View Abstract

CONTROL ID: 3522950

CURRENT CATEGORY: Microbiome & Microbial Therapy

CURRENT SUBCATEGORY/DESCRIPTORS: COVID and Interactions with the Microbiome and COVID and Immune Defense

PRESENTATION TYPE: AGA Institute Oral or Poster

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ABSTRACT

TITLE: ORAL TANNINS REDUCE PROINFLAMMATORY CYTOKINES ASSOCIATED WITH DIARRHEA AND PNEUMONIA IN HOSPITALIZED COVID-19 PATIENTS.

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ABSTRACT BODY:

Abstract Body: INTRODUCTION: There is evidence that the gut microbiota and its relationship with the immune system could be involved in the pathogenesis of COVID-19. SARS-CoV-2 can cause gastrointestinal symptoms during the early phases of the disease. Intestinal dysfunction induces changes in intestinal microbes, and an increase in inflammatory cytokines. Therefore, microbiota modulation could play a role in COVID-19 treatment. Tannins have been shown to work as prebiotics on the gastrointestinal microbiota. In particular, quebracho and chestnut tannins have shown to regulate the immune response and decrease in vitro-cytokines production, through microbiota fermentation-secondary metabolites, such as quercetin and SCFAs.

OBJECTIVE: To evaluate the efficacy and the effect on cytokine levels of a tannin specific natural extract in COVID-19 patients.

MATERIAL AND METHODS: This prospective, double-blind, and randomized study was approved by the Hospital de Clínicas, José de San Martín (Buenos Aires, Argentina). Blood and stool samples were collected at baseline (Day 0) and after treatment (Day 14) during July-October 2020, with final follow-up in November 2020. We randomly assigned 124 RT-PCR confirmed COVID-19 cases (>18 years) to receive oral dry extracts of quebracho and chestnut tannins (240 mg) and B12 vitamin (0.72 µg) or placebo, twice daily for 14 days as adjunct treatment to their standard of care management. 27- pro and anti-inflammatory cytokines were measured on day 0 and 14 (Bio-Plex Pro™, Bio- Rad). Final enrollment of 140 patients with matched fecal microbiome characterization (16S, WGS and metabolites) is expected.

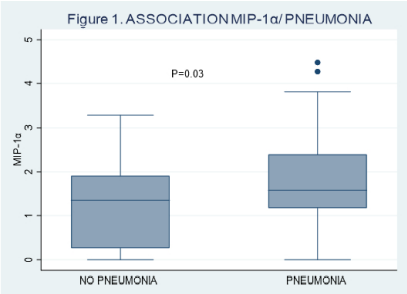
RESULTS. Of 124 patients who were randomized (mean age 55+/-15, 63 [50.81%] male), 121 (97.58%) completed the trial. No adverse events were observed in the tannin group. Patients presenting with diarrhea (13%) had a trend to have elevated blood MIP-1α levels, which were significantly reduced by tannin treatment (Table 1). At baseline, higher levels of MIP-1α were also associated with diagnosis of pneumonia (Fig. 1), which was maintained after adjusting for confounders (age, sex, diabetes; p=0.04). Moreover, at baseline there was a positive correlation between MIP-1 α and IL-1ra, IL-2, MIP-1b and TNF- α, with all of these cytokines decreasing mostly with tannin treatment.

CONCLUSION: To our knowledge, this clinical trial represents the first study to target the gut microbiome in

hospitalized COVID-19 patients. Oral tannins as adjunct treatment with standard-of-care management of these patients significantly reduced proinflammatory cytokine levels that are generally associated with poor predictive outcomes, i.e. pneumonia and diarrhea. Further, our prospective studies will determine which microbiome-mediated mechanisms may attenuate the cytokine storm that is evident in COVID-19 disease pathogenesis.

Table 1. Comparison of Cytokines levels at day 0 and 14

	Tannin n=62			Placebo n=62			P
	Day 0	Day 14	Difference (IQR)	Day 0	Day 14	Difference (IQR)	
CYTOKINES (pg/ml). Median (IQR)	N=51	N= 48		N=49	N= 45		
IL-1ra	385,47 (219,18-532,35)	280,44 (140,71-537,65)	-33,62 (-179,1-108,46)	343,07 (254,33-603,82)	359,88 (219,18-513,23)	8,35 (-156,17-121,65)	0,67
IL-2	0,78 (0-2,1)	0 (0-0,78)	-0,19 (-1,32- 0)	1,22 (0,44-2)	0,78 (0-1,22)	0 (-0,89-0)	0,58
MIP-1α	1,39 (0,74-2,07)	0,87 (0,29-1,69)	-0,25 (-0,95-0,35)	1,58 (1,17-2,36)	1,66 (1,28-2,56)	0 (-0,47-0,94)	0,03
MIP-1β	79,62 (64,76-95,61)	85,11 (64,2-96,39)	-0,91 (-6,93-10,46)	79,76 (66,89-89,76)	87,1 (72,49-93,74)	4,68 (-7,89-13,59)	0,48
TNF-α	44,26 (33,82-67,32)	39,48 (28,2-53,83)	-6,99 (-11,28- -1,33)	40,48 (31-48,03)	39,53 (31-45,21)	-2,78 (-11,18-4,73)	0,08



DISCLOSURE

The following authors have completed their 2021 DDW disclosure: Ana Pisarevsky: Disclosure completed | Fabiana Lopez Mingorance: Disclosure completed | Patrica Vega: Disclosure completed | Juan Stefanolo: Disclosure completed | Julieta Repetti: Disclosure completed | Guillermina Ludueña: Disclosure completed | Pablo Pepa: Disclosure completed | Juan Olmos: Disclosure completed | Marcelo Rodríguez Fermepin: Disclosure completed | Silvia Molino: Disclosure completed | Tatiana Uehara: Disclosure completed | Elisa Viciani: Disclosure completed | Sonia Villapol: Disclosure completed | Andrea Castagnetti: Disclosure completed | Tor Savidge: Disclosure completed | Todd Treangen: Disclosure completed | Maria Piskorz: Disclosure completed