

THE MEDICAL IMPORTANCE OF CHLOROPHYLLS AND THEIR DERIVATIVES

Kanaan Al-Tameemi^{1*}, Rana Nassour² and Abdullah Hamad³¹Department of Biochemistry and Microbiology, Faculty of Pharmacy, University of Al-Arabia, Hama, Syria.²Department of Botany, Faculty of Sciences, Tishreen University, Latakia, Syria.³Faculty of Pharmacy, Al Andalus University for Medical Sciences, Tartous, Syria.***Corresponding Author: Dr. Kanaan Al-Tameemi**

Department of Biochemistry and Microbiology, Faculty of Pharmacy, University of Al-Arabia, Hama, Syria.

Email id:

Article Received on 28/07/2022

Article Revised on 18/08/2022

Article Accepted on 07/09/2022

ABSTRACT

Plant pigments exist in varied forms, some with highly complex chemical structures. Chlorophylls represent the most important natural plant pigments. They are the green pigments that contribute in photosynthesis, and they are found in all the organisms performing this process. Chlorophylls are complex liposoluble organic compounds, consisting of a porphyrin ring (tetrapyrroles macrocycle) with a central magnesium atom, a cyclopentanone ring and a side phytol chain. Two forms of chlorophylls (chlorophyll a and chlorophyll b) are embedded within the thylakoid membranes of higher plants' chloroplasts. Chlorophylls have various semi-synthetic derivatives, and chlorophyllins are the most studied among them. The synthesis of different chlorophyllins occurs by removing the phytol chain to increase the solubility in water, and replacing the central magnesium by a divalent cation such as copper, iron or zinc, which is important to retain the green colour of the pigments. Decades ago, human have taken chlorophylls to treat many medical conditions. In this review, we will summarize the potential health benefits and side effects for chlorophylls and their derivatives.

KEYWORDS: Chlorophyll, chlorophyllin, antioxidants, antimicrobial, cancer.

INTRODUCTION

Pigments are chemical compounds that absorb visible light.^[1] Plant pigments are categorized into four main types: chlorophylls, carotenoids, anthocyanins and betalains.^[2] These natural pigments are essential secondary metabolites, which play several roles in plant physiology. Not to mention their importance in food (as natural colourants) and medical industries.^[3,4,5]

The name of Chlorophylls is derived from the Greek words *chloros* meaning "green" and *phyllon* meaning "leaf".^[6] Chlorophylls are the greenish photosynthetic pigments found in all photosynthetic organisms. In algae and plants, these pigments are embedded in the thylakoid membranes within the chloroplasts. They occur in almost every green part of plant, i.e. leaves and herbaceous stems and fruits.^[6]

THE CHEMICAL STRUCTURE OF NATURAL CHLOROPHYLLS

Chlorophylls are derivatives of porphyrin. Chlorophyll molecule consists of a porphyrin ring (tetrapyrroles macrocycle) with a central magnesium atom, a cyclopentanone ring conjugated with the third pyrrole ring and a side phytol chain on the fourth pyrrole ring of the porphyrin.^[7,8] Thus, chlorophyll molecule possess two distinct parts: a hydrophilic part (porphyrin ring) and

a hydrophobic part (phytol chain).^[8] The hydrophobic part of the chlorophyll makes it liposoluble and insoluble in water.^[9,10]

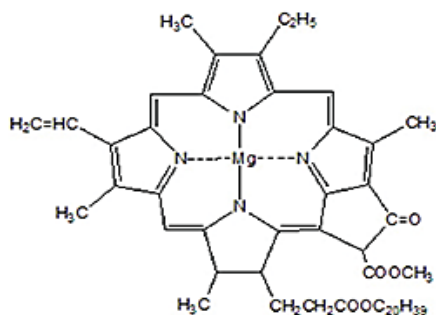
There are several known forms of chlorophylls, including:

- 1) Chlorophyll a, which has a bluish green colour. It is found in almost all photosynthetic organisms, including cyanobacteria.^[6,8]
- 2) Chlorophyll b, which has a bright green colour. It is found in higher plants and many algal groups such as green algae.^[6,8]
- 3) Chlorophyll c, which has a yellowish green colour. It is found in brown algae and diatoms.^[6,8,11]
- 4) Chlorophyll d, which has a bright forest green colour. It is found in red algae.^[6,8,11]
- 5) Chlorophyll e, which is a rare type of chlorophyll. It is found in some genera of yellow green algae like *Vaucheria hamata* and *Tribonema bombycinum*.^[6,12]
- 6) Chlorophyll f, which is the most recently discovered chlorophyll. It appears in emerald green colour, and can be found in some cyanobacteria.^[6,8,13,14]
- 7) Protochlorophyll, which is found in the inner coat of pumpkin seeds and the dark-grown yellow leaves of seedlings.^[6]
- 8) Bacteriochlorophyll, which is the main chlorophyll of various photosynthetic bacteria like purple and

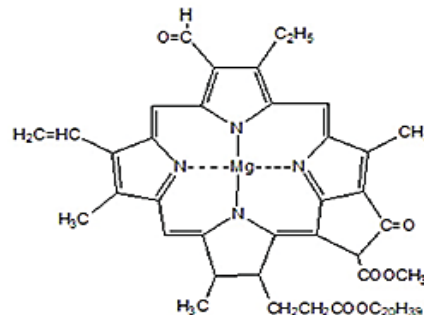
green bacteria. It has many forms: a, b, c, d, e and g.^[6]

- 9) Chlorobium chlorophylls, which are abundantly found in green-sulfur bacteria, and sometimes work in association with bacteriochlorophylls.^[6]

Generally, the chlorophyll types differ from each other in the saturation of the pyrrole rings, or the side groups attached to them.^[8]



Chlorophyll a



Chlorophyll b

Fig. 1: Difference between Chlorophyll a and chlorophyll b.^[10]

THE ESSENTIAL ROLE OF CHLOROPHYLLS

Chlorophyll a is the most abundant of all chlorophylls, representing about 75% of the natural green pigment. In plants, chlorophyll a is found within the thylakoid membranes in both light harvesting complexes (antennas) and both reaction centres of photosystem II and photosystem I. It functions as the main electron donor in the reaction centres to both photosystems.^[6,15,16] In another words, chlorophyll a is the only form of chlorophylls that have the ability to convert the light energy into chemical energy that is used to build up carbohydrate molecules through photosynthesis.^[6,11]

On the other hand, chlorophyll b is considered an accessory pigment found only in the light harvesting complexes of both photosystems.^[6,15,17] This pigment absorbs light and transfers excitation energy to chlorophyll a of the reaction centre where photochemical reaction takes place.^[15]

CHLOROPHYLL DERIVATIVES

There are many metallo-chlorophyll derivatives that can be chemically synthesized and commonly used as

additives to medicines.^[10,18] The chlorophyllins are semi-synthetic derivatives of chlorophyll, and they represent the most studied metallo-chlorophyll derivatives.^[10] After chlorophyll extraction, the synthesis of different chlorophyllins types starts with the saponification (alkaline hydrolyzation) of natural chlorophyll in alkaline medium, which removes the phytol group to increase the solubility of the pigment in water. Sodium (Na^+) or potassium (K^+) ions may bind to the carboxylic groups of the porphyrin ring in order to stabilize its structure. After saponification (or instead of it), the central magnesium (Mg^{2+}) can be replaced by copper (Cu^{2+}) by adding copper sulphate in acidic medium, which increase the chemical stability of the pigment (Fig. 2). Besides Cu^{2+} , divalent cations like iron (Fe^{2+}) and zinc (Zn^{2+}) can be used to replace the central Mg^{2+} . This is important to retain the green colour of processed green food products.^[9,10]

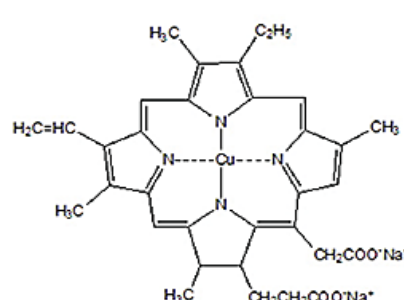
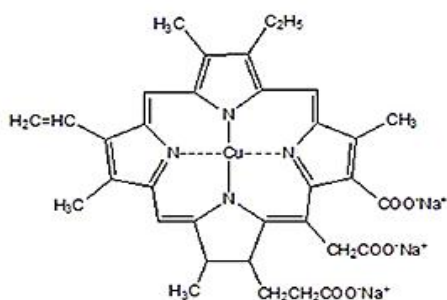


Fig. 2: Examples of chlorophyllins.^[10]

THE PHARMACEUTICAL FORMS TO CHLOROPHYLLS

Humans don't have the ability to synthesize chlorophyll, but they can obtain it from their diet or take its derivative forms.^[6] Animal model studies show that only 1-3% of dietary chlorophyll is absorbed, while the rest goes out of the body with faeces.^[10]

The chlorophyll supplements can be obtained as liquid (drops), ointments, sprays, pills or capsules.^[19,20] Most of them contain chlorophyllin, which is a water-soluble derivative of natural chlorophyll and potentially better absorbed by the body compared to other forms of chlorophyll.^[19,21,22,23,24]

THE MEDICAL IMPORTANCE FOR CHLOROPHYLLS AND THEIR DERIVATIVES

Chlorophylls and their derivatives have long been studied because of their significant role in plant physiology and food industry.^[6] On the other hand, they have many suggested health benefits to human, as the following:

- They are used to boost energy^[22, 25] and prevent or treat chronic fatigue and fibromyalgia^[19,26]
- They are powerful antioxidants and effective scavengers of reactive oxygen species that are associated with cell damage and different medical conditions (when excessively produced)^[9,19,21,23,26,27,28,29,30] According to studies, applying a gel containing chlorophyllin to the skin reduces the signs of photoaging and prevents age prematurely^[19,26,29]
- They may help treating skin conditions, when applied topically.^[19,21,24,26,28,30] Topical chlorophyll may be useful in acne treatment, as a gel containing chlorophyllin helps reducing facial acne and large pores. Besides, a combination of topical chlorophyll and phototherapy results in less oily skin, less severe acne and fewer acne lesions.^[19,20,23,28] Yet, these findings may not be relevant for all skin types.^[19]
- They may be helpful in treating haemoglobin deficiency disorders, such as thalassemia and anaemia, considering that the main structure of chlorophylls is a porphyrin ring similar to the structure of haem in haemoglobin, except that the central atom in haem is iron instead of magnesium.^[10,19,20,29,31]
- They may prevent and slow the progression of certain types of cancers, such as stomach, intestinal, colon, pancreatic and lung cancers based on animal researches and *in vitro* ones on human tissues.^[10,18,19,20,25,16,28,29] Besides, chlorophylls and their supplements can form complexes with known or suspected carcinogens, such as polyaromatic hydrocarbons found in tobacco smoke and aflatoxin-B1.^[10,18,20,32,33] This interferes with gastrointestinal absorption of potential carcinogens, reducing their risk on susceptible tissues.^[10]
- They improve the liver's natural ability to remove waste and toxins from the body (detoxification). It

was found that chlorophyllin boost detoxification process, which in its turn help minimizing liver damage.^[26,29]

- They may aid reducing inflammation and inflammatory pain as in the case of arthritis and inflammatory bowel disease.^[19,26,31,34] Besides, chlorophyllin supplements reduce fatalities related to inflammatory bowel disease, intestinal epithelial damage and infiltration of inflammatory cells.^[34,35]
- They are potential antimicrobial agents^[36,37], as they may inhibit the growth of some resistant Gram-positive bacteria^[36,38,39] and *Candida albicans*.^[26,31,32,40]
- They have the potential to promote wound-healing, as chlorophyllin reduces inflammation and bacterial growth in skin wound.^[19,20,24,25,31,32]
- They can improve digestion and reduce constipation.^[9, 25, 29]
- They may support healthy weight loss, as some evidence suggests that diets rich in chlorophyll can elevate satiety, which reduce hunger and appetite^[19,21,25,26,28,29,30,32] Besides, chlorophyll may enhance the gut microbiome that could help with weight management^[28].
- They may reduce internal body odour^[19, 20, 25, 26, 27]. Chlorophyll supplements have deodorizing effects on foul-smelling wounds, urinary and faecal odour in trimethylaminuria, incontinent, colostomies, ileostomies and geriatric patients.^[9,10,23,27,31,41]

However, further studies are needed to characterize the previously mentioned potential benefits.^[19,20,26]

THE SAFETY OF CHLOROPHYLLS AND THEIR DERIVATIVES

According to the Food and Drug Administration (FDA), adults > 12 years old can safely consume 100-200 mg chlorophyll daily, and not more than 300 mg per day.^[30] Natural chlorophylls don't have any toxic effects on humans.^[18] As for supplemental chlorophylls (chlorophyllins), some people may experience the one or more of the following side effects, especially when consuming liquid chlorophyll:

- Green discoloration of urine or faeces.^[10,18,26,28,29,41]
- False positive results on guaiac card test.^[10]
- Yellow or black discoloration of the tongue.^[10,18]
- Nausea.^[21,26,28,29,42]
- Vomiting.^[26,28,29,42]
- Stomach cramps.^[19,26,28,29,41,42]
- Diarrhoea.^[10,18,21,41]
- Mild burning or itching, when applied topically on wounds.^[10,18]

Of note, chlorophyll supplements should be avoided during pregnancy and lactation until doing adequate safety studies.^[10,18,19,42]

CONCLUSION

Chlorophylls and their supplements have been used for a long time to treat various medical conditions. These green pigments are potent antioxidant, antiaging, antimicrobial, antiinflammation and anticancer agents. Besides their potential ability to treat skin conditions and haemoglobin deficiency disorders. Still, extensive studies should be conducted to confirm and characterize the health benefits of these pigments. Unlike natural chlorophylls, chlorophyll supplements may cause some minor side effects such as green discoloration of urine or faeces, nausea, vomiting, stomach cramps and diarrhoea.

REFERENCES

- Delgado-Vargas F, Jiménez AR, Paredes-López O. Natural Pigments: Carotenoids, Anthocyanins, and Betalains - Characteristics, Biosynthesis, Processing, and Stability. *Critical Reviews in Food Science and Nutrition*, 2000; 40(3): 173-289.
- Dikshit R, Tallapragada P. Comparative Study of natural and artificial flavoring agents and dyes, In: Grumezescu AM and Holban AM (eds). *Natural and artificial flavoring agents and food dyes*, UK; Elsevier Inc., 2018; 83-112.
- Yeum KJ, Russell RM. Biological functions of plant pigment phytochemicals in humans, In: Laheri I (ed). *Systems biology of free radicals and antioxidants*. Berlin, Heidelberg; Springer, 2014; 4023-4045.
- Nassour R, Ayash A, Al-Tameemi K. Anthocyanin pigments: Structure and biological importance. *Journal of Chemical and Pharmaceutical Sciences*, 2020; 13(4): 45-57.
- Al-Tameemi K, Nassour R. Betalains's structure, existence and biological importance. *Journal of Chemical and Pharmaceutical Sciences*, 2021; 14(3): 37-44.
- Pareek S, Sagar NA, Sharma S, Kumar V, Agarwal T, González-Aguilar GA, Yahia EM. Chlorophylls: Chemistry and Biological Functions. In: Yahia EM (ed). *Fruit and vegetable phytochemicals chemistry and human health*, USA; John Wiley & Sons Ltd., 2018; 269-284.
- Ngamwonglumlert L, Devahastin S, Chiewchan N. Natural colorants: Pigment stability and extraction yield enhancement via utilization of appropriate pretreatment and extraction methods. *Critical Reviews in Food Science and Nutrition*, 2017; 57(15): 3243-3259.
- Queiroz MI, Fernandes AS, Deprá MC, Jacob-Lopes E, Zepka LQ, Introductory Chapter: Chlorophyll Molecules and Their Technological Relevance. In: Jacob-Lopes E, Zepka LQ and Queiroz MI (eds), *Chlorophyll, ExLi4EvA*, 2017; 1-6.
- Solymosi K, Mysliwa-Kurczel B. Chlorophylls and their Derivatives Used in Food Industry and Medicine. *Mini-Reviews in Medicinal Chemistry*, 2017; 17(13): 1194-1222.
- Drake VJ. Chlorophyll and metallo-chlorophyll derivatives. Oregon State University, 2021. (<https://lpi.oregonstate.edu/mic/dietary-factors/phytochemicals/chlorophyll-metallo-chlorophyll-derivatives>).
- İnanç AL. Chlorophyll: Structural properties, health benefits and its occurrence in virgin olive oils. *Akademik Gıda*, 2011; 9(2): 26-32.
- Kumar HD, Singh HN. Xanthophyta, In: Kumar HD, Singh HN (eds). *A Textbook on Algae*. London; Palgrave, 1979; 123-130.
- Chen M, Li Y, Birch D, Willows RD. A cyanobacterium that contains chlorophyll f--a red-absorbing photopigment. *FEBS Letters*, 2012; 586(19): 3249-3254.
- Behrendt L, Brejnrod A, Schliep M, Sørensen SJ, Larkum AWD, Kuhl M. Chlorophyll f-driven photosynthesis in a cavernous cyanobacterium. *International Society for Microbial Ecology Journal*, 2015; 9: 2108-2111.
- Melkozernov AN, Blankenship RE. Photosynthetic Functions of Chlorophylls. In: Grimm B, Porra RJ, Rüdiger W, Scheer H. *Chlorophylls and Bacteriochlorophylls. Advances in Photosynthesis and Respiration*, Dordrecht; Springer, 2006; 25: 397-412.
- Pessaraki M. *Handbook of photosynthesis*, 3rd edition. USA; Taylor & Francis Group, 2016; 447-505.
- Voitsekhevskaja OV, Tyutereva EV. Chlorophyll b in angiosperms: Functions in photosynthesis, signaling and ontogenetic regulation. *Journal of Plant Physiology*, 2015; 15: 51-64.
- Brennan D. Health Benefits of Chlorophyll. WebMD, 2020; November 7.
- Berry J. What are the benefits of chlorophyll?. *MedicalNewsToday*, 2018; July 4.
- Bowman J, Seladi-Schulman J. The Benefits of Chlorophyll. *Healthline*, 2020; November 9.
- Alexander H. 6 things to know about chlorophyll. MD Anderson Center, 2021; April 21.
- Mark J. Health Benefits of Chlorophyll Supplements. *lifeextension*, 2021; May.
- Silva L. Liquid Chlorophyll: Everything You Need To Know. *FrobesHealth*, 2022; July 20.
- <https://www.webmd.com/vitamins/ai/ingredientmono-712/chlorophyll> (accessed on 17 August 2022).
- <https://health.clevelandclinic.org/are-there-health-benefits-to-using-liquid-chlorophyll/> (written on 23 November 2021, accessed on 18 August 2022)
- Mutchler C. The Benefits of Chlorophyll. This green pigment in plants is available in liquid, capsule, and tablet form. *Verywell health*, 2022; July 8.
- Solymosi K, Latruffe N, Morant-Manceau A, Schoefs B. Food colour additives of natural origin. In: Scotter MJ, *Colour Additives for Foods and Beverages*. UK; Elsevier Ltd., 2015; 3-34.
- Heger E. Dietitians weigh in on the risks and benefits of drinking liquid chlorophyll. *Insider*, 2022; April 18.

29. Muinos L. The Health Benefits of Liquid Chlorophyll. Verywellfit, 2022; August 3.
30. Morgan M. 5 Best Liquid Chlorophyll 2022: Top Chlorophyll Supplements. HealthCanal, 2022; June 16.
31. Mead T, 9 healing benefits of 'Green Blood' (fight *Candida* and more). Thealternativedaily, <https://www.thealternativedaily.com/the-healing-benefits-of-chlorophyll> (Access on August 18, 2022).
32. Group E. 10 Amazing Benefits of Chlorophyll. GlobalHealing, 2014; January 6.
33. Zhong S, Bird A, Kopec RE. The metabolism and potential bioactivity of chlorophyll and metallo-chlorophyll derivatives in the gastrointestinal tract. *Molecular Nutrition & Food Research*, 2021; 65(7): e2000761.
34. Henderson E. Oral chlorophyllin supplement alleviates inflammatory bowel disease. *News-medical*, 2022; 17 August.
35. Zhang T, Zhang R, Zhao G, Liu W, Pan L, Tong Y, Jiang M, Zhang H, Xiao Z, Pandol SJ, Fu X, Han YP, Zheng X. Plant green pigment of chlorophyllin attenuates inflammatory bowel diseases by suppressing autophagy activation in mice. *American Journal of Physiology Gastrointestinal and Liver Physiology*, 2022; 323: G102–G113.
36. Wang E, Braun MS, Wink M. Chlorophyll and chlorophyll derivatives interfere with multi-drug resistant cancer cells and bacteria. *Molecules*, 2019; 24: Article 2968.
37. Suvorov N, Pogorilyy V, Diachkova E, Vasil'ev Y, Mironov A, Grin M. Derivatives of Natural Chlorophylls as Agents for Antimicrobial Photodynamic Therapy. *International Journal of Molecular Sciences*, 2021; 22: 6392.
38. Mowbray S. The Antibacterial Activity of Chlorophyll. *British Medical Journal*, 1957; 1(5013): 268–270.
39. Kustova AV, Belykh DV, Smirnova NL, Venediktov EA, Kudayarova TV, Kruchin SO, Khudyaeva IS, D. B. Berezin DB. Synthesis and investigation of water-soluble chlorophyll pigments for antimicrobial photodynamic therapy. *Dyes and Pigments*, 2018; 149: 553-559.
40. Maekawa LE, Lamping R, Marcacci S, Maekawa MY, Nassri MRG, Koga-Ito CY. Antimicrobial activity of chlorophyll-based solution on *Candida albicans* and *Enterococcus faecalis*. *RSBO*, 2007; 4(2): 36-40.
41. Cunha JP. Chlorophyll. RxList, 2021; August 19.
42. Griffin RM. Chlorophyll: Uses and Risks. WebMD, 2021; January 19.