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Use of Nasoil® via intranasal to control the harmful effects of Covid-19

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ABSTRACT

In the absence of vaccines and antiviral drugs available to prevent and treat COVID-19, it becomes imperative to find or use all those products with the potential to fight this virus. This article is an attempt to propose ways to prevent, treat and control the COVID-19 virus, using a product based on plant extracts with the potential to reduce the symptoms caused by the SARS-CoV-2 virus. Nasoil® counts as one of its main components, *Asclepias curassavica* extracts, and in the present study it has been shown that it is an effective adjuvant in the treatment of Covid-19, increasing the respiratory capacity of the patients (SpO2> 90%) and reducing the symptoms from the first application, improving the patients around the fifth to the eighth application. At a preventive level, the individuals in this study who have applied it (400 individuals) only a 3.15% of these presented symptoms, disappearing when increasing the weekly applications.

1. Introduction

The virus that caused the COVID 19 pandemic spread globally with an increase in deadly infections in most countries, especially Iran, Italy, South Korea, Spain, the US, Brazil and Mexico. The U.S. with an estimated fatality rate of about 3.5% [1–4]. COVID-19 is caused by SARS-coronavirus-2 (SARS-CoV-2), which belongs to the coronavirus family and is related to Severe Acute Respiratory Syndrome (SARS) and Middle East Respiratory Syndrome (MERS) virus. Structurally, SARS-CoV-2 is a virus wrapped with a positive-sense single-stranded RNA genome [5]. Proteins on the surface of the virion are responsible for compromising the angiotensin-converting enzyme 2 (ACE2) receptor to enter susceptible host cells; the initial infection is predominantly directed at the epithelial cells of the lungs and throat [6]. Spray microdroplets are thought to be the primary mode of viral transmission [7]. There are currently no vaccines or antiviral drugs available to prevent and treat COVID-19.Clinical trials have been conducted quickly, but it has been despite this that it is likely that vaccines and effective medicines will take months to reach the global market.

Patients hospitalized with severe or critical infections are treated with a selection of antiviral agents (e.g. oseltamivir, lopinavir, ritonavir, remdesivir), combinations of antibiotics and/or glucocorticoids depending on the clinical condition of patients, in addition to assisted ventilation when breathing capacity is compromised [8–10]. With the current magnitude of contagious infections and associated deaths caused by COVID-19, there is an urgency to employ additional strategies to find treatment options capable of reducing deaths. Although there are encouraging results with some therapies, there is still a need for other strategies, particularly specific approaches such as nutritional intervention, inmunoenhancer, coronavirus-specific treatments such as coronavirus protease inhibitors, etc. (trials are currently being conducted around the world) [11,12].

Patients with COVID-19 develop clinical manifestations of high fever, cough, myalgia, dyspnoea with or without diarrhea and pneumonia, these manifestations are among the first recognized, every day new symptoms are put associated with COVID-19 virus, but usually

Abbreviations: ACE2, Angiotensin I Converting Enzyme 2; ARDS, Acute Respiratory Distress Syndrome; CNS, Central Nervous System; COPD, Chronic Obstructive Pulmonary Disease; COVID-19, Coronavirus disease 2019; CoV-2, Coronavirus −2; ICU, Intensive care Unit; NETs, Neutrophils Extracellular Traps; PCR, Polymerasa Chain Reaction; MERS, Middle East Respiratory Syndrome; SARS, Severe Acute Respiratory Syndrome; SpO2, peripheral capillary oxygen saturation.

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patients have gastrointestinal problems such as nausea, vomiting, diarrhea, abdominal pain, in addition to shortness of breath, headache, sore throat, colds, breathing problems, myalgia, nasal congestion and inflammation of the mucous membranes that cover the inside of the sinuses and nasal discharge, also in some cases occur injuries to the central nervous system [13–20].

According to Trisha Greenhalgh et al. (2020) [21], the best clinical signs for predicting adult acquired pneumonia are a temperature above 38 °C, a breathing rate greater than 20 breaths/minute and a heart rate greater than 100 beats/minute; low urine flow is also a worrying symptom [21]. Two of the main symptoms of Covid-19 include anosmia (loss of smell) and ageusia (loss of taste). Chemosensory dysfunction is necessarily associated with Covid-19 infection and should be considered when detecting symptoms. Understanding the timing and association of odor/taste loss in Covid-19 can help facilitate early detection and isolation of cases. There is a strong association between an olfactory and taste deficiency with a Covid-19 infection. Loss of odors/flavors can be used as a symptom of increased detection of Covid-19 infections to reduce the risk of disease transmission from mildly symptomatic cases [22].

To date, no adequate vaccine or treatment has been found to combat the pandemic. Some researchers encourage the use of traditional herbal medicine to decrease spread while waiting for the introduction of a vaccine, especially in developing countries; but it must be done according to the guidelines of modern medicine in patient care [23–25]. Integrating traditional medicine into conventional treatment can be an alternative approach and event to combat resource scarcity. Clinical studies are needed to evaluate the efficacy and safety of traditional medicines and provide clinical evidence [26].

Taking into account the above and the wealth of plants in the Mexican Republic, we proceeded to look for plants that could have the best capacity to help control the symptoms caused by the SARS-CoV-2 virus, in addition to standardizing a protocol to obtain the extracts, having everything ready proceeded to the registration of Nasoil® has different plant extracts, of which one of these extracts are *Asclepias curassavica* (Apocynaceae) which has different uses, among which they stand out against respiratory, cardiotonic, analgesic and dermatological conditions. The interest *in A. curassavica* is not only given for its use in traditional Mexican medicine, but even the use of this species in different countries worldwide, highlighting even the name used to a species of this genus in the United States of America which is Pleurisy root, since it allows to cure respiratory conditions, deflating the pleura and lung [27].

The properties of the species *A. curassavica* in particular are sneezing, febrifuge and expectorant. Allowing to cure a constipated cold by sneezing the patient, reducing fever and, as we note, reduces inflammation of the pleura (coating of the lungs) due to lung infections hence its name in English [28]. Different studies have shown that extracts obtained through different solvents such as chloroform, alcohols and aqueous *A. curassavica* presents antimicrobial, anti-inflammatory, alexitic, activities, this due to its proteolitic, indirect hemolytic and coagulating capacity. As you can see this plant has a great capacity to modify structures, since it presents some compounds such as cardiotonic glycosides (cardenolides) and various types of alkaloids derived from 2-methoxy-pyrrazine, indole, pyridine or phenantroindolizidine, as well as flavonoids, occasionally tannins, steroids, coumarins, free triterpenes and sesquiterpene lactones [29–33]. With this context and observing the properties of *A. curassavica,* which together with the other extracts and molecules have the ability to modify elastic proteins, in addition to helping patients to control the symptoms of the SARS-CoV-2 virus,is that we make available this new product based on extracts from medicinal plants to fight the COVID-19 pandemic.

2. Materials and methods

2.1. Medicines

Invasive mechanical ventilation for 10 individuals hospitalized with their respective parameters according to the patient's weight and the degree of loss of respiratory capacity, according to guidelines for patient care by Covid-19, published by the Government of Mexico in February 2020.500 mg azithromycin, broad-spectrum antibiotic for 5 days.500 mg Clarithromycin, respiratory tract antibiotic, 500 mg paracetamol, analgesic and antipyretic, for fever control every 4 h, Intramuscular Dexamethasone 8 mg, steroid, anti-inflammatory.

2.2. Nasoil®

Nasoil® is a product with an industrial secret and in patent process that contains extracts of *Asclepias currasavica* and as well as molecules that help to modify the elastic proteins of the respiratory system and decrease symptoms caused by respiratory diseases.

The protocol for the application of Nasoil® for patients with symptoms to different degrees of severity without reaching hospitalization was 2 drops of intranasal application per day, i.e. one drop per nostril, for 3 days in a row, and subsequently three applications per week, in case symptoms disappeared earlier or decreased, apps change to 1–2 apps per week, until 20 apps are completed. For patients without symptoms or healthy, the dose was 2 intranasal drops per day per week until 15 applications were completed.

2.3. Patients

Our study population were 600 individuals dividing them into 6 groups:

GROUP 1: 100 patients confirmed with Covid-19 through laboratory test belonging to the Mexican health sector
GROUP 2: it was made up of 100 patients with symptoms (high fever, loss of smell and appetite, diarrhea, phlegm cough) related to SARS-CoV-2 but had no confirmation of positives.
GROUP 3: 99 healthy individuals without symptoms, but at high risk of contagion as they belong to the public health sector.
GROUP 4: 100 individuals at high risk of contagion, since in their family or nearby circle there was at least one patient confirmed with Covid-19.
GROUP 5: 100 high-risk individuals with chronic respiratory diseases (asthma, rhinitis, sinusitis, bronchitis, smokers, allergies and loss of smell from inhalation of toxics related to their field of work.) and senior citizens with chronic metabolic diseases, such as diabetes, hypercholesterolemia, hypertension and tumor history.
GROUP 6: 101 individuals at low risk of contagion, healthy, disease-free, unrelated with individuals to Covid-19, athletes and ages under the age of 45.

2.4. Statistics

The IBM SPSS Statistics 27.0 program was used to perform inter-observer agreement analysis using Cohen's kappa. And the Pearson correlation was performed to determine the degree of relationship between the observed results.

3. Results

Testing with Nasoil® began on April 20, 2020, and these observations were completed on July 15, 2020. The effect of Nasoil® was studied in a total of 600 individuals of which 348 were men and 252 women, the average age was 44.27 years, with ages ranging from 20 to 78 years.

Antibiotics azithromycin were used in 76% of patients confirmed with COVID-19, and in the case of patients with symptoms but without confirmation 10% used this same antibiotic, in addition to this antibiotic, 88 individuals in group 1 used paracetamol 500 mg every 4 h. In group 2, 40% of individuals use this analgesic and antipyretic to control some of the symptoms related to Covid-19, in addition as isolated cases it is worth mentioning, the use of the antibiotic clarithromycin 500 mg by an individual in group 1 and another individual in this same group used intramuscular 8 mg dexamethasone, the rest of the individuals (472) included part of group 2 and all individuals from groups 3 to 6, they did not take medications to control symptoms related to Covid-19.

The 90% of patients in group 1 and 2 had the following symptoms: fever, headache, cough, asthenia, anosmia and ageusia with different degree of severity, 10% of patients had only anosmia and ageusia, such loss of smell did not link it to SARS-CoV-2 since there was no presence of any other symptoms (Table 1).

When the drops were placed in the nostrils, immediately all individuals manifested one or some of the reactions shown in Table 2. Other reactions were also present which they were discarded, these were the presence of febriculas, diarrhea, low blood sugar levels which were observed mainly in patients confirmed to Covid-19 and sporadically in unconfirmed patients and being null for groups with individuals without symptoms.

From these reactions, it was determined whether they were unique to the application of Nasoil® droplets or was a reaction as a result of the disease or respiratory discomfort suffered by individuals. Reactions occur in a large number of individuals, such as burning, tearing, nasal flow, and coughing in all groups. Cohen's Kappa was carried out to determine that data obtained by two groups of observers (homeopathic physicians and researchers) were not randomly obtained data, and the Landis and Koch scale (1977) was considered, which is frequently used to qualitatively express the force of concordance between observers (Table 3).

According to Landis and Koch, (1977) [34] the Kappa concordance coefficient of our two observer groups for each study group is almost perfect, as it is in that range according to Table 3, it should be clarified that in this study each group of observers checked separately approximately 50 different individuals for each group, subsequently the information was collected in a total of all observed individuals, using the value 1 for those who had had a reaction x and zero for those responses that did not include such a reaction, obtaining as a first impression the percentages shown in Table 2.

The observations made by the two research groups are consistent that Nasoil® provokes reactions in all study groups, being almost perfect for groups 1 and 2 (Table 4) which are the groups where individuals with symptoms related to Covid-19 are concentrated, having the lower values for Kappa, for the group of individuals considered high risk (group 4) working in the health sector, and the low-risk group considered to be healthy individuals (group 6), all values are in the near-perfect range according to Table 3.

In Table 5 shows the obtained values for each reaction per study group, having values in the ranges of almost perfect concordance in most groups for each reaction, having values of considerable in the tearing reaction and headache for group 5 and moderate in headache for group 6.

Each observer team was composed, the first, by 3 homeopathic physicians, and the second by 3 researchers, subsequently proceeded to determine whether there was a correlation of reactions with the presence of the SARS-CoV-2 virus or were reactions considered to be of Nasoil® side effect of no relevance to the health problems presented by the patients, for this proceeded to perform the Pearson correlation, to see if there was any correlation (Table 6).

With Pearson's values (Table 6), it is observed that burning and tearing are the exclusive consequence of the placement of Nasoil® intranasally, since there is a very high and high significant correlation in each group for these reactions. In the case of tearing, the correlation between groups 3 to 6 (considered groups in preventive status) has values with high and moderate significance with respect to the group of patients confirmed with Covid-19, this group have a very high significance with the group of unconfirmed patients but with all symptoms to this disease.

The nasal flow by action of Nasoil® occurs but that it will depend on the severity of the disease for to occur abundance in nasal flow. Within groups of 3–6 there are individuals with nasal flow who possibly depends the other respiratory diseases, it should be mentioned that even within the group of healthy it is manifested that by placing the drops improve their breathing.

It is clear that headache and dizziness, sneeze and cough in general, are responses caused by Nasoil® but due to the presence of the SARS-

Table 1
Symptoms with increased presence related to Covid-19, and the percentage present in groups 1 and 2.

	Group 1	Group 2
High fever with values of more than 40°	100%	89%
Trouble breathing (Dyspnoea)	100%	70%
Headaches	100%	90%
Body aches	99%	80%
Dry cough attacks	100%	90%
Asthenia	100%	95%
Anosmia	100%	100%
Ageusia	100%	100%
Threw up	70%	30%
Diarrhea	60%	40%

Table 2
Percentage of individuals and reactions presented in each group instantly placing Nasoil® drops.

Symptoms that appear when using Nasoil®	Group 1 (%)	Group 2 (%)	Group 3 (%)	Group 4 (%)	Group 5 (%)	Group 6 (%)
Burning nose	85	80	80	80	81	79
Tearing	75	71	60	60	60	59
Runny nose	80	70	49	51	52	49
Cough (with phlegms or dry)	95	85	34	34	35	33
Headaches and/or dizziness	80	60	6	8	11	5
Burst sneeze	100	90	10	10	11	9

Table 3
Assessment of Kappa coefficient (Landis and Koch, 1977)[n].

0.00	Poor
0.01–0.20	Slight
0.21–0.40	Fair
0.41–0.60	Moderate
0.61–0.80	Subtantial
0.81–1	Almos perfect

Table 4
Intra-observer concordance, Kappa test, by study group.

Group1	1 (100%)
Group 2	1 (100%)
Group 3	0.947 (94.7%)
Group 4	0.96 (96%)
Group 5	0.954 (95.4%)
Group 6	0.947 (94.7%)

Table 5
Intra-observer concordance, Cohen's Kappa test for Nasoil® reactions per study group.

	Group 1	Group 2	Group 3	Group 4	Group 5	Group 6
Burning nose	0.866 (86.6%)	0.925 (92.5%)	0.935(93.52%)	0.968 (96.8%)	0.935 (93.5%)	1(100%)
Tearing	0.896 (89.6%)	0.942 (94.2%)	0.979 (97.9%)	1 (100%)	0.650(65%)	1(100%)
Headaches and/or dizziness	1 (100%)	0.920 (92%)	0.847 (84.7%)	0.826 (82.6%)	0.754 (75.4%)	0.597 (59.7%)
Burst sneeze	1 (100%)	0.834 (83.1%)	0.889 (88.9%)	0.947 (94.7%)	1 (100%)	0.942 (94.2%)
Cough (with phlegms or dry)	0.904 (90.4%)	0.987 (98.7%)	1 (100%)	0.976 (97.6%)	0.976 (97.6%)	1 (100%)
Runny nose	0.884 (88.4%)	0.911 (91.1%)	0.939 (93.9%)	0.940(94%)	0.960(96%)	0.980(98%)

Table 6
Pearson correlation between each study group.

	group1/ group2	group1/ group3	group1 /group4	group1/ group5	group1/ group6	group2 /group3	group2 /group4	group2 /group5	group2 /group6
Burning nose	0.932[a] (93.2%)	0.873[b] (87.3%)	0.901[a] (90.1)	0.967[a] (96.7%)	0.867[b] (86.4%)	0.937[a] (93.7%)	0.967[a] (96.7%)	0.967[a] (96.7%)	0.934[a] (93.4%)
Tearing	0.903[a] (90.3%)	0.702[b] (70.2%)	0.737[b] (73.7%)	0.816[b] (81.6%)	0.693[c] 69.3%)	0.740[b] (74%)	0.740[b] (74%)	0.745[b] (74.5%)	0.693[c] (69.3%)
Runny nose	0.733[b] (73.3%)	0.478[d] (47.8%)	0.488[d] (48.8%)	0.459[d] (45.9%)	0.451[d] (45.1%)	0.665[c] (66.5%)	0.626[c] (62.6%)	0.652[c] (65.2%)	0.622[c] (62.2%)
Headaches and/or dizziness	0.631[c] (63.1%)	0.130[e] 13%)	0.152[e] (15.2%)	0.181[e] (18.1%)	0.118[e] (11.8%)	0.206[e] (20.6%)	0.241[e] (24.1%)	0.287[e] (28.7%)	0.187[e] (18.7%)
Burst sneeze	0.559[c] (55.9%)	0.059[e] (5.9%)	0.059[e] (5.9%)	0.062[e] (6.2%)	0.045[e] (4.5%)	0.105[e] (10.5%)	0.105[e] (10.5%)	0.105[e] (105%)	0.094[e] (9.4%)
Cough (with phlegms or dry)	0.579[c] (57.9%)	0.181[e] (18.1%)	0.181[e] (18.1%)	0.185[e] (18.5%)	0.163[e] (16.3%)	0.313[d] (31.3)	0.313[d] (31.3%)	0.320[d] (32%)	0.299[e] (29.9%)

The correlation is significant at the 0.01 level (bilateral).
[a] = Very high correlation; [b] = High correlation; [c] = Moderate correlation; [d] = Low correlation; [e] = Negligible correlation.

CoV-2 virus, in fact, sneeze and cough, in patients with hospitalization has been helpful, so that the improvement is rapidly since coughing, in the case of patients with severe degrees of disease allowed the expulsion of phlegms, which allowed for a better breathing ability. Nasoil® was recommended, for all individuals in groups 1 and 2, a daily application for three days in a row and then two weekly applications until 20 doses are completed.

For groups 3 to 6 Nasoil® was applied one dose per day per week, at first, modifying from the second week as some individuals pointed to the occurrence of symptoms related to Covid-19 (Fig. 1), the dose was changed to these individuals by one application per day for three days a week until completing 14 doses, disappearing symptoms in the fourth week of application.

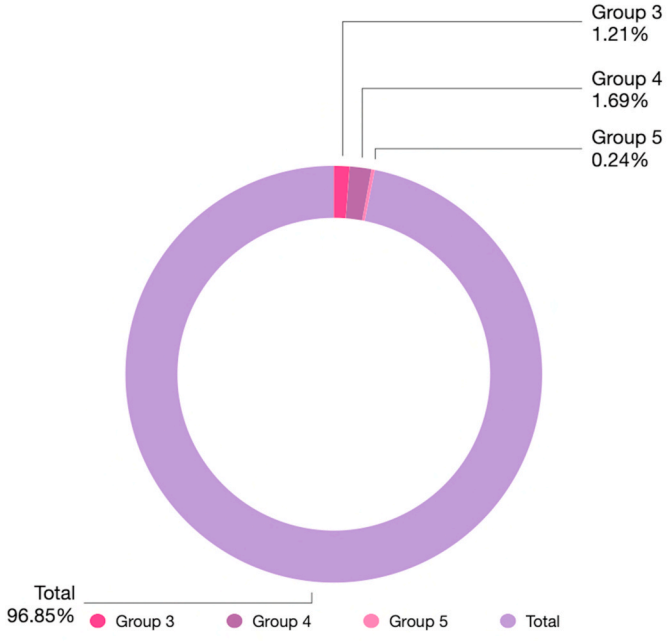

Fig. 1. Percentage of the individuals in groups 3 to 6 who had possible symptoms to Covid-19.

Anosmia is one of the symptoms that together with ageusia occurred in 100% of individuals with symptoms to Covid-19, being the two main and sometimes unique symptoms in young people between the ages of 20 and 30, predominating 60% in women, these individuals noted that immediately after the burning that occurs by the placement of Nasoil®, they felt the nostrils decongestant and immediately afterwards they could breathe better and begin to perceive the smells slightly.

The 100% of individuals with both confirmed and unconfirmed Covid-19 symptoms initiated the placement of Nasoil® drops between 4 and 17 days after the first discomfort began. 12 of the individuals initiated the drops hospitalized or when leaving the hospital. In Fig. 2 the percentage of all individuals with symptoms related to Covid-19 (Groups 1 and 2 of study) and their status during this study is observed. Of the number of hospitalized (12 individuals), 10 individuals (7 men and 3 women) were already in that state at the beginning of the present work, and a couple was hospitalized after the use of the droplets. In the case of the 10 hospitalized individuals, they were with invasive mechanical ventilation, of which 8 (5 men and 3 women) were applied Nasolil® during their hospitalization and 2 (both men) began post-hospitalization application.

The 8 individuals who were applied to Nasoil® in the hospital, had acute respiratory distress syndrome (ARDS) in addition to having onset of chronic obstructive pulmonary disease (COPD), having SpO2 values less than 40%. At the time of use of Nasoil® all 8 patients no longer required mechanical ventilation from the first intake, and even one of the 3 women referred that ventilation will be removed at the minute of the application of the droplets, all patients were discharged without any complication, having SpO2 values greater than 90%.

Of the 2 patients who were with invasive mechanical assistance, but were not given the drops during their hospitalization but after it, they spent 17 days in the hospital, being 2 male individuals aged 38 and 57, the individual aged 38, has no harm, however he was discharged with oxygen assistance, and recurrent extreme weakness and dry cough that prevented rest, at the time of the use of Nasoil® the help of oxygen by

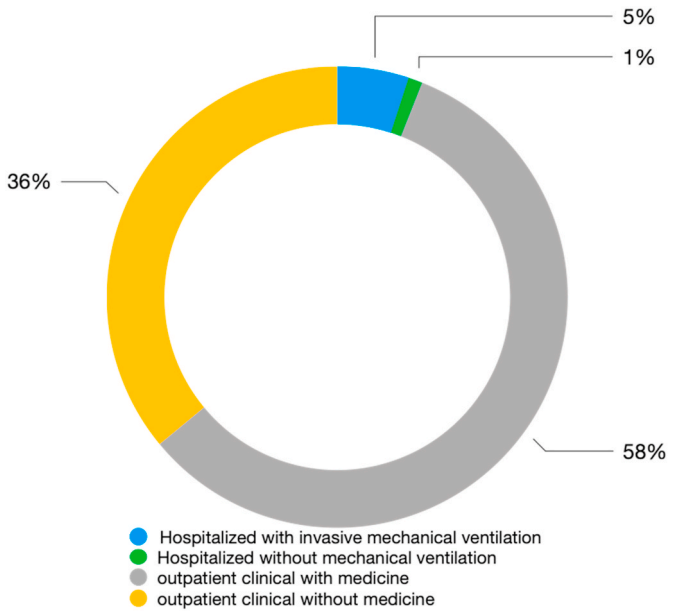

Fig. 2. Percentage of the status of all individuals with symptoms related to Covid 19 (groups 1 and 2 of this study). Total sample number 200.

mask, flung phlegms with abundant nasal flow was withdrawn, which allowed him to improve his breathing and the recurrent dry cough disappeared.

The patient aged 57 years was discharged with a pulmonary microthrobosis and cerebral hypoxia, maintaining SpO2 values less than 90%, extreme tiredness that prevented him from walking and even sitting in the bed itself, at the time of use of Nasoil® did not require the help of oxygen by mask, his oxygenation in blood increased to 96%, tiredness and constant cough remitted, it should be mentioned that this individual has started to take his first steps with help, will prolong the application of Nasoil® hopefully improve even more.

Two individuals who were given the drops after hospitalization, are a couple with ages 64 for the woman and 67 years the man, the first to be hospitalized was the man, he applied the drops, only once four days before being hospitalized, the reason for the application was the presence of flu symptoms, he stopped using them, and was subsequently hospitalized, in his hospitalization did not require invasive mechanical ventilation, and during the 14 days of his hospital was given Nasoil® only one occasion, at the time of being transferred to another hospital confirming that he had Covid-19, and due to the protocols available to the public health sector could not be applied the drops, at the time of stopping using them, his SpO2 under 70%, however it did not require assisted ventilation, once outside the hospital, returned to the application of the drops, maintaining a SpO2 between 92 and 96%, expulsion of phlegms and abundant nasal flow, improving its breathing capacity, and completely eliminated fever and general discomfort. The woman at the time of hospitalization her husband, start with azithromycin treatment for 5 days, and then start with the application of Nasoil®, was hospitalized 4 days after Nasoil® use, she removed the application of the drops, lowering her SpO2, to 80%, however did not require invasive ventilation, lasting 7 days in the hospital, restarting Nasoil® applications when finished her boarding hospital and after the 14th application of Nasoil® was found discharged.

The rest of the individuals positive to Covid-19 had improvements in some cases almost immediately, 60% of the individuals mentioned that they felt improvement from the first application and even though the fever in almost 80% of them remained, all noting that tiredness and shortness of breath had disappeared.

Group 2 all improved, immediately, and those who had severe symptoms felt their improvement between the 5 and 8 application. Groups 3 to 6, regardless of the 13 individuals who indicated that they started with the presence of symptoms (Fig. 1), are all found without the presence of symptoms or discomfort. The reactions caused by Nasoil® in all individuals in which they occurred lasted no longer than a few seconds in the case of burning and tearing, a couple of minutes for nasal flow, sneeze in a burst and cough, and for the discomfort of the head either pain or dizziness, about 5–10 min.

Dizziness occurred consistently in individuals who claimed to have recurrent hearing infections, or even those who indicated a problem at the nasal septum level. However, this discomfort was not prolonged and in 100% of cases was not an impediment to pursuing its tasks.

4. Discussion

Nasoil® has as one of its main components extracts of *Asclepias curassavica* and was mainly intended to improve the elastic capacity of the lung, since information is reported on its ability to modify proteins [35], to activate change at the cellular level [36,37], act as protease causing protein degradation due to modification of intramolecular changes [35–38] with these characteristics is intended to resolve some respiratory diseases such as pulmonary emphysema, due to the current contingency he proceeded to study whether he could be an assistant to reduce the number of deaths by Covid-19, and above all as a preventative, by improving breathing capacity, a fact seen in hospitalized patients who went from having SpO2 values $< 40\%$ and when using the drops the values were SpO2 $> 90\%$.

Of the main symptoms seen in Table 1 that individuals infected with the SARS-CoV-2 virus improve from the first application is their ability to breathe, as mentioned above, this improvement in breathing is accompanied by an improvement in asthenia, anosmia and eugesia, the next symptom that improves with applications is fever which although present ceases to be high, the decrease in these malaises present by Covid-19 may be due to the addition of *Asclepias curassavica* extracts has been shown in some studies to have their analgesic, antipyretic, and anti -inflammatory capacity [39,40].

The reason for the use of Nasoil® via intranasal administration is in order to affect steroid receptors, as it has been shown that, by this means, there is a greater benefit in neuroinflamation-related problems, both in infectious and non-infectious neuropathologies, and there is clear evidence that better control of neuroinflammation problems is related to clear clinical benefits, an example is the work done by Meneses et al. (2017) those who verified the effect of intranasal use of dexamethazone, in this study even point out as a conclusion that administration of glucocorticoids via intranasal is a new therapeutic alternative of potential value in different neuropathologies in which neuroinflammation is related to the disease. They emphasize that the intranasal pathway may overcome the undesirable effects mediated by the high systemic doses that should be used to achieve therapeutic levels of glucocorticoids to control the inflammation of the central nervous system (CNS) [41]. *Asclepias* is a family of plants that has been used in a traditional way to deflate the pulmonary pleura in fact in the United States of America is known as Pleurisy Root to the Tuberous *Asclepias* L. which they recommend for pneumonia, as it contains some glucocorticoids reduce the inflammation the pleura.

In addition to the use of Nasoil® intranasal route to aid neuronal anti-inflammation, it is the way in which it allows access to all the upper airways, to introduce the greatest amount of compounds intended for the control of the pulmonary pleura and the decrease of progressive clinical manifestations of acute respiratory distress syndrome (ARDS), as well as decreasing the neutrophilia that occurs in patients with severe damage caused by the SARS-CoV-2 virus, all with the presence of some enzymes intended to modify the main structure of the elastic proteins of the lung, mainly elastin, which is severely affected due to the presence of elastase enzyme released by neutrophils.

In fact, excessive neutrophils and neutrophil extracellular traps (NETs) has been directly correlated with the severity acute lung injury in

influenza-infected patients. Elevated plasma levels of neutrophilic enzymes serve markers of sever pneumonia in patients with influenza. In addition, a severe influenza blood test identifies a "dominated by neutrophils" immune response that requires patients to enter the intensive care unit (ICU) in this disease [42–44].

The current emergency treatments for patients with severe COVID-19 complications generally require the use of external pulmonary ventilation devices. However, the use of ventilators can be dangerous as NETs markers increase in alveolar spaces in patients with ventilator-associated pneumonia (VPN)· NETs and a high activity of elastase has been detected which generates activation of TGF-ß, apoptosis, dispersion of matrix elastin and abnormalities in the structure of the lung in mouse models with mechanical ventilation. Neutrophil counts at the beginning and throughout breathing and administration of drugs that prevent neutrophil recruitment and activity can effectively mitigate pathological complications of alveolitis and vascular injury in patients with COVID-19 [45,46].

Nasoil® is indirectly observed to help decrease neuroinflamation, neutrophilia and vascular injury three important factors seen in severe outpatients or with invasive ventilation. The 8 patients who were hospitalized with severe neutrophilia and with an advanced state of acute respiratory distress syndrome (ARDS), and who were given Nasoil® during their stay in the hospital, had a clear improvement within minutes of dropping drops even one of the individuals who were with mechanical ventilation immediately increased their oxygen saturation and reported the non-need for the ventilation.

In the individuals patients who lasted 17 days hospitalized and discharged, had severe damage at the lung level and even one was discharged with a pulmonary microthrombosis and cerebral hypoxia, at the time of the use of Nasoil® started with abundant nasal flow and removal of phlegms by cough, this patient, like the patient who also applied the drops after their hospitalization had a cough that did not allow them to sleep, and with the lung problems present maintained a state of severe fatigue, as Nasoil applications progressed®, both had decreased cough and ability to breathe improvement. It is clear that Nasoil® produced anti-inflammation, and decreases the microthrombosis caused by hypercoagulation due to polymerization and fibrin formation [47], it is inferred that this last effect on coagulation is given to the characteristic observed in *Asclepias* extracts decrease coagulation caused by some poisons, through the cardiotonic glycosides present in this plant [48], these two actions, anti -inflammation and decreased clotting, help to have a better ability to breathe.

Nasoil® emerges as a product with the ability to modify the elastic proteins of the respiratory system, mainly to modify elastin, since if this elastic protein is damaged, due to inflammation, pressure of the alveoli is lost and air circulation is reduced, effects observed by COVID-19 and chronic obstructive pulmonary disease (COPD) in both diseases there is an inflammation that causes a fixed narrowing of the small airways and the destruction of the alveolar wall (emphysema).

Chronic obstructive pulmonary disease is characterized by an increase in the number of alveolar macrophages, neutrophils and cytotoxic T lymphocytes, and the release of multiple inflammatory mediators (lipids, chemokines, cytokines, growth factors). An elevated level of oxidative stress may amplify this inflammation. There is also increased elastolysis and more findings of involvement of various elastolytic enzymes, including serine proteases, catepsins, and matrix metalloproteinases [49].

During aging there are also changes in the lung, perhaps as a result of these changes older adults are more susceptible to COVID-19, in the lung parenchyma most of the structural changes have to do with a modification of the elastic properties of the lung. When the rib cage of an elderly person is opened, it is observed that the lungs have a lower capacity to retract and that the length of the different pulmonary tissue elements is greater. Under normal conditions, the lung has an internal support formed by radial connective tissue elements extending from the pleura to the pulmonary hilum through the intersegmental and interlobar septa, axial connective tissue elements surrounding the ducts and alveolar sacs and fibrous crosses, distributed throughout the lung tissue, which connect the radial and axial elements. These connective elements are made up of elastin fibers, collagen fibers and proteoglycans produced by the fibroblasts. Some authors have shown that, in old age, there is an increase in the concentration of elastin at the pleural and septal level [50].

On the other hand, the elastic fibres around the more distal airways and alveolar sacs change in their location and orientation and become thinner [50]. Therefore, reinforcing elastin or stimulating other critical residues that assume a new role and allow it to form new interactions that would prevent its degradation or structural modification, which would prevent the loss of lung activity. The individuals in group 5 were made up of individuals who presented other respiratory problems, such as bronchitis, asthma, allergies, sinusitis, and even patients who did not have respiratory diseases, but were smokers, 100% presented improvement in their conditions and even smokers showed an improvement in their breathing which has manifested itself with improvement at bedtime. In the same way within the other groups, there were people with some similar problems to those of this particular group, and in the same way they presented improvement to the use of Nasoil®.

Anfinsen points out that the three-dimensional structure of a protein is determined by the sequence of amino acids. This dogma has been a central principle of molecular biology and biochemistry, however, it is not entirely true since the inability of x-ray crystallography to resolve the structures of many proteins and protein segments, often, Anfinsen's dogma applies only to the domains of a protein since proteins can also exist in inherently disordered states and cannot be described by a single atomic resolution conformation.

The relative disposition of the domain may change through large-scale conformational transitions following interaction with small ligands, other proteins, nucleic acids and even microenvironmental changes such as pH, temperature etc., a review of Anfinsen's dogma is necessary [51,52]. Clarke (2020) points out that, the sequence of amino acids of a protein must encode both order and disorder, or perhaps complete that the protein sequence allows changes depending on the microenvironment [52], since some authors have demonstrated the role of the microenvironment in the final structure of a protein, such as the work of Dalle-Donne et al. (2001), in which they put actin in contact with oxidizing agents such as HOCl, which causes a change in the structure of the protein, causing exposure to tyrosine and allowing the formation of dithryrosine-type bonds, such exposure increases as the environment becomes more oxidizing [53].

In the work of Welker et al. (2001), they use ferritin, which was considered to be due to stabilization by means of disulphide bridges. However, these authors conclude that the cysteines presented by this enzyme are not for the formation of disulfide, but for the oxidation or reduction of the protein in these residues. Consequently, ferritin changed its conformation and caused the formation of new bonds which are responsible for the stabilization and activity of this protein [54]. According to the results obtained by Welch et al. (2002) [55] and Dalle-Donne et al. (2001) [53], the presence of critical residues and a specific microenvironment is necessary for the formation of bonds in proteins, but these bonds can be modified by modifying the environment.

In Morales' (2010) work with wheat proteins, mainly gluten proteins, which are elastic proteins, he observed that using different substances he had the capacity to generate diverse links in the proteins [56]. Nasoil® being a combination of plant extracts that have the capacity to modify the tissue microenvironment by oxidizing or reducing depending on the state in which the proteins are found, is that they provide immediately the improvement in the respiratory capacity.

If the elastic proteins are compromised it is necessary that they are modified to retake their capacity, this of indirect form is observed, since 95% of the individuals with confirmation of COVID-19 or associated

symptoms without confirmation manifest at the moment of the placement of the drops the imperative need to cough, being with phlegm in 90% of the cases, with nasal flow in 80% and sneeze in 80% of the cases and these manifestations allowed them once they passed, in questions of minutes, a generalized improvement. In addition, 50% of the individuals confirmed with SARS-CoV-2 when performing new PCR test are negative, this indicates that the structural modification probably helps to prevent the replication of the virus.

The other indirect observation of the change at a structural level is in the individual with pulmonary microthrombosis, who after the applications of Nasoil® can breathe without external help, has been able to leave the extreme fatigue that prevented him from moving, in this case we are not seeing a preventive aspect, but a reversion to the structural damage of the lung.

5. Conclusions

Out of a population of 600 individuals analyzed, 100% show an improvement in breathing, including individuals belonging to groups 3 to 6 considered preventive or healthy, most of them showing blood oxygen values higher than 96%.

Nasoil® presents a way of action for the control of the symptoms present in the infected individuals with the SARS-CoV-2 virus and is the one of modifying the pulmonary microenvironment, promoting a change in the microstructure of the elastic proteins, which allows to reduce the inflammation and the coagulation, improving with it the capacity of the individuals to breathe.

As a preventive, Nasoil® presents a high percentage of protection to the presence of symptoms (~96%), this does not mean that the individuals do not get infected, but that they do not show in an aggressive way the problems caused by the SARS-CoV-2 virus, and even allowing an immediate improvement in case these symptoms appear.

Nasoil® does not affect the SARS-CoV-2 virus but its action is to improve the capacity of the lungs, improving their elastic capacity and preventing the possible hypercoagulation, and the exaggerated action of the immune system of the individuals (neutrophilia), by stimulating the elastic proteins.

In individuals with severe Covid-19 disease, Nasoil® acts as a stimulant of the action to eliminate the phlegm caused by the lung inflammation, and as a mechanism to expel the virus by mechanical action, such as coughing, nasal flow and even diarrhea in some individuals.

Of the total number of confirmed with Covid-19 all improved and 50% of them were negative when new PCR test. Currently in Mexico, homeopathic physican are using it as a co-adjuvant to treat the symptoms of Covid-19 and other respiratory diseases.

Much work remains to be done to better determine the ways in which Nasoil® acts on the body to improve its condition, as well as to determine the actions on other respiratory diseases, which were seen during the performance of this work. Nasoil® is not a cure or a vaccine, is an adjuvant for the control of symptoms and discomfort caused by the SARS-CoV-2 virus.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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