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Clinical Safety Evaluation of an Herbal Gel Containing 2.5% *Arrabidaea chica* Verlot Standardized Extract

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Abstract

Oral Mucositis (OM) is a quite common adverse event due to cancer treatments. There are effective laser treatments for the prevention and therapy of OM, however, the lack of trained professionals difficult the use of this technique in Brazil´s public hospitals, being necessary alternative treatments to circumvent this issue. Non-clinical studies conducted by our group to elucidate the mechanism of action of *A. chica* extract with further toxicity on genotoxicity and mutagenicity reports provided necessary data to apply for authorization to conduct clinical trial with the herbal gel containing 2.5% *Arrabidaea chica* Verlot standardized extract. The open-label clinical trial protocol aims to access safety issues of the herbal gel on oral mucosa of healthy research participants. This clinical trial was approved by the ethics committee of research in humans at the Faculty of Medical Sciences of University of Campinas (report no. 007891/2015). Results of this trial demonstrated that herbal gel is safe, which culminated in the approval of the phase 2 clinical study protocols.

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Introduction

Clinical trials are a way to test new methods of diagnosing, treating, or preventing health conditions. The goal is to determine whether something is both safe and effective. Clinical trials take place in four different phases during which different questions are asked. Each phase provide evidence on safety and efficacy issues related to the intervention under study. Drug developments proceed throughout all four phases over a long period of time. With phase four being a surveillance phase after post marketing to monitor safety issues with broaden use. Phase I focuses on safety issues with participant groups that range from 20 to 100 research participants, generally with healthy individuals aiming to determine which is the highest dose humans can tolerate without serious side effects. Investigators monitor this phase closely to see the drug candidate's outcome on participants' health [1].

These studies are fundamental to identify new products for the relief of symptoms that cause patients suffering, seeking to improve patient's life quality. Among diseases that are life-threatening with various side effects arising from treatment are neoplasia. Oral Mucositis (OM) is a frequent event in patients treated with radiotherapy and/or chemotherapy, which tends to appear in buccal and labial surfaces, the ventral surface of the tongue, the floor of the mouth, and the soft palate of patients. This side effect interferes in patient's life quality since oral mucositis is associated with considerable pain and dysphagia which also complicates nutritional intake, increases susceptibility to infections, and leads to cancer treatment interruption, that has outcomes on total treatment increased cost [2-6].

The Brazilian government published the RENISUS list that consist of plants that are of interest to further study for the purpose to apply in the public system of health (SUS) [7]. *Arrabidaea chica* (Humb. & Bonpl.) Verlot, was included in this list as result of previous reports indicating healing and antiulcerogenic activity in preclinical studies [8,9]. The crude standardized *A. chica* extract, enriched with anthocyanins, demonstrated calcaneus tendons healing in animal model [10], along with reduction of cutaneous 'ulcerations, evaluated in experimental *in vivo* healing experimental model with semisolid basis incorporated extract [11]. *Arrabidaea chica* extract decreased 96% wound area in dermal ulcer models of male Wistar rats. In diabetic Wistar rats, *A. chica* extract decreased the ulcerated area by 85% [12].

Preclinical toxicity study with *A. chica* extract evaluated on Salmonella test and *in vivo*

micronucleus test from mice bone marrow confirmed that the sample tested did not present any mutagenic or genotoxic potential, inferring the extract to be genetically safe [13]. In gastrointestinal tract mucositis and oral mucositis experimental models induced by 5-fluoracil in mice and hamsters showed that animals treated with *A. chica* extract had an increase in survival lifespan in comparison with the negative control. Furthermore a decrease of diarrhea and increase of food intake was also observed [14]. Recently Wiziack Zago et al. reported that at low concentrations, *A. chica* extract showed promising cytoprotective effects against zoledronic acid induced damage.

These results contributed to the development of the phase I clinical study protocol with the objective of identifying possible adverse events and toxicity signs of the herbal medicine containing *A. chica* extract applied to healthy participants.

Clinical Experience with Phase 1 Studies

In the order to evaluate the safety of an herbal gel containing 2.5% *Arrabidaea chica* Verlot standardized extract on the oral mucosa of healthy research participants a phase 1 clinical trial protocol submitted to the Research Ethics Committee (CEP) was developed. This clinical trial was approved by the ethics committee of research in humans at the Faculty of Medical Sciences of University of Campinas (report no. 007891/2015).

Twenty research participants were selected after laboratory, clinical, and dental evaluation. Ten men and ten women, who were framed within the concept of healthy individuals. Following Resolution 466 of December 2012 [1], participants signed the Informed Consent Form (ICF) before entering the open-label study carried out during 30 days. On May 19th, 2016, after medical, dental, and pharmaceutical anamnesis, 1 pump pack containing the herbal medicine (the study object) was dispensed. The herbal medicine was given to participants every 10 days within 30 calendar days.

The instructions were to use the gel three times a day, morning, afternoon, and night, in 4 different oral mucosa regions (palate, right and left cheek, under the tongue). Before each application, participants were guided to sanitize the oral cavity by brushing and flossing teeth with no further water and food intake for 30 min after product application. The participants remained in their routine activities and maintained their normal general diets.

Each participant had a paper file for registering any discomfort or pertinent observation, during the 30 days of gel application, such as burning, use of concomitant medication or even forgetting to apply the gel. Weekly, the participants were submitted to clinical pharmaceutical, medical, and dental evaluations. At the end of the 30 days of gel application, all the participants repeated the laboratory tests which, together with the diary and the clinical annotations of the medical records were analyzed to evaluate the possible adverse events generated by the use of the herbal medicine.

There are no reports of adverse events found in the literature for the crude extract of *Arrabidaea chica*, therefore, for patient follow-up, the events described in the package insert of a mucoadhesive herbal gel already commercialized and prescribed for mucositis, such as dry mouth, rash, itching, coughing, redness in the face, among other hypersensitivity reactions that could arise were monitored. The extract's red coloring was also taken into account, since the extract could stain mucosa and teeth. Also any discomfort caused by the texture of the gel associated with the sweet taste due to the natural sugars present in the extract was assessed regarding the presence of nausea and even vomiting at the time of application. For security monitoring purposes, the participants were monitored daily and any and every report thoroughly analyzed.

According to the report of all the at the application sites, the oral mucosa, as well as the nearby teeth, were stained with "bright" red, but after a few hours, this color was no longer visible. During the study, the following adverse events were observed:

* A participant, displayed throat inflammation after medical evaluation that was promptly treated with anti-inflammatory drugs, nevertheless this event after a thorough clinical evaluation was proven not to have relationship with the test medication.

* Complaint of migraine, from a participant after using the herbal medicine for the first time. As the first application of the gel was assisted by the research team, the medical and dental evaluation was immediate, where the use of an analgesic was advised. The second application was then carried out under the supervision of the research investigator and there was no further complaint. The adverse event, after clinical evaluations, therefore did not have relationship with the use of the gel.

* Report of unpleasant taste by a participant but without signs of nausea or rejection of the gel.

* A participant reported that the gel had better grip on the cheeks and felt a numbness in the region of the tongue. After dental evaluation, this reported event may be related to the use of the test medication.

* A participant reported pain in the dental arch after the tenth day of the study. Self-medicated with an analgesic and reported pain improvement. The day after the report, a dental evaluation was performed and this event was not related to the use of the test medication, but to a tension in the dental arch.

These results were submitted to the CEP, through a report for the evaluation of the execution of the study as well as of all medical, dental, and pharmaceutical clinical evaluations carried out and of the cases of the reported adverse events. The report was approved culminating in the development of the Phase 2 study protocol, which, after approval by the same ethics committee, is undergoing for the assessment of safety and efficacy [2].

Conclusion

The complexity of developing a clinical protocol coupled with low financial investment in the areas of research on natural products discourages translational progress from pre-clinical to clinical phases. Therefore, herein insight to the importance of investing on the discovery of new products for the relief of patients' suffering, seeking life quality is a positive influence for the treatment of diseases of life-threatening neoplasia with the various side effects resulting from treatment. Furthermore, data provided herein permitted to apply for the ongoing phase II trial, stimulating research progress with products from natural sources.

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References

1. ANVISA. 2020 [cited 2020 Oct 27] www.anvisa.gov.br.
2. Queiroz NDCA, Jorge MP, Sousa IMDO, Lima CSP, Matias MCDM, Rio ACD, et al. Arrabidaea chica for oral mucositis in patients with head and neck cancer: A protocol of a randomized clinical trial. BMJ Open. 2018;8(10):e019505.
3. Sonis ST, Oster G, Fuchs H, Bellm L, Bradford WZ, Edelsberg J, et al. Oral mucositis and the clinical and economic outcomes of hematopoietic stem-cell transplantation. J Clin Oncol. 2001;19(8):2201-5.
4. Rubenstein EB, Peterson DE, Schubert M, Keefe D, McGuire D, Epstein J, et al. Clinical practice guidelines for the prevention and treatment of cancer therapy-induced oral and gastrointestinal mucositis. Cancer. 2004;100(9 Suppl):2026-46.
5. Lalla RV, Bowen J, Barasch A, Elting L, Epstein J, Keefe DM, et al. MASCC/ISOO clinical practice guidelines for the management of mucositis secondary to cancer therapy. Cancer. 2014;120(10):1453-61.
6. Sanz M, Beighton D, Curtis MA, Cury JA, Dige I, Dommisch H, et al. Role of microbial biofilms in the maintenance of oral health and in the development of dental caries and periodontal diseases. Consensus report of group 1 of the Joint EFP/ORCA workshop on the boundaries between caries and periodontal disease. J Clin Periodontol. 2017;44(Suppl 18):S5-11.
7. BRASIL. Relação Nacional de Plantas Medicinais de interesse ao SUS (Renisus), Brasília, 2009.
8. Jorge MP. Atividade cicatrizante do extrato bruto de Arrabidaea chica Verlot [Dissertação]. Campinas: Universidade Estadual de Campinas, Faculdade de Ciências Médicas. 2008.
9. Jorge MP, Madjarof C, Ruiz ALTG, Fernandes AT, Rodrigues RAF, Sousa IMdO, et al. Evaluation of wound healing properties of arrabidaea chica verlot extract. J Ethnopharmacol. 2008;118(3):361-6.
10. Aro AA, Simões GF, Esquisatto MAM, Foglio MA, Carvalho JE, Oliveira ALR, et al. Arrabidaea chica extract improves gait recovery and changes collagen content during healing of the Achilles tendon. Injury. 2013;44(7):884-92.
11. Sousa IMO. Avaliação da estabilidade do Extrato seco e formulações de bases semi sólidas contend Arrabidaea chica Verlot, para uso em cicatrização. Dissertação de Mestrado Instituto de Biologia. 2013.
12. Jorge MP. Atividade cicatrizante de microencapsulados de extrato bruto etanólico obtido de Arrabidaea chica (Humb. & Bonpl.) Verlot. Tese de Doutorado, Faculdade de Ciências Médicas, Universidade Estadual de Campinas. 2013.
13. dos Santos VC, Longo TB, Garcia ALH, Richter MF, Guecheva TN, Henriques JAP, et al. Evaluation of the mutagenicity and genotoxicity of Arrabidaea chica Verlot (Bignoneaceae), an amazon plant with medicinal properties. J Toxicol Environ Health A. 2013;76(6):381-90.
14. Servat-Medina L. Arrabidaea chica Verlot: Formulações de liberação sustentada para aplicação em úlceras de mucosa e pele. Tese de Doutorado,Faculdade de Odontologia de Piracicaba da Universidade Estadual de Campinas. 2014.