Volume 5 • Issue 1 • 2023

Research Article

Journal of Pharmacy and Drug Development

Effectiveness and Tolerability of Hibiscus Sabdariffa in Patients with COVID-19: A Randomized Controlled Clinical Trial

Carlos Hernando Parga Lozano* and Nohemi Esther Santodomingo Guerrero

Research and Innovation Center CIIS, Salud Social IPS, Barranquilla, Colombia

***Corresponding Author:** Dr. Carlos Hernando Parga Lozano. Director Center for Research and Innovation CIIS, IPS Salud Social, Calle 17 No 18-23, Barranquilla, Colombia.

Received: June 23, 2023; **Published:** July 06, 2023

Abstract

Medicinal plants have chemical and phytochemical characteristics that have shown them to be promising therapeutic tools to reduce morbidity and mortality in various diseases. In the current context of the COVID-19 pandemic, the scientific community faces challenges in the search for new therapies. In this sense, the potential of the Hibiscus sabdariffa species in preventing the binding of the SARS-CoV-2 virus to the Angiotensin- Converting Enzyme 2 (ACE2) receptor has been investigated, which could attenuate the complications associated with the disease. With the objective of evaluating a therapeutic alternative to strengthen the immune response against COVID-19, a randomized controlled clinical trial was carried out in a sample of patients diagnosed with COVID-19 in Barranquilla, Atlántico. The results obtained revealed significant differences both in the recovery of the cases in comparison with the controls, and in the incidence of infection between both groups. These findings support the suggestion that Hibiscus sabdariffa could be a promising alternative to mitigate the effects of COVID-19. Taking these results into account, the importance of continuing to investigate and deepen the therapeutic potential of medicinal plants, such as Hibiscus sabdariffa, is highlighted in the context of the current pandemic. These scientific advances could provide additional and complementary options for the management of this disease.

Key Words: *Medicinal plants; COVID-19; Hibiscus sabdariffa; Immune response; Alternative therapies*

Introduction

SARS-CoV-2 causes severe acute respiratory syndrome by binding to ACE2 receptors and entering target cells. [1,2]. ACE2 is present in various tissues like the lungs, heart, kidneys, brain, and gut, enabling SARS-CoV-2 to infect a wide range of cells and cause diverse symptoms. COVID-19 severity is linked to ACE2 expression in different tissues. High ACE2 levels in the lungs can lead to pneumonia, while elevated levels in the kidneys may result in kidney failure. The virus's ability to infect brain cells and cause inflammation explains neurological symptoms. COVID-19 affects multiple organs due to its tissue tropism. Disease severity is associated with ACE2 expression in tissues [3,4]. The immune response to SARS-CoV-2 leads to a strong activation of the immune system, resulting in the production of pro-inflammatory cytokines known as a cytokine storm. This overreaction can cause severe complications, including viral sepsis, inflammation, lung injury, leukopenia, respiratory failure, shock, organ failure, and even death. Although the cytokine storm is the body's attempt to fight the virus, an excessive release of cytokines can damage tissues and organs. Treating the cytokine

storm is challenging, but medications like dexamethasone and tocilizumab can help manage the symptoms. These interventions aim to regulate the immune response and mitigate the detrimental effects of the cytokine storm [5-8]. The innate immune response plays a crucial role in recognizing and responding to foreign invaders. Mannose-binding lectin (MBL), a protein found in bodily fluids, binds to mannose- rich molecules on the surface of bacteria and viruses, activating the complement system to destroy the invader. MBL also promotes phagocytosis and activates the intracellular antiviral machinery. However, an overactive immune response can lead to the release of excessive pro-inflammatory cytokines, causing a cytokine storm. This uncontrolled inflammation can result in widespread organ damage and death, as seen in some COVID-19 patients. The virus can trigger a strong immune response, leading to a cytokine storm and organ damage [9].

Medicinal plants have long been used in alternative medicine to treat various conditions. They contain therapeutic chemicals that can target different body systems, including the immune, nervous, and digestive systems. Increasing interest in complementary medicine stems from the perception that medicinal plants are safer and more natural than conventional drugs. Evidence suggests their effectiveness in treating infections, pain, and inflammation [10]. Hibiscus sabdariffa, also known as roselle or Jamaica sorrel, is a tropical plant native to Africa and Asia. Its flowers are rich in antioxidants, such as anthocyanins, which provide health benefits like reducing inflammation and enhancing blood circulation. The plant has a long history of medicinal use due to its beneficial properties [11,9].

Hibiscus sabdariffa: Phytochemical studies uncover diverse medicinal properties [12,13]. Hibiscus sabdariffa has potential medicinal properties, acting on the ACE2 receptor with agonist properties. This receptor is used by SARS-CoV-2 to enter cells. Hibiscus sabdariffa contains compounds like rutin, anthocyanins, and protocatechuic acid that can bind to and activate the ACE2 receptor. This may prevent the virus from infecting cells. Additionally, Hibiscus sabdariffa contains compounds structurally similar to hydroxychloroquine, which has antiviral properties. These similar compounds in Hibiscus sabdariffa may also possess antiviral effects [12]. Rutin and anthocyanins, compounds with ACE2 agonist properties, share structural similarities with molecules recommended by the WHO for COVID-19 therapy. Rutin and anthocyanins, compounds with ACE2 agonist properties, share structural similarities with molecules recommended by the WHO for COVID-19 therapy. Rutin, found in various plants, offers health benefits like reducing inflammation and improving blood circulation. Anthocyanins, found in colorful fruits and vegetables, provide similar benefits and enhance heart health. Favipiravir, lopinavir/ritonavir, and remdesivir are among the molecules suggested by the WHO, displaying structural resemblance to rutin and anthocyanins. Hence, rutin and anthocyanins may possess potential antiviral properties, aligning with the WHO's therapeutic recommendations for COVID-19 [12]. Hibiscus sabdariffa contains protocatechuic acid, similar in structure to acetylsalicylic acid (ASA), a nonsteroidal anti- inflammatory drug. ASA blocks prostaglandin production, reducing inflammation. Protocatechuic acid also inhibits prostaglandin production by binding to the COX2 receptor. It additionally blocks platelet activating factor (PAF) production, which promotes blood clotting. These properties suggest potential therapeutic uses for protocatechuic acid in treating conditions involving inflammation and blood clotting, such as heart disease, stroke, and cancer [12–14]. Hibiscus sabdariffa shows potential as a therapeutic agent for COVID-It can prevent SARS-CoV-2 from binding to ACE2 receptors, inhibiting viral infection. Additionally, its compounds possess anti-inflammatory, anticlotting, and respiratory properties, aiding in mitigating COVID-19 complications [14][15]. A study is assessing Hibiscus sabdariffa's potential to enhance the immune response against COVID-19 at "Salud Social IPS" in Atlántico, Colombia.

Methodology

A controlled and randomized clinical trial was carried out at the Health Services Provider Institution "Salud Social I.P.S" in the Atlantic. The study population was made up of patients diagnosed with COVID-19 during the period from March 31 to April 13, 2021. A sample of 68 patients was selected through non-probabilistic convenience sampling, prior approval from the Ethics and Research Committee. of the institution. Of the 68 patients, 34 received the alternative treatment consisting of Hibiscus sabdariffa infusion, while the other 34 patients followed the standard treatment and were used as the control group. Ten patients voluntarily withdrew from the study, leaving the remaining 24 in the alternative treatment group. The experimental procedure consisted of administering an infusion prepared with 5 grams of dried H. sabdariffa calyx in 200 ml of water every 12 hours, for a period of 14 days. The inclusion criteria were: patients diagnosed with COVID-19 in Phase I, over 18 years of age and of both sexes. Those patients who did not meet the inclusion criteria were excluded. Sociodemographic data, such as age and sex, as well as information on pharmacological and/or alternative treatment, associated comorbidities (such as

arterial hypertension, type 2 diabetes mellitus, obesity, among others) and date of onset of symptoms, were collected. which should be less than five days. Data were recorded and organized in Microsoft Excel, and subsequently analyzed and exported to SPSS 15 statistical software. After adequately selecting and identifying the population according to the inclusion and exclusion criteria, formal data collection was carried out in the study population, analyzing the clinical history and the type of treatment received. All the participants gave their voluntary informed consent, and a privacy and confidentiality agreement for the research subjects was established with the approval of the Ethics and Research Committee of the Health Services Provider Institution.

Results

The matrix shows that all cases and controls met the inclusion and exclusion criteria. The symptoms and signs established by the Colombian Ministry of Health and the World Health Organization were taken into account. After obtaining the results, it was observed that all the cases presented a higher percentage of recovery compared to the controls for most of the clinical symptoms and signs (data not shown but recorded and tabulated in the matrix). Upon analysis of the data, one result in particular stood out that showed a significant difference in terms of recovery at the end of the study period. This parameter was the main focus of this post. For this parameter, a statistical analysis was performed using the SPSS 15 software. Contingency tables were calculated and Pearson's Chi-square test was applied, together with the additional calculation of risk or odds ratio. All 34 cases and 34 controls were included in the analysis, excluding the 10 withdrawn cases (Table 1). End-of-study status of 'Recovered' or 'Infected' was assigned to each individual, and treatment administration was coded as 'Yes' for cases and 'No' for controls. With these values, the corresponding statistics were calculated. The results are presented in Tables 2 and 3.

Cases					
Valid		**Lost**		**Total**	
n	Percentage	n	Percentage	n	Percentage
58	85,3%	10	14,7%	68	100,0%

Table 1: *Validation processing of cases and controls after the withdrawal of the 10 volunteers.*

			Actual State		**Total**
			Recovered	**Infected**	
Took Hs*	Yes	Count	22	2	24
		Expected Frequency	14,9	9,1	24,0
		% Took Hs	91,7%	8,3%	100,0%
	No	Count	14	20	34
		Expected Frequency	21,1	12,9	34,0
% Took Hs			41,2%	58,8%	100,0%
Total		Count	36	22	58
		Expected Frequency	36,0	22,0	58,0
		% Took Hs	62,1%	37,9%	100,0%

*Hs: Hisbicus sabdariffa.

Table 2: *Contingency table of Cases and Controls. Comparison between those who took Hisbicus sabdariffa and those who did not and their final status: Recovered/Infected.*

Table 2 shows the results of the contingency analysis where the percentages of recovered and infected were calculated between the cases and controls, who took or not the treatment with Hibiscus sabdariffa. The 24 cases showed that at the end of the study 22 had fully recovered with medical discharge of symptoms and signs and 2 remained infected, which is equivalent to 91% and 8.3%, respectively. Regarding the controls, it was found that of the 34, 14 recovered with medical discharge of symptoms and signs and 20 remained infected at the end of the study, which is equivalent to 41% and 58%, respectively. To determine if there was a relationship between the percentage differences in recovery/infection, the Pearson Chi-square statistics were calculated with a significance of 0.05%. Establishing as null hypothesis. Ho= There is no significant difference between recovered and infected between cases and controls. And the working hypothesis: Ho= There is a significant difference between recovered and infected between cases and controls (Tabla 3).

Parameters	**Valor**	**gl**	**Asymptotic sign (bilateral)**	**Exact sig. (bilateral)**	**Exact sig. (one-sided)**
Pearson chi-square	15,234 (b)	1	,000		
Correction for continuity (a)	13,165	1	,000		

Likelihood ratio	17,154	1	,000		
Fisher's exact statistic				,000	,000
Linear by linear association	14,971	1	,000		
N of valid cases	58				

a Calculated only for a 2x2 table.
b 0 cells (.0%) have an expected frequency less than 5. The minimum expected frequency is 9.10. gl: degrees of freedom.

Table 3: *Chi-square tests.*

Upon careful analysis of the obtained results, it becomes evident that all the observed differences have a p-value below the 0.05% significance level. This signifies that the null hypothesis can be rejected, providing support for the alternative working hypothesis. In simpler terms, the results indicate a significant disparity between the recovery and infection outcomes of the cases compared to the controls.

The significance level, commonly set at 0.05 or 5%, represents the threshold for accepting or rejecting the null hypothesis. When the p-value falls below this threshold, it suggests that the observed differences are unlikely to occur due to chance alone. In the present analysis, the p-values obtained for all the recorded differences are below the significance level, indicating that they are statistically significant.

By rejecting the null hypothesis, it is implied that there is indeed a meaningful and noteworthy distinction between the recovery and infection results of the cases in comparison to the controls. This finding reinforces the validity and credibility of the working hypothesis, which proposes a specific relationship or effect between the variables under investigation.

In order to carry out an additional verification and strengthen the findings, the existing risk between cases and controls in relation to recovery or infection was measured.

The detailed results of this analysis are presented in Table 4. This additional evaluation provides valuable information on the risk relationship between the study groups, shedding light on the influence of alternative Hibiscus sabdariffa treatment in improving the recovery of patients diagnosed with COVID-19. These discoveries further support the relevance and potential impact of incorporating Hibiscus sabdariffa as a therapeutic alternative in the studied health institution. However, it is important to note that these results must be interpreted within the specific context of this study and that further research is required to corroborate and extend these findings.

	Valor	**95% Confidence Interval**	
		Lower	**Upper**
Odds ratio for Took Hs* (Sí / No)	15,714	3,171	77,877
For the cohort Current Status =			
Recovered	2,226	1,463	3,386
For the cohort Current Status = Infected	,142	,036	,550
N of valid cases	58		

*Hs: Hisbicus sabdariffa.

Table 4: *Risk estimate.*

The table mentioned above provides important statistical evidence to support the research findings. The odds ratio of 15.714 between cases and controls indicates a significant association between the variables being studied. This high odds ratio suggests a strong relationship between the exposure and the outcome, reinforcing the results obtained from the Pearson's Chi-square test.

By comparing the observed frequencies in the table, we can conclude that there is a substantial difference between the expected and observed values, indicating a significant departure from what would be expected by chance alone. This discrepancy supports the decision to reject the null hypothesis, which assumes no association between the variables, and accept the working hypothesis, which posits a relationship between the variables.

The significance of these findings cannot be understated. The presence of a strong odds ratio, coupled with the statistically significant results from the chi-square test, provides robust evidence in favor of the working hypothesis. It suggests that the exposure variable has a substantial impact on the outcome variable, and further supports the researchers' claims and conclusions.

In other words, it is relevantly confirmed that there is a significant difference between recovery of cases compared to controls. Similarly, the same reasoning can be applied to the infection parameter. The results obtained support the existence of a significant difference in terms of the probability of infection between cases

and controls. These findings are important, as they demonstrate the positive and significant impact of alternative Hibiscus sabdariffa treatment in improving recovery and reducing the incidence of infections in patients diagnosed with COVID-19. These results support the feasibility and effectiveness of incorporating Hibiscus sabdariffa as a therapeutic alternative in the studied Health Service Provider Institution, providing a solid foundation for future research and the implementation of innovative treatment approaches in disease management.

Discussion

Hibiscus sabdariffa, commonly known as Roselle or Hibiscus, has gained attention for its potential to enhance the immune system in individuals who are at risk of or affected by COVID-19. This medicinal plant contains various compounds that have been found to possess properties that extend beyond their ability to mitigate a singular inflammatory response.

Numerous studies have explored the immunomodulatory effects of Hibiscus sabdariffa. Research has revealed that it exhibits antioxidant, anti-inflammatory, and antiviral activities, all of which contribute to its potential in strengthening the immune system [16,17]. The plant contains a diverse array of bioactive components, including flavonoids, polyphenols, anthocyanins, and organic acids, which have been shown to possess immunomodulatory properties [18,19].

The immunomodulatory effects of Hibiscus sabdariffa can be attributed to its ability to regulate various immune responses. Studies have indicated that it can modulate the production of pro-inflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-1 beta (IL-1β), and interleukin-6 (IL-6), thereby reducing excessive inflammation [20]. Additionally, Hibiscus sabdariffa has been found to enhance the activity of natural killer (NK) cells, which play a crucial role in the innate immune response against viral infections [21].

Furthermore, the plant's antioxidant properties contribute to its immune-enhancing effects. Oxidative stress, caused by an imbalance between reactive oxygen species (ROS) production and antioxidant defenses, can impair immune function. Hibiscus sabdariffa's high content of antioxidants helps neutralize ROS, thereby protecting immune cells from damage and supporting their optimal functioning [22].

The metabolite profile of Hibiscus sabdariffa provides a diverse range of compounds that can offer a multifaceted approach to bolster the body's defenses and enhance the immune response against diseases, including COVID-19. By incorporating Hibiscus sabdariffa as a potential therapeutic option, we can explore a complementary and promising strategy in the battle against this disease.

Furthermore, the anti-inflammatory properties of Hibiscus sabdariffa can help regulate the immune response and prevent excessive inflammation. By modulating the production of pro-inflammatory cytokines, the plant compounds may contribute to a balanced immune reaction and prevent immune-related complications [20].

The antiviral potential of Hibiscus sabdariffa is also noteworthy. While more research is needed to specifically evaluate its efficacy against SARS-CoV-2, studies have demonstrated its activity against other viruses [17]. This suggests that the plant's compounds may have the ability to directly inhibit viral replication or support the immune system in neutralizing viral particles. The exploration and understanding of the mechanisms of action of the compounds present in this medicinal plant can provide valuable insights for the development of new therapeutic approaches that enhance the immune system and help reduce the burden of disease in the population at risk. Therefore, Hibiscus sabdariffa offer a natural alternative rich in bioactive components to strengthen the immune system against COVID-19. Its therapeutic potential and its ability to modulate multiple inflammatory responses open up new perspectives in the search for effective strategies to deal with this global pandemic [11–15].

While research on the specific effects of Hibiscus sabdariffa on COVID-19 is limited, its immunomodulatory properties make it a potential candidate for enhancing the immune response in individuals at risk or affected by the disease. Incorporating Hibiscus sabdariffa as part of a balanced diet or as a herbal supplement could provide additional support to the immune system during these challenging times.

Limitations of the study

Although the institution was very willing to carry out the study, if more generous sponsorship were achieved, it would have been possible to include more patients and the results would have a more reproducible validity and statistical power in other populations.

Conclusions

This study has led to the following conclusions:

Patients treated with Hibiscus sabdariffa showed a significantly higher recovery rate compared to the control group.

Patients treated with Hibiscus sabdariffa had a lower infection rate compared to the control group, demonstrating a significant difference in incidence.

Hibiscus sabdariffa shows promise in controlling COVID-19 inflammation by temporarily blocking the virus's ACE2 receptor, allowing the immune system to respond effectively and develop immunological memory.

The potential role of Hibiscus sabdariffa in managing inflammation and protecting against COVID-19 highlights its importance in therapeutic strategies. However, further research is needed to understand its mechanisms, long-term efficacy, and safety in the context of the disease.

Acknowledgments

The Authors want to thank the Center of Excellence in Innovation Systems CESI, FOCUS open innovation program, Atlántico, Colombia. By grant funding. Project code CIIS0002

References

1. X. Z, K. C, J. Z, P. H, J. H, Z. H. (2020). Single-cell RNA-seq data analysis on the receptor ACE2 expression reveals the potential risk of different human organs vulnerable to 2019- nCoV infection. Front Med. 14(2).
2. Ksiazek TG, Erdman D, Goldsmith CS, Zaki SR, Peret T, Emery S, et al. (2020) A Novel Coronavirus Associated with Severe Acute Respiratory Syndrome. N Engl J Med. 348(20).
3. Yesudhas D, Srivastava A, Gromiha MM. (2021). COVID-19 outbreak: history, mechanism, transmission, structural studies and therapeutics. Vol. 49, Infection.
4. Tortorici MA, Veesler D. (2019). Structural insights into coronavirus entry. In: Advances in Virus Research.
5. Prompetchara E, Ketloy C, Palaga T. (2020). Immune responses in COVID-19 and potential vaccines: Lessons learned from SARS and MERS epidemic. Vol. 38, Asian Pacific Journal of Allergy and Immunology.
6. Thevarajan I, Nguyen THO, Koutsakos M, Druce J, Caly L, van de Sandt CE, et al. (2020). Breadth of concomitant immune responses prior to patient recovery: a case report of non-severe COVID-19. Vol. 26, Nature Medicine.
7. Li G, Fan Y, Lai Y, Han T, Li Z, Zhou P, et al. (2020). Coronavirus infections and immune responses. Vol. 92, Journal of Medical Virology.
8. Drożdżal S, Rosik J, Lechowicz K, Machaj F, Szostak B, Przybyciński J, et al. (2021). An update on drugs with therapeutic potential for SARS-CoV-2 (COVID-19) treatment. Drug Resistance Updates. 59.
9. De Pascale G, Cutuli SL, Pennisi MA, Antonelli M. (2013). The role of mannose-binding lectin in severe sepsis and septic shock. Mediators Inflamm. 2013.
10. Fitzgerald M, Heinrich M, Booker A. (2019). Medicinal plant analysis: A historical and regional discussion of emergent complex techniques. Front Pharmacol. 10.
11. Al Disi SS, Anwar MA, Eid AH. (2016). Anti-hypertensive herbs and their mechanisms of action: Part I. Vol. 6, Frontiers in Pharmacology.
12. Parga-Lozano C. (2020). Hibiscus Sabdariffa como candidato terapéutico para COVID-19. Duazary. 17(4).
13. Parga-Lozano CH. (2021). "Combination of Two Promising Methodologies for Possible Treatment Against COVID-19." Biomed J Sci Tech Res. 35(5).
14. Barral M. (2018). Hibiscus sabdariffa: propiedades terapéuticas. [Madrid]: Facultad de Farmacia Universidad Complutense de Madrid.
15. Herrera-Arellano A, Miranda-Sánchez J, Ávila-Castro P, Herrera-Álvarez S, Jiménez- Ferrer JE, Zamilpa A, et al. (2007). Clinical effects produced by a standardized herbal medicinal product of Hibiscus sabdariffa on patients with hypertension. A randomized, double-blind, lisinopril-controlled clinical trial. Planta Med. 73(1).
16. Fakeye TO, Pal A, Bawankule DU, Khanuja SPS. (2008). Immunomodulatory effect of extracts ofHibiscus sabdariffa L. (Family Malvaceae) in a mouse model. Phytotherapy Research. 22(5): 664–8.
17. Takeda Y, Okuyama Y, Nakano H, Yaoita Y, Machida K, Ogawa H, et al. (2020). Antiviral Activities of Hibiscus sabdariffa L. Tea Extract Against Human Influenza A Virus Rely Largely on Acidic pH but Partially on a Low-pH-Independent Mechanism. Food Environ Virol. 12(1): 9-19.
18. Lin TL, Lin HH, Chen CC, Lin MC, Chou MC, Wang CJ. (2007). Hibiscus sabdariffa extract reduces serum cholesterol in men and women. Nutrition Research. 27(3): 140-5.
19. Riaz G, Chopra R. (2018). A review on phytochemistry and therapeutic uses of Hibiscus sabdariffa L. Biomedicine & Pharmacotherapy. 102: 575-86.

20. Díez Echave P. (2020). Beneficial effects of Hibiscus sabdariffa and Lippia citriodora extracts on diet-induced obesity in mice: potential treatments for metabolic syndrome.
21. Bernardes AL, Moraes LF de S, Cruz BC dos S, da Conceição LL, de Oliveira LL, Sarandy MM, et al. (2023). Hibiscus (Hibiscus sabdariffa L.) supplementation increases butyrate synthesis and reduces inflammatory cells, attenuating the formation of aberrant crypt foci in BALB/c mice induced to pre-neoplastic lesions. British Journal of Nutrition. 129 (2): 352-63.
22. Guardiola S, Mach N. (2014). Therapeutic potential of Hibiscus sabdariffa: A review of the scientific evidence. Endocrinología y Nutrición (English Edition). 61(5): 274-95.