

LETTER

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Potential Role of Acacia Senegal (Gum Arabic) as Immunomodulatory Agent among newly diagnosed COVID 19 Patients: A structured summary of a protocol for a randomised, controlled, clinical trial

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Abstract

Objectives: To investigate the potential efficacy of Acacia Senegal extract Gum Arabic (GA) supplementation as immunomodulatory and anti-inflammatory dietary intervention among newly diagnosed COVID 19 Sudanese patients. To study the effect of GA on the level of cytokines, TNF α , IL8, IL6 IL10, CRP and the viral load. Secondary outcomes will be the effect of GA oral intake on mortality rate and days of hospital admission.

Trial design: Quadruple blind, randomized placebo-controlled clinical trial Phase II & III. Prospective, two-arm, parallel-group, randomised (1:1 allocation ratio) superiority trial of oral GA among seropositive COVID-19 patients.

Participants: Inclusion criteria:

COVID-19 infected (newly diagnosed) as proved by real-time PCR within 72 hours of PCR.

Age 8-90 years

Both genders

Exclusion criteria:

Intubated patients on parenteral treatment

Allergy to Gum Arabic

The study will be conducted in COVID Isolation Centres and Soba University Hospital Khartoum State Sudan.

Intervention and comparator: Experimental: Intervention Group

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This arm will receive 100% natural Gum Arabic provided in a powder form in 30-grams-dose once daily for four weeks
 Placebo Comparator: Control group: This group will be provided with pectin powder provided as one-gram-dose once daily for four weeks

Both GA and placebo will be in addition to standard care treatment based on local clinical guidelines.

Main outcomes: Mean change from baseline score of Immune Response to end of the trial. Changes of the level of Tumor Necrosis Factor (TNF α), interleukin IL8, IL6, and IL10 from the baseline values (Four weeks from the start of randomization).

Mortality rate: The percentage of deaths among COVID 19 patients received Gum Arabic compared to placebo (Four weeks from the start of randomization)).

Randomisation: Randomization (1:1 allocation ratio) and will be conducted using a sequence of computer-generated random numbers by an independent individual.

Each participating centre will be assigned a special code generated by the computer. The randomization will be kept by the PI and a research assistant.

Blinding (masking): Quadruple (Participant, Care Provider, Investigator, Outcomes Assessor)

Numbers to be randomised (sample size): 110 eligible patients will be randomly assigned to either GA (n=55) or placebo (n=55) groups.

Trial Status: Protocol Version no 2, 30th June 2020. Recruitment will start on 15th September 2020. The intended completion date is 15th January 2021.

Trial registration: ClinicalTrials.gov Identifier: [NCT04381871](https://clinicaltrials.gov/ct2/show/study/NCT04381871). Date of trial registration: 11 May 2020.

Full protocol: The full protocol is attached as an additional file, accessible from the Trials website (Additional file 1). In the interest in expediting dissemination of this material, the familiar formatting has been eliminated; this Letter serves as a summary of the key elements of the full protocol.

Keywords: COVID-19, Randomised controlled trial, protocol, Gum Arabic, cytokines, Immunomodulation

Supplementary information

Supplementary information accompanies this paper at <https://doi.org/10.1186/s13063-020-04707-2>.

Additional file 1. Full Study Protocol.

Acknowledgements

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Authors' contributions

LK, RB, SS and MN participated in the study design. LK, RB, MN, ME, SS and AS will be involved in all aspects of the study conduction. RB, SS, NA, and SA will collect the data from the centres. MM and SA will conduct the laboratory work. LK, RB, NE, ME and MN will analyse the data. All authors approved the final version of the manuscript.

Funding

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Availability of data and materials

The datasets used and/or analysed during the current study will be available from the corresponding author on reasonable request

Ethics approval and consent to participate

The study was approved by the Central Institutional Review Board at Al-Neelain University 23rd April 2020 (NUM-IRP-20-09-04-1). We confirm that this trial has received ethical approval from the appropriate ethical

committee described above. Written informed consent will be obtained from each participant prior to enrolment or from the legal guardian for patients aged less than 18 years old.

Consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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Date Received:

00

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Part2

1. Title of Proposal:

Protective effect of Gum Arabic (*Acacia Senegal*) supplementation on immune responses and inflammatory markers among COVID 19 Patients

Double Randomized two arms clinical trial

Introduction:

COVID 19 Coronavirus disease (COVID-19) is caused by SARS-COV2 and represents the causative agent of a potentially fatal disease caused global public concern. The disease spreads rapidly compared to the previous pandemics, which makes it more difficult to contain. Due to this, there is an urgent need for fast diagnosis, preventive and therapeutic measures. Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-inflammatory cytokines. Main mechanism for ARDS (Acute Respiratory Distress Syndrome) is the cytokine storm, uncontrolled systemic inflammatory response resulting from the release of pro-inflammatory cytokines. The cytokine storm will trigger a violent attack by the immune system to the body, cause ARDS and multiple organ failure, and finally death in severe cases. Current investigations, demonstrated that T cell numbers are negatively correlated to serum IL-6, IL-10 and TNF- α concentration, and proposed T cells as potential therapeutic target.

Butyrate, is an epigenetic regulator via its capacity to act as a histone deacetylase (HDAC) inhibitor. This may be directly relevant to the modulation of covid-19 infection. Although data on the biological interactions of covid-19 with human physiology have still to be published, HDAC inhibition is a common regulator of the effects of many viruses, including the influenza virus. The inhibition of HDAC1, as induced by butyrate, decreases influenza-driven pneumonia infections.

Gum Arabic (GA) is a safe dietary fibres approved by FDA and WHO. It is high molecular weight polysaccharide retrieved from *Acacia Senegal* and *Acacia Seyal* trees. GA fermentation produced short chain fatty acids mainly propionate and butyrate. Gum Arabic has anti-inflammatory effect

which has been investigated in various diseases and conditions.

Scientific Background:

COVID 19 Pathogenesis:

COVID 19 Coronavirus disease (COVID-19) is caused by SARS-COV2 and represents the causative agent of a potentially fatal disease that is of great global public health concern(1, 2).

Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-inflammatory cytokines(1-3). Additionally, a value of 16.16 mg/L of blood C-reactive protein was noted which is above the normal range (0–10 mg/L)(2). Patients infected with COVID-19 showed higher leukocyte numbers, abnormal respiratory findings, and increased levels of plasma pro-inflammatory cytokines. Significantly high blood levels of cytokines and chemokines were noted in patients with COVID-19 infection that included IL1- β , IL1RA, IL7, IL8, IL9, IL10, basic FGF2, GCSF, GMCSF, IFN γ , IP10, MCP1, MIP1 α , MIP1 β , PDGFB, TNF α , and VEGFA(1) The latest report shows the number of CD4+ and CD8+ T cells in the peripheral blood of SARS-CoV-2-infected patients significantly is reduced, Similarly, the acute phase response in patients with SARS-CoV is associated with severe decrease of CD4+ T and CD8+ T cells(3). The report in Lancet shows ARDS is the main death cause of COVID-19. Of the 41 SARS-CoV-2-infected patients admitted in the early stages of the outbreak, six died from ARDS(3). Main mechanism for ARDS is the cytokine storm, the deadly uncontrolled systemic inflammatory response resulting from the release of large amounts of pro-inflammatory cytokines (3).The cytokine storm will trigger a violent attack by the immune system to the body, cause ARDS and multiple organ failure, and finally lead to death in severe cases of SARS-CoV-2 infection(1, 2) . IFN-I(IFN- α and IFN- β) has a protective effect on SARS-CoV and MERS-CoV infection, but the IFN-I pathway is inhibited in infected mice(4). n Number of total T cells, CD4+ and CD8+ T cells were dramatically reduced in COVID-19 patients, especially among elderly patients (≥ 60 years of age) and in patients requiring Intensive Care Unit (ICU)(3). Statistical analysis demonstrated that T cell numbers are negatively correlated to serum IL-6, IL-10 and TNF- α concentration, potential therapeutic targets preventing cytokine storm.

Gum Arabic mechanism of action:

Gum Arabic fermentation increased the level of serum butyrate. Butyrate, including in its nutraceutical form, sodium butyrate, is an epigenetic regulator via its capacity to act as a histone deacetylase (HDAC) inhibitor. This may be directly relevant to the modulation of covid-19 infection(5). Although data on the biological interactions of covid-19 with human physiology have still to be published, HDAC inhibition is a common regulator of the effects of many viruses, including the influenza virus. The inhibition of HDAC1, as induced by butyrate, decreases influenza-driven pneumonia infections(5)

Gum Arabic (GA) is a safe dietary fibres approved by FDA and WHO(6). It is high molecular

weight non-starch polysaccharide retrieved from Achaia Senegal and Achaia Seyal trees(6, 7). GA is mainly fermented by colonic bacteria instead of been digested among humans(8) and animals (6, 7). GA fermentation produced short chain fatty acids mainly propionate and butyrate (6-8). The latter discovered as physiological modifier for different body function like modulation of cell proliferation, apoptosis, regulation of angiogenesis and inflammation(9). Gum Arabic anti-inflammatory effect has been investigated in various diseases and conditions (10-12). GA exerted local anti-inflammatory effects by modifying nuclear factor- κ B (NF- κ B) on the small intestine(13).

Gum Arabic as anti-inflammatory agent:

Gum Arabic anti-inflammatory effect has been investigated in clinical trials (10,12). An anti-inflammatory effect of GA was demonstrated via the application of GA in drinking water given to rats with diabetes mellitus by a decrease of TNF α and IL-1 β and increase of IL-10 (14).

Interestingly, Bovo et al. investigated the effect of GA on the complement system, as arabinogalactans are reported to be complement system modulators. The authors showed a pro-inflammatory activity of GA by activation of the classical and alternative pathways of the complement system (15). GA exerted local anti-inflammatory effects by modifying nuclear factor- κ B (NF- κ B) on the small intestine (12). In addition, a reduction of oxidative stress was shown after GA supplementation of drinking water in the liver tissue of rats with type I diabetes (16) and oral GA supplementation in humans suffering from sickle cell anemia (17). GA significantly increased oxidative burst/ROS production of bovine and human granulocytes in a dose-dependent manner (18,19). Similarly, arabinogalactan–protein (AGP) of GA may have pro-inflammatory properties on certain parts of the immune system(18, 20).

From all the above the main pathogenesis of COVID 19 is due to inflammatory process and cytokine storm. Gum Arabic is a prebiotic dietary fibers with proven anti-inflammatory properties and immunomodulatory agent. Nowadays, most of research have carried out on corona-virus are in the primary stages and the exact mechanisms remains unknown, infection spread and deaths are increasing in daily bases, the urge for vaccine and protective elements against the immunological response of the body against the virus is needed.

Justification:

A novel corona virus from Wuhan in central China, named 2019- nCoV, has recently caused an epidemic of pneumonia in humans and posed a huge threat to global public health. To the Date according to national ECDPC -nCoV has led to more than 2744744 cases including 195387 deaths. Which put heath system word wide in great challenge because no licensed vaccine and specific treatment. Identification of natural products with direct antimicrobial effects or also immunomodulatory effects to boost the innate immune defense is a promising strategy to identify and characterize new treatment or prevention strategies. GA is a well-known traditional herbal medication from Acacia Senegal. Gum Arabic is prebiotic agent, with immune modulator properties. Enhancing natural immunity and ameliorate the cytokines storm, will be of great

benefits for COVID 19 patients to overcome the disease.

3. Objectives

General objective:

Explore the role of Gum Arabic as immune modulator among COVID 19 Sudanese patients.

Specific objectives:

- 1- To understand the immune response of disease progression and physiological pathway in patients consuming Gum Arabic (Acacia Senegal) for one month.
- 2- To study the innate and acquired mechanisms of defense against the coronavirus (cytokine and antibody responses) in placebo and experimental groups in each.
- 3- To assess clinical progression of the disease in group treated with Gum Arabic (Acacia Senegal)
- 4- Measure the level of anti-inflammatory marker (CRP & TNF α , IL6, IL10, IF γ) before and after GA ingestion

4. Methodology

- Study Plan: (Phases, Activities)

Phase III clinical trial

Method:

Study design: Double blind, randomized placebo controlled clinical trial Phase III.

The study will be conducted on patients with COVID 19 infection for 4 weeks.

Study setting: The study will be conducted in Khartoum Isolation centers and Soba hospital Khartoum State Sudan

Sample size: All Patients who presented to Gabra and Soba hospital and confirmed with COVID 19 during the study period will be included after satisfying the inclusion criteria

Study population: (inclusion and exclusion criteria)

(Inclusion criteria:)

1-COVID 19 infected as proved by real time PCR. (Newly diagnosed)

2-Age 8-90 years

3-Both gender

Exclusion criteria:

1-Intubated patients on parental treatment

2- Pregnancy

3- Gum Arabic allergy

Randomization and blinding:

The subjects, after stratification by age and sex, will randomly assigned to receive coded and indistinguishable Gum Arabic or placebo. Randomization will be conducted by using a sequence of computer-generated random numbers by independent individual.

Each participating center will be assigned a special code generated by the computer. The

randomization will be kept by the PI and a research assistant. The assessor for clinical outcomes would be blinded to the randomization status. The research staffs who perform the intervention would not know the assessment results. After the eligibility assessment by viral screening, laboratory and clinical assessments would be conducted at the baseline (after completion of informed consent), at first, second and 4th week

Gum Arabic administration:

GA in powder form, it is a 100% natural extract powder produced mechanically from the wildy grown Acacia Senegal tree with a particle size less than 210 µm. The daily dose is 45 gram per day. It will be given in one sachet to be consumed in the early morning dissolved in 200 ml of water. The GA will be provided to the participants weekly for four weeks (7 sachets for each visit). Standardized questionnaire and check list will be used to collect data about patients' physical examination, weight, height, severity of the symptoms and any side effects. Gum Arabic will be purchased from nature gum company, Khartoum Sudan.

Placebo will be pectin one gram per day. It will be given in one sachet to be consumed in the early morning dissolved in 200 ml of water for 4 weeks.

Investigations:

The procedures for screening will be performed within one week before dosing, except where otherwise stated, and included the following:

- 1- Medical history,
- 2- Physical examination, including weight, height and vital signs.

3- The following routine laboratory tests: (A) CBC (B) serum chemistry

including renal function tests (RFT) and Liver function test (LFT)

(serological tests)

- i. **Real time PCR:** To determine the viral load
- ii. **Flowcytometry:** To measure the CD4 counts.
- iii. **ELISA for cytokines**

Study protocols:

Each patient will receive daily dose

The patients will be followed every week and the following investigation will be done during the visit for follow up: CBC, and urine analysis. LFT and RFT will be done weekly

Blood samples will be collected by certified nurse and will be used solely for the research purposes and will be destructed after completing the project.

Primary outcome:

Mean change from baseline score of Immune Response to end of the trial (Time Frame: up to 4 weeks)

Secondary outcome:

1-clinical improvement and hospital discharge [Time Frame: from the date of assignment until the date of hospital discharge for the last assigned case, whichever comes first, assessed up to two months]

2-Time of discharge from hospital after full recovery

5. Data analysis (Methods used for Data analysis)

Data will be collected and coded and entered in excel sheet.

SPSS .24 and Graph prism will be used. Paired *t* test will be used to determine statistical significance between baseline and post treatment results. *P* equal to or less than .05 will consider statistically significant. Data will be presented as means ($\pm$ SD).

- **References:**

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- **Annexes:**

-Ethics consideration

بروتوكول البحث -

-Relevant C.V for Principal investigator

الأخلاقية الإعتبارات -

-Declaration of the authority responsible for research

الذاتية للباحث الاساسي السيرة

-Declaration of Agreement for Participation in the Research

اقرار الجهة المسؤولة عن البحث -

إقرار موافقة للمشاركة في البحث-

استمارة تقييم الوحدات البحثية للجهات التي يسمح فيها إجراء -
التجارب الطبية

- إحضار عقد الجهة البحثية والجهة الممولة للبحث

