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Proceeding Paper

Effects of *Spirulina* on CD4+ T-Lymphocyte Count in Patients with HIV Infection: A Literature Review †

Michele Antonelli [1,*] and Davide Donelli [2]

[1] Department of Public Health, AUSL-IRCCS of Reggio Emilia, Via Giovanni Amendola 2, 42122 Reggio Emilia, Italy
[2] Cardiology Unit, University Hospital of Parma, 43121 Parma, Italy; donelli.davide@gmail.com
* Correspondence: michele.antonelli@ausl.re.it
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Abstract: The aim of this review is to understand if Spirulina can significantly improve the CD4+ cell count in patients with HIV. PubMed was searched up to February 2022 for relevant trials, and seven studies were found to match our inclusion criteria. Overall, the available evidence indicates that Spirulina might be useful to improve the CD4+ T-lymphocyte count in patients with HIV. A more pronounced effect is likely to be observed for a 10 g daily dose of Spirulina for 6 months, while smaller amounts given for shorter periods of time seem to be less effective. High-quality Spirulina-derived products are necessary to ensure the best clinical safety and avoid contaminants. Further studies on the topic are needed.

Keywords: spirulina; nutraceutical; immune system; lymphocytes; HIV; review

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1. Introduction

Spirulina (*Arthrospira platensis*) is a biomass of edible cyanobacteria or blue-green algae, which is well-known for its nutritional properties, as it is sometimes recommended to patients with metabolic problems [1,2] (Figure 1). Usually, 100 g of Spirulina can contain between 35 g and 70 g of proteins, up to 7 g of crude fiber, different micronutrients (B vitamins, carotenoids, tocopherol, minerals), and diverse functional compounds (phenols, flavonoids, phycocyanin, polysaccharides), which can account for antioxidant, anti-inflammatory, and immunostimulatory effects [1]. For a combination of easy production and favorable nutritional profile, Spirulina has been proposed as a potential candidate to help eradicate malnutrition [3] and to improve immunity in patients with HIV (human immunodeficiency virus) infection [1], two health conditions that tend to overlap, especially in low-income countries where nutrition-related issues and a high prevalence of HIV infection are both of great concern in public health [4]. A Cochrane review published in 2013 reported that it is not possible to draw firm conclusions on the efficacy of Spirulina for reducing morbidity and mortality in people with HIV infection, since the existing evidence is limited [5]. However, a more recent literature review, published in 2017, described Spirulina as a functional food with potential beneficial effects on patients with different diseases, including HIV infection [1]. Additionally, field studies conducted in Africa seem to support its usefulness for the nutritional rehabilitation of HIV-positive subjects suffering from malnutrition [6,7].

HIV is a retrovirus responsible for the so-called "Acquired Immuno-Deficiency Syndrome" (AIDS), with millions of infected patients worldwide [8]. Untreated HIV infection leads to progressive CD4+ T-lymphocyte loss and to a wide range of immunological abnormalities associated with an increased risk of developing opportunistic infections and neoplasms [8]. Even though there are now pharmacological treatments capable of slowing the disease progression, improving symptoms, and reducing viral replication [9], these treatment options can have side effects and, most importantly, they cannot be afforded by many patients in poor countries [10].

Figure 1. Spirulina powder. A spoon of Spirulina powder. Picture distributed under the CC0 Public Domain license and available online at: https://pxhere.com/it/photo/1178244 (accessed on 5 March 2022).

The aim of this review is to understand if Spirulina administration can significantly improve the CD4+ cell count in patients with HIV infection.

2. Methods

This research was designed as a narrative review of the scientific literature. No study protocol was registered prior to conducting this literature research.

Firstly, PubMed was searched from inception up to November 2021 for clinical studies about the effects of Spirulina administration on CD4+ T-cell count in patients with HIV infection. A second search was conducted in Google Scholar to screen the gray literature as well. The entire search was run again in February 2022. No restrictions were imposed in terms of publication year. For consideration for inclusion, relevant studies had to be written in English, or, at least, their content had to be summarized in an English abstract.

The following PICOS criteria were chosen for study inclusion:

- P (population): patients with HIV infection, regardless of their gender, age, disease severity, and comorbidities.
- I (intervention): oral intake of Spirulina powder on a daily basis for any number of days.
- C (comparator): any type, including no control.
- O (outcomes): changes in CD4+ T-lymphocyte count.
- S (study design): clinical studies (laboratory experiments were excluded).

Articles were excluded when their full-text version was irretrievable or when they had no English abstract/summary.

Key words such as "Spirulina", "Arthrospira", "HIV", "CD4", and "immun*" were used. The search strategy used for PubMed was: ("Spirulina" [Mesh Terms] OR "Arthrospira" [Title/Abstract]) AND ("HIV" [Mesh Terms] OR "CD4" [Title/Abstract] OR "immun*" [Mesh Terms]).

One author (M.A.) screened all research items retrieved after the database search, while the other author (D.D.) performed a second check to ensure reproducibility. Data were collected and manually extracted by one author (M.A.) using an Excel spreadsheet. In the case of disagreements, the two authors (M.A. and D.D.) discussed the matter until a consensus was reached.

The following data were extracted from studies eligible for inclusion: the number of patients involved, the most important characteristics of intervention and control, whether the standard antiretroviral therapy was administered or not to the patients, baseline and post-test values of CD4+ cell count, and the study design.

Relevant study results were summarized in a table and critically discussed in a qualitative way.

3. Results

After searching the scientific literature, 134 articles were retrieved, and among them, seven studies were found to match our PICOS criteria for inclusion (Table 1) [7,11–16]. All but two studies [11,12] were randomized trials, mostly placebo-controlled. The number of study participants ranged from 11 to 169 (median = 73), and females were generally over-represented across different trials. Almost all included trials, except for one [12], involved adult patients. In one study, described in a preprint, the group assigned to intervention was given Spirulina in adjunct to standard antiretroviral therapy, while the control group received the pharmacological treatment only [15]. In the other included studies, participants were naive to standard HIV therapy (Table 1). Intervention consisted of Spirulina powder administration, either encapsulated as a dietary supplement, or added to meals as a functional food: the daily dose ranged from 5 g to 10 g, and the treatment duration lasted from a minimum of 8 weeks to a maximum of 6 months (Table 1).

The study results can be briefly summarized as follows:

- In four studies, the CD4+ cell count significantly increased after intervention ($p < 0.05$) [12–15].
- In two studies, the CD4+ cell count tended to increase after intervention, but this variation was not statistically significant [11,15].
- In one study, the CD4+ cell count significantly decreased after intervention ($p < 0.05$) [16].

Table 1. Summary of scientific evidence about the effects of Spirulina administration on CD4+ cell count of patients with HIV.

Population (HIV+)	Intervention (Spirulina) (n—per-Protocol Analysis)	ART	Control (n—per-Protocol Analysis)	Baseline CD4+ Cell Count (Cells/μL)	Post-Test CD4+ Cell Count (Cells/μL)	Change §	Study Design	Ref.
169 adults (119F/50M)	Spirulina (10 g/day) for 6 months (*n* = 79)	No	No intervention (*n* = 66)	Mean ± SD: 596.32 ± 198 (int.) vs. 569.40 ± 179.89 (con.) (NS)	Mean ± SD: 6 months: 609.07 ± 149.14 (int.) vs. 464.86 ± 200.33 (con.) * 12 months: 614.92 ± 179.43 (int.) vs. 429.04 ± 177.19 (con.) *	↑	RCT	[13]
160 adults (F > M)	Spirulina (10 g/day) for 6 months (*n* = 67)	No	Placebo (*n* = 61)	Mean: 249.5 (int.) vs. 238.5 (con.) (NS)	Mean: 6 months: 271.1 (int.) vs. 276.9 (con.) (NS)	↑	RCT	[14]
86 adults (F > M)	ART plus Spirulina (10 g/day) for 6 months (*n* = 31)	Yes	ART only (*n* = 31)	Median (IQR): 443 (332–626) (int.) vs. 397 (321–497) (con.)	Median (IQR): 6 months: 504 (395–609) (int.) vs. 401 (272–492) (con.)	=	RCT	[15]
73 adults (73F/0M)	Spirulina (5 g/day) for 3 months (*n* = 28)	No	Placebo (*n* = 30)	Median (IQR): 440 (415–550) (int.) vs. 462 (413–558) (con.) (NS)	Median (IQR): 3 months: 406 (320–499) (int.) vs. 417 (311–486) (con.) (NS)	↓	RCT	[16]
69 children aged less than 2 years old (?)	Spirulina (10 g/day divided into two administrations along with traditional meals) for 8 weeks (*n* = 46)	No	Irrelevant for this review (Spirulina in HIV-negative children) (*n* = 23)	Median (IQR): 1339 (152–4000)	Median (IQR): 8 weeks: 2088 (244–4214)	↑	Case-control study	[12]
56 adults (34F/18M)	Spirulina (dosage calculated to provide 25% of the RDA for proteins) for 12 weeks (*n* = 26)	No	Soya beans consumption (*n* = 26)	Mean ± SD: 96 ± 58 (int.) vs. 97 ± 49 (con.) (NS)	Mean ± SD: 12 weeks: 195 ± 90 (int.) vs. 143 ± 69 (con.) *	↑	RCT	[7]
11 adults (7F/4M)	Spirulina (6 g/day), Undaria (5 g/day) or Spirulina plus Undaria (3 + 2.5 g/day) for a maximum of 3 months (*n* = 6)	No	/	Mean ± SE: 447 ± 47	Mean ± SE: 3 weeks: 475 ± 65 3 months: 484 ± 67	=	Pre-post study	[11]

Table legends: ART = AntiRetroviral Therapy. Con. = Control. F = Females. Int. = Intervention. IQR = Inter Quartile Range. M = Males. N—per-protocol analysis = Number of participants who completed the study. NS = non-significant difference between groups. RCT = Randomized Controlled Trial. RDA = Recommended Dietary Allowance. SD = Standard Deviation. SE = Standard Error; Table symbols: * = significant difference between groups ($p < 0.05$); § = pre-post test changes in the CD4+ cell count ("↑" stands for "significant increase"; "↓" stands for "significant decrease"; "=" stands for "no significant variation"). Threshold for statistical significance was set at $p < 0.05$.

4. Discussion

Most available evidence indicates that Spirulina administration can significantly improve the CD4+ T-cell count in patients with HIV infection [12–15], especially if Spirulina is taken at high doses (10 g/day) for long periods of time (6 months). In one study, the number of participants was too low to detect any significant effect of intervention [11]; however, beneficial trends were observed in those who were not lost to follow-up. In the clinical trial where all participants took antiretroviral therapy, no significant variations in the CD4+ T-cell count were reported, but the group taking Spirulina in adjunct to standard therapy had better control over viral replication and improved their oxidant/antioxidant balance [15], thus suggesting that Spirulina may also have a role as an integrative dietary supplement along with standard therapy. In a study involving a cohort of female patients, either placebo or Spirulina administered at a dose of 5 g/day for 3 months were associated with a decreased CD4+ T-cell count [16]: it is possible to hypothesize that this dose may be insufficient to produce clinically relevant effects, as underscored by other authors too [12].

In general, Spirulina can have antioxidant, cardio-protective, and lipid-lowering effects in patients with HIV, and it can also help them against malnutrition, since it represents a good source of proteins and micronutrients [1,2,17]. Given its low cost and easy availability, it is important to further study the potential efficacy of Spirulina as a dietary supplement with medicinal properties to help patients who cannot afford the standard antiretroviral therapy, especially in poor countries with a high prevalence of HIV infections, where effective and low-cost therapeutic strategies are urgently needed to tackle this important public health issue. Spirulina may also be a useful complementary remedy in patients who have access to standard treatment options in order to possibly improve its efficacy and reduce any side effects.

Spirulina is categorized as "generally safe" by the US Food and Drug Administration [18]. Nevertheless, case reports of autoimmune disease flares associated with Spirulina consumption are described in the scientific literature [19,20]. Moreover, poor-quality Spirulina, sometimes harvested in polluted lakes, can contain high levels of toxic substances, thus urging health authorities to enact strict controls over marketed products [21,22]. Some Spirulina-derived polysaccharides may have anticoagulant activity [23], and this is important to consider in patients taking blood thinners or those genetically prone to bleeding. Finally, allergy to Spirulina is more frequent in patients suffering from allergic rhinitis [24], and cross-reactivity with pollen and other volatile allergens has been hypothesized. For all these reasons, medical supervision is strongly recommended.

In conclusion, Spirulina might be useful to improve the CD4+ T-lymphocyte count in patients with HIV infection. A more pronounced effect is likely to be observed for a 10 g daily dose of Spirulina administered for 6 months, while smaller amounts given for shorter periods of time seem to be less effective. Further trials on the topic are needed to better investigate the potential role of Spirulina in HIV integrative management.

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