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Review Article

Arthrospira Platensis – Potential in Dermatology and Beyond

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Abstract

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 Fare 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 (IC_{50}) 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 ± 0.012 μM. 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 μg/mL and HaCaT cells with an IC50 of 0.07 μg/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 1.5μg/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-phycocyanin 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 - phycocyanin was investigated for anti-inflammatory and anti-hyperalgesic effects. C - phycocyanin 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 -alfa 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 Maresometrade 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 µg 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].

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