

Arthrospira Platensis – Potential in Dermatology and Beyond

Uwe Wollina^{1*}, Cristiana Voicu², Serena Gianfaldoni³, Torello Lotti³, Katlein França⁴, Georgi Tchernev^{5,6}

¹Städtisches Klinikum Dresden - Department of Dermatology and Allergology, Dresden, Sachsen, Germany; ²Polisano Clinic - Department of Dermatology and Venereology, Piscului 16, Corbeanca, Ilfov 077065, Romania; ³University G. Marconi of Rome - Dermatology and Venereology, Rome, Italy; ⁴Department of Dermatology and Cutaneous Surgery, Department of Psychiatry & Behavioral Sciences; Institute for Bioethics and Health Policy, University of Miami Miller School of Medicine, Miami, FL, USA; ⁵Department of Dermatology, Venereology and Dermatologic Surgery, Medical Institute of Ministry of Interior, Sofia, Bulgaria; ⁶Onkoderma, Policlinic for Dermatology and Dermatologic Surgery, Sofia, Bulgaria

Abstract

Citation: Wollina U, Voicu C, Gianfaldoni S, Lotti T, França K, Tchernev G. Arthrospira Platensis – Potential in Dermatology and Beyond. Open Access Maced J Med Sci. 2018 Jan 25; 6(1):176-180. <https://doi.org/10.3889/oamjms.2018.033>

Keywords: Microalgae; Arthrospira platensis; Calcium spirulan; Gamma-linolenic acid; Phycocyanin

***Correspondence:** Uwe Wollina. Städtisches Klinikum Dresden - Department of Dermatology and Allergology, Dresden, Sachsen, Germany. E-mail: wollina-uw@khdf.de

Received: 24-Sep-2017; **Revised:** 23-Nov-2017; **Accepted:** 24-Nov-2017; **Online first:** 10-Jan-2018

Copyright: © 2018 Uwe Wollina, Cristiana Voicu, Serena Gianfaldoni, Torello Lotti, Katlein França, Georgi Tchernev. This is an open-access article distributed under the terms of the Creative Commons Attribution-NonCommercial 4.0 International License (CC BY-NC 4.0)

Funding: This research did not receive any financial support

Competing Interests: The authors have declared that no competing interests exist

The search for natural products with benefits for health in general and of potential for treating human disease has gained wider interest world-wide. Here, we analyse current data on the microalga Arthrospira platensis (AP), that has been used in nutrition since ancient times in Far East and African communities, for medical purposes with a focus on dermatology. Extracts of AP have been investigated in vitro and in vivo. The alga is rich in proteins, lipopolysaccharides and gamma-linolenic acid. AP extracts, phycocyanin compounds and polysaccharide calcium spirulan (Ca-SP) have been evaluated in various models. It could be demonstrated, that AP has significant antioxidant activity, prevents viruses from entry into target cells and inhibits the colonisation of wounds by multi-resistant bacteria. Furthermore, anti-cancer activity was documented in models of oral cancer, melanoma, and UV-induced non-melanoma skin cancer.

Introduction

Arthrospira (formerly: Spirulina) platensis (AP) is one of the photoautotrophic, planktonic, filamentous green-blue algae that have become of medical interest. It has been used as a protein-rich nutrient since ancient times for instance by the Kanem in Tchad, in Japan and Korea. Seventy percent of dry matter of AP is proteins [1]. The water-soluble fraction of proteins contains molecules between 11,000 and > 300,000 kDa [2]. This plant is very rich in gamma-linolenic acid (GLA) which is produced by the alga by direct desaturation of linoleic acid [1][3][4]. AP also has a high content of vitamin B complex, carotene, and ascorbic acid [5].

The whole cells of AP and

lipopolysaccharides isolated from these cells are immunomodulatory in rabbits leading to the production of macro - and microglobulin antibodies [6].

In this review, we focus on medical indications for the possible use of AP in dermatology.

Antiviral activities

An aqueous extract of AP containing lipopolysaccharides as well as a fraction depleted of polysaccharides and tannins inhibited HIV - 1 replication in human T - cell lines, peripheral blood mononuclear cells (PBMC), and Langerhans cells (LC). The 50% inhibitory concentration (IC₅₀) of

extract for PBMC growth ranged between 0.8 and 3.1 mg/ml. In vitro, the extract inactivated HIV - 1 directly, i.e. viral entry and fusion [7].

In a small phase I trial, five HIV - infected, treatment naïve adult patients took algae extracts from either AP or brown seaweed *Undaria pinnatifida* or a mixture of both for 3 to 13 months. No toxicities were observed, but a bB stabilisation of the CD4 cell count and virus load was found. Both parameters improved after 13 months [8].

Allophycocyanin from AP neutralised in vitro the enterovirus 71 - induced cytopathic effects in both human rhabdomyosarcoma cells and African green monkey kidney cells with an IC50 of approximately $0.045 \pm 0.012 \mu\text{M}$. Allophycocyanin was active in the state of viral adsorption and post-adsorption, respectively. However, the antiviral activity was superior when added to the cell cultures before viral infection. Allophycocyanin delayed the viral RNA synthesis in infected cells and reduced thereby enterovirus - 71 - induced apoptosis [8].

Aqueous extracts of AP and purified calcium spirulan (Ca-SP) were investigated for their potential in human herpes simplex virus 1 (HHV1) and 8 (HHV8) infections. Ca-SP represents a sulfated polysaccharide mainly composed of rhamnose, that is capable of chelating calcium. In vitro, Ca-SP inhibited HHV1 infection of Vero cells with an IC50 of 0.04 $\mu\text{g}/\text{mL}$ and HaCaT cells with an IC50 of 0.07 $\mu\text{g}/\text{mL}$. AP extract was lesser effective. Ca - SP inhibited the delivery of viral protein VP16, that is necessary for viral attachment to target cells, in a dose-dependent manner. In an observational trial, 198 adult female patients, who underwent a procedure for permanent lip makeup and had a history of previous herpes labialis, were included. Patients received herpes prophylaxis with either topical ointment containing AP extract and Ca - SP, topical acyclovir or systemic acyclovir/ valacyclovir. Herpes reactivation was observed in about 20% with systemic medications, 90% with topical acyclovir, and 60% with topical AP extract/ Ca-SP [10]. In conclusion, topical AP extract/ Ca - SP was more effective in this open trial than topical acyclovir.

HHV8 is responsible for cutaneous Kaposi sarcoma. Tissue cultures of human RPE - 1 cells were infected by HHV8. The IC50 for Ca-SP for HHV8 titer reduction and reduction of DNA copies in treated versus untreated controls was 1.5 $\mu\text{g}/\text{mL}$. Ca - SP inhibited the uptake of viral ORF45 tegument protein by target cells in a dose-dependent manner [10].

Antioxidant activity

It was shown that a protean extract of AP is a potent free-radical scavenger for both hydroxyl and

peroxyl radicals and inhibits microsomal lipid peroxidation. The major component of this activity is the phycobiliprotein C - phycocyanin [11].

C - phycocyanin has been evaluated in several models of inflammation. It was shown to reduce oedema, histamine release from mast cells, myeloperoxidase activity of macrophages, and the concentrations of prostaglandin-E2 and leukotriene LTB4 in inflammatory lesions [12].

Chinese researchers succeeded in the crystallisation of the selenium-containing phycocyanin from the selenium-rich by the hanging-drop vapour diffusion techniques [13]. Indian researchers developed a method of purification of C - phycocyanin [14].

Experimental studies have been performed to analyse the potential of AP as a matrix for the production of selenium - and iodine-containing pharmaceuticals [15].

More recently, the potential of algae extracts on diabetic nephropathy was investigated in a mouse model. Oral administration of phycocyanin (300 mg/kg) for ten weeks protected against albuminuria and renal mesangial expansion. The compound also normalised tumour growth factor- β and fibronectin expression. Phycocyanin was capable of normalising urinary and renal oxidative stress markers and the expression of NAD(P)H oxidase components. Similar antioxidant effects were observed following oral administration of phycocyanobilin (15 mg/kg) for two weeks. Phycocyanobilin also inhibited NADPH dependent superoxide production in cultures of renal mesangial cells [16].

By the use of one-step high-speed counter-current chromatography (HSCCC) with ethanol-ammonium sulfate, another major antioxidant could be isolated: a α - acidic polysaccharide, composed of major glucose, slight rhamnose and mannose, with a molecular weight of 12.33 kDa [17].

Reactive oxygen species and mitochondrial dysfunction have been implicated in doxorubicin-induced and tilmicosin-induced cardiotoxicity [18][19] and ciclosporin A-induced and cisplatin-induced nephrotoxicity [20][21]. In mice and rat models of these diseases, extracts from AP exhibited dose-dependent cytoprotective activities. Concerning cardiomyocytes, C - pyocyanin has been identified as the most active compound to protect cells from mitochondrial dysfunction, lipid and protein peroxidation thereby diminishing apoptosis [22].

Liver injury by liver toxins like dibutyl nitrosamine precursors [23], carbon tetrachloride [24], lead acetate [25], deltamethrin [26], and drugs such as acetaminophen [27] or cisplatin [28] can be diminished by AP extracts.

Anti-inflammatory, anti-pyretic, and anti - hyperalgesic effects

C-phycoerythrin is a selective inhibitor of cyclooxygenase - 2 (COX-2), that is upregulated during inflammation and induces apoptosis in macrophages [29][30]. In a carrageenan-induced thermal hyperalgesia animal model C - phycoerythrin was investigated for anti-inflammatory and anti-hyperalgesic effects. C - phycoerythrin inhibited the overproduction of nitric oxide (NO) and prostaglandin E2 by suppression of inducible NO synthase and COX-2. Also, there was an attenuation of TNF - α formation and tissue infiltration by neutrophilic granulocytes [31].

Antipyretic activity of AP was demonstrated in Brewer's Yeast induced pyrexia in rats. The anti-inflammatory potential had been evaluated in rat paw oedema induced by prostaglandin E2 injection. In both models, AP extract revealed dose-dependent efficacy [32].

Wound healing potential

Using an in vitro model with cultivated human dermal fibroblast various extracts of AP have been screened for a wound healing promotion. Aqueous extracts stimulated both proliferation and migration of fibroblasts and enhanced the closure rate of wounds within 24 hours after treatment. Methanolic and ethanolic extracts supported fibroblast proliferation too but failed to support migration and wound closure. The plant extracts were further characterised: Cinnamic acid, narigenin, kaempferol, temsirolimus, phosphatidylserine isomeric derivatives and sulphoquinovosyl diacylglycerol supported proliferation. The authors concluded that AP might pose potential medical use to treat chronic wounds especially in diabetes mellitus patients [33].

Colonization of chronic wounds with bacteria including methicillin-resistant *Staphylococcus aureus* (MRSA) is an increasing health problem [34]. Of interest for wound treatment is the fact that topical Maresmetrade mark containing lipids and all other components of microalgae in an encapsulated form, is capable of inhibiting dermal colonisation by several MRSA strains and by vancomycin-resistant strain MU50. In animal models, MRSA colonisation was reduced by 3 - 4 log units in comparison to controls [35].

Gunes et al. (2017) used an aqueous AP crude extract in a concentration of 1.125% in a skin cream. The formulation enhanced wound healing in HS2 keratinocyte cell cultures [36].

Anti-cancer potential

The first published data on the possible anti-cancer potential of AP extracts came from dimethylbenz(a)anthracene - induced squamous cell carcinomas (SCC) of hamster buccal pouch as a model of oral SCC. Phylogenies from algae extract induced complete response in 30% and partial response in 70% of animals treated twice weekly by intratumoral injections [37].

In a model investigating the early epithelial changes leading to oral SCC, buccal pouches of the Syrian hamsters were painted with 7, 12 - dimethylbenz[a]anthracene. Supplementation of the diet with AP extracts diminished epithelial dysplasia during 14 weeks of this study [38] and 32 weeks in a long-term study [39]. In the latter study, the progression to SCC was reduced by AOP extracts as well.

By using an in vitro model of invasion of tumour cells through reconstituted basement membrane (Matrigel)/fibronectin-coated filters, the potential of Ca-SP isolated from AP was evaluated. Ca-SP significantly inhibited the invasion of B16 - BL6 melanoma, Colon 26 M3.1 carcinoma and HT - 1080 fibrosarcoma cells. Ca - SP also inhibited migration of tumour cells on laminin but failed on fibronectin. This effect was accompanied by prevented adhesion of B16-BL6 melanoma cells to Matrigel and laminin but did not affect the adhesion to fibronectin. Experimental lung metastasis was significantly reduced by co-injection of B16-BL6 cells with Ca - SP. In B16-BL6 spontaneous lung metastasis model, several intra-venous injections 100 μ g of Ca - SP diminished the tumours lung colonisation [40].

Non-melanoma skin cancer is induced by ultraviolet (UV) light exposure, natural and artificial. UVB (280 - 320nm) irradiation of skin induces the formation of 8-oxo - 7,8-dihydroguanine (8 - oxoG) by UV-induced reactive oxygen species. Ogg1 gene encodes a repair enzyme that removes 8 - oxoG - DNA. Ogg1 - knock out (KO) mice, missing the repair enzyme, have become an established model for UVB-induced skin cancer [41]. In Ogg1 - KO mice fed with AP extracts, skin tumours developed about seven weeks later than in control animals without AP extracts. Furthermore, the number of tumours was lower in AP-treated animals, but the ratio of malignant versus benign skin tumours remained unaffected by AP. The authors could further demonstrate, that AP lead to a reduced acute UVB-induced inflammation (ear swelling and erythema). AP downregulated signalling proteins such as p38 mitogen-activated protein kinase, kinase/c-Jun N-terminal kinase, and extracellular signal-regulated kinase after UVB exposure in mice [42]. AP extracts from their anti-inflammatory, and anti-oxidative potential may be beneficial in UV - induced skin cancer. However, studies in humans are warranted before conclusions.

In conclusion, AP is a source of various, partially identified and purified compounds with potential health benefits and activities in the prevention or treatment of some human pathologies, ranging from infections to environmental disorders, chronic wounds and cancer. Despite the vast advantages in basic research and in in vitro and in vivo models of disease, human trials are sparse. A better standardization of natural products and randomized controlled trials in human disease are necessary before final conclusions. Nevertheless, the potential of natural products as AP should not be underestimated [43].

References

- Clement G. [Production and characteristic constituents of the algae *Spirulina platensis* and *maxima*]. [Article in French] *Ann Nutr Aliment*. 1975; 29(6):477-88. PMID:824992
- Voronkova SS, Sadkova NP, Al'bitskaia ON, Pavlova SA, Rogozhin SV. [Physico-chemical properties of water-soluble proteins from *Spirulina platensis*]. [Article in Russian] *Prikl Biokhim Mikrobiol*. 1980; 16(3):363-71. PMID:7433430
- Nichols BW, Wood BJ. The occurrence and biosynthesis of gamma-linolenic acid in a blue-green alga, *Spirulina platensis*. *Lipids*. 1968; 3(1):46-50. <https://doi.org/10.1007/BF02530968> PMID:17805841
- Cohen Z, Didi S, Heimer YM. Overproduction of gamma-linolenic and eicosapentaenoic acids by algae. *Plant Physiol*. 1992; 98(2):569-72. <https://doi.org/10.1104/pp.98.2.569> PMID:16668678 PMID:PMC1080227
- Baianova Iul, Trubachev IN. [Comparative evaluation of the vitamin composition of unicellular algae and higher plants grown under artificial conditions]. [Article in Russian] *Prikl Biokhim Mikrobiol*. 1981; 17(3):400-7. PMID:6801639
- Besednova NN, Smolina TP, Mikheïskaia LV, Ovodova RG. [Immunostimulating activity of the lipopolysaccharides of blue-green algae]. [Article in Russian] *Zh Mikrobiol Epidemiol Immunobiol*. 1979; 1):75-9.
- Ayehunie S, Belay A, Baba TW, Ruprecht RM. Inhibition of HIV-1 replication by an aqueous extract of *Spirulina platensis* (*Arthrospira platensis*). *J Acquir Immune Defic Syndr Hum Retrovirol*. 1998; 18(1):7-12. <https://doi.org/10.1097/00042560-199805010-00002> PMID:9593452
- Teas J, Irahimeh MR. Dietary algae and HIV/AIDS: proof of concept clinical data. *J Appl Phycol*. 2012; 24(3):575-82. <https://doi.org/10.1007/s10811-011-9766-0> PMID:22661829 PMID:PMC3354323
- Shih SR, Tsai KN, Li YS, Chueh CC, Chan EC. Inhibition of enterovirus 71-induced apoptosis by allophycocyanin isolated from a blue-green alga *Spirulina platensis*. *J Med Virol*. 2003; 70(1):119-25. <https://doi.org/10.1002/jmv.10363> PMID:12629652
- Mader J, Gallo A, Schommartz T, Handke W, Nagel CH, Günther P, Brune W, Reich K. Calcium spirulan derived from *Spirulina platensis* inhibits herpes simplex virus 1 attachment to human keratinocytes and protects against herpes labialis. *J Allergy Clin Immunol*. 2016; 137(1):197-203.e3. <https://doi.org/10.1016/j.jaci.2015.07.027> PMID:26341274
- Pi-ero Estrada JE, Bermejo Bescós P, Villar del Fresno AM. Antioxidant activity of different fractions of *Spirulina platensis* protean extract. *Farmacol*. 2001; 56(5-7):497-500. [https://doi.org/10.1016/S0014-827X\(01\)01084-9](https://doi.org/10.1016/S0014-827X(01)01084-9)
- Romay C, González R, Ledón N, Remírez D, Rimbau V. C-phycocyanin: a biliprotein with antioxidant, anti-inflammatory and neuroprotective effects. *Curr Protein Pept Sci*. 2003; 4(3):207-16. <https://doi.org/10.2174/1389203033487216> PMID:12769719
- Li L, Zhang J, Jiang T, Guo B, Chang W, Liang D. Purification, crystallization and preliminary crystallographic investigations of selenium-containing phycocyanin from selenium-rich algae (*Spirulina platensis*). *Sci China C Life Sci*. 2001; 44(4):337-44. <https://doi.org/10.1007/BF02879600> PMID:18726414
- Kumar D, Dhar DW, Pabbi S, Kumar N, Walia S. Extraction and purification of C-phycocyanin from *Spirulina platensis* (CCC540). *Indian J Plant Physiol*. 2014; 19:184-8. <https://doi.org/10.1007/s40502-014-0094-7> PMID:25089058 PMID:PMC4113674
- Mosulishvili LM, Kirkesali EI, Belokobylsky AI, Khizanishvili AI, Frontasyeva MV, Pavlov SS, Gundorina SF. Experimental substantiation of the possibility of developing selenium- and iodine-containing pharmaceuticals based on blue-green algae *Spirulina platensis*. *J Pharm Biomed Anal*. 2002; 30(1):87-97. [https://doi.org/10.1016/S0731-7085\(02\)00199-1](https://doi.org/10.1016/S0731-7085(02)00199-1)
- Zheng J, Inoguchi T, Sasaki S, Maeda Y, McCarty MF, Fujii M, Ikeda N, Kobayashi K, Sonoda N, Takayanagi R. Phycocyanin and phycocyanobilin from *Spirulina platensis* protect against diabetic nephropathy by inhibiting oxidative stress. *Am J Physiol Regul Integr Comp Physiol*. 2013; 304(2):R110-20. <https://doi.org/10.1152/ajpregu.00648.2011> PMID:23115122
- Wu X, Li R, Zhao Y, Liu Y. Separation of polysaccharides from *Spirulina platensis* by HSCCC with ethanol-ammonium sulfate ATPS and their antioxidant activities. *Carbohydr Polym*. 2017; 173:465-72. <https://doi.org/10.1016/j.carbpol.2017.06.023> PMID:28732888
- Khan M, Shobha JC, Mohan IK, Naidu MU, Sundaram C, Singh S, Kuppasamy P, Kutala VK. Protective effect of *Spirulina* against doxorubicin-induced cardiotoxicity. *Phytother Res*. 2005; 19(12):1030-7. <https://doi.org/10.1002/ptr.1783> PMID:16372368
- Ibrahim AE, Abdel-Daim MM. Modulating effects of *Spirulina platensis* against tilmicosin-induced cardiotoxicity in mice. *Cell J*. 2015; 17(1):137-44. PMID:25870843 PMID:PMC4393661
- Khan M, Shobha JC, Mohan IK, Rao Naidu MU, Prayag A, Kutala VK. *Spirulina* attenuates cyclosporine-induced nephrotoxicity in rats. *J Appl Toxicol*. 2006; 26(5):444-51. <https://doi.org/10.1002/jat.1159> PMID:16858688
- Mohan IK, Khan M, Shobha JC, Naidu MU, Prayag A, Kuppasamy P, Kutala VK. Protection against cisplatin-induced nephrotoxicity by *Spirulina* in rats. *Cancer Chemother Pharmacol*. 2006; 58(6):802-8. <https://doi.org/10.1007/s00280-006-0231-8> PMID:16552571
- Khan M, Varadharaj S, Shobha JC, Naidu MU, Parinandi NL, Kutala VK, Kuppasamy P. C-phycocyanin ameliorates doxorubicin-induced oxidative stress and apoptosis in adult rat cardiomyocytes. *J Cardiovasc Pharmacol*. 2006; 47(1):9-20. <https://doi.org/10.1097/01.fjc.0000191520.48404.27> PMID:16424780
- Ismail MF, Ali DA, Fernando A, Abdraboh ME, Gaur RL, Ibrahim WM, Raj MH, Ouhitit A. Chemoprevention of rat liver toxicity and carcinogenesis by *Spirulina*. *Int J Biol Sci*. 2009; 5(4):377-87. <https://doi.org/10.7150/ijbs.5.377> PMID:19521547 PMID:PMC2695150
- Kepekçi RA, Polat S, Çelik A, Bayat N, Saygideger SD. Protective effect of *Spirulina platensis* enriched in phenolic compounds against hepatotoxicity induced by CCl₄. *Food Chem*. 2013; 141(3):1972-9. <https://doi.org/10.1016/j.foodchem.2013.04.107> PMID:23870917
- El-Tantawy WH. Antioxidant effects of *Spirulina* supplement against lead acetate-induced hepatic injury in rats. *J Tradit Complement Med*. 2015; 6(4):327-31. <https://doi.org/10.1016/j.itcme.2015.02.001> PMID:27774414 PMID:PMC5067858
- Abdel-Daim M, El-Bialy BE, Rahman HG, Radi AM, Hefny HA, Hassan AM. Antagonistic effects of *Spirulina platensis* against sub-acute deltamethrin toxicity in mice: Biochemical and histopathological studies. *Biomed Pharmacother*. 2016; 77:79-85. <https://doi.org/10.1016/j.biopha.2015.12.003> PMID:26796269

27. Lu J, Ren DF, Wang JZ, Sanada H, Egashira Y. Protection by dietary *Spirulina platensis* against D-galactosamine- and acetaminophen-induced liver injuries. *Br J Nutr*. 2010; 103(11):1573-6. <https://doi.org/10.1017/S0007114509993758> PMID:20102673
28. Bhattacharyya S, Mehta P. The hepatoprotective potential of *Spirulina* and vitamin C supplementation in cisplatin toxicity. *Food Funct*. 2012; 3(2):164-9. <https://doi.org/10.1039/C1FO10172B> PMID:22119940
29. Reddy MC, Subhashini J, Mahipal SV, Bhat VB, Srinivas Reddy P, Kiranmai G, Madyastha KM, Reddanna P. C-Phycocyanin, a selective cyclooxygenase-2 inhibitor, induces apoptosis in lipopolysaccharide-stimulated RAW 264.7 macrophages. *Biochem Biophys Res Commun*. 2003; 304(2):385-92. [https://doi.org/10.1016/S0006-291X\(03\)00586-2](https://doi.org/10.1016/S0006-291X(03)00586-2)
30. Pham TX, Lee JY. Anti-inflammatory effect of *Spirulina platensis* in macrophages is beneficial for adipocyte differentiation and maturation by inhibiting nuclear factor- κ B pathway in 3T3-L1 adipocytes. *J Med Food*. 2016; 19(6):535-42. <https://doi.org/10.1089/jmf.2015.0156> PMID:27206252 PMID:PMC4904162
31. Shih CM, Cheng SN, Wong CS, Kuo YL, Chou TC. Antiinflammatory and antihyperalgesic activity of C-phycocyanin. *Anesth Analg*. 2009; 108(4):1303-10. <https://doi.org/10.1213/ane.0b013e318193e919> PMID:19299804
32. Somchit MN, Mohamed NA, Ahmad Z, Zakaria ZA, Shamsuddin L, Omar-Fauzee MS, Kadir AA. Anti-inflammatory and anti-pyretic properties of *Spirulina platensis* and *Spirulina lonar*: a comparative study. *Pak J Pharm Sci*. 2014; 27(5):1277-80. PMID:25176383
33. Syarina PN, Karthivashan G, Abas F, Arulselvan P, Fakurazi S. Wound healing potential of *Spirulina platensis* extracts on human dermal fibroblast cells. *EXCLI J*. 2015; 14:385-93. PMID:27004048 PMID:PMC4800779
34. Jockenhöfer F, Gollnick H, Herberger K, Isbary G, Renner R, Stücker M, Valesky E, Wollina U, Weichenthal M, Karrer S, Klode J, Dissemond J. Bacteriological pathogen spectrum of chronic leg ulcers: Results of a multicenter trial in dermatologic wound care centers differentiated by regions. *J Dtsch Dermatol Ges*. 2013; 11(11):1057-63. <https://doi.org/10.1111/ddg.12170>
35. Lukowski G, Lindequist U, Mundt S, Kramer A, Julich WD. Inhibition of dermal MRSA colonization by microalgal micro- and nanoparticles. *Skin Pharmacol Physiol*. 2008; 21(2):98-105. <https://doi.org/10.1159/000113066> PMID:18198493
36. Gunes S, Tamburaci S, Dalay MC, Deliloglu Gurhan I. In vitro evaluation of *Spirulina platensis* extract incorporated skin cream with its wound healing and antioxidant activities. *Pharm Biol*. 2017; 55(1):1824-32. <https://doi.org/10.1080/13880209.2017.1331249> PMID:28552036
37. Schwartz J, Shklar G. Regression of experimental hamster cancer by beta carotene and algae extracts. *J Oral Maxillofac Surg*. 1987; 45(6):510-5. [https://doi.org/10.1016/S0278-2391\(87\)80011-3](https://doi.org/10.1016/S0278-2391(87)80011-3)
38. Grawish ME. Effects of *Spirulina platensis* extract on Syrian hamster cheek pouch mucosa painted with 7,12-dimethylbenz[*a*]anthracene. *Oral Oncol*. 2008; 44(10):956-62. <https://doi.org/10.1016/j.oraloncology.2007.11.014> PMID:18262461
39. Grawish ME, Zaher AR, Gaafar AI, Nasif WA. Long-term effect of *Spirulina platensis* extract on DMBA-induced hamster buccal pouch carcinogenesis (immunohistochemical study). *Med Oncol*. 2010; 27(1):20-8. <https://doi.org/10.1007/s12032-008-9164-x> PMID:19156551
40. Mishima T, Murata J, Toyoshima M, Fujii H, Nakajima M, Hayashi T, Kato T, Saiki I. Inhibition of tumor invasion and metastasis by calcium spirulan (Ca-SP), a novel sulfated polysaccharide derived from a blue-green alga, *Spirulina platensis*. *Clin Exp Metastasis*. 1998; 16(6):541-50. <https://doi.org/10.1023/A:1006594318633> PMID:9872601
41. Kunisada M, Sakumi K, Tominaga Y, Budiyanto A, Ueda M, Ichihashi M, Nakabeppu Y, Nishigori C. 8-Oxoguanine formation induced by chronic UVB exposure makes Ogg1 knockout mice susceptible to skin carcinogenesis. *Cancer Res*. 2005; 65(14):6006-10. <https://doi.org/10.1158/0008-5472.CAN-05-0724> PMID:16024598
42. Yogianti F, Kunisada M, Nakano E, Ono R, Sakumi K, Oka S, Nakabeppu Y, Nishigori C. Inhibitory effects of dietary *Spirulina platensis* on UVB-induced skin inflammatory responses and carcinogenesis. *J Invest Dermatol*. 2014; 134(10):2610-19. <https://doi.org/10.1038/jid.2014.188> PMID:24732403
43. Finamore A, Palmery M, Bensehaila S, Peluso I. Antioxidant, immunomodulating, and microbial-modulating activities of the sustainable and ecofriendly *Spirulina*. *Oxid Med Cell Longev*. 2017; 2017:3247528. <https://doi.org/10.1155/2017/3247528> PMID:28182098 PMID:PMC5274660