



# Potential plants for inflammatory dysfunction in the SARS-CoV-2 infection

Diorge Jônatas Marmitt<sup>1</sup>

Received: 31 January 2022 / Accepted: 21 March 2022 / Published online: 7 April 2022  
© The Author(s), under exclusive licence to Springer Nature Switzerland AG 2022

## Abstract

The inflammatory process is a biological response of the organism to remove injurious stimuli and initiate homeostasis. It has been recognized as a key player in the most severe forms of SARS-CoV-2, characterized by significantly increased pro-inflammatory cytokine levels, the so-called "cytokine storm" that appears to play a pivotal role in this disease. Therefore, the aim of this systematic review was to select clinical trials with anti-inflammatory plants and relate the activity of these plants to inflammatory markers of SARS-CoV-2 infection. PRISMA guidelines are followed, and studies of interest are indexed in PubMed and ClinicalTrials.gov databases. As a result, 32 clinical trials encompassing 22 plants were selected. The main anti-inflammatory mechanisms described in the studies are the inhibition of inflammatory cytokines, such as IL-6, TNF- $\alpha$ , IFN- $\gamma$ , and IL-1; decreased CRP and oxidative marker levels; increased endogenous antioxidant levels; modulation of cardiovascular risk markers. The data found are not directly related to SARS-CoV-2 infection. However, they provide possibilities for new studies as plants have a wide array of phytochemicals, and detecting which ones are responsible for anti-inflammatory effects can provide invaluable contribution to studies aiming to evaluate efficacy in scenarios of SARS-CoV-2 infection.

**Keywords** Inflammation · SARS-CoV-2 · Plants · Therapeutic effects

## Introduction

When the immune system responds to harmful stimuli, such as damaged cells, pathogens, irradiation, and toxic compounds, it triggers the inflammatory process, which acts to restore cell homeostasis. It is an essential defence mechanism for the health (Chen et al. 2018). In general, cellular and molecular interactions effectively minimize any impending injury or infection during acute inflammatory responses. Nevertheless, acute inflammation might become chronic when it is uncontrolled, and it is involved in the pathogenesis of a variety of chronic diseases, such as cardiovascular diseases (CVDs) and cancer (Medzhitov 2010).

Studies indicate that pulmonary inflammatory dysfunction is likely a leading cause of lethality in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection, which induces acute lung injury, mostly from the aggressive

inflammation initiated by viral replication. Hence, SARS-CoV-2 infection induces increased secretion of interleukin-6 (IL-6), tumour necrosis factor- $\alpha$  (TNF- $\alpha$ ), interleukin-1 $\beta$  (IL-1 $\beta$ ), Interferon-gamma (IFN- $\gamma$ ), interleukin-8 (IL-8), interferon- $\gamma$ -inducible protein 10 (IP-10), Monocyte chemoattractant protein-1 (MCP-1), interleukin-4 (IL-4), and interleukin-10 (IL-10), resulting in a potential cytokine storm associated with disease severity, manifested clinically by severe acute respiratory distress syndrome (SARDS) and systemic consequences, such as disseminated intravascular coagulation (Fu et al. 2020).

Therefore, exacerbated inflammation causes multi-organ damage, particularly in the hepatic, cardiac, and renal systems. Aside from direct damages resulting from the virus, uncontrolled inflammatory cell infiltration ultimately leads to damage to the lung via the excessive secretion of reactive oxygen species (ROS) and proteases (Tay et al. 2020). Together, they result in diffuse alveolar damage, including hyaline membrane formation, desquamation of alveolar cells, and pulmonary oedema. This scenario decreases the effective gas exchange in the lung, causing difficulty in breathing and low blood oxygen levels. Moreover, the lung becomes more vulnerable to other infections (Xu et al. 2020a).

✉ Diorge Jônatas Marmitt  
diorgemarmitt@yahoo.com.br

<sup>1</sup> Programa de Pós-Graduação em Biotecnologia,  
Universidade Do Vale Do Taquari - Univates, Avelino Talini  
Street, 171, Lajeado, RS 95914-014, Brazil

Considering how aggressive this disease is, new therapeutic options are required along with the vaccines that have already been developed, mainly to prevent or mitigate the damage induced by inflammatory dysfunction. During the early pandemic, the previous use of non-steroidal anti-inflammatory drugs (NSAIDs) was suggested as a factor that could lead to disease severity in SARS-CoV-2 infection (Little 2020). However, new studies have shown that the use of NSAID is not associated with higher mortality or increased severity (Drake et al. 2021). A great number of NSAIDs are produced from plants, such as acetylsalicylic acid (Aspirin®) (Reis Nunes et al. 2020). Thus, medicinal plants arise as an important source of studies in the search for new therapeutic options (Marmitt et al. 2021a). South America has one of the most abundant flora, and the therapeutic potential contained here is immeasurable (Barlow et al. 2018). A survey published in 2017 on the diversity of vascular plants in the Americas shows that there are 124,993 species, 6227 genera, and 355 families, which correspond to 33% of the 383,671 vascular plant species already identified worldwide. Differences in relief, climate, and altitude help to explain this diversity, and most of these species have several therapeutic applications, some already analysed and characterized. Nevertheless, there still is scope for further research (Ulloa Ulloa et al. 2017).

The increased use of medicinal plants has cultural, economic, and therapeutic reasons (Ekor 2013). However, only a small portion of these plants has undergone thorough scientific analyses to prove their pharmacological effects. The actual number of plants native to South America that are used to treat inflammations is rather unknown. However, the knowledge that plants can be used to treat inflammations has led to an increase in experimental and clinical investigations designed to analyse anti-inflammatory properties (French et al. 2017). This is important because pharmacological treatments have some disadvantages, including drug resistance (reduction in efficiency), side effects, and even toxicity (Bindu et al. 2020; Fendrick and Greenberg 2009). Thus, new studies are required so that efficacy and safety are ensured, as they are in clinical trials. Therefore, the present study aimed to select South American plants in clinical trials with anti-inflammatory properties, and relate them to the hyper-inflammation of SARS-CoV-2, analysing the potential mechanism these plants have for inhibiting/decreasing inflammatory markers.

## Methodology

### Search strategy

This systematic review focused on clinical trials analysing South American plants with anti-inflammatory properties.

All open access texts published up to May 2021 were considered, regardless of language. The studies of interest are indexed in two important electronic databases, PubMed and the ClinicalTrials.gov portal. Since there were numerous manuscripts on inflammation and plants, the search focused on clinical trials.

### Stages of study

Data analysis and interpretation were based on the same key items that guided the method; these items are described in Tables 1 and 2. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline was followed in the design of this systematic review. The flowchart in Fig. 1 shows the study stages.

In the first stage, the keywords used to search the PubMed database were the scientific names of native South American plants, following the National Relation of Medicinal Plants of Interest to the Unified Health System (RENISUS) of Brazil (Marmitt et al. 2021b; Marmitt and Shahrajabian 2021) and the books: Medicinal and Aromatic plants of South America Vol. 1 and 2 (Albuquerque et al. 2018; Máthé and Bandoni 2021), Medicinal Plants of Latin America (Duke 2008), and Pharmacological Properties of Native Plants from Argentina (Alvarez 2019). Additionally, terms such as 'inflammation', 'inflammatory bowel diseases', 'inflammatory rheumatism', 'inflammatory arthritis', and 'inflammatory myopathy' were used, as well as 'clinical trials'. A wide array of studies were found through these terms but only the clinical trials (Clinical Trial Phase I, II, III, IV; Clinical Study; Clinical Trial Protocol; Randomized Controlled Trial; Controlled Clinical Trial) were selected. To refine the search for more specific results in the ClinicalTrials.gov portal, an advanced search was performed using the following filters: Condition or disease (oxidative stress; oxygen radical damage; free radical oxidation of tissue); other terms (scientific name of native South American plants); Study Results (Study with Results); Status: Recruitment (Active, not recruiting; Terminated; Completed). Plant names were checked using The Plant List (TPL). The second stage was to analyse the clinical trials through their abstracts. The third and last stage consisted of analysing the clinical trials by reading their full texts.

### Inclusion and exclusion criteria

Inclusion criteria were as follows: clinical trials (stage one); anti-inflammatory effects of plants (stage two); and therapeutic evidence (positive results over placebo) in clinical trials with methods or formulations using plants (stage three). In vitro and in vivo studies, comments, reviews, semi-structured interviews, conferences, letters, guidance articles, and studies that only mentioned the empirical use of plants were

**Table 1** Overview of clinical inflammatory studies published on PubMed or ClinicalTrials.gov with native South American plants with completed/terminated status

Part of the plant/compound and concentration	Main results	Intervention/identifier number
<p><i>Acmella oleracea</i> (L.) R. K. Jansen — Compositae (Amazon) 350 mg of the lecithin-based formulation of <i>Zingiber officinale</i> Roscoe (37.5 mg) and <i>A. oleracea</i> (7.5 mg) standardized extracts for 4 weeks with two tablets/day</p>	<p>Fifty subjects with moderate knee osteoarthritis (OA) (mean age: 62.46), treatment decreased WOMAC levels (baseline: 44.31 ± 15.28; 30 days: 38.14 ± 15.19), C-reactive protein (CRP) (mg/L) (baseline: 0.33 ± 0.65; 30 days: 0.21 ± 0.47), Visual Analogue Scale (VAS) of Pain (baseline right knee: 4.4; 30 days right knee: 2.7) (baseline left knee: 4.37; 30 days left knee: 2.6)</p>	<p>Clinical trial NCT03907787 (Rondanelli et al. 2020)</p>
<p><i>Aloysia citriodora</i> Palau — Verbenaceae (Chile and Brazil) 400 mg lemon verbena extract (Recoverben®) once daily or placebo</p>	<p>In forty-four healthy males and females, which were 22–50 years old and active in sports, after 48 h of analysis, Glutathione Peroxidase (GPx) was increased levels (extract: 0.204; Placebo: 0.5895 U/L), Creatine kinase (CK) decreased levels (extract: 0.94; Placebo: 1.88 U/L), and IL-6 (differences between groups <math>p = 0.5824</math>)</p>	<p>Randomized, placebo-controlled, double-blind study (NCT02923102) (Buchwald-Werner et al. 2018)</p>
<p><i>Bertholletia excelsa</i> Bonpl. — Lecythidaceae (Amazon) Supplementation of 1 unit of Brazil nut (0.75 g of protein, 0.45 g of carbohydrates, and 3.53 g of lipids, for a total of 36.7 kcal and 290.5 µg of selenium) a day, during 3 months</p>	<p>In Forty maintenance hemodialysis (HD) patients, was increased oxidative markers levels (GPx before: 33.6 ± 5.1; after: 40.0 ± 8.5 nmol/mL/min), inflammatory (interleukin 6 (IL-6) before: 64.8 ± 10.6; after: 14.0 ± 1.6 pg/mL; tumor necrosis factor alpha (TNF-α) before: 21.0 ± 0.3; after: 14.3 ± 8.8 pg/mL), and in the lipid profile (high-density lipoprotein cholesterol (HDL-c) before: 38.5 ± 15.4; after: 46.6 ± 15.1 mg/dL; Low-density lipoprotein cholesterol (LDL-c) before: 86.5 ± 28.3; after: 75.2 ± 30.2 mg/dL; total cholesterol (TC) before: 149.5 ± 31.5; after: 154.0 ± 63.1 mg/dL) suggesting that the consumption of Brazil nut was effective to reduce the inflammation, thereby increasing the antioxidant defenses in HD patients</p>	<p>Clinical Trial (Stockler-Pinto et al. 2014)</p>
<p><i>B. excelsa</i> Brazil nuts: 0, 5, 20 and 50 g/day during 30 days</p>	<p>In 10 healthy individuals (mean age 24.7 ± 3.4 y), tested four times regarding intake of different portions of Brazil nuts, consumption of a single intake of Brazil nuts (20 or 50 g) caused a significant decrease in serum IL-1 (baseline: 130; after: 115 pg/mL), IL-6 (baseline: 135; after: 123 pg/mL), TNF-α (baseline: 147; after: 132 pg/mL), and Interferon-gamma (IFN-γ) levels (baseline: 145; after: 132 pg/mL), whereas serum levels of IL-10 were significantly increased (baseline: 55; after: 80 pg/mL), showing the long-term effect of regular Brazil nut consumption on inflammatory markers should be better investigated</p>	<p>Randomized crossover study (Colpo et al. 2014)</p>

Table 1 (continued)

Part of the plant/compound and concentration	Main results	Intervention/identifier number
<i>Campomanesia xanthocarpa</i> Berg. — Myrtaceae (Brazil) 500 mg (CX 500), 750 mg (CX 750) or 1000 mg (CX 1000) of encapsulated <i>C. xanthocarpa</i> , for 90 days	A total of 156 individuals were divided into two groups: individuals with TC levels between 200 and 240 mg/dL (undesirable level individuals — UL) and individuals with TC levels > 240 mg/dL (hypercholesterolemic individuals — HL). A decrease in LDL levels was observed in HL individuals from the CX 500 group (reduction of 41 ± 5% to levels before treatment) compared to Placebo. Also, a significant reduction in oxidative stress and inflammatory process components (reduction of 52 ± 11% in advanced oxidation protein products (AOPPs), 32 ± 10% in ischemia-modified albumin (IMA), and 57 ± 7% in hs-CRP) was observed in HL individuals in the CX 1000 group when compared to Placebo group	Randomized, placebo-controlled, double-blind study (Viecelli et al. 2014)
<i>Carica papaya</i> L. — Caricaceae (Amazon) Supplementation of 6 g Fermented papaya preparation (FPP®)/day for a period of 14 weeks	CRP levels (mg/L) significantly decreased with supplementation of FPP® (baseline: 1.519 ± 1.115; after: 1.317 ± 0.715), uric acid (mg/dL) (baseline: 6.654 ± 1.472; after: 6.525 ± 1.315), and LDL/HDL ratio was considerably changed (baseline: 2.923 ± 0.906; after: 2.829 ± 0.663) decreasing risk for diseases worsened by overt inflammation and oxidative stress	Randomized controlled clinical trial (Somanah et al. 2012)
<i>C. papaya</i> - Patients were orally supplemented 9 g (3 g/dose, 3 doses/day) with FPP daily	In 19 patients, wound closure in FPP-supplemented patients, compared with standard of care (SoC) showed improvement (wound volume %) (SoC: 82; FPP: 45), by increased NADPH oxidase (NOX) activity in immune cells at the wound site (fold change) (SoC: 0.8; FPP: 1.6) after 2 weeks of supplementation	Clinical Trial (NCT02332993) (Das et al. 2018)
<i>Caryocar brasiliense</i> A.St.-Hil. — Caryocaraceae (Brazil) 400 mg <i>C. brasiliense</i> oil capsules for 14 days	Capsules ingestion decreases high-sensitivity C-reactive protein (hs-CRP) levels (Before: 1.59 ± 0.21; after: 1.55 ± 0.17 mg/dL), TC (Before: 187.78 ± 3.53; after: 187.29 ± 3.22 mg/dL), LDL (Before: 110.82 ± 2.94; after: 108.7 ± 2.64 mg/dL), Thiobarbituric acid reactive substances (TBARS) (Before: 0.0267 ± 0.001; after: 0.0264 ± 0.001 nmol/mL of malondialdehyde — MDA), hypothesizing that pequi oil could reduce exercise-induced inflammation and blood pressure	Clinical Trial (Miranda-Vilela et al. 2009)

**Table 1** (continued)

Part of the plant/compound and concentration	Main results	Intervention/identifier number
<i>Euterpe edulis</i> Mart. — Arecaceae (Brazil) 5 g juçara freeze-dried pulp for 6 weeks	Twenty-seven obese participants (BMI between 30.0 and 39.9 kg/m <sup>2</sup> ) of both genders from 31 to 59-year-old, post-treatment, <i>E. edulis</i> reduced Toll-like receptor 4 (TLR4) (Placebo: 1.5; <i>E. edulis</i> : 0.5), and IL-6 (Placebo: 0.5; <i>E. edulis</i> : 0.1) mRNA. IL-6 (Placebo: + 310%; <i>E. edulis</i> : -290%), TNF- $\alpha$ (Placebo: -190%; <i>E. edulis</i> : -540%), and Monocyte chemoattractant protein 1 (MCP-1) (Placebo: + 80%; <i>E. edulis</i> : -20%) production by monocytes were reduced and IL-10 levels increased (Placebo: + 220%; <i>E. edulis</i> : + 240%) in post-treatment compared to pre-treatment levels	Placebo-controlled, randomized double-blind trial (Santamarina et al. 2020)
<i>Euterpe oleracea</i> Mart. — Arecaceae (Suriname) Açai-beverage in 37 individuals with metabolic syndrome who were randomized to consume 325 mL twice per day for 12 weeks	Consumption of açai-beverage induce hs-CRP decreased levels (Baseline: 2.60; Week 12: 2.22 mg/L), TNF- $\alpha$ (Baseline: 26.56; Week 12: 23.16 pg/mL), and IFN- $\gamma$ (Baseline: 13.99; Week 12: 3.33 pg/mL). The selected dose of açai polyphenols may be beneficial in metabolic syndrome	Randomized Controlled Trial (Kim et al. 2018)
<i>Ilex paraguariensis</i> A.St.-Hil. — Aquifoliaceae (Argentina, Paraguay, Brazil) Drink 200 ml of water (control) and, in the second phase, they consumed 200 ml of soluble mate tea (SMT), was taken three times per day (morning, afternoon, and night) for 7 days	In nine men that SMT ingestion, subjects' plasma levels of hs-CRP were below 1.35 mg/l (range: 0.17—1.31 mg/L), suggesting no subclinical inflammation. The expression of p47 <sup>phox</sup> protein in CD16b/CD14 cells decreased 22% (p=030) in SMT treatment. Serum TNF- $\alpha$ and IL-6 levels were 56% and 52% lower in SMT than in control, respectively. Plasma total phenols increased 30% (p=004) after SMT consumption. Blood glutathione (GSH) was 16.5% higher in SMT than in the control treatment. SMT ingestion favorably affected inflammatory cytokine and antioxidants levels in peripheral blood, which may help decrease oxidative stress and low-grade inflammation	Controlled Clinical Trial (Panza et al. 2019)
<i>I. paraguariensis</i> 3 g of a preparation containing soluble yerba mate plus maltodextrin and artificial peach flavor, corresponding to 107 mg/g total phenols, or mate-placebo for 15 days each, alternating by a washout period of 15 days	In 92 individuals on antiretroviral therapy for at least six months and at viral suppression, mean values of HDL-c (mg/dL) at baseline and after receiving yerba mate and placebo mate were 50.6 $\pm$ 15, 50.3 $\pm$ 14.6, respectively. Fibrinogen levels were within the normal range in 71.7% of the subjects. Leukocyte, neutrophil, lymphocyte, and monocyte counts were within the normal range in most subjects (87%, 92.4%, 97.8%, and 95.7%, respectively)	Cross-over, placebo-controlled, double-blind, randomized clinical trial (Petrilli et al. 2016)
<i>Manihot esculenta</i> Cramtz — Euphorbiaceae (South America) Daily, 6 days/week, for 18.5 weeks, provitamin A-rich cassava (mean content: 1460 $\mu$ g $\beta$ -carotene/day)	In 342 children aged 5–13 y that receive provitamin A-rich cassava, CRP concentration decreased (Control: 3.7; Yellow cassava: 2.7 mg/L). Consumption of yellow cassava increased serum $\beta$ -carotene concentration by 524% and led to modest gains in serum retinol concentrations	Randomized Controlled Trial (NCT01614483) (Talsma et al. 2016)

Table 1 (continued)

Part of the plant/compound and concentration	Main results	Intervention/identifier number
<i>Myrciaria dubia</i> (Kunth) McVaugh — Myrtaceae (Amazon) Daily 70 ml of 100% camu-camu juice, corresponding to 1050 mg of vitamin C (camu-camu group; n = 10) for 7 days	In 20 male smoking volunteers, considered to have an accelerated oxidative stress state, oxidative stress markers such as the levels of urinary 8-hydroxy-deoxyguanosine (8-OHdG) (9.0 to 7.0 ng/mg) and total reactive oxygen species (ROS) (128 to 123 Unit) and inflammatory markers such as serum levels of hs-CRP (0.05 to 0.02 mg/dL), interleukin IL-6 (6.0 to 5.1 pg/mL), and IL-8 (24.8 to 22.4 pg/mL) decreased significantly in the camu-camu group, suggesting that camu-camu juice may have powerful anti-oxidative and anti-inflammatory properties, that may be due to the existence of unknown anti-oxidant substances besides vitamin C	Randomized Controlled Trial (Inoue et al. 2008)
<i>Miconia albicans</i> (Sw.) Steud. — Melastomataceae (tropical and temperate regions of South America) <i>M. albicans</i> (1000 mg/day) was applied orally for 30 days	In Twenty-four osteoarthritis patients, means of Osteoarthritis Index Total (WOMAC) for <i>M. albicans</i> presented a statistically significant difference (mean day 0 = 57.19; mean day 30 = 31.02), demonstrating the analgesic and anti-inflammatory effect on knee osteoarthritis from <i>M. albicans</i>	Clinical Trial (Gomes et al. 2021)
<i>Passiflora edulis</i> Sims — Passifloraceae (Brazil) Piceatannol compound from <i>P. edulis</i> , (20 mg/day) for eight weeks	On 39 subjects, including 10 overweight men and 9 overweight women (BMI $\geq 25$ ), as well as 10 non-overweight men and 10 non-overweight women (BMI < 25), piceatannol in women decreased hs-CRP levels (ng/mL) (Start: 212.6 $\pm$ 233.1; 8 week: 117.6 $\pm$ 56.9), IL-6 (Start: 1.50 $\pm$ 0.41; 8 week: 1.32 $\pm$ 0.38), diacron reactive oxygen metabolite (dROM) (U. Carr) (Start: 354.2 $\pm$ 37.8; 8 week: 308.6 $\pm$ 30.7), biological antioxidant potential (BAP) (Start: 486.8 $\pm$ 182.9; 8 week: 2120.0 $\pm$ 207.7), and in men decreased Flow Mediated Dilatation (FMD) (%) (Start: 6.6 $\pm$ 4.8; 8 week: 8.4 $\pm$ 2.7). Supplementation can improve metabolic health	Randomized, Placebo, Controlled Trial (Kitada et al. 2017)
<i>Persea americana</i> Mill. — Lauraceae (South America) Avocado diet include 1 Hass avocado (~136 g) per day, for 5 weeks	With 45 subjects, aged 21–70 y, with overweight or obesity and elevated LDL-c (25th–90th percentile), compared with baseline, avocado significantly decreased circulating oxidized LDL (oxLDL) (Baseline: 65.8 $\pm$ 2.4; 5 weeks: 58.0 $\pm$ 2.1) and increased plasma lutein concentration (19.6 nmol/L, + 68.7%) decreasing susceptible biomarkers levels to in vivo oxidation and associated with increased risk of cardiovascular disease (CVD)	Randomized, crossover, controlled feeding trial (NCT01235832) (Wang et al. 2020a, b)

Table 1 (continued)

Part of the plant/compound and concentration	Main results	Intervention/identifier number
<i>P. americana</i> 250 g hamburger patty alone (ca. 436 cal and 25 g fat) or together with 68 g of avocado flesh (an additional 114 cal and 11 g of fat for a total of 550 cal and 36 g fat)	Eleven healthy subjects, in peripheral blood mononuclear cells, isolated from postprandial blood samples, the Ikappa-B alpha (IkB $\alpha$ ) protein concentration show was a significant preservation of IkB $\alpha$ (131% vs. 58%) when avocado was consumed with the meat compared to meat alone, showing reduced activation of the NF-kappa B (NF $\kappa$ B) inflammatory pathway. IL-6 levels increased significantly after consumption of the hamburger, but no change was observed when avocado was added. Results suggest beneficial anti-inflammatory and vascular health effects	Randomized Controlled Trial (NCT01397071) (Li et al. 2013)
<i>Phyllanthus amarus</i> Schumacher & Thonn. — Phyllanthaceae (Amazon) Standardized ethanol extract of <i>P. amarus</i> leaves (PHYLL-PRO™), ten days daily oral supplementation of 750 mg/day followed by intoxication	In 15 subjects (21–50 years old) after alcohol intoxication, PHYLLPRO decreased inflammatory cytokine levels, TNF- $\alpha$ (Placebo: $5.30 \pm 1.16$ ; treatment: $5.16 \pm 1.68$ pg/mL), IFN- $\gamma$ (Placebo: $6.18 \pm 2.32$ ; treatment: $5.78 \pm 1.9$ pg/mL) and Vascular endothelial growth factor (VEGF) (Placebo: $62.12 \pm 37.67$ ; treatment: $54.89 \pm 29.34$ pg/mL)	Randomized Controlled Trial (George et al. 2019)
<i>P. amarus</i> Treatment group received <i>P. amarus</i> (15 cases) from pharmacologist preparation, once daily for 10 sessions, by ultrasound therapy	In 30 subjects with mild-to-moderate degree of OA, decreased TNF- $\alpha$ levels (pg/mL) (Control: 65; <i>P. amarus</i> : 55), Nitric oxide (NO) (nmol/ $\mu$ L) (Control: 110; <i>P. amarus</i> : 90) besides increased levels of superoxide dismutase (SOD) (inhibitory rate%) (Control: 40; <i>P. amarus</i> : 65), and total antioxidant capacity (TAC) (nmol/ $\mu$ L) (Control: 4.5; <i>P. amarus</i> : 6.5), significantly reducing anti-inflammatory effects in OA patients	Randomized, double-blind, placebo-control, parallel-group, clinical trial (Decha et al. 2019)
<i>Phyllanthus niruri</i> L. — Phyllanthaceae (Amazon) <i>Nigella sativa</i> L. and <i>P. niruri</i> extract (NSPN extract) capsules containing 360 mg <i>N. sativa</i> and 50 mg <i>P. niruri</i> extracts, were orally administered 3 times, 1 capsule daily for 7 days	With 186 patients analyzed, NSPN reduced pharyngitis score (mean) (Placebo: 3.6; NSPN: 3.5), sore throat pain intensity scale (STPIS) (mean) (Placebo: 71.84; NSPN: 70.73), pain rating (%) (Placebo: 64; NSPN: 60), change in difficulty in swallowing scale (CDSS) (%) (Placebo: 48; NSPN: 37), showing a significantly greater proportion of patients in the NSPN group than in the placebo group had their sore throat completely relieved	Comparative, parallel, randomized, double-blind, placebo-controlled study (Dirjomuljono et al. 2008)
<i>Plukenetia volubilis</i> L. — Euphorbiaceae (Peru) 15 mL of commercial oil seeds of <i>P. volubilis</i> (998 cal, 65% from fats—SFA 30%, MUFA 20%, PUFA 15%). Were randomly assigned to a sequence of two test meals on two separate days with a 2 weeks washout period	Twenty metabolically healthy (MH) and 22 metabolically unhealthy (MU) subjects, the addition of <i>P. volubilis</i> seeds attenuated the LPS increase produced by High-fat meal (HFM) intake (HFM: 1.15 EU/mL; <i>P. volubilis</i> : 1.04 EU/mL) and <i>P. volubilis</i> seeds were associated with IL-6 decrease in serum (HFM: 1.4 pg/mL; <i>P. volubilis</i> : 0.8 pg/mL)	Randomized, crossover clinical trial (Alayón et al. 2019)

Table 1 (continued)

Part of the plant/compound and concentration	Main results	Intervention/identifier number
<i>Psidium guajava</i> L. — Myrtaceae (South America) 200 g guava ingestion, in 14 days pre-experimental period with oral hygiene instructions, scaling, prophylaxis and supplementation	Study with 16 students, Plaque Index (PI) the guava group developed significantly less plaque compared to the control group (Guava: 1.30; Control: 1.79). Similarly, Gingival Index (GI) increase was significantly less than the increase in the control group (Guava: 0.10; Control: 0.87), showed a preventive effect on the development of experimental gingivitis	Randomized Controlled Trial (Amaliya et al. 2018)
<i>Smallanthus sonchifolius</i> (Poepp.) H. Rob. — Compositae (Andes) Daily intake of 150 mL of synbiotic beverage (soy extract and <i>S. sonchifolius</i> , containing <i>Bifidobacterium animalis</i> ssp. lactis BB-12)	In twenty-nine volunteers (over 65 years age), for 8 weeks: a prefeeding period (2 weeks), followed by a feeding period (4 weeks) and a postfeeding period (2 weeks), synbiotic beverage decreased IL-6 concentrations (synbiotic: 518.32 ± 157.98; Placebo: 564.38 ± 220.35 pg/mL), and increased anti-inflammatory interleukin-10 (IL-10) (Synbiotic: 121.42 ± 44.87; Placebo: 56.47 ± 11.41)	Randomized, double-blinded, placebo-controlled trial (Manzoni et al. 2017)
<i>Solanum tuberosum</i> L. Solanaceae — (Andes) 150 g of cooked white (WP), yellow (YP), or purple-flesh potatoes (PP) once per day for 6 weeks	Twelve free-living healthy men (18–40 y), 8-OHdG concentrations in the YP (30.3 ± 2.4 mg/L) and PP (26.0 ± 1.5 mg/L) groups were lower than in the WP group (38.0 ± 2.3 mg/L). Plasma CRP concentrations in the PP group were 57% lower than in the YP group at week 6. Concentrations of plasma IL-6 in the YP and PP groups were lower compared with the WP group (at week six) (YP: 18; PP: 18; WP: 33 ng/L)	Randomized Controlled Trial (Kaspar et al. 2011)
<i>S. tuberosum</i> Yellow potatoes with or without purple potato extract (PPE) rich in acylated anthocyanins (152 mg) and other phenolics (140 mg)	In 17 healthy male volunteers, PPE affected some inflammation markers after the meal; for example, fibroblast growth factor 19 (FGF-19) levels were elevated at 240 min (0 min: 2.13; 240 min: 3.74), besides of C-C motif chemokine 20 (CCL20, p < 0.001). Results suggest PPE affects postprandial inflammation	Randomized cross-over trial (Jokioja et al. 2020)
<i>Uncaria guianensis</i> (Aubl.) J.F. Gmel. — Rubiaceae (Amazon) Group (n = 30) received 100 mg of freeze-dried cat's claw (1 capsule of 100 mg daily) four-week trial	For thirty patients with OA, pain score for <i>U. guianensis</i> treatment was lower when compared to placebo (Placebo: 6; <i>U. guianensis</i> : 3.5), the better score of disease activity (Placebo: 3; <i>U. guianensis</i> : 2), decrease the measure of pain (Placebo: 4.17 ± 0.69; <i>U. guianensis</i> : 3.06 ± 0.37), besides show anti-TNF-α activities (73%; EC <sub>50</sub> : 10.9 ng/mL)	Clinical Trial (Piscoya et al. 2001)
<i>Theobroma cacao</i> L. — Malvaceae (South America) Cocoa (13 g/unit; 1 g cocoa/unit, 6 units/d; 465 kcal/d) added to a low saturated fat diet for 4 weeks	One hundred and thirteen volunteers (age range: 43–65 years) who were pre-hypertensive, stage-1 hypertensive, and hypercholesterolemic received the cocoa cream product. Compared to control, cocoa reduced LDL-c by 11.2%, Apolipoprotein B (ApoB) by 8.1%, and ApoB/ApoA ratio by 7.8%, decreased hs-CRP by 33.4% and oxidized LDL (oxLDL) by 5.9%, showing anti-inflammatory and antioxidant effects	Multi-centered, randomized, controlled, double-blind, parallel trial (NCT00511420) (Solà et al. 2012)



**Table 1** (continued)

Part of the plant/compound and concentration	Main results	Intervention/identifier number
<i>T. cacao</i> Twenty adults consumed a controlled diet for 5 days along with four cocoa beverages containing 30–900 mg flavanol per day	The cocoa flavanols significantly affected the biomarkers of oxidative stress and inflammation, such total 8-isoprostane (Placebo: 5.3; Cocoa: 4.8 pg/mL), CRP (Placebo: 6.3; Cocoa: 5.6 mg/L), Fibrinogen (Placebo: 436.1; Cocoa: 430.3 mg/dL), and IL-6 concentrations (Placebo: 2.2; Cocoa: 2.1 pg/mL)	Randomized crossover design (Stote et al. 2012)
<i>T. cacao</i> Natural cocoa-containing product (12.7 g natural cocoa, 148 kcal/serving) for 4 weeks, with a 2-week washout period between treatment	Twenty-four young (19–35 years) women of differing body mass indices, compared to placebo, following natural cocoa consumption, haptoglobin levels significantly declined by 18% in the obese group. Cocoa consumption, induced decreases in Elevated endothelial microparticles (EMPs) for obese (−31%) and overweight (−13%). Also, in the obese subjects found a 21% decrease in haptoglobin levels and a 20% decrease in proinflammatory monocyte adhesion molecule expression (CD62L)	Randomized Controlled Trial (McFarlin et al. 2015)
<i>T. cacao</i> 40 g cocoa powder with 500 mL skim milk/d (C+M) or only 500 mL skim milk/d (M) for 4 weeks	Forty-two high-risk volunteers (19 men and 23 women; mean ± SD age: 69.7 ± 11.5 y) cocoa powder reduced hs-CRP levels (mg/dL) (Baseline: 0.52; 4 weeks: 0.50), P-selectin (ng/mL) (Baseline: 255.02; 4 weeks: 235.39), Intercellular Adhesion Molecule 1 (ICAM-1) (ng/mL) (Baseline: 359.07; 4 weeks: 331.47), suggesting that the intake of cocoa polyphenols may modulate inflammatory mediators in patients at high risk of cardiovascular disease	Randomized crossover feeding trial (ISRCTN75176807) (Monagas et al. 2009)
<i>T. cacao</i> Consume 2 cups cocoa (960 mg) beverage on 2 separate post-prandial study days	Eighteen type 2 diabetes adults, after 6 h of intervention cocoa decreased postprandial serum levels of inflammatory cytokines, such IL-6 (pg/mL) (Placebo: 5.0 ± 2.6; Cocoa: 4.5 ± 1.3), IL-1β (pg/mL) (Placebo: 4.2 ± 0.6; Cocoa: 4.0 ± 0.4), IL-18 (pg/mL), (Placebo: 339 ± 15; Cocoa: 250 ± 9), besides Nitrite (μM) (Placebo: 13.8 ± 3.0; Cocoa: 12.2 ± 2.3)	Randomized cross-over controlled trial (NCT01886989) (Davis et al. 2020)

**Source:** Research data, 2021

**Table 2** Anti-inflammatory drugs with completed/terminated clinical trials in SARS-CoV-2 infection published in PubMed or *ClinicalTrials.gov* portal

Drug/mechanism of action	Primary details	Study identifier	Study phase
Anakinra® (IL-1 receptor antagonist)	The following were assessed in the studies with SARS-CoV-2 patients with biochemical signs of hyperinflammation at baseline or during follow-up: the effect of intervention on thrombotic markers (D-dimer), pneumonia, efficacy, and safety of early anti-inflammatory treatment. Anakinra improved overall survival and invasive ventilation-free survival and was well tolerated by patients with ARDS and decreased severe respiratory failure (SRF), and restored the pro-/anti-inflammatory balance	EU 2020-001739-28; NCT04330638; NCT04357366	Open-label multicenter randomized clinical trial (Vanasse et al. 2020); Clinical trial — Phase III (Maes et al. 2020); Observational Study (Bozzi et al. 2021; Franzetti et al. 2021); Controlled Clinical Trial (Kyriazopoulou et al. 2021; Pontali et al. 2021)
Aspirin® (Platelet aggregation inhibitor)	Aspirin was tested (alone or associated with other drugs) in mild or moderate cases of ARDS, pneumonia, COVID-19 patients with severe pneumonia-associated respiratory failure who underwent treatment with continuous positive airway pressure (CPAP), and SARS-CoV-2 patients on chronic treatment with anticoagulants or antiplatelet agents. Clinical evolution (survival and thromboembolic complications) was evaluated, as well as the use of adjuvant therapies compared to the control group. Treatment was associated with a significantly lower cumulative incidence of in-hospital death. In adults with cardiovascular diseases, low-dose aspirin medication (100 mg/day) was associated with a lower mortality risk compared to the control group	NCT04425863; NCT04757792; NCT04368377; NCT04518735; CTRI/2020/07/026791	Prospective Cohort (Carvallo, 2021); Retrospective multicenter study (Alkholy, 2021; Sant Pau, 2020; Meizlish et al. 2021); Clinical trial — Phase II (Flumignan et al. 2020); Open-label, randomized control trial (Ghati et al. 2020); Observational Study (Qiang et al. 2021)

Table 2 (continued)

Drug/mechanism of action	Primary details	Study identifier	Study phase
Baricitinib® (Janus kinase (JAK) inhibitor)	SARS-CoV-2 patients (515 were assigned to the treatment combined with Remdesivir) who received baricitinib 2 mg ( $\leq 14$ days) had a median recovery time of 7 days, compared with 8 days in the placebo group, and a clinical status 30% higher at day 15. Patients receiving high-flow oxygen or noninvasive ventilation at admission had a recovery time of 10 days of treatment while the control group (with placebo) had a recovery time of 18 days. The treatment group had a 28-day mortality of 5.1% while the placebo group had 7.8%. Severe adverse events were less frequent in the treatment group than in the placebo group (16.0% vs. 21.0%), as well as new infections (5.9% vs. 11.2%).	NCT04401579	Clinical trial — Phase III (Kalil et al. 2021)
Bevacizumab® (Monoclonal anti-vascular endothelial growth factor — VEGF antibody)	A study with 26 severe SARS-CoV-2 patients found that bevacizumab plus standard care markedly improved partial arterial oxygen pressure to fraction of inspiration O <sub>2</sub> ratio (PaO <sub>2</sub> /FiO <sub>2</sub> ) ratios at days 1 and 7. By day 28, 24 (92%) patients had improved their oxygen-support status, 17 (65%) patients had been discharged, none had worse oxygen-support status, and there were no deaths	NCT04275414	Single-arm trial (Pang et al. 2021)
Canakinumab® (Anti-IL-1 $\beta$ monoclonal antibody)	A total of 45 patients were randomized: 15 subjects received 600 mg of intravenous canakinumab (8 mg/kg if $\leq 40$ kg), 15 subjects received 300 mg of intravenous canakinumab (4 mg/kg if $\leq 40$ kg), and 15 patients received a placebo infusion. The aim was to demonstrate that early treatment with canakinumab prevents progressive heart and respiratory failure in SARS-CoV-2 patients	NCT04365153	Clinical trial — Phase II (Cremer, 2021a)

Table 2 (continued)

Drug/mechanism of action	Primary details	Study identifier	Study phase
Dexamethasone® (Corticosteroid)	Assays showed that clinical, radiological, and biochemical parameters improved in either hospitalized SARS-CoV-2 patients, or patients with established moderate-to-severe ARDS, after receiving treatment with steroids (methylprednisolone or dexamethasone). Mean ventilator-free days were 6.6 in dexamethasone patients during the first 28 days vs 4.0 ventilator-free days in the standard care group. Thirty-three patients (21.9%) in the dexamethasone group vs 43 (29.1%) in the standard care group experienced secondary infections. Forty-seven (31.1%) vs 42 (28.3%) needed insulin for glucose control, and 5 (3.3%) vs 9 (6.1%) experienced other serious adverse events	NCT04425863; NCT04603729; NCT04746430; NCT04325061; NCT04327401; NCT04654416	Prospective Cohort (Carvallo 2021; Pinzón 2020); Clinical trial — Phase III (Syeda 2020; Villar et al. 2020); Clinical trial — Phase IV (Kocks 2021; Tomazini et al. 2020)
Mavrilimumab® (Monoclonal antibody for granulocyte macrophage colony-stimulating factor receptor alpha (GM-CSFR $\alpha$ ))	In SARS-CoV-2 inpatients, 12 (57%) patients in the mavrilimumab group were alive and off supplemental oxygen therapy <i>versus</i> nine (47%) patients in the placebo group. There were no treatment-related deaths, and adverse events were similar between groups	NCT04399980	Clinical trial — phase II (Cremer et al. 2021)
Celecoxib® (Inhibitor of cyclooxygenases (COXs))	Thirty-seven SARS-CoV-2 cases received Celebrex as adjuvant (full dose: 0.2 g, <i>bid</i> ; half dose: 0.2 g, <i>qd</i> ) for 7–14 days. Remission rates in midterm were 100%, 82%, and 57% of the full dose, half dose, and control group, respectively, and the discharged rate was 100% at the Celebrex group. Treatment significantly reduced the PGE2 levels	NCT04757792; ChiCTR2000031630	Retrospective multicenter study (Alkholy 2021); Prospective clinical study (Hong et al. 2020)
Colchicine® (Downstream inhibition of inflammation)	Studies show that SARS-CoV-2 inpatients with mild, moderate, or severe pneumonia treated with colchicine have decreased peak high-sensitivity cardiac troponin values. CRP protein levels were the clinical primary endpoint rate. Mean event-free survival time, the median time for required supplemental oxygen, and median time of hospitalization were also lower in the colchicine group	NCT04527562; NCT04392141; NCT04654416; NCT04350320; NCT04326790; NCT04328480; NCT04322682; RBR-8jyhxx	Randomised, double-blinded, placebo-controlled clinical trial (Rahman 2020; Pinzón 2020; Lopes et al. 2021); Clinical trial — phase II (Mostafaie 2020; Deftereos et al. 2020); Clinical trial — Phase III (Figueroa et al. 2020; Mehta et al. 2020; Tardif 2020)

Table 2 (continued)

Drug/mechanism of action	Primary details	Study identifier	Study phase
Infliximab® (anti-TNF- $\alpha$ monoclonal antibody)	In infliximab-treated patients with inflammatory bowel disease and confirmed SARS-CoV-2 infection, seroconversion was observed in fewer infliximab-treated patients, and the magnitude of anti-SARS-CoV-2 reactivity was lower	ISRCTN45176516	Clinical trial (Kennedy et al. 2021)
Ixekizumab® (Immunoglobulin G subclass 4 (IgG4) monoclonal antibody)	A study analyzed SARS-CoV-2 patients aged 18–75 with increased Interleukin IL-6 levels. The primary outcome was a change in pulmonary severity score, analyzed on the 7th day, 14th day, or at discharge	ChiCTR2000030703	Open-label, randomized controlled pilot trial (Liu et al. 2020)
Naproxen® (Inhibitor of COXs)	Treatment with naproxen (250 mg twice and lansoprazole 30 mg daily to prevent stress-induced gastropathy) in addition to standard of care was compared to standard of care alone in terms of 30-day mortality analysis (30 participants). A study suggested that naproxen could combine a broad-spectrum antiviral activity with its well-known anti-inflammatory property, which could help reduce severe respiratory mortality associated with COVID-19	NCT04325633	Randomized parallel assignment (Adnet 2020)
Ruxolitinib® (JAK inhibitor)	The study assessed the efficacy and safety of ruxolitinib (5 mg tablets twice daily (b.i.d.) for 14 days) + standard-of-care (SoC) therapy, in SARS-CoV-2 patients aged $\geq$ 12 years	NCT04362137	Clinical trial — Phase III (Novartis Pharmaceuticals 2021)
Siltuximab® (IL-6 receptor antagonist)	The researchers tested the safety and efficacy of blocking IL-6 in SARS-CoV-2 patients with acute hypoxic respiratory failure and systemic cytokine release syndrome. The primary endpoint was time to clinical improvement, measured daily until day 28, discharge from the hospital, or death	NCT04330638	Clinical trial — Phase III (Maes et al. 2020)

Table 2 (continued)

Drug/mechanism of action	Primary details	Study identifier	Study phase
Tocilizumab® (IL-6 receptor antagonist)	Studies analyzed treatment with tocilizumab in adult SARS-CoV-2 inpatients with radiographic pulmonary infiltrates, fever, and CRP. The treatment caused fever resolution, and CRP decline consistent with IL-6 pathway abrogation, and decreased number of patients who required invasive ventilation. Median time to clinical recovery was shorter. Clinically presumed and/or cultured bacterial superinfections decreased. Moreo-ver, oxygenation and inflammatory biomarkers improved, with higher survival than expected. Treatment was associated with rapid improvement in clinical and laboratory hyperinflammation measures, and may be of value in prolonging survival in patients with severe COVID-19. Furthermore, it provides a novel strategy for treating COVID-19-in-duced cytokine release syndrome	NCT04331795; NCT04730323	Clinical trial — Phase II (Sirohbehn et al. 2021); Observational Study (Price et al. 2020; Tian et al. 2021; Chachar et al. 2021); Clinical Trial (Dastan et al. 2020)

Source: Research data, 2021

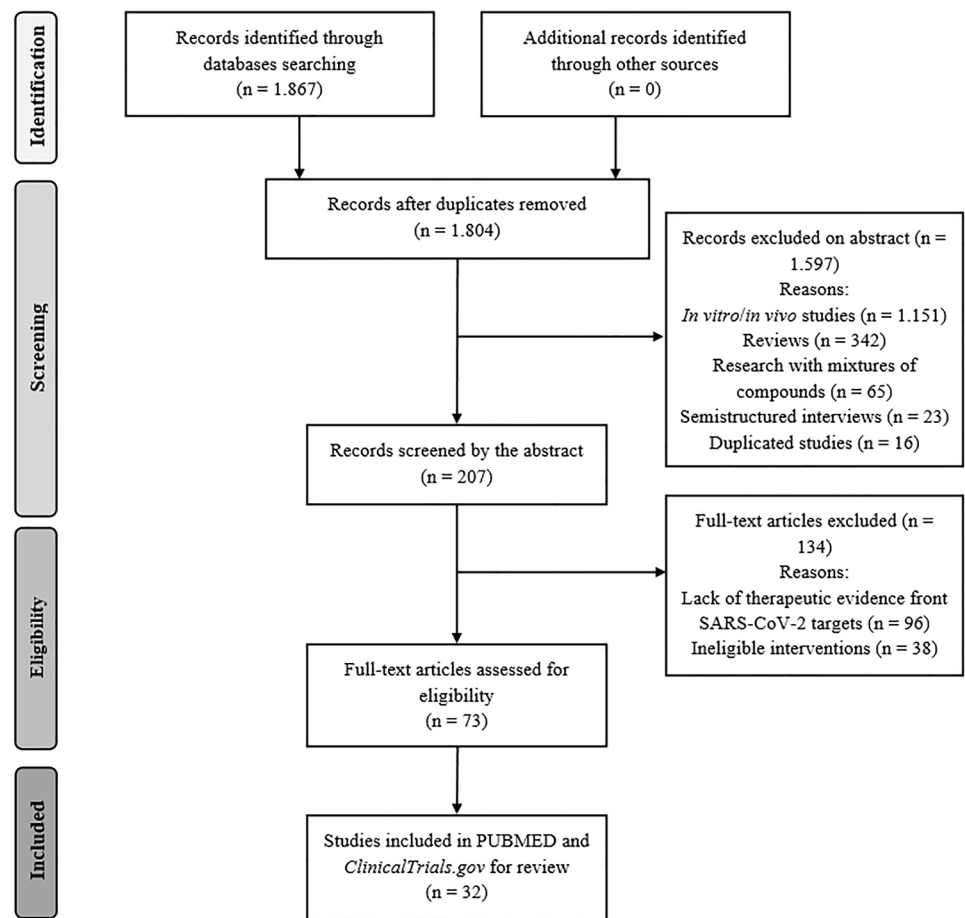
excluded. Duplicate studies and those that did not fall within the search scope have not been considered. Limitations of the study were risk of biases that may affect study evidence (e.g. publication bias, duplicated papers, and 'in vitro' and 'in vivo' studies, which were not considered); and limited results (restricted to two databases and limited by the presence or absence of the keywords used in the present study).

## Results

The results in Table 1 show South American plants studied in clinical trials concerning the inflammatory process. Thirty-two studies were found in the databases searched within the study scope, encompassing twenty-two native plants from different places in South America (Fig. 2).

Among the major anti-inflammatory mechanisms involved in clinical studies with selected plants, the following stand out: decrease in CRP levels (Rondanelli et al. 2020; Vicili et al. 2014; Somanah et al. 2012; Miranda-Vilela et al. 2009; Kim et al. 2018; Panza et al. 2019; Talsma et al. 2016; Inoue et al. 2008; Kitada et al. 2017; Kaspar et al. 2011; Solà et al. 2012; Stote et al. 2012; Monagas et al. 2009); cytokines and pro-inflammatory markers such as: IL-6 (Buchwald-Werner et al. 2018; Stockler-Pinto et al. 2014; Colpo et al. 2014; Santamarina et al. 2020; Panza et al. 2019; Kitada et al. 2017; Li et al. 2013; Alayón et al. 2019; Manzoni et al. 2017; Kaspar et al. 2011; Stote et al. 2012; Davis et al. 2020), TNF- $\alpha$  (Stockler-Pinto et al. 2014; Colpo et al. 2014; Santamarina et al. 2020; Kim et al. 2018; Panza et al. 2019; George et al. 2019; Decha et al. 2019; Piscocoya et al. 2001), IFN- $\gamma$  (Colpo et al. 2014; Kim et al. 2018; George et al. 2019), IL-1 (Colpo et al. 2014; Davis et al. 2020), IL-8 (Inoue et al. 2008), IL-18 (Davis et al. 2020), MCP-1 (Santamarina et al. 2020), ICAM-1 (Monagas et al. 2009); increased cytokine level and anti-inflammatory modulator IL-10 (Colpo et al. 2014; Santamarina et al. 2020; Manzoni et al. 2017) and FGF-19 (Jokioja et al. 2020); inhibition of NF- $\kappa$ B pathway (Li et al. 2013); decreased oxidative markers (TBARS, ROS, NO, 8-OHdG, dROM) (Miranda-Vilela et al. 2009; Inoue et al. 2008; Gomes et al. 2021; Kitada et al. 2017; Decha et al. 2019; Davis et al. 2020); increased levels of non-enzymatic antioxidants (GPx, GSH and SOD) (Buchwald-Werner et al. 2018; Stockler-Pinto et al. 2014; Panza et al. 2019; Decha et al. 2019); modulation of proteins associated with cholesterol (HDL-c, LDL-c, and ApoB) (Stockler-Pinto et al. 2014; Vicili et al. 2014; Somanah et al. 2012; Miranda-Vilela et al. 2009; Petrilli et al. 2016; Wang et al. 2020a; Solà et al. 2012); decreased cardiovascular risk markers such as FMD in the brachial artery (Kitada et al. 2017), fibrinogen (Petrilli et al. 2016; Stote et al. 2012), CK (Buchwald-Werner et al. 2018), VEGF (George et al. 2019), and increased NOX (Das et al.

**Fig. 1** Flow diagram of the literature search and study selection process following PRISMA guidelines



2018). Decreased OA levels (Rondanelli et al. 2020; Gomes et al. 2021; Decha et al. 2019; Piscocya et al. 2001), reduced uric acid levels (Somanah et al. 2012), TLR4 (Santamarina et al. 2020), haptoglobin (McFarlin et al. 2015), p47<sup>phox</sup> protein (Panza et al. 2019), as well as reduced pharyngitis score (Dirjomuljono et al. 2008) and plaque gingival index (Amaliya et al. 2018) (Table 1).

Table 2, on the other hand, shows the major anti-inflammatory drugs that have already been tested against the SARS-CoV-2 infection in clinical trials. Results of fifteen medications were found in the databases used. These drugs act to inhibit the activity of interleukins (Anakinra (Vanassche et al. 2020; Maes et al. 2020; Bozzi et al. 2021; Kyriazopoulou et al. 2021; Franzetti et al. 2021; Pontali et al. 2021), Canakinumab (Cremer 2021), Siltuximab (Maes et al. 2020), Tocilizumab — Strohhahn et al. 2021; Price et al. 2020; Tian et al. 2021; Dastan et al. 2020; Chachar et al. 2021), COXs (Celecoxib — Alkholly 2021; Hong et al. 2020), Naproxen — Adnet 2020), platelet aggregation (Aspirin — Carvalho 2021; Alkholly 2021; Flumignan et al. 2020; Sant Pau 2020; Ghati et al. 2020; Meizlish et al. 2021; Qiang et al. 2021), action of JAKs (Baricitinib — Kalil et al. 2021; Ruxolitinib — Novartis Pharmaceuticals 2021), VEGFs

(Bevacizumab — Pang et al. 2021), downstream inhibition of inflammation (Colchicine — Rahman 2020; Mostafaie 2020; Pinzón 2020; Figal 2020; Deftereos et al. 2020; Mehta et al. 2020; Tardif 2020), immunoglobulin monoclonal antibody (Infliximab — Kennedy et al. 2021; Ixekizumab — Liu et al. 2020), or as corticosteroids (Dexamethasone — Carvalho 2021; Syeda 2020; Kocks 2021; Tomazini et al. 2020; Villar et al. 2020; Pinzón 2020). These studies have good results, such as decreased clinical and laboratory inflammation levels, and increased prolonged survival in SARS-CoV-2 patients. However, none of these drugs has yet shown unequivocal clinical use against SARS-CoV-2 infection. Treatment results are summarized, providing evidence for new studies.

Except for the study (NCT04810728) in both databases, no results were found relating the scientific names of native South American plants to SARS-CoV-2, COVID-19, Middle East respiratory syndrome coronavirus (MERS-CoV), or SARS-CoV, up to May 2021. This randomized clinical trial (phase III — NCT04810728) hypothesized the anti-viral efficacy of *P. guajava* extract (two capsules of the extract, three times daily) in increasing neutrophil, lymphocyte, and monocyte counts, and decreasing hs-CRP, thus causing a

**Fig. 2** South American anti-inflammatory plants. Source: VectorStock



shorter SARS-CoV-2 seroconversion into mild and symptomless cases (Heppy 2020).

## Discussion

There are thousands of published studies involving the inflammatory process. This is because chronic inflammation is involved in the pathogenesis of several diseases, including SARS-CoV-2 (Medzhitov 2010). The selected clinical trials (Table 1) show that plant effects are induced via different anti-inflammatory mechanisms. In SARS-CoV-2 patients, the severe inflammatory responses induced by a cytokine storm (Fig. 3) start locally and spread systemically, causing collateral damage in tissues (Gupta et al. 2020). There are increased serum levels of pro-inflammatory cytokines that are also observed in SARS-CoV and MERS-CoV infections, which lead to several adverse reactions in the human body (Prompetchara et al. 2020).

CRP levels are correlated with inflammation intensity. It is an important marker for the diagnosis and assessment of severe pulmonary infectious diseases. Its levels can be used in the early diagnosis of pneumonia, and patients presenting with severe pneumonia have high CRP levels (Chalmers et al. 2019). This suggests that CRP levels can cause lung lesions and increase disease severity in the early stage

of SARS-CoV-2, and can be used as a key indicator for infection monitoring (Wang 2020). In the present review, many native South American plants analysed in clinical trials showed potential to decrease CRP levels; namely, *A. oleracea* (Rondanelli et al. 2020), *C. xanthocarpa* (Viecili et al. 2014), *C. papaya* (Somanah et al. 2012), *C. brasiliense* (Miranda-Vilela et al. 2009), *E. oleracea* (Kim et al. 2018), *I. paraguariensis* (Panza et al. 2019), *M. esculenta* (Talsma et al. 2016), *M. dubia* (Inoue et al. 2008), *P. edulis* (Kitada et al. 2017), *S. tuberosum* (Kaspar et al. 2011), and *T. cacao* (Solà et al. 2012; Stote et al. 2012; Monagas et al. 2009).

Inhibition of the NF- $\kappa$ B pathway plays a therapeutic role in alleviating the severe form of SARS-CoV-2 infection, as the activation of NF- $\kappa$ B in some cells (e.g. the macrophages in the lung, liver, kidney, gastrointestinal system, central nervous system, and cardiovascular system) leads to the production of several cytokines, such as IL-1, IL-6, IL-8, TNF- $\alpha$ , and several chemokines. Thus, immunomodulation at the level of NF- $\kappa$ B activation and inhibitors of NF- $\kappa$ B (I $\kappa$ B) degradation together with TNF- $\alpha$  inhibition can result in reduced cytokine storm levels and mitigate the severity of SARS-CoV-2 infection (Hariharan et al. 2021). *P. americana* induces inhibition of the NF- $\kappa$ B signalling pathway (Li et al. 2013).

Severe SARS-CoV-2 patients show high levels of IL-6, which play a major role in coagulation; this provides a

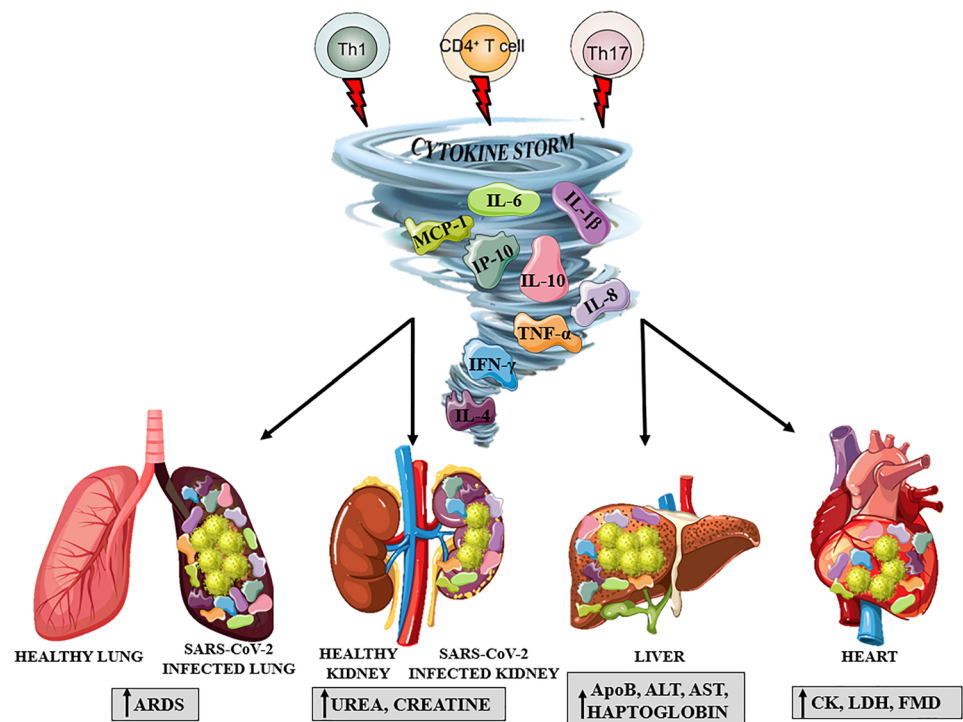


major contribution to tissue damage and inflammation, and to atherogenesis (Smail et al. 2021). Studies show that even moderate IL-6 levels (higher than 80 pg/mL) are sufficient to identify SARS-CoV-2-infected patients with a high risk of respiratory failure (Herold et al. 2020). It was also suggested that a serial measurement of circulating IL-6, IL-8, and TNF- $\alpha$  might be important in identifying disease progression, and it might predict the next respiratory failure (Del Valle et al. 2020). In this review, *A. citriodora* (Buchwald-Werner et al. 2018), *B. excelsa* (Stockler-Pinto et al. 2014; Colpo et al. 2014), *E. edulis* (Santamarina et al. 2020), *I. paraguariensis* (Panza et al. 2019), *P. edulis* (Kitada et al. 2017), *P. americana* (Li et al. 2013), *P. volubilis* (Alayón et al. 2019), *S. sonchifolius* (Manzoni et al. 2017), *S. tuberosum* (Kaspar et al. 2011), and *T. cacao* (Stote et al. 2012; Davis et al. 2020), decreased IL-6 levels in clinical trials.

A major component in deteriorating lung function in SARS-CoV-2 patients is capillary leak resulting from inflammation caused by key inflammatory cytokines (TNF- $\alpha$ , IL-1, IL-6, IL-8, and VEGF) that up-regulate adhesion molecules and disrupt endothelial barrier in blood vessels. TNF- $\alpha$  is a cell signalling inflammatory cytokine and acts as an inflammation amplifier (Robinson et al. 2020). In blood and tissue samples of SARS-CoV-2 patients, the presence of TNF- $\alpha$  molecules was observed (Wang et al. 2020b). *B. excelsa* (Stockler-Pinto et al. 2014; Colpo et al. 2014), *E. edulis* (Santamarina et al. 2020), *E. oleracea* (Kim et al. 2018), *I. paraguariensis* (Panza et al. 2019), *P. amarus* (George et al. 2019; Decha et al. 2019), *U.*

*guianensis* (Piscoya et al. 2001) are plants with inhibitory activity against TNF- $\alpha$ . *B. excelsa* (Colpo et al. 2014) and *T. cacao* (Davis et al. 2020) decreased IL-1 $\beta$  levels, which are released from cells undergoing pyroptosis (an inflammatory form of programmed cell death observed in infections with cytopathic viruses, such as CoVs) and are high in serum and bronchoalveolar fluid (BALF) of patients with severe SARS-CoV-2 infection. Cytokine also increases tissue inflammation, fibrosis, and fever (Liao et al. 2020). IL-8 is another biomarker to predict different disease severities and prognoses of COVID-19 patients. Serum IL-8 is easily detectable in COVID-19 patients with mild syndromes (Li et al. 2020). The Amazonian plant *M. dubia* showed potential to inhibit IL-8 in clinical trials (Inoue et al. 2008). On the other hand, after viral infection, IL-18 release induces ferritin synthesis, which explains the hyperferritinemia observed in viral infections. Aside from the cytokine storm, the pathogenesis of SARS-CoV-2 is also characterized by hyperferritinemia. Moreover, serum concentrations of IL-18 correlate with other inflammatory markers and can predict disease outcomes (Satış et al. 2021). *T. cacao* (Davis et al. 2020) decreased serum IL-18 concentrations. It is important to understand the role played by IFN- $\gamma$  in SARS-CoV-2 pathogenesis since it is still ambiguous. This cytokine is essential for antiviral defence, it downregulates virus replication and activates cytokine production by T cells, increasing the killing activity of cytotoxic T lymphocytes. Nevertheless, persistently high levels of IFN- $\gamma$  worsen systemic inflammation, increasing tissue injury and organ failure

**Fig. 3** The potential mechanisms of 'cytokine storm' induced by Th1, CD4+ T, and Th17 cells, culminating in multiple organ damage. Source: VectorStock



(Gadotti et al. 2020). *B. excelsa* (Colpo et al. 2014), *E. oleracea* (Kim et al. 2018), *P. amarus* (George et al. 2019) are plants that induce decrease in IFN- $\gamma$  levels in humans. In contrast, there are elevated amounts of anti-inflammatory cytokine, IL-10, in the serum of COVID-19 patients, which is generally regarded as an immune-inhibitory mechanism, stimulated by the rapid accumulation of pro-inflammatory cytokines as a negative feedback loop (Zhao 2020). However, some lines of clinical evidence suggest that the early and dramatic IL-10 rise during SARS-CoV-2 infection might play a detrimental pathological role in COVID-19 severity (Lu et al. 2021). *B. excelsa* (Colpo et al. 2014), *E. edulis* (Kim et al. 2018) and *S. sonchifolius* (Manzoni et al. 2017) increased IL-10 levels.

SARS-Cov-2 levels are high in the first week, and then, decrease sharply in the second week of infection (Petrilli et al. 2016). Therefore, antiviral therapy can be initiated at an early stage of infection. In general, when patients seek medical help, the disease has already developed into the second or third stage, with respiratory difficulties and organ failures. Therefore, studies should look further, beyond the virus, focusing on the cytokine storm and on the action of free radicals as the actual pathogens (Wu 2020). The pathogenic role of free radical damage is clear in inflammations and in respiratory virus infection. IL-6 and TNF- $\alpha$  have been reported to lead to production of superoxide in neutrophils, and hydrogen peroxide can stimulate IL-6 production (Kharazmi et al. 1989). Inhibition of NO synthesis can decrease IL-6 production by more than 50%. In summary, it is essential to understand that free radicals are the downstream product of the cytokine storm, causing direct damage to cells and many organs (Willis et al. 1994). Therefore, the present study found that South American plants showed inhibitory potential against some free radicals, such as TBARS (Miranda-Vilela et al. 2009) (*C. brasiliense*), ROS (Inoue et al. 2008) (*M. dubia*), NO (Decha et al. 2019; Davis et al. 2020) (*P. amarus* and *T. cacao*), 8-OHdG (Inoue et al. 2008; Kaspar et al. 2011) (*M. dubia* and *S. tuberosum*), as well as dROM (Kitada et al. 2017) (*P. edulis*). On the other hand, natural antioxidant substances play a preventive role in protecting against the production of free radicals and are, therefore, a therapeutic agent to reduce the conditions triggered by oxidative stress, e.g. inflammation (Marmitt et al. 2021c). It has been suggested that there is an inverse relationship between consuming natural antioxidant plant sources and the prevalence of chronic illnesses (Arulsevan et al. 2016). The selected clinical trials show good results with plants that stimulate increased levels of endogenous antioxidants; *A. citriodora* (Buchwald-Werner et al. 2018) and *B. excelsa* (Stockler-Pinto et al. 2014) increased GPx levels, *I. paraguariensis* increases GSH levels (Panza et al. 2019), and *P. amarus* (Decha et al. 2019) up-regulated SOD levels.

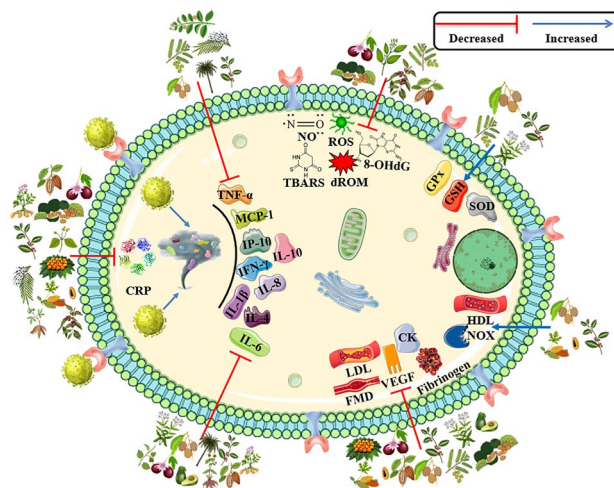
The association between cardiovascular events and infectious diseases is well established (Collard et al. 2021). In short, the presence of more than one CVD marker, such as fibrinogen, haptoglobin, and hyperCKemia (increased CK levels), in SARS-CoV-2 inpatients might indicate a mortality risk higher than 50%. The accumulation of CVD risk factors (presence of coronary artery disease, smoking, and obesity) is associated with mortality, regardless of age or sex. These results are consistent with previous SARS-CoV and MERS-CoV infections (Nishiga et al. 2020). The present review relates decrease in CVD markers with some plants in clinical trials on inflammation; for instance, decreased CK by *A. citriodora* (Buchwald-Werner et al. 2018), decreased NOX by *C. papaya* (Das et al. 2018), decreased FMD by *P. edulis* (Kitada et al. 2017), decreased fibrinogen by *I. paraguariensis* and *T. cacao* (Petrilli et al. 2016; Stote et al. 2012), and decreased haptoglobin by *T. cacao* (McFarlin et al. 2015). Similarly, studies have also reported that patients with comorbidities and risk factors such as obesity are more susceptible to a more serious SARS-CoV-2 infection. Cholesterol (LDL-high levels) is an important risk factor in CVDs. It has been suggested that it is involved in regulating the entry of the SARS-CoV-2 virus into the host cell. Higher membrane cholesterol coincides with a more effective SARS-CoV-2 entry (Koçar et al. 2021). Conversely, SARS-CoV-2 patients show low levels of blood cholesterol, such as LDL. HDL already seems to play an array of roles, ranging from virus scavenger, immune modulator, to mediator of viral entry. Clinical studies with the following plants inducing a decrease in LDL levels were found; *B. excelsa* (Stockler-Pinto et al. 2014), *C. xanthocarpa* (Viecili et al. 2014), *C. papaya* (Somanah et al. 2012), *C. brasiliense* (Miranda-Vilela et al. 2009), *P. americana* (Wang et al. 2020a), and *T. cacao* (Solà et al. 2012), which also decreased ApoB levels, which is the primary LDL apolipoprotein, responsible for transporting cholesterol to tissues. Some plants induce increase in HDL levels, e.g. *B. excelsa* (Stockler-Pinto et al. 2014), *C. papaya* (Petrilli et al. 2016), and *I. paraguariensis* (Petrilli et al. 2016). Analysing these results, Fig. 4 shows a potential mechanism through which these plants can provide their anti-inflammatory effects.

The NCT04810728 study (Heppy 2020) showed an antiviral effect based on in vitro studies, indicating that guava leaves contain a large amount of flavonoids, especially quercetin. The study on type 2 Dengue virus (DEN-2) found that quercetin significantly inhibited DEN-2 virus activity (IC<sub>50</sub>: 53  $\mu$ g/mL). Quercetin also inhibited the enzyme reverse transcriptase, HIV-1(RT), with an inhibitory concentration of 0.6  $\mu$ M. Another study found that quercetin in *P. guavaja* inhibits RNA polymerase, which is important in Dengue virus replication. In addition, quercetin can inhibit protease enzyme, helicase domain, and viral ATPase enzyme. Considering antiviral effects, these results may be

important for future analyses of treatments against SARS-CoV-2 infection.

Even considering other scientific study levels (in vitro, in vivo), the only studies related to SARS-CoV-2 in the databases are with *P. edulis*, *P. amarus*, *S. tuberosum*, and *T. cacao*. The compounds in these four plants with inhibitory potential against SARS-CoV-2 were analysed in silico using molecular docking. *P. edulis* showed that lucenin, isoorientin, oleanolic acid, luteolin, isochaphoside, schaftoside, and saponarin are potential ligands with ACE2 protease, with binding energy higher than  $-8.0$  kcal/mol (Yalçın et al. 2021). Phytochemicals from *P. amarus* (astragalin, kaempferol, quercetin, quercetin-3-O-glucoside, quercetin, corilagin, furosin, and geraniin) had a binding docking score lower than  $-6.0$  kcal/mol (Hiremath et al. 2021). The compounds curcumenol, *N*-desmethylselegiline, phentermine, and sphingolipid, which are derived from *S. tuberosum*, have been suggested as selective candidates for the effective modulation of ACE2 and TMPRSS2 receptors (Dave et al. 2020). Isorhoifolin and rutin are *T. cacao* compounds that already stand out due to their more negative binding to the SARS-CoV-2 major viral protease (Yañez et al. 2021). The phytochemicals present in these plants might have a potential effect on multiple target sites of SARS-CoV-2, providing further possibilities for experiments aiming to validate these molecules as inhibitors of SARS-CoV-2 protease.

It is also worth noting that from 1981 to 2019, 53 of the 1,881 drugs produced were anti-inflammatory; of these, fifteen derived from natural products or their derivatives (Newman and Cragg, 2020). Two of the fifteen anti-inflammatory drugs selected in Table 2 are natural, plant-produced drugs. Colchicine is a poisonous alkaloid, originally extracted from *Colchicum autumnale* L. — Colchicaceae. It has been used in the treatment of several diseases such as gout, pericarditis, and inflammatory arthritis. Additionally, it has had novel applications within oncology, immunology, cardiology, and dermatology, yet it has been used on a smaller scale due to its high toxicity (Dasgeb et al. 2018). Acetylsalicylic acid (Aspirin) was originally synthesized from the bark of white willow (*Salix alba* L. — Salicaceae) (Montinari et al. 2019) and it is important to describe the benefits of salicylates, such as salicylic acid (SA), which is the major aspirin metabolite, and a compound that reduces inflammation. A genome-analysis identified potential SA-binding proteins (SABPs) using in vitro cells. Approximately 2000 proteins were identified. Pathway analysis with 95 proteins candidate SABPs (cSABPs) revealed a potential involvement of SA in multiple biological pathways, including glycolysis, cytoskeletal assembly and/or signalling, and NF- $\kappa$ B-mediated immune signalling (Choi et al. 2019). SA is an endogenous signal for innate immunity in plants. Researchers have identified pathways through which SA



**Fig. 4** The suggested mechanism through which plants could exert their inhibitory/inducing effects in SARS-CoV-2 infection. Source: VectorStock

can be synthesized, numerous proteins that regulate SA synthesis and metabolism, as well as some of the signalling components that act downstream of SA, including a large number of SA targets or receptors. Thus, numerous SABPs might be required to mediate myriad effects of SA. Therefore, while the primary mode of action of aspirin in humans has been ascribed to the inhibition of cyclooxygenases COX1 and COX2, several lines of evidence argue that additional SA targets exist, as potential of salicylates in the anti-viral activity (Klessig et al. 2016). In addition, a significant SA-mediated antiviral activity against DNA and RNA viruses, including different coronaviruses, has been documented. The use of SA in patients with different types of infections has been associated with lower rates of clinical complications and in-hospital mortality, as well as reduced thrombo-inflammation. However, safety issues related to the risk of adverse effects, such as the risk of bleeding and of developing rare liver and brain damage should be considered (Bianconi et al. 2020). Moreover clinical trials show the potential of SA (Goldfine et al. 2008, 2016), since the randomized controlled studies ( $n = 35$ ) showed that high doses of salicylate (up to 4 g/day) reduce inflammation, glucose and triacylglycerols, improve insulin sensitivity, and reduce adipose tissue NF- $\kappa$ B activity, suggesting a therapeutic potential in impaired fasting glucose and/or impaired glucose tolerance in the randomized controlled study ( $n = 35$ ). These data support the targeting of inflammation and NF- $\kappa$ B as a therapeutic approach in type 2 diabetes.

Clinical results of anti-inflammatory drugs tested against SARS-CoV-2 infection (Table 2) are important but not definitive, as most treatments have not shown significant improvement in the survival of the severe form of SARS-CoV-2

infection. It is worth considering that the prognosis of healing from hyperinflammation is generally unfavourable (Herold et al. 2020). NSAIDs such as aspirin work as inhibitors of the COX enzyme, which is responsible for the production of inflammatory prostaglandins. The World Health Organization (WHO) has contraindicated the use of NSAIDs in the early COVID-19 pandemic since NSAIDs down-regulate ACE2 in the respiratory system, which decreases pulmonary function. However, NSAIDs also up-regulate ACE2 especially in diabetic patients and patients that take ACE2 receptor inhibitors (Rinott et al. 2020), and therefore, the over-expression of ACE2 receptors could facilitate the entry of SARS-CoV-2 and increase the chances of infection. However, the WHO soon became favourable to the use of NSAIDs, as findings showed that not only these drugs are not contraindicated but also their use could help in the treatment of SARS-CoV-2 infection (WHO 2020). In addition, the reasons for not using NSAIDs do not hold since the up-regulation of ACE2 occurs during the chronic use of drugs, which renders the person vulnerable to the disease. On the other hand, the evidence of ACE2 up-regulation by these drugs was obtained in *in vivo* studies, and may be not transferable to clinical trials (NICE 2020).

Similarly, immunotherapeutic drugs mostly act as anti-inflammatory agents; however, their side effects should be considered since decreased immunity delays virus clearance and increases the chances of the patient having a bacterial infection (Singanayagam et al. 2018). In addition, most immunotherapeutic drugs have a specific target, as they inhibit only one cytokine, such as JAK inhibitors or IL-6 blockers, which renders the inflammation difficult to control (Zidek et al. 2009). Targeting the IL-6 signalling pathway is a potential strategy for relieving inflammation symptoms in SARS-CoV-2 infection (Salomé and Magen 2020). Six clinical trials with findings on Tocilizumab, an anti-IL-6 receptor antibody, were selected for SARS-CoV-2 mitigation (Strohbehn et al. 2021; Price et al. 2020; Tian et al. 2021; Dastan et al. 2020; Chachar et al. 2021). Moreover, tocilizumab has been approved by China for the treatment of SARS-CoV-2 infection through the clinical trial (ChiCTR2000029765); its results showed rapidly controlled fever and improved respiratory function in patients with severe COVID-19, and all patients recovered (Xu et al. 2020b). There was a Phase III Clinical trial with another IL-6 blocker, Siltuximab (Maes et al. 2020). Inhibitors of the JAK signalling pathway are powerful anti-inflammatory agents that are effective against the effects of high cytokine levels. Baricitinib and ruxolitinib are selective JAK inhibitors that have been used in SARS-CoV-2 infection, and have been selected in the present review (Kalil et al. 2021; Novartis Pharmaceuticals 2021). Baricitinib was administered to SARS-CoV-2 patients associated with direct-acting antivirals, and reduced viral replication and inflammatory response (Stebbing et al.

2020). However, the risks and benefits of cytokine inhibition must be carefully assessed in the administration of these treatments (Schett et al. 2020).

## Conclusion

The clinical results found are not directly related to the context of the SARS-CoV-2 infection. However, they provide possibilities for further studies with native South American plants considering their anti-inflammatory activity by inhibiting levels of cytokines that play a role in hyperinflammation or even other inflammatory markers detected in SARS-CoV-2 patients. Plants have a variety of compounds, and identifying which ones are responsible for anti-inflammatory effects can help in studies conducted with the aim to evaluate their efficacy in scenarios of SARS-CoV-2 infection.

**Acknowledgements** This work was supported by the University of Taquari Valley, Brazil and Coordination of Improvement of Higher Education Personnel — Brazil (CAPES).

**Author contributions** DM has elaborated, designed, and analysed the data; he has also written the paper.

**Funding** This work was supported in part by CAPES — Brazil (CAPES) — Finance Code 001.

## Declarations

**Conflict of interest** There are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

## References

- Adnet F (2020) Efficacy of addition of naproxen in the treatment of critically ill patients hospitalized for COVID-19 infection (ENA-COVID). Clinical trials. Available in: <https://clinicaltrials.gov/ct2/show/NCT04325633>
- Alayón AN, Ávila JGO, Jiménez IE (2019) Metabolic status is related to the effects of adding of sacha inchi (*Plukenetia volubilis* L.) oil on postprandial inflammation and lipid profile: randomized, crossover clinical trial. *J Food Biochem* 43(2):e12703. <https://doi.org/10.1111/jfbc.12703>
- Albuquerque UP, Patil U, Máthé A (2018) Medicinal and aromatic plants of South America, vol. 486. Springer Nature, Berlin. Doi: <https://doi.org/10.1007/978-94-024-1552-0>
- Alkholi AF (2021) Back to the traditional: anti-COX drugs can improve the outcome of COVID-19 patients admitted to ICU. Clinical trials. Available in: <https://clinicaltrials.gov/ct2/show/study/NCT04757792>
- Alvarez MA (2019) Pharmacological properties of native plants from Argentina, vol. 255. Springer Nature, Berlin. <https://doi.org/10.1007/978-3-030-20198-2>
- Amaliya A, Risdiana AS, Van der Velden U (2018) Effect of guava and vitamin C supplementation on experimental gingivitis: a

- randomized clinical trial. *J Clin Periodontol* 45(8):959–967. <https://doi.org/10.1111/jcpe.12922>
- Arulselvan P, Fard MT, Tan WS, Gothai S, Fakurazi S, Norhaizan ME et al (2016) Role of antioxidants and natural products in inflammation. *Oxid Med Cell Longev* 2016:5276130. <https://doi.org/10.1155/2016/5276130>
- Barlow J, França F, Gardner TA, Hicks CA, Lennox GD, Berenguer E et al (2018) The future of hyperdiverse tropical ecosystems. *Nature* 559:517–526. <https://doi.org/10.1038/s41586-018-0301-1>
- Bianconi V, Violi F, Fallarino F, Pignatelli P, Sahebkar A, Pirro M (2020) Is acetylsalicylic acid a safe and potentially useful choice for adult patients with COVID-19. *Drugs* 80(14):1383–1396. <https://doi.org/10.1007/s40265-020-01365-1>
- Bindu S, Mazumder S, Bandyopadhyay U (2020) Non-steroidal anti-inflammatory drugs (NSAIDs) and organ damage: a current perspective. *Biochem Pharmacol* 180:114147. <https://doi.org/10.1016/j.bcp.2020.114147>
- Bozzi G, Mangioni D, Minoia F, Filocamo G, Gori A, Bandera A et al (2021) Anakinra combined with methylprednisolone in patients with severe COVID-19 pneumonia and hyperinflammation: an observational cohort study. *J Allergy Clin Immunol* 147(2):561–566.e4. <https://doi.org/10.1016/j.jaci.2020.11.006>
- Buchwald-Werner S, Naka I, Wilhelm M, Schütz E, Schoen C, Reule C (2018) Effects of lemon verbena extract (Recoverben®) supplementation on muscle strength and recovery after exhaustive exercise: a randomized, placebo-controlled trial. *J Int Soc Sports Nutr* 15:5. <https://doi.org/10.1186/s12970-018-0208-0>
- Carvalho HE (2021) Ivermectin, aspirin, dexamethasone and enoxaparin as treatment of Covid 19 (IDEA). *Clinical trials*. Available in: <https://clinicaltrials.gov/ct2/show/NCT04425863>
- Chachar AZK, Khan KA, Iqbal J, Shahid AH, Asif M, Fatima SA et al (2021) “Tocilizumab-an option for patients with COVID-19 associated cytokine release syndrome: a single center experience”, a retrospective study-original article. *Ann Med Surg* 63:102165. <https://doi.org/10.1016/j.amsu.2021.02.011>
- Chalmers S, Khawaja A, Wieruszewski PM, Gajic O, Odeyemi Y (2019) Diagnosis and treatment of acute pulmonary inflammation in critically ill patients: the role of inflammatory biomarkers. *World J Crit Care Med* 8(5):59–71. <https://doi.org/10.5492/wjccm.v8.i5.59>
- Chen L, Deng H, Cui H, Fang J, Zuo Z, Deng J, et al. (2018) Inflammatory responses and inflammation-associated diseases in organs. *Oncotarget* 9(6):7204–7218. <https://doi.org/10.18632/oncotarget.23208>
- Choi HW, Wang L, Powell AF, Strickler SR, Wang D, Dempsey DMA et al (2019) (2019) A genome-wide screen for human salicylic acid (SA)-binding proteins reveals targets through which SA may influence development of various diseases. *Sci Rep* 9:13084. <https://doi.org/10.1038/s41598-019-49234-6>
- Collard D, Nurmohamed NS, Kaiser Y, Reeskamp LF, Dormans T et al (2021) Cardiovascular risk factors and COVID-19 outcomes in hospitalised patients: a prospective cohort study. *BMJ Open* 11(2):e045482. <https://doi.org/10.1136/bmjopen-2020-045482>
- Colpo E, Vilanova CDDA, Reetz LGB, Duarte MMFD, Farias ILG, Meinerz DF et al (2014) Brazilian nut consumption by healthy volunteers improves inflammatory parameters. *Nutrition* 30(4):459–465. <https://doi.org/10.1016/j.nut.2013.10.005>
- Cremer PC (2021a) Canakinumab in Covid-19 cardiac injury (The Three C Study). *Clinical trials*. Available in: <https://clinicaltrials.gov/ct2/show/NCT04365153>
- Cremer PC, Abbate A, Hudock K, McWilliams C, Mehta J, Chang SY et al (2021) Mavrilimumab in patients with severe COVID-19 pneumonia and systemic hyperinflammation (MASH-COVID): an investigator initiated, multicentre, double-blind, randomized, placebo-controlled trial. *Lancet Rheumatol* 3(6):e410–e418. [https://doi.org/10.1016/S2665-9913\(21\)00070-9](https://doi.org/10.1016/S2665-9913(21)00070-9)
- Das A, Dickerson R, Ghatak PD, Gordillo GM, Chaffee S, Saha A et al (2018) May dietary supplementation augment respiratory burst in wound-site inflammatory cells? *Antioxid Redox Signal* 28(5):401–405. <https://doi.org/10.1089/ars.2017.7304>
- Dasgeb B, Kornreich D, McGuinn K, Okon L, Brownell I, Sackett DL (2018) Colchicine: an ancient drug with novel applications. *Br J Dermatol* 178(2):350–356. <https://doi.org/10.1111/bjd.15896>
- Dastan F, Saffaei A, Haseli S, Marjani M, Moniri A, Abtahian Z et al (2020) Promising effects of tocilizumab in COVID-19: A non-controlled, prospective clinical trial. *Int Immunopharmacol* 88:106869. <https://doi.org/10.1016/j.intimp.2020.106869>
- Dave GS, Rakholiya KD, Kaneria MJ, Galvadiya BP, Vyas SR, Kanbi VH (2020) High affinity interaction of *Solanum tuberosum* and *Brassica juncea* residue smoke water compounds with proteins involved in coronavirus infection. *Phytother Res* 34(12):3400–3410. <https://doi.org/10.1002/ptr.6796>
- Davis DW, Tallent R, Navalta JW, Salazar A, Lyons TJ, Basu A (2020) Effects of acute cocoa supplementation on postprandial apolipoproteins, lipoprotein subclasses, and inflammatory biomarkers in adults with type 2 diabetes after a high-fat meal. *Nutrients* 12(7):1902. <https://doi.org/10.3390/nu12071902>
- Decha P, Kanokwan K, Jiraporn T, Pichaya J, Pisittawoot A (2019) Phonopheresis associated with nanoparticle gel from *Phyllanthus amarus* relieves pain by reducing oxidative stress and proinflammatory markers in adults with knee osteoarthritis. *Chin J Integr Med* 25(9):691–695. <https://doi.org/10.1007/s11655-019-3202-8>
- Deftereos SG, Giannopoulos G, Vrachatis DA, Siasos GD, Giotaki SG, Gargalianos P et al (2020) Effect of colchicine vs standard care on cardiac and inflammatory biomarkers and clinical outcomes in patients hospitalized with coronavirus disease 2019: the GRECCO-19 randomized clinical trial. *JAMA Netw Open* 3(6):e2013136. <https://doi.org/10.1001/jamanetworkopen.2020.13136>
- Del Valle DM, Kim-Schulze S, Gnajatic S (2020) An inflammatory cytokine signature predicts COVID-19 severity and survival. *Nat Med* 26:1636–1643. <https://doi.org/10.1038/s41591-020-1051-9>
- Dirjomuljono M, Kristyono I, Tjandrawinata RR, Nofiarny D (2008) Symptomatic treatment of acute tonsillo-pharyngitis patients with a combination of *Nigella sativa* and *Phyllanthus niruri* extract. *Int J Clin Pharmacol Ther* 46(6):295–306. <https://doi.org/10.5414/cpp46295>
- Drake TM, Fairfield CJ, Pius R, Knight SR, Norman L, Girvan M et al (2021) Non-steroidal anti-inflammatory drug use and outcomes of COVID-19 in the ISARIC Clinical Characterisation Protocol UK cohort: a matched, prospective cohort study. *Lancet Rheumatol*. [https://doi.org/10.1016/S2665-9913\(21\)00104-1](https://doi.org/10.1016/S2665-9913(21)00104-1)
- Duke JA (2008) Medicinal plants of Latin America, vol. 832. CRC Press, Boca Raton. ISBN 9781420043167
- Ekor M (2013) The growing use of herbal medicines: issues relating to adverse reactions and challenges in monitoring safety. *Front Pharmacol* 4:177. <https://doi.org/10.3389/fphar.2013.00177>
- Fendrick AM, Greenberg BP (2009) A review of the benefits and risks of nonsteroidal anti-inflammatory drugs in the management of mild-to-moderate osteoarthritis. *Osteopath Med Prim Care* 3:1. <https://doi.org/10.1186/1750-4732-3-1>
- Figal DAP (2020) Trial to study the benefit of colchicine in patients with COVID-19 (COL-COVID). *Clinical trials*. Available in: <https://clinicaltrials.gov/ct2/show/NCT04350320>
- Flumignan RL, Tinôco JDS, Pascoal PI, Areias A, Cossi MS, Fernandes MICD, et al. (2020) Prophylactic anticoagulants for people hospitalised with COVID-19. *Cochrane Database Syst Rev* 10:CD013739. <https://doi.org/10.1002/14651858.CD013739>
- Franzetti M, Forastieri A, Borsa N, Pandolfo A, Molteni C, Borghesi L et al (2021) IL-1 receptor antagonist anakinra in the treatment of COVID-19 acute respiratory distress syndrome: a retrospective.

- Obs Study J Immunol 206(7):1569–1575. <https://doi.org/10.4049/jimmunol.2001126>
- French JA, Koeppe M, Naegelin Y, Vigeveno F, Auvin S, Rho JM et al (2017) Clinical studies and anti-inflammatory mechanisms of treatments. *Epilepsia* 58(Suppl 3):69–82. <https://doi.org/10.1111/epi.13779>
- Fu Y, Cheng Y, Wu Y (2020) Understanding SARS-CoV-2-mediated inflammatory responses: from mechanisms to potential therapeutic tools. *Virus Res* 35(3):266–271. <https://doi.org/10.1007/s12250-020-00207-4>
- Gadotti AC, Castro Deus M, Telles JP, Wind F, Goes M, Ossoski RGC et al (2020) IFN- $\gamma$  is an independent risk factor associated with mortality in patients with moderate and severe COVID-19 infection. *Virus Res* 289:198171. <https://doi.org/10.1016/j.virusres.2020.198171>
- Ghati N, Roy A, Bhatnagar S, Bhati S, Bhushan S, Mahendran M et al (2020) Atorvastatin and aspirin as adjuvant therapy in patients with SARS-CoV-2 infection: a structured summary of a study protocol for a randomized controlled trial. *Trials* 21(1):902. <https://doi.org/10.1186/s13063-020-04840-y>
- George A, Udani JK, Yusof A (2019) Effects of *Phyllanthus amarus* PHYLLPRO TM leaves on hangover symptoms: a randomized, double-blind, placebo-controlled crossover study. *Pharm Biol* 57(1):145–153. <https://doi.org/10.1080/13880209.2019.1585460>
- Goldfine AB, Silver R, Aldhahi W, Cai D, Tatro E, Lee J et al (2008) Use of salsalate to target inflammation in the treatment of insulin resistance and type 2 diabetes. Use of salsalate to target inflammation in the treatment of insulin resistance and type 2 diabetes. *Clin Transl Sci* 1(1):36–43. <https://doi.org/10.1111/j.1752-8062.2008.00026.x>
- Goldfine AB, Conlin PR, Halperin F, Koska J, Permana P, Schwenke D et al (2016) A randomised trial of salsalate for insulin resistance and cardiovascular risk factors in persons with abnormal glucose tolerance. *Diabetologia* 56:714–723. <https://doi.org/10.1007/s00125-012-2819-3>
- Gomes TPO, Souza JIN, Somerlate LC, Mendonça VA, Lima NM, Carli GP et al (2021) *Miconia albicans* and *Curcuma longa* herbal medicines positively modulate joint pain, function and inflammation in patients with osteoarthritis: a clinical study. *Inflammopharmacol* 29(2):377–391. <https://doi.org/10.1007/s10787-020-00781-9>
- Gupta KK, Khan MA (2020) Storm SSKCIC: a major threat to human health. *J Interferon Cytokine Res* 40:19–23. <https://doi.org/10.1089/jir.2019.0085>
- Hariharan A, Hakeem AR, Radhakrishnan S, Reddy MS, Rela M (2021) The role and therapeutic potential of NF-kappa-B pathway in severe COVID-19 patients. *Inflammopharmacol* 9:91–100. <https://doi.org/10.1007/s10787-020-00773-9>
- Heppy F (2020) Efficacy of Psidii Guava's extract for COVID-19. Clinical trials. Available in: <https://clinicaltrials.gov/ct2/show/NCT04810728>
- Herold T, Jurinovic V, Arnreich C, Hellmuth JC, Von Bergwelt-Baildon M, Klein M, et al. (2020) Level of IL-6 predicts respiratory failure in hospitalized symptomatic COVID-19 patients. medRxiv 20047381. <https://doi.org/10.1101/2020.04.01.20047381>
- Hiremath S, Kumar HDV, Nandan M, Mantesh M, Shankarappa KS, Venkataravanappa V, et al. (2021) *In silico* docking analysis revealed the potential of phytochemicals present in *Phyllanthus amarus* and *Andrographis paniculata*, used in Ayurveda medicine in inhibiting SARS-CoV-2. *3 Biotech* 11(2):44. <https://doi.org/10.1007/s13205-020-02578-7>
- Hong W, Chen Y, You K, Tan S, Wu F, Tao J et al (2020) Celebrex adjuvant therapy on coronavirus disease 2019: an experimental study. *Front Pharmacol* 11:561674. <https://doi.org/10.3389/fphar.2020.561674>
- Inoue T, Komoda H, Uchida T, Node K (2008) Tropical fruit camu-camu (*Myrciaria dubia*) has anti-oxidative and anti-inflammatory properties. *J Cardiol* 52(2):127–132. <https://doi.org/10.1016/j.jjcc.2008.06.004>
- Jokioja J, Linderborg KM, Korteniemi M, Nuora A, Heinonen J, Sainio T et al (2020) Anthocyanin-rich extract from purple potatoes decreases postprandial glycemic response and affects inflammation markers in healthy men. *Food Chem* 310:125797. <https://doi.org/10.1016/j.foodchem.2019.125797>
- Kalil AC, Patterson TF, Mehta AK, Tomashek KM, Wolfe CR, Ghazaryan V et al (2021) Baricitinib plus remdesivir for hospitalized adults with Covid-19. *N Engl J Med* 384(9):795–807. <https://doi.org/10.1056/NEJMoa2031994>
- Kaspar KL, Park JS, Brown CR, Mathison BD, Navarre DA, Chew BP (2011) Pigmented potato consumption alters oxidative stress and inflammatory damage in men. *J Nutr* 141(1):108–111. <https://doi.org/10.3945/jn.110.128074>
- Kennedy NA, Goodhand JR, Bewshea C, Nice R, Chee D, Lin S et al (2021) Anti-SARS-CoV-2 antibody responses are attenuated in patients with IBD treated with infliximab. *Gut* 70(5):865–875. <https://doi.org/10.1136/gutjnl-2021-324388>
- Kharazmi A, Nielsen H, Rehnitz C, Bendtzen K (1989) Interleukin 6 primes human neutrophil and monocyte oxidative burst response. *Immunol Lett* 21(2):177–184. [https://doi.org/10.1016/0165-2478\(89\)90056-4](https://doi.org/10.1016/0165-2478(89)90056-4)
- Kim H, Simbo SY, Fang C, McAlister L, Roque A, Banerjee N, et al. (2018) Açai (*Euterpe oleracea* Mart.) beverage consumption improves biomarkers for inflammation but not glucose- or lipid-metabolism in individuals with metabolic syndrome in a randomized, double-blinded, placebo-controlled clinical trial. *Food Funct* 9(6):3097–3103. <https://doi.org/10.1039/c8fo00595h>
- Kitada M, Ogura Y, Maruki-Uchida H, Sai M, Suzuki T, Kanasaki K et al (2017) The effect of piceatannol from passion fruit (*Passiflora edulis*) seeds on metabolic health in humans. *Nutrients* 9(10):1142. <https://doi.org/10.3390/nu9101142>
- Klessig DF, Tian M, Choi HW (2016) Multiple targets of salicylic acid and its derivatives in plants and animals. *Front Immunol* 7:206. <https://doi.org/10.3389/fimmu.2016.00206>
- Kočar E, Režen T (1866) Rozman D (2021) Cholesterol, lipoproteins, and COVID-19: basic concepts and clinical applications. *Biochim Biophys Acta Mol Cell Biol Lipids* 2:158849. <https://doi.org/10.1016/j.bbalip.2020.158849>
- Kocks J (2021) COVID-19 primary care platform for early treatment and recovery (COPPER) study (COPPER). Clinical trials. Available in: <https://clinicaltrials.gov/ct2/show/NCT04746430>
- Kyriazopoulou E, Panagopoulos P, Metallidis S, Dalekos GN, Poulakou G, Gatselis N et al (2021) An open label trial of anakinra to prevent respiratory failure in COVID-19. *Elife* 10:e66125. <https://doi.org/10.7554/eLife.66125>
- Li Z, Wong A, Henning SM, Zhang Y, Jones A, Zerlin A et al (2013) Hass avocado modulates postprandial vascular reactivity and postprandial inflammatory responses to a hamburger meal in healthy volunteers. *Food Funct* 4(3):384–391. <https://doi.org/10.1039/c2fo30226h>
- Li L, Li J, Gao M, Fan H, Wang Y, Xu X et al (2020) Interleukin-8 as a biomarker for disease prognosis of coronavirus disease-2019 patients. *Front Immunol* 11:602395. <https://doi.org/10.3389/fimmu.2020.602395>
- Liao M, Liu Y, Yuan J, Wen Y, Xu G, Zhao J et al (2020) Single-cell landscape of bronchoalveolar immune cells in patients with COVID-19. *Nat Med* 26:842–844. <https://doi.org/10.1038/s41591-020-0901-9>
- Little P (2020) Non-steroidal anti-inflammatory drugs and covid-19. *BMJ*. <https://doi.org/10.1136/bmj.m1185>

- Liu P, Huang Z, Yin M, Liu C, Chen X, Pan P et al (2020) Safety and efficacy of ixekizumab and antiviral treatment for patients with COVID-19: a structured summary of a study protocol for a pilot randomized controlled trial. *Trials* 21(1):999. <https://doi.org/10.1186/s13063-020-04925-8>
- Lopes MI, Bonjorno LP, Giannini MC, Amaral NB, Menezes PI, Musse S et al (2021) Beneficial effects of colchicine for moderate to severe COVID-19: a randomised, double-blinded, placebo-controlled clinical trial. *RMD Open* 7:e001455. <https://doi.org/10.1136/rmdopen-2020-001455>
- Lu L, Zhang H, Dauphars DJ, He YW (2021) A potential role of interleukin 10 in COVID-19 pathogenesis. *Trends Immunol* 42(1):3–5. <https://doi.org/10.1016/j.it.2020.10.012>
- Maes B, Bosteels C, De Leeuw E, Declercq J, Van Damme K, Delporte A et al (2020) Treatment of severely ill COVID-19 patients with anti-interleukin drugs (COV-AID): a structured summary of a study protocol for a randomized controlled trial. *Trials* 21(1):468. <https://doi.org/10.1186/s13063-020-04453-5>
- Manzoni MSJ, Rossi EA, Pauly-Silveira ND, Pinto RA, Roselino MN, Carlos IZ, et al. (2017) Consumption effect of a synbiotic beverage made from soy and yacon extracts containing *Bifidobacterium animalis* ssp. lactis BB-12 on the intestinal polyamine concentrations in elderly individuals. *Food Res Int* 99(Pt 1):495–500. <https://doi.org/10.1016/j.foodres.2017.06.005>
- Marmitt DJ, Goettert MI, Rempel C (2021a) Compounds of plants with activity against SARS-CoV-2 targets. *Expert Rev Clin Pharmacol* 14(4):1–12. <https://doi.org/10.1080/17512433.2021.1903317>
- Marmitt DJ, Shahrajabian MH, Goettert MI, Crempel C (2021b) Clinical trials with plants in diabetes mellitus therapy: a systematic review. *Expert Rev Clin Pharmacol* 14(4):1–14. <https://doi.org/10.1080/1751.2433.2021.1917380>
- Marmitt DJ, Bitencourt S, Silva GR, Goettert MI, Rempel C (2021c) Traditional plants with antioxidant properties in clinical trials—a systematic review. *Phytother Res* 35(10):5647–5667. <https://doi.org/10.1002/ptr.7202>
- Marmitt DJ, Shahrajabian MH (2021) Plant species used in Brazil and Asia regions with toxic properties. *Phytother Res* 35(4):1–24. <https://doi.org/10.1002/ptr.7100>
- Máthé A, Bandoni A (2021) Medicinal and aromatic plants of South America, vol. 2. Springer Nature, Berlin, pp 551. <https://doi.org/10.1007/978-3-030-62818-5>
- McFarlin BK, Venable AS, Henning AL, Prado EA, Sampson JNB, Vingren JL et al (2015) Natural cocoa consumption: potential to reduce atherogenic factors? *J Nutr Biochem* 26(6):626–632. <https://doi.org/10.1016/j.jnutbio.2014.12.015>
- Medzhitov R (2010) Inflammation 2010: new adventures of an old flame. *Cell* 140:771–776. <https://doi.org/10.1016/j.cell.2010.03.006>
- Meizlish ML, Goshua G, Liu Y, Fine R, Amin K, Chang E et al (2021) Intermediate-dose anticoagulation, aspirin, and in-hospital mortality in COVID-19: a propensity score-matched analysis. *Am J Hematol* 96(4):471–479. <https://doi.org/10.1002/ajh.26102>
- Mehta P, McAuley DF, Brown M, Sanchez E, Tattersall RS, Manson JJ, et al. (2020) HLH Across Speciality Collaboration, UK. COVID-19: consider cytokine storm syndromes and immunosuppression. *The Lancet* 395(10229):1033–1034. [https://doi.org/10.1016/S0140-6736\(20\)30628-0](https://doi.org/10.1016/S0140-6736(20)30628-0)
- Miranda-Vilela AL, Pereira LCS, Gonçalves CA, Grisolia CK (2009) Pequi fruit (*Caryocar brasiliense* Camb.) pulp oil reduces exercise-induced inflammatory markers and blood pressure of male and female runners. *Nutr Res* 29(12):850–858. <https://doi.org/10.1016/j.nutres.2009.10.022>
- Monagas M, Khan N, Andres-Lacueva C, Casas R, Urfí-Sardà M, Llorach R et al (2009) Effect of cocoa powder on the modulation of inflammatory biomarkers in patients at high risk of cardiovascular disease. *Am J Clin Nutr* 90(5):1144–1150. <https://doi.org/10.3945/ajcn.2009.27716>
- Montinari MR, Minelli S, De Caterina R (2019) The first 3500 years of aspirin history from its roots—a concise summary. *Vascu Pharmacol* 113:1–8. <https://doi.org/10.1016/j.vph.2018.10.008>
- Mostafaie A (2020) Colchicine plus phenolic monoterpenes to treat COVID-19. *Clinical trials*. Available in: <https://clinicaltrials.gov/ct2/show/NCT04392141>
- Newman DJ, Cragg GM (2020) Natural products as sources of new drugs over the nearly four decades from 01/1981 to 09/2019. *J Nat Prod* 83:770–803. <https://doi.org/10.1021/acs.jnatprod.9b01285>
- NICE (2020) The National Institute for Health and Care Excellence (NICE). Acute Use of Non-steroidal Antiinflammatory Drugs (NSAIDs) for people with or at risk of COVID-19 UK.
- Nishiga M, Wang DW, Han Y, Lewis DB, Wu JC (2020) COVID-19 and cardiovascular disease: from basic mechanisms to clinical perspectives. *Nat Rev Cardiol* 17:543–558. <https://doi.org/10.1038/s41569-020-0413-9>
- Novartis Pharmaceuticals (2021) Study to assess the efficacy and safety of ruxolitinib in patients with COVID-19 associated cytokine storm (RUXCOVID). *Clinical trials*. Available in: <https://clinicaltrials.gov/ct2/show/NCT04362137>
- Pang J, Xu F, Aondio G, Li Y, Fumagalli A, Lu M et al (2021) Efficacy and tolerability of bevacizumab in patients with severe Covid-19. *Nat Commun* 12(1):814. <https://doi.org/10.1038/s41467-021-21085-8>
- Panza VP, Brunetta HS, de Oliveira MV, Nunes EA, da Silva EL et al (2019) Effect of mate tea (*Ilex paraguariensis*) on the expression of the leukocyte NADPH oxidase subunit p47<sup>phox</sup> and on circulating inflammatory cytokines in healthy men: a pilot study. *Int J Food Sci Nutr* 70(2):212–221. <https://doi.org/10.1080/09637486.2018.1486393>
- Petrilli AA, Souza SJ, Teixeira AM, Pontilho PM, Souza JMP, Luzia LA et al (2016) Effect of chocolate and yerba mate phenolic compounds on inflammatory and oxidative biomarkers in HIV/AIDS individuals. *Nutrients* 8(5):132. <https://doi.org/10.3390/nu8050132>
- Pinzón MA (2020) Clinical outcome of patients with COVID-19 pneumonia treated with corticosteroids and colchicine. *Clinical trials*. Available in: <https://clinicaltrials.gov/ct2/show/NCT04654416>
- Piscocoy J, Rodriguez Z, Bustamante SA, Okuhama NN, Miller MJS, Sandoval M (2001) Efficacy and safety of freeze-dried cat's claw in osteoarthritis of the knee: mechanisms of action of the species *Uncaria guianensis*. *Inflamm Res* 50(9):442–448. <https://doi.org/10.1007/PL00000268>
- Pontali E, Volpi S, Signori A, Antonucci G, Castellaneta M, Buzzi D et al (2021) Efficacy of early anti-inflammatory treatment with high doses of intravenous anakinra with or without glucocorticoids in patients with severe COVID-19 pneumonia. *J Allergy Clin Immunol* 147(4):1217–1225. <https://doi.org/10.1016/j.jaci.2021.01.024>
- Price CC, Altice FL, Shyr Y, Koff A, Pischel L, Goshua G et al (2020) Tocilizumab treatment for cytokine release syndrome in hospitalized patients with coronavirus disease 2019: survival and clinical outcomes. *Chest* 158(4):1397–1408. <https://doi.org/10.1016/j.chest.2020.06.006>
- Promptchara E, Ketloy C, Palaga, T (2020) Immune responses in COVID-19 and potential vaccines: lessons learned from SARS and MERS epidemic. *Asian Pac J Allergy Immunol* 38:1–9. <https://doi.org/10.12932/AP-200220-0772>
- Qiang L, Na H, Anni L, Yuanhong Z, Liang L, Xinyu S et al (2021) Effect of low-dose aspirin on mortality and viral duration of the hospitalized adults with COVID-19. *Medicine (baltimore)* 100(6):e24544. <https://doi.org/10.1097/MD.00000000000024544>

- Rahman M (2020) Colchicine in moderate symptomatic COVID-19 patients (COLCOVIDBD). Clinical trials. Available in: <https://clinicaltrials.gov/ct2/show/study/NCT04527562>
- Reis Nunes C, Arantes MB, Pereira SMF, Da Cruz LL, Passos MS, de Moraes LP et al (2020) Plants as sources of anti-inflammatory agents. *Molecules* 25(16):3726. <https://doi.org/10.3390/molecules25163726>
- Rinott E, Kozler E, Shapira Y, Bar-Haim A, Youngster I (2020) Ibuprofen use and clinical outcomes in COVID-19 patients. *Clin Microbiol Infect* 26(9):1259. <https://doi.org/10.1016/j.cmi.2020.06.003>
- Robinson PC, Richards D, Tanner HL, Feldmann M (2020) Accumulating evidence suggests anti-TNF therapy needs to be given trial priority in COVID-19 treatment. *Lancet Rheumatol* 2(11):E653–E655. [https://doi.org/10.1016/S2665-9913\(20\)30309-X](https://doi.org/10.1016/S2665-9913(20)30309-X)
- Rondanelli M, Riva A, Allegrini P, Faliva MA, Naso M, Peroni G et al (2020) The use of a new food-grade lecithin formulation of highly standardized ginger (*Zingiber officinale*) and *Acmella oleracea* extracts for the treatment of pain and inflammation in a group of subjects with moderate knee osteoarthritis. *J Pain Res* 13:761–770. <https://doi.org/10.2147/JPR.S214488>
- Salomé B, Magen A (2020) Dysregulation of lung myeloid cells in COVID-19. *Nat Rev Immunol* 20:277. <https://doi.org/10.1038/s41577-020-0303-8>
- Santamarina AB, Jamar G, Mennitti LV, Cesar HC, Vasconcelos JR, Oyama LM, et al. (2020) Obesity-related inflammatory modulation by juçara berry (*Euterpe edulis* Mart.) supplementation in Brazilian adults: a double-blind randomized controlled trial. *Eur J Nutr* 59(4):1693–1705. <https://doi.org/10.1007/s00394-019-02024-2>
- Sant Pau (2020) Evolution of COVID-19 in anticoagulated or antiaggregated patients (CORONA study) (CORONA). Clinical trials. Available in: <https://www.clinicaltrials.gov/ct2/show/NCT04518735>
- Satış H, Özger HS, Yıldız PA, Hizel K, Gulbahar Ö, Erbaş G et al (2021) Prognostic value of interleukin-18 and its association with other inflammatory markers and disease severity in COVID-19. *Cytokine* 137:155302. <https://doi.org/10.1016/j.cyto.2020.155302>
- Schett G, Sticherling M, Neurath MF (2020) COVID-19: risk for cytokine targeting in chronic inflammatory diseases? *Nat Rev Immunol* 20:271–272. <https://doi.org/10.1038/s41577-020-0312-7>
- Singanayagam A, Glanville N, Johnston SL (2018) Corticosteroid suppression of antiviral immunity increases bacterial loads and mucus production in COPD exacerbations. *Nat Commun* 9(1):2229. <https://doi.org/10.1038/s41467-018-04574-1>
- Smail SW, Saeed M, Alkasalies T, Khudhur ZO, Younus DA, Rajab MF et al (2021) Inflammation, immunity and potential target therapy of SARS-COV-2: a total scale analysis review. *Food Chem Toxicol* 150:112087. <https://doi.org/10.1016/j.fct.2021.112087>
- Solà R, Valls RM, Godàs G, Perez-Busquets G, Ribalta J, Girona J et al (2012) Cocoa, hazelnuts, sterols and soluble fiber cream reduces lipids and inflammation biomarkers in hypertensive patients: a randomized controlled trial. *PLoS ONE* 7(2):e31103. <https://doi.org/10.1371/journal.pone.0031103>
- Somanah J, Aruoma OI, Gunness TK, Kowlessur S, Dambala V, Murad F et al (2012) Effects of a short term supplementation of a fermented papaya preparation on biomarkers of diabetes mellitus in a randomized Mauritian population. *Prev Med* 54(Suppl):S90–97. <https://doi.org/10.1016/j.ypmed.2012.01.014>
- Stebbing J, Phelan A, Griffin I, Tucker C, Oechsle O, Smith D et al (2020) COVID-19: combining antiviral and anti-inflammatory treatments. *Lancet Infect Dis* 20:400–402. [https://doi.org/10.1016/S1473-3099\(20\)30132-8](https://doi.org/10.1016/S1473-3099(20)30132-8)
- Strohbehn GW, Heiss BL, Rouhani SJ, Trujillo JA, Yu J, Kacew AJ et al (2021) COVIDOSE: a phase II clinical trial of low-dose tocilizumab in the treatment of noncritical COVID-19 pneumonia. *Clin Pharmacol Ther* 109(3):688–696. <https://doi.org/10.1002/cpt.2117>
- Stockler-Pinto MB, Mafra D, Moraes C, Lobo J, Boaventura GT, Farage NE, et al. (2014) Brazil nut (*Bertholletia excelsa*, H.B.K.) improves oxidative stress and inflammation biomarkers in hemodialysis patients. *Biol Trace Elem Res* 158(1):105–112. <https://doi.org/10.1007/s12011-014-9904-z>
- Stote KS, Clevidence BA, Novotny JA, Henderson T, Radecki SV, Baer DJ (2012) Effect of cocoa and green tea on biomarkers of glucose regulation, oxidative stress, inflammation and hemostasis in obese adults at risk for insulin resistance. *Eur J Clin Nutr* 66(10):1153–1159. <https://doi.org/10.1038/ejcn.2012.101>
- Syeda AF (2020) Comparison of efficacy of dexamethasone and methylprednisolone in moderate to severe Covid 19 disease (covid19). Clinical trials. Available in: <https://clinicaltrials.gov/ct2/show/NCT04603729>
- Talsma EF, Brouwer ID, Verhoef H, Mbera GNK, Mwangi AM, Demir AY et al (2016) Biofortified yellow cassava and vitamin A status of Kenyan children: a randomized controlled trial. *Am J Clin Nutr* 103(1):258–267. <https://doi.org/10.3945/ajcn.114.100164>
- Tardif JC (2020) Colchicine coronavirus SARS-CoV2 trial (COLCORONA) (COVID-19). Clinical trials. Available in: <https://clinicaltrials.gov/ct2/show/NCT04322682>
- Tay MZ, Poh CM, Rénia L, MacAry PA, Ng LFP (2020) The trinity of COVID-19: immunity, inflammation and intervention. *Nat Rev Immunol*. <https://doi.org/10.1038/s41577-020-0311-8>
- Tian J, Zhang M, Jin M, Zhang F, Chu Q, Wang X et al (2021) Repurposed tocilizumab in patients with severe COVID-19. *J Immunol* 206(3):599–606. <https://doi.org/10.1093/jimmunol.2000981>
- Tomazini BM, Maia IS, Cavalcanti AB, Berwanger O, Rosa RG, Veiga VC et al (2020) Effect of dexamethasone on days alive and ventilator-free in patients with moderate or severe acute respiratory distress syndrome and COVID-19: the CoDEX randomized clinical trial. *JAMA* 324(13):1307–1316. <https://doi.org/10.1001/jama.2020.17021>
- Ulloa Ulloa C, Acevedo-Rodríguez P, Beck S, Belgrano MJ, Bernal R, Berry PE et al (2017) An integrated assessment of the vascular plant species of the Americas. *Science* 358(6370):1614–1617. <https://doi.org/10.1126/science.aao0398>
- Vanassche T, Engelen MM, Van Thillo Q, Wauters J, Gunst J, Wouters C et al (2020) A randomized, open-label, adaptive, proof-of-concept clinical trial of modulation of host thromboinflammatory response in patients with COVID-19: the DAWn-Antico study. *Trials* 21(1):1005. <https://doi.org/10.1186/s13063-020-04878-y>
- Vieçili PRN, Borges DO, Kirsten K, Malheiros J, Vieçili E, Melo RD et al (2014) Effects of *Campomanesia xanthocarpa* on inflammatory processes, oxidative stress, endothelial dysfunction and lipid biomarkers in hypercholesterolemic individuals. *Atherosclerosis* 234(1):85–92. <https://doi.org/10.1016/j.atherosclerosis.2014.02.010>
- Villar J, Añón JM, Ferrando C, Aguilar G, Muñoz T, Ferreres J et al (2020) Efficacy of dexamethasone treatment for patients with the acute respiratory distress syndrome caused by COVID-19: study protocol for a randomized controlled superiority trial. *Trials* 21(1):717. <https://doi.org/10.1186/s13063-020-04643-1>
- Xu Z, Shi L, Wang Y, Zhang J, Huang L, Zhang C et al (2020a) Pathological findings of COVID-19 associated with acute respiratory distress syndrome. *Lancet Respir Med* 8:420–422. [https://doi.org/10.1016/S2213-2600\(20\)30076-X](https://doi.org/10.1016/S2213-2600(20)30076-X)
- Xu X, Han M, Li T et al (2020b) Effective treatment of severe COVID-19 patients with tocilizumab. *Proc Natl Acad Sci USA* 117:10970–10975. <https://doi.org/10.1073/pnas.2005615117>



- Wang L, Tao L, Hao L, Stanley TH, Huang KH, Lambert JD et al (2020a) A moderate-fat diet with one avocado per day increases plasma antioxidants and decreases the oxidation of small, dense LDL in adults with overweight and obesity: a randomized controlled trial. *J Nutr* 150(2):276–284. <https://doi.org/10.1093/jn/nxz231>
- Wang L, He W, Yu X, Hu D, Bao M, Liu H (2020b) Coronavirus Disease 2019 in elderly patients: characteristics and prognostic factors based on 4-week follow-up. *J Infect* 80(6):639–645. <https://doi.org/10.1016/j.jinf.2020.03.019>
- Wang L (2020) C-reactive protein levels in the early stage of COVID-19. *Med Mal Infect* 50(4):332–334. <https://doi.org/10.1016/j.medmal.2020.03.007>
- WHO (2020) The use of non-steroidal anti-inflammatory drugs (NSAIDs) in patients with COVID-19. Available in: [https://www.who.int/news-room/commentaries/detail/the-use-of-non-steroidal-anti-inflammatory-drugs-\(nsaids\)-in-patients-with-covid-19](https://www.who.int/news-room/commentaries/detail/the-use-of-non-steroidal-anti-inflammatory-drugs-(nsaids)-in-patients-with-covid-19)
- Willis RA, Nussler AK, Fries KM, Geller DA, Phipps RP (1994) Induction of nitric oxide synthase in subsets of murine pulmonary fibroblasts: effect on fibroblast interleukin-6 production. *Clin Immunol Immunopathol* 71(2):231–239. Doi: <https://doi.org/10.1006/clin.1994.1077>
- Wu J (2020) Tackle the free radicals damage in COVID-19. *Nitric Oxide* 102:39–41. <https://doi.org/10.1016/j.niox.2020.06.002>
- Yağın S, Yağınkaya S, Ercan F (2021) In silico detection of inhibitor potential of *Passiflora* compounds against SARS-CoV-2(Covid-19) main protease using molecular docking and dynamic analyses. *J Mol Struct* 1240:130556. <https://doi.org/10.1016/j.molstruc.2021.130556>
- Yañez O, Osorio MI, Areche C, Vasquez-Espinal A, Bravo J, Sandoval-Aldana A, et al. (2021) *Theobroma cacao* L. compounds: theoretical study and molecular modeling as inhibitors of main SARS-CoV-2 protease. *Biomed Pharmacother* 140:111764. <https://doi.org/10.1016/j.biopha.2021.111764>
- Zhao Y (2020) Longitudinal COVID-19 profiling associates IL-1RA and IL-10 with disease severity and RANTES with mild disease. *JCI Insight*. <https://doi.org/10.1172/jci.insight.139834>
- Zídek Z, Anzenbacher P, Kmoníčková E (2009) Current status and challenges of cytokine pharmacology. *Br J Pharmacol* 157(3):342–361. <https://doi.org/10.1111/j.1476-5381.2009.00206.x>

**Publisher's Note** Springer Nature remains neutral with regard to jurisdictional claims in published maps and institutional affiliations.