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Herbal medicines for treating HIV infection and AIDS: a systematic review and meta-analysis

Plantas medicinais para o tratamento da infecção pelo HIV e AIDS: uma revisão sistemática e meta-análise

Plantas medicinales para el tratamiento de la infección por VIH y SIDA: una revisión sistemática y un metanálisis

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Abstract
The present meta-analysis evaluated the use of medicinal plants, phytotherapics and/or phytopharmaceuticals associated or not to antiretroviral therapy, using as primary outcome the lymphocyte count, and, among which, the $CD4^+$ count. Studies were considered eligible for the present systematic review if they comprised the following criteria: randomized clinical trials using as intervention medicinal plants, phytotherapics, and/or phytopharmaceuticals associated or not with antiretroviral therapy. The search strategy included terms related to the intervention (medicinal plants, medicinal plants extracts, phytotherapics, and/or phytopharmaceuticals associated or not with antiretroviral therapy), to the primary outcome (in which was verified if there was a decreasing in lymphocytes, among which $CD4^+$ cells), as well as terms that were used to improve sensitivity in a search for clinical trials. From 2.747 records of potential relevance identified on the databases, remaining two eligible randomized placebo-controlled clinical trials. The present systematic review and meta-analysis showed on the forest plot that there was no difference between control and intervention groups when the two included studies were taken into consideration.
Keywords: Meta-analysis; HIV; Medicinal plants; $CD4^+$ count; Phytotherapics; Antiretroviral therapy.

Resumo
A presente meta-análise avaliou o uso de plantas medicinais, fitoterápicos e/ou produtos fitofarmacêuticos associados ou não à terapia anti-retroviral, usando como principal resultado a contagem de linfócitos e, entre os quais, a contagem de CD4 +. Estudos foram considerados elegíveis para a presente revisão sistemática se eles compreendia os seguintes critérios: estudo randomizado clínicos usando como plantas medicinais de intervenção, fitoterápicos e/ou produtos fitofarmacêuticos associados ou não com terapia anti-retroviral. A estratégia de pesquisa incluiu termos relacionados à intervenção (plantas medicinais, extratos de plantas medicinais, fitoterápicos e/ou produtos fitofarmacêuticos associados ou não com a terapia anti-retroviral), para o resultado primário (no qual verificou-se lá foi uma diminuição em linfócitos, entre os quais células $CD4^+$), bem como os termos que foram usados para melhorar a sensibilidade em busca de ensaios clínicos. De 2,747 registros de relevância potencial identificado nos bancos de dados, permanecendo dois elegíveis placebo-controlado ensaios clínicos randomizados. Rever o presente sistemático e meta-análise sobre a trama de floresta mostrou que não houve diferença entre os grupos controle e intervenção quando dois estudos incluídos foram tidos em consideração.
Palavras-chave: Meta-análise; HIV; Plantas medicinais; Contagem CD4 +; Fitoterápicos; Terapia anti-retroviral.

Resumen
El presente metanálisis evaluó el uso de plantas medicinales, hierbas medicinales y/o productos fitosanitarios asociados o no a la terapia antirretroviral, utilizando como resultado principal el recuento de linfocitos y, entre los cuales, el recuento de $CD4^+$. Los estudios se consideraron elegibles para esta revisión sistemática si comprendían los siguientes criterios: estudios clínicos aleatorizados que utilizaron la intervención como plantas medicinales, hierbas medicinales y/o productos fitosanitarios asociados o no con el tratamiento antirretroviral. La estrategia de investigación incluyó términos relacionados con la intervención (plantas medicinales, extractos de plantas medicinales, productos herbarios y/o fitosanitarios asociados o no a la terapia antirretroviral), para el resultado primario (en el que se verificó que hubo una disminución de linfocitos, incluidas las células CD4+), así como los términos que se utilizaron para mejorar la sensibilidad en busca de ensayos clínicos. De los 2.747 registros de relevancia potencial identificados en las bases de datos, quedan dos ensayos clínicos aleatorios controlados con placebo elegibles. La revisión del presente sistemático y el metanálisis en la parcela forestal mostraron que no hubo diferencias entre los grupos de control e intervención cuando se tuvieron en cuenta dos estudios incluidos.
Palabras clave: Meta-análisis; VIH; Plantas medicinales; Recuento de CD4+; Hierbas medicinales; Terapia antirretroviral.

1. Introduction

AIDS is a public health issue since due to its global dissemination and to the psychosocial burden associated to bearing the disease (Costa et al. 2015; Zanon et al. 2016). This large scale pandemics derives from the ease of spread of the disease, which occurs mainly by means of sexual transmission, as well as the lack of a solid investment on education towards prevention of transmission and/or changes in behaviour linked to sexual activities (Unaids 2015).

As the early diagnosis plays a crucial role in reducing mortality by secondary causes in the immunocompromised patient, the absence of efficient public health policies in most parts of the world results in underdiagnosis, lack of therapeutic adhesion and no investment in the psychosocial support for patients (Villela & Barbosa, 2017).

The proper reduction of morbidity and mortality in patients with AIDS is achieved by means of effective pharmacotherapy. The early discovery of zidovudine as an antiretroviral agent and the later development of protease inhibitors enhanced the effectiveness of available treatments in reducing HIV burden below detectable levels, which in turn allowed patients who bear the virus a better quality of life (Bonolo et al. 2007).

The guidelines provided by the World Health Organization call for treatment of every patient with HIV, with the aim that 30 million people will be able to have access to proper pharmacotherapy by 2020, among the current nearly 37 millions who are estimated to bear the virus (Unaids 2017).

The use of medicinal plants has always been a common practice in therapeutics. In spite of that, only in past decades there has been global effort to provide supporting evidence of their efficacy in some conditions and thus rationalize their applications in modern medicine, especially in chronic diseases such as AIDS (Liu et al. 2005). In addition, the high costs associated to the antiretroviral agents in impoverished countries restrict the access to adequate treatment by a large number of patients and therefore the use of medicinal plants may comprise a viable alternative in such regions (Vella & Palmisano, 2000). Based on the aforementioned premises this study aims to assess the use of medicinal plants, phytotherapy and phytomedicines, including in conjunction with conventional antirretroviral drugs, in patients with HIV.

2. Materials and Methods

2.1 Study selection and search strategy

Studies were considered eligible for the present systematic review if they comprised the following criteria: randomized clinical trials using as intervention medicinal plants, phytotherapics, and/or phytopharmaceuticals associated or not with antiretroviral therapy.

In order to carry out this review we adopted the Preferred Reporting Items for Systematic Reviews and Meta-Analyses – PRISMA guidelines. We included terms related with the intervention (medicinal plants, medicinal plants extracts, phytotherapics, and/or phytopharmaceuticals associated or not with antiretroviral therapy), the primary outcome (in which we

verified if there was a decrease in $CD4^+$ cells), as well as terms that improved sensitivity in a search for clinical trials (Robinson & Dickersin, 2002).

We evaluated only English papers and carried out the search between March 2016 and March 2018 in the following databases: ClinicalTrias.gov, LILACS, MEDLINE, CENTRAL, Scopus and SciELO. Furthermore we sought non-peer-reviewed databases which included ClinicalEvidence.com, OpenGrey.eu, NYAM.org and DissOnline.de.

2.2 Assessment of the eligibility of the study

The previously described search strategy was used to identify titles and abstracts of relevance to the meta-analysis. Researchers independently selected abstracts that were identified on the initial search and each researcher was able to classify a study as relevant and to include the study on the analysis. The full articles were then obtained, and their content was assessed, also independently. Any disagreements between researchers were resolved by discussion to establish a consensus. In cases of queries regarding a specific study, the author of the paper was contacted.

2.3 Risk of bias assessment

We also followed the recommendations of the Cochrane Manual (Turner et al. 2013) in order to assess the risk of bias. Therefore, the quality of the investigations was assessed by researchers in an independent way and then classified into one out of five categories, namely allocation concealment, sequence generation, blinding of outcome assessors, missing data manipulation and selective outcome report.

2.4 Statistical analysis

Dichotomous data of all included randomized clinical trials (RCTs) were combined to estimate the risk ratio (RR) combined with a 95% confidence interval (Cl), using a random effects model. We aimed for the most complete information about the outcomes of participating patients and we managed to contact some authors to obtain those details.

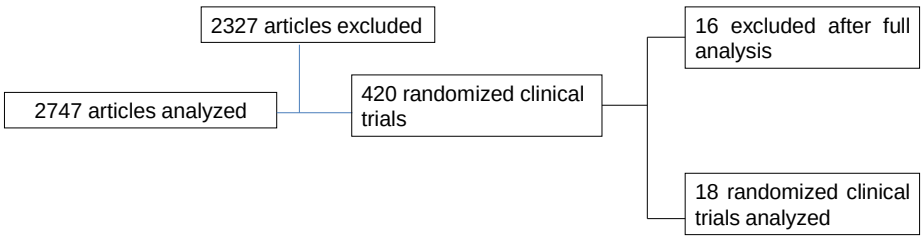
To identify heterogeneity on the findings, we applied statistical techniques to verify if the differences observed could be explained by chance. The chi-square test was used to assess the significance of $p<0.05$. The magnitude of heterogeneity was investigated by I^2 calculation and we considered an I^2 value superior to 50% as substantial heterogeneity and, above 75%, as considerable heterogeneity (Santos 2013).

3. Results

Characteristics of the included studies

From 2.747 records of potential relevance identified on the databases, 18 full text articles comprised the eligibility criteria and were used for posterior evaluation. Among these selected papers, 16 were excluded after full text analysis, remaining two eligible randomized placebo-controlled clinical trials. The motives for exclusions are shown on the supplemental material. Studies were heterogeneous in terms of participants, intervention, and results (Figure 1).

Figure 1. Flow chart of the studies analyzed on the meta-analysis.



Source: Authors.

Risk of bias of the included studies

The two included trials were double-blinded, placebo-controlled in parallel groups, being randomized and non-multicentre studies. Sequence generation and allocation concealment were not reported. The motives for dropouts did not change between experimental groups as well as the proportion of losses was similar between groups. The absence of an intention-to-treat analysis is a strong bias. The judgment regarding risk of bias was of high risk (Wang et al. 2006).

On the trial performed by Wilson et al. (2015), regarding sequence generation and allocation concealment, the eligible participants were sequentially assigned to a patient identification number (PIN) in order to obtain a proper allocation. Intention-to-treat analysis was performed. Risk of bias judgement was of low risk.

Blindness was adequate for individuals, including participants, investigators, and caretakers. Both studies reported numbers and reasons for exclusions/dropouts and used the intention-to-treat principle in their data analysis (Wang et al. 2006; Wilson et al. 2015). The sample size varied from 72 to 133 participants. In general, the methodological quality of trials was considered adequate.

Effects of interventions on the included studies

Randomized clinical trials aiming to evaluate the antiretroviral action of phytotherapics versus placebo were performed by Wang et al. (2006) and Wilson et al. (2015) with Zhongyan-4 (ZY-4) and *Sutherlandia frutescens* L., respectively (Table 1).

Table 1. Randomized clinical trials using phytotherapics and placebo.

Study	Country	Sample size	Mean age	Allocation	Type of blindness	$CD4^+$ count	Duration	Type of analysis	Risk of bias assessment
Wang et al, 2006	China	72 patients	18 -55 years old	Not reported	Double-blinded	100-400 cells/mm^3.	6 months	Per-Protocol	High risk
Wilson et al, 2015	South Africa	133 patients	21 – 64 years old	Participant's identification number	Double-blinded	>350 cells/μL	6 months	Intention-to-treat	Low risk

Source: Authors.

The restricted amount of randomized clinical trials and the small sampling of these investigations leads to data that are far from being conclusive about the complementary Chinese therapy and the therapy using the species *S. frutescens*, which is native from South Africa, on the treatment of patients with infection by HIV and AIDS. Compared to placebo, intervention with Zhongyan-4 (ZY-4) showed positive effects on the increasing of $CD4^+$ cells (Wang et al. 2006) (Table 1).

In contrast, the second intervention regarding *S. frutescens* showed no impact on $CD4^+$ T lymphocyte count when compared to negative control. The authors concluded that the consumption of 1.200 mg of *S. frutescens* had no beneficial effect on patients since the duration of infections was reported to be even longer in these patients in comparison with those taking placebo alone. This occurred because two patients developed tuberculosis during the treatment with *S. frutescens*, despite the administration of Isoniazid preventive therapy (IPT) (Table 1).

Wang et al. (2006) performed a clinical study with 72 patients diagnosed with HIV/AIDS, 44 men and 28 women, aged from 18 to 55 years old and whose $CD4^+$ count ranged between 100-400/mm^3.

The intervention was performed using the oral phytotherapic Zhongyan-4 (ZY-4), which has in its composition: *Ginseng raiz, Radix astragali, Fructus lycii, Radix frichosanthis, Radix scutellariae* e *Herba vilae*, on a proportion of 1: 2 : 1 : 1 : 1: 1, 5 per granulated dose of 7.5 g. The therapeutic regimen was of twice per take, twice per day. Placebo was used as control using the same therapeutic scheme of ZY-4.

The use of other anti-HIV drugs was not allowed during the clinical trial; however, the treatment of opportunistic infections was allowed. In addition, cell count of CD45 RA^+ and $CD8^+$ lymphocytes showed that the action of ZY-4 might involve multiple targets. However, it has a delayed onset of action since its effects were only observed after three months, not reaching its peak at the end of six months. The observation also showed that ZY-4 affects the effectiveness index of serum Interleukin-2 (IL-2).

The composed formulation of Zy-4 was based on pre-clinical and experimental studies under the use of de Zhongyan-1 e Zhongyan-2 (Wang et al. 2002). The phytotherapic contains *Radix* astragali, Ginseng root, *Fructus lycii*, *Radix frichosanthis*, *Radix scutellariae* and *Herba Vilae*. Several pharmacological investigations reported the immunomodulatory effects of Ginseng root, *Radix astragali*, and *Fructus lycii* whereas others describe the inhibition of HIV activity by *Radix frichosanthis* and *Radix scutellariae* (Lu 1994).

Sutherlandia frutescens

The research performed by Wilson et al. (2015) occurred in two phases. On phase 1, 56 random participants were selected to receive a twice-daily treatment with 400, 800, or 1200 mg of *Sutherlandia frutescens* or placebo for 24 weeks.

On phase 2, 77 participants were included randomly with administration of 1200 mg of *S. frutescens* or placebo. Combined data from phases 1 and 2 were used on the final analysis, comprising a total of 107 participants (54 with 1200 mg of *S. frutescens* and 53 with placebo).

A possible explanation to the interaction between *S. frutescens* and IPT may be related to the antioxidant potential of *S. frutescens* (Fernandes et al. 2004; Tobwala et al. 2014) which are thought to interfere with the mechanisms of action of Isoniazid (Timmins & Deretic, 2006).

HIV-serum positive adults aged between 21 and 64 years old with $CD4^+$ T lymphocyte count higher than 350 cells/μL and viral load of HIV>1.000 copies/mL were considered eligible for the study. The only adjuvant treatment administered was Isoniazid and Pyridoxine in order to prevent tuberculosis. Data obtained from the results suggest that treatment with *S. frutescens* in daily doses up to 2.400 mg do not cause significant side effects in HIV-serum positive adults. However, some side effects were observed in patients with diabetes or adrenal imbalances *S. frutescens* (MacKenzie et al., 2009). Therefore, more studies are needed to better describe interactions between antiretroviral drugs and phytotherapics.

Characteristics of the excluded studies

The motives that lead to the exclusion of the articles were the absence of data related to $CD4^+$ (Matsabisa et al. 2012; Joshi et al. 2008). Marques et al. (2016); studies without mean and standard deviation (Dabaghzadeh et al. 2014; Petrilli et al. 2016; Nikolaeva et al. 2008); non-randomized clinical studies (Oladele et al. 2012; Jiang et al. 2013); randomized clinical trials that were not placebo controlled (Nikolaeva et al. 2008; Onifade et al. 2013; Ayuba et al. 2014); a random pilot study (Burack et al. 1996); a study without standard deviation (Weber et al. 1999); studies without CD4 values (Galarza et al. 2007; Ellis et al. 2009; Shi-qing et al. 2011); a study with the absence of full text (Gil del Valle et al. 2010).

In a double-blinded placebo controlled trial carried out by Matsabisa et al. (2012). Four treatment groups were randomly assigned to patients. The first group comprised a daily dose of 1.835,2 mg of standard IMUNITI Wellness Pack, while the second and third groups received, respectively, two and three times the recommended daily dose. These three groups altogether received as well 150 ml of *Aloe vera* juice. Lastly, the control group received placebo and. 150 ml of water aromatized with *Aloe vera* to blind the treatment. The investigation continued over consecutive 5 weeks and the results showed the IMUNITI was safe for patients since no significant alterations for hematological, renal and biochemical parameters (Matsabisa et al. 2012).

A phase II double-blinded clinical trial carried out by Joshi et al. (2008), in 2015 divided 100 patients into two different groups. The first group received Praneem tablets containing 80 mg of *Azadirachta indica* leaves, 40 mg of purified saponins from *Sapindus mukerosi* and 20 mg of Mentha citrate oil. In addition, each formulation also had 20 mg of quinine hydrochloride. The other group comprised patients taking only placebo. The data obtained from the study revealed that the Praneem tablet was safe for vaginal use in phase I studies in low risk HIV-negative women after 6 months of use (Joshi et al. 2008). There were no statistical significant differences regarding reported adverse events between patients enrolled on group Praneem when compared to the negative control group. The most frequently experienced condition by users was genital discomfort manifested as genital pruritus, burning, and ache. However, the long-term safety of polyherbal Praneem must be assessed by a full pre-clinical evaluation (Joshi et al. 2008).

Marques et al. (2016) evaluated the effects of passion fruit peel flour with diet therapy and therapeutic counseling in 36 patients with HIV lipodystrophy that were on a ambulatorial clinic of a teaching hospital. Patients were divided into two groups. One group received 30 g of passion fruit peel flour daily during 90 days and therapeutic counseling. The other group received only nutritional counseling. The metabolic changes were analyzed before and after the intervention with a significance level set at $p \leq 0.05$. The use of passion fruit peel flour was effective in reducing total cholesterol and triglycerides after 30 days. Patients presented undetectable levels of HIV as well as $CD4^+$ T lymphocyte count of 300 cells/mm^3. The concentrations of LDL-C decreased, whereas the HDL-C increased in the blood of patients with lipodystrophy after 90 days of treatment with passion fruit peel flour.

On a randomized clinical trial performed by Dabaghzadeh et al. (2014), 102 HIV-positive patients that attended an HIV hospital clinic participated on this double-blinded study, which had a duration of two years. Participants received, randomly, 500 mg of *Zingiber officinale* or placebo, twice a day, before each dose of antiretroviral for 14 days. Patients participated the study for two years. Nauseas and vomits are common side effects of antiretroviral therapy (ART) and generally occur early during HIV treatment. Despite these adverse gastrointestinal effects are generally self-limited and vanish with continuous treatment, they may affect the adherence to ART (Dabaghzadeh et al. 2014).

A total of 90,2% and 56,4% patients of group placebo and the group that received ginger, respectively, experienced nausea during the first two weeks of treatment ($p = 0.001$). Moderated and severe nauseas were significant smaller in group receiving the herbal medicine ($p=0.001$). In addition, 47.1% and 9.8% of patients on groups placebo and ginger, respectively, reported at least one episode of vomit during the treatment ($p = 0.01$) (Dabaghzadeh et al. 2014).

Petrili et al. (2016) assessed the effects cocoa and yerba mate ingestion on several biomarkers of individuals with HIV, including anthropometric, inflammatory, oxidative, and immunological parameters. A double-blinded, placebo controlled, randomized clinical trial assigned 92 individuals undergoing ART during at least six months in 2 groups, one of which receiving 65 g of chocolate or 3 g of yerba mate and the other group comprising the patients taking placebo. Results showed that the intake of 65 g of dark chocolate was enough to increase the concentrations of HDL-C, while the supplementation with 3 g of yerba mate did not change significantly biomarkers on these individuals (Petrili et al. 2016).

On the research performed by Nikolaeva et al. (2008), patients not treated with antiretrovirals were assigned into two equal groups. The positive control group received standard anti-tuberculosis treatment, while the other group received HRZSE and 50 drops of Dzherelo, a hydroalcoholic concentrated extract of several medicinal plants, diluted in 100 ml of water twice a day. Results showed that following two months of treatment led to increased total $CD3^+$ and $CD4^+$ T lymphocytes in the group receiving the herbal medicine but decreased levels of both cells in control group (Nikolaeva et al. 2008).

There were no significant changes on ATT alone, i.e. 182 (24.2%) to 203 (24.5%); $p = 0.063$ ($p = 0.28$), whereas the treatment with Dzherelo significantly increased the count of helper cells from 174 (23.3%) to 257 cells (27.3%); $p = 0.00003$ ($p = 0.0004$). At the end of the second month, lymphocytes increased to 174 (25.3%) and 283 (31%) with probability values of $p = 0.13$ and $P=0.0000004$ for treatments A and B, respectively (Nikolaeva et al., 2008).

Ten young women diagnosed with HIV in a Nigerian hospital that did not fit national criteria for antiretroviral use participated on a randomized clinical trial. Treatment was performed with *Aloe barbadensis* Miller with daily administration of 30-40 ml. $CD4^+$ count was monitored over one year. Results were similar for both groups, suggesting that *A. vera* consumption may be an alternative for individuals infected by HIV in the tropics, given its availability and low cost. One patient had a bad reaction to the antiretroviral drug and started to use *Aloe vera*. The average increase of $CD4^+$ count among patients was 153,7 cells/L in comparison to 238.85 cells/L among controls ($p = 0.087$), and no side effects were reported for both groups (Oladele et al. 2012).

Jiang et al. (2013) performed a clinical study that included 34 ambulatorial patients with HIV/AIDS. Changes in serum levels of $CD3^+$, $CD4^+$, $CD8^+$, $CD3^+$, $CD4^+$, $CD38^+$, $CD3^+$, $CD4^+$, HLA-DR^+, $CD3^+$, $CD8^+$, $CD38^+$, e $CD3^+$, $CD8^+$, HLA-DR^+ were analyzed in patients treated with FZPDG, a concentrated granules of herbs that has in its composition Huangqi (*Radix astragali mongolici*), Rensen (*Radix ginseng*), Chaobaizhu (Roasted *rhizoma atractylodis macrocephalae*), Fuling (*Poria*), Chenpi (*Pericarpium citri reticulatae*), Sharen (*Fructus amomi*), Yiyiren (*Semen coicis*), Bajitian (*Radix morindae officinalis*), Rouconrong (*Herba cistanche deserticolae*), Yinyanghuo (*Herba epimedii brevicornus*), Lianqiao (*Fructus forsythiae suspensae*), Danggui (*Radix angelicae sinensis*), and Gancao (*Radix glycyrrhizae*).

In this research, patients with HIV/AIDS received half of a FZPDG sachet orally, twice a day, with boiled water for six months and presented an immune activation profile after treatment, with acts modulating the immunological activation of $CD4^+$ and $CD8^+$ T cells (Jiang et al. 2013).

The changes on serum levels of $CD3^+$, $CD4^+$, $CD8^+$, $CD3^+$, $CD4^+$, $CD38^+$, $CD3^+$, $CD4^+$, HLA-DR^+, $CD3^+$, $CD8^+$, $CD38^+$ e $CD3^+$, $CD8^+$, HLA-DR^+ (human leukocyte antigen) in patients with HIV/AIDS treated with FZDPG for six months were examined by flux cytometry and compared with levels of health controls. The initial count of $CD4^+$ T lymphocytes in patients with HIV/AIDS was of 38-595 (247±133) cells/ml. Specifically, 15 patients had a $CD4^+$ T cell count inferior to 200 cells/mL and 7 had a count of over 350 cells/ml. Patients with HIV/AIDS showed better immunological profile after receiving FZPDG (Jiang et al. 2013). The herbal medicine Zam was investigated by Onifade et al. (2013). It contains *Nigella sativa* and honey on a 60:40 proportion in its composition. The recommended posology for adults is about 10 ml diluted in about 50 ml of warm water, three times daily after each meal. For monthly monitoring, data and contact information of each patient were registered.

Patients were counted daily and visited regularly after the beginning of treatment with the herbal preparation to assess its efficacy, side effects, and toxicity. The findings suggest improvement on symptoms and signs related to HIV infection disappeared within 20 days after the beginning of treatment with statistical difference ($p < 0.05$). In addition the results also pointed for increased body weight, decreased viral load to undetectable levels of ≤50 copies/ml, and improved $CD4^+$ levels, from 227 ± 9 to 680 ± 12 mm3/uL. This study concluded that Zam is effective on the treatment of HIV infection based on a significant improvement on both clinical and laboratorial parameters (Onifade et al. 2013).

Godwin et al. (2014) performed a investigated the effects of a 8 weeks treatment with the herbal medicine Jobelyn in 10 patients not receiving antiretroviral treatment. The therapeutic schedule comprised of twice-daily dose of 500 mg. Patients that received ART presented a statistical significant improvement on $CD4^+$ T lymphocyte count during the study period of 12 weeks ($p < 0.01$). On the other hand, patients that received ART associated to Jobelyn showed a faster improvement within 6 weeks of treatment ($p < 0.001$). Futhermore, data suggest that the intake of Jobelyn contributed to improve $CD4^+$ T lymphocyte count (Ayuba et al. 2014).

Another trial carried out by Burack et al. (1996), in 1996 aimed at the investigation of a Chinese formulation of (IGM-1) composed by 31 medicinal plants and its effects on HIV-related symptoms. Participants were stratified by $CD4^+$ count in two groups ($0.200\text{-}0.349 \times 10^9$/L e $0.350\text{-}0.499 \times 10^9$/L) and then were assigned to treatment groups using a series of random numbers for each group. Among the ingredients contained in the 650 mg pill, the ones present in high concentrations included *Andrographis paniculata, Astragalus membranaceus, Ganoderma lucidum, Isatis tinctoria, Laminaria japonica, Lonicera japonica, Milletia reticulate* and *Oldenlandia diffusa*. The negative control group received placebo pills composed mainly by microcrystalinne cellulose (Burack et al. 1996).

On the study of Weber (1999), a total of 68 adults infected with HIV, and with $CD4^+$ lymphocyte count $<0.5 \times 10^{(9)}$ / L were included. The patients were assigned randomly to receive doses of seven pills which included 35 Chinese herbs or placebo and to be taken over six months on a daily basis. However, the treated individuals showed no signs of improvement regarding clinical manifestations, $CD4^+$ lymphocyte counts or serum viral load.

Galarza et al. (2007) performed a double-blinded, randomized study with HIV-related eosinophilic folliculitis. Sample was comprised by 40 patients with HIV-related eosinophilic folliculitis that were assigned by systematic random sample in two groups, one receiving different therapies. Therapy 1 consisted of 0,075% of Capsaicin, whereas therapy 2 comprised 1% Menthol. Treatment on the affected area was performed every 6 hours for 45 days. Response was good in 90% of patients that received 0.075% of Capsaicin, in comparison with 40% of the group treated with 1% Menthol ($p = 0.001$). The effectiveness of topical therapies was modified by $CD4^+$ T lymphocyte count ($p < 0.001$). The presence of opportunistic diseases ($p = 0.252$) did

not affect therapy effectiveness. Topical therapy with Capsaicin was effective and safe on the treatment of pruritus on HIV-related eosinophilic folliculitis (Galarza et al. 2007).

Ellis et al. (2009), in a double-blinded clinical trial, assessed the effects of Cannabis sativa on neuropathic pain refractory to analgesics in HIV-positive patients. The concentrations of the active constituent, Delta-9-tetrahydrocannabinol, ranged from 1 to 8% in the formulations given to patients. The therapeutic scheme consisted of an alternated two weeks treatment, in which the patients had to smoke *Cannabis* 4 times a day during 5 days in each week of treatment. The trial considered 34 individuals eligible and 28 out of the total concluded the study. The data gathered from the investigation suggest that the pain relief was enhanced by the use of *Cannabis*, when compared to the negative control placebo. Furthermore, the side effects experienced by the patients were mild and self-limited, with the exception of two individuals with limiting toxicities. Therefore, the use of *Cannabis* was well tolerated and effective when used for analgesic therapy on patients with refractory pain (Ellis et al. 2009).

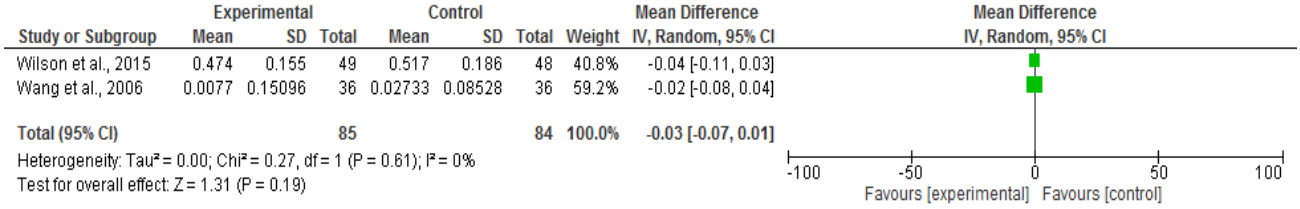
On a double-blinded randomized study, 58 patients used oral capsules of Jingyuankang and ART, and the other 58 patients used Leucogen pill and ART for 6 weeks. Hematological parameters were monitored in order to stablish the effects of Jingyuankang capsules on the leucocytes count in HIV-positive patients. The results showed that the herbal formulation could improve blood cells count with minor to non-existent secondary or side effects during the trial (Shi-qing et al. 2011).

Outcome of primary outcome

There were no statistically significant differences between the intervention and placebo groups in the study compared to any of the variables examined in the $CD4^+$ lymphocyte count. One of the factors that may have influenced the small number of randomized clinical trials included in the study.

According to these studies, the reduction of $CD4^+$ lymphocytes. There was no significant difference in relation to placebo, with ($p = 0.19$) (Figure 2).

Figure 2. Forest plot for the outcome CD4+ lymphocyte count.



Source: Authors.

Considering infection vulnerability and HIV/AIDS treatment, the knowledge regarding the taking of antiretroviral drugs and the use of phytotherapics and medicinal plants is of utmost importance.

The forest plot depicted above shows that there was no difference between control and intervention groups when the two included studies were taken into consideration.

The study performed by Wang et al. (2006) showed a standard deviation superior to the mean value, which represents contrasting results. On the other hand, the study performed by Wilson et al. (2015) presented standard deviation inferior to the mean value, indicating less data variation.

The magnitude of heterogeneity was verified mainly by I^2 calculation, which ranges from 0 to 100%. An I^2 superior to 50% indicates substantial heterogeneity and, above 75%, indicates considerable heterogeneity. The questioning about the

validity of combine results increases with greater heterogeneity. It was verified a heterogeneity of 0%, which represented a satisfactory result (Pereira & Galvão, 2014).

The results of the clinical effectiveness of ZY-4 in patients with AIDS pointed that the herbal medicine is better than placebo in enhancing $CD4^+$ lymphocytes levels, besides reducing HIV viral load, increasing body mass, and the improving the symptoms. The use of other anti-HIV drugs was not allowed during the clinical trial; however, the treatment of opportunistic infections was allowed on patients (Wang et al. 2006).

On the other hand, the results from the clinical trial with *S. frutescens* were not as good, since the herbal medicine did not induce a decrease in viral load neither an increase on lymphocyte levels. The parameters analyzed during the investigation were similar to the negative control during the whole interval of treatment. In addition, two cases of tuberculosis in individuals with Isoniazid preventive therapy (IPT), induced an increase in the mean load and total of infection in patients taking on *S. frutescens* (Wilson et al. 2015).

Therefore, drug interactions between *S. frutescens* and Isoniazid require additional studies. Adherence to treatment of tuberculosis (TB) and HIV/AIDS is of important for infection control, in view that, even considering them as chronic infections, the treatment of tuberculosis lasts six to nine months, depending on the type of TB, while HIV/AIDS treatment lasts the whole life (Unaids 2015). The coinfection HIV/TB results in mortality rates higher than infection of HIV alone (Vilela et al. 2017; Lemos et al. 2012).

This study had several limitations. HIV-positive symptomatic adults were included in a single place in KwaZulu-Natal. The inclusion of participants with a more advanced HIV infection may have altered the results of the study in unpredictable ways. However, known interactions between *S. frutescens* and antiretroviral drugs prevented their inclusion on this study (Wilson et al. 2015; Mills et al. 2005; Minocha et al. 2011).

Most participants of this study were women. This gender bias for inclusion in clinical studies is a limiting factor, yet it has been observed in several other contexts. In addition, different forms of preparing *S. frutescens* for consume may alter the chemistry and the availability of any bioactive compounds (Wilson et al. 2015).

The small number of included randomized clinical trials on this study may have influenced on the absence of statistical significant differences between intervention groups using herbal medicines and placebo.

4. Final Considerations

The data selected to comprise this meta-analysis may be influenced by publication bias which is a trend to publish results that are systematically different from reality. The non-publication of results might be explained by a decision from the author or the research financier to not submit unfavorable findings for publication; or the editors of scientific journals that might not be interested in publishing results without statistical significance.

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