min[88].

In patients with hepatic impairment, due to a case report of pseudojaundice, chlorophyll should be used cautiously[89]. In patients with known allergy or hypersensitivity to chlorophyll or any of its metabolites, as allergic photosensitive rash has been reported, chlorophyll should be avoided[90]. There is not enough reliable information about the safety of taking chlorophyll during pregnancy or breastfeeding or in children.

Conclusion

There are several different types of chlorophylls that are sold as herbal supplements. Chlorophyll a and chlorophyll b occur naturally in all plants, while chlorophyllin copper complex is an isolate derived from plant chlorophyll. Natural chlorophyll is fat-soluble, therefore its products usually contain fat-soluble vitamins including vitamin K that can interact with warfarin when use in cocomittent. However, most that is sold on the market is a chlorophyllin copper complex, which is a water-soluble form of chlorophyll that does not contain vitamin K.

Chlorophyll products are sold in many forms, such as tablets, capsules, and gel caps, etc. The solid forms usually contain natural chlorophyll and vitamin K. Therefore, patients who are on warfarin therapy should avoid using these kinds of product. Chlorophyll liquid is water-soluble and when in the forms of chlorophyll drops or chlorophyll water (drink) is likely to be safer for patients on warfarin since they contain the least amount of, or are without, vitamin K.

There is no known interaction between chlorophyll and warfarin in the clinical records. It is difficult to interpret data about the interactions between chlorophyll itself and warfarin, as the evidence is mainly based on in vitro and in vivo studies, rather than a large scale human study and case reports. However, chlorophyllin can inhibit CYP3A4, while the R-isomer of warfarin (the less potent isomer) is metabolized via CYP3A4. This pharmacokinetic interaction may result in increased INRs. Patients on warfarin along with chlorophyll products are specifically advised to have their INR measured within two weeks of starting the product to be on the safe side. While the consistency of such reports still needs to be weighed up, the interactions relating to chlorophyll should be closely monitored.

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