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Evaluation of the Clinical Effects of an Antiviral, Immunostimulant and Antioxidant Phytotherapy in Patients Suffering from COVID-19 Infection: An Observational Pilot Study

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Abstract: Background: In the last two years, the COVID-19 pandemic has spread all over the world, affecting millions of people. The same infection can manifest in different clinical conditions, ranging from mild situations to severe patient impairment, up to their death. The COVID-19 infection can activate innate and adaptive immune systems and cause massive inflammatory responses that is important to treat as soon as possible. Methods: In the initial phase of the pandemic, a group of 240 unvaccinated subjects with COVID-19 disease was administered phytotherapy with immunostimulant and antioxidant property to evaluate the role of this phytotherapeutic preparation in counteracting the progression of the COVID-19 disease both in duration and complexity. Results: 161 patients were treated with phytotherapy alone and the prevailing symptoms in the acute phase were rhinitis, fever, cough, osteo-muscular pains; the other 79 patients were given a therapy with NSAIDs, symptomatic drugs, monoclonal antibodies, corticosteroids, antibiotics, and/or heparin. The coexistence of comorbidity (such as diabetes, hypertension, gastro-intestinal disease) was recorded in 74 out of 240 subjects, more frequently in the older subjects; there was no statistically significant correlation between the presence of comorbidity and the duration of disease. Hospitalization rate in this population was 1.6% and lethality rate was 0%. Conclusion: The use of phytotherapy can represent a valid weapon against COVID-19, since it showed no side effects and can also be used in association with other pharmacological therapies to reduce the massive inflammatory responses of this infection.

Keywords: population health; infectious diseases; phytotherapy

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1. Introduction

In December 2019, a zoonosis was identified in the Chinese city of Wuhan that would soon turn into a global pandemic. According to updates from the World Health Organization (WHO) made in March 2022, there were about 476,000,000 confirmed cases in the world since the beginning of the pandemic and 6,000,000 deaths [1]. In Italy, there were about 14,000,000 cases and 158,000 deaths in the same period. Although unique in its transmission and virulence, COVID-19 is similar to zoonotic diseases, including other variants of SARS (Severe Acute Respiratory Syndrome), such as SARS-CoV and MERS (Middle East Respiratory Syndrome), in causing severe symptoms similar to influenza and respiratory infections. Additionally, at the molecular level, many parallels

have been identified between SARS and COVID-19, so much so that the COVID-19 virus has been called SARS-CoV-2 [2,3]. These similarities have provided several opportunities to treat COVID-19 patients using clinical approaches that have been shown to be effective against SARS. The COVID-19 infection can activate innate and adaptive immune responses and cause massive inflammatory responses in a more advanced stage of the disease [4,5]. The severity of the COVID-19 disease as well as the risk of progression to relevant clinical forms with systemic involvement, and the decrease in respiratory and circulatory capacity until death, depends on the concomitance of several factors, some of which are related to the virus, such as virulence and viral load, with others related to the infected host, including age, sex, obesity, the degree of effectiveness of the immune response [6–9], the genetic predisposition to develop a cytokine and coagulative hyper-inflammatory response [10] resulting in local and systemic organ damage, and the number of associated comorbidities. The strategy of using phytotherapy [11,12] in a very early stage of the disease, at the onset of symptoms, when usually the viral load is still low, combining in a single tablet, several active ingredients with different activities on the virus and on the host organism, has been documented in various in vitro and animal clinical studies [13,14]. Little is known about the effect of this approach on humans. The present study therefore aims to evaluate the role of a phytotherapeutic preparation in counteracting the progression of the COVID-19 disease at various levels, with the main objective of reducing the risk of hospitalization and death.

Our primary aim was to report a descriptive analysis of the COVID-19 patients enrolled in the studies, and who were followed during symptomatic SARS-CoV-2 infection, before the vaccination period; the secondary aim was to evaluate the clinical effects of a phytotherapeutic preparation, called Immuno Complex, with antiviral and immunostimulant/immunomodulating action on the severity of COVID-19 disease and on the hospitalization rate in symptomatic patients affected by SARS-CoV-2.

2. Materials and Methods

2.1. Patients' Characteristics and Assessment

In the period between September 2020 and December 2021, a total of 240 unvaccinated patients aged between 8 and 96 years, of both sexes (males n.111, females n.129), with symptomatic COVID-19 disease, documented by rhino-oropharyngeal molecular swab by genetic research of viral RNA, were recruited on a voluntary basis. After receiving the approval of the University Research Committee of Rome Foro Italico University (Protocol Number: CAR 103/2021), patients were recruited by a group of family doctors who practiced in Rome. Before the enrolment, all participants were informed verbally about the procedures of the study and gave their verbal informed consent.

Patients who had completed the vaccination course or who had received at least 1 dose of vaccine (incomplete vaccination) were excluded from the evaluation. Asymptomatic patients throughout the course of the disease were not included. The microbiological diagnosis of the COVID-19 infection was performed on all patients with suspected symptoms, as early as possible, at the onset of symptoms. This diagnosis was ascertained through the use of nasopharyngeal swabs by searching for specific genetic material of SARS-CoV-2, with the RT-PCR method, based on the search for one or more genomic portions of the SARS-CoV-2 virus, gene E, N gene and RdRp / S gene, validated and approved by the scientific community and used for all tests performed within the NHS (National Health Service) [15]. Patients' characteristics were reported in Table 1.

Table 1. Patients' Characteristics.

	Value/Mean ± SD	Range
Age (years)	37.15 ± 20.5	8–96
Sex	111 M–129 F	
Microbiological Disease—Positive Swab (days)	18 ± 8	2–49
Clinical Disease—Symptoms (days)	10 ± 7	2–36
Lowest value of O_2 saturation (%)	96 ± 2	90–99
Body temperature (°C)	37.4 ± 1	36–40
Presence of Comorbidity	74	
Subjects who need Hospitalization	3	
Subjects who died	0	

2.2. Phytotherapeutic Preparation and Administration

One tablet of the phytotherapeutic preparation (PTP) contains: green tea polyphenols 285 mg (Camellia sinensis, leaves dry extract titrated to 95% polyphenols, 40% epigallocatechin gallate, EGCG), ascorbic acid 250 mg, quercetin 200 mg (Sophora japonica, dry extract titrated at 98% in quercetin), polyphenols from red wine 190 mg (Vitis vinifera semi dry extract titrated at 95% in polyphenols). All monitored patients were treated with antiviral immune-phytotherapy, regardless of age, sex, risk factors and comorbidities, and other drugs taken for specific underlying pathologies, except in the case of documented interactions between active ingredients. In patients under 14 years of age and in those with mild symptoms and/or exclusively affecting the upper respiratory tract, the daily dosage was equal to 2 tablets/day, one every 12 h. In all other patients, the dosage administered was 3 tablets/day, one every 8 h. Patients' adherence to therapy was verified with daily phone calls. All patients enrolled in the study regularly continued the specific pharmacological treatments necessary for underlying chronic diseases diagnosed before the COVID-19 infection. In accordance with current WHO and NHS guidelines [16], patients were treated, in individual specific cases and when deemed appropriate or necessary, with specific pharmacological therapies, such as low molecular weight enoxaparin, at the posology of 4000/6000 IU sc/day, depending on body weight, in bedridden or semi-bedridden patients, antibiotics such as azithromycin at a dosage of 500 mg/day × 3–6 days or other antibiotics in cases of proven or strongly suspected over-infection, cortisone such as dexametazone 6 mg/day, in the advanced forms, with significant pulmonary commitment and in the most critical situations and deserving of oxygen therapy and hospitalization. To alleviate pain and inflammation NSAIDs (non-steroidal anti-inflammatory drugs) were used as needed and at the recommended doses. Everyone was advised to have adequate hydration. Starting from April 2021, in the Lazio region, the possibility of performing therapy with monoclonal antibodies was activated in accordance with the guidelines of the WHO and of our NHS. In this study, 2 patients belonging to this category were recruited. Patients were followed at home for the entire course of the disease, from the moment of diagnostic suspicion, until the negativization of the molecular swab (microbiological recovery) or complete remission of clinical symptoms (clinical recovery) and also in the convalescence phase, post COVID-19, for a variable period of 3–6 months. Clinical monitoring of patients was carried out daily, remotely, by telephone, on-line, video-call, etc. for the entire course of the acute phase of the disease. In case of worsening of the respiratory and general clinical symptoms, signs and symptoms of disease progression, especially in the presence of comorbidities and/or additional risk factors and elements, the patient was hospitalized, as suggested by the NHS guidelines.

The patients were all monitored and followed up daily, at home, for the entire course of the disease, by filling in a clinical-anamnestic form, recording of all the information useful for the study:

- Personal data: age, sex, etc.;
- Anamnestic data: date of execution of molecular swabs (first positive swab and negative swab at the end of the disease), date of onset of symptoms, duration of symp-

toms in days, co-morbidities, current and previous pathologies, therapies assumed, modalities and circumstances of the infection, etc.;
- Symptoms and trend of symptoms (at the onset and throughout the course);
- Clinical parameters: body temperature, heart rate, blood pressure, respiratory rate, O_2 Saturation by means of a pulse oximeter/digital oximeter and at rest in ambient air;
- Start date of phytotherapeutic administration and dosage.

In some circumstances, such as in more critical situations or in the case of interpretative doubt, the O_2 saturation was also detected after physical exercise, such as walking test, step test, chair test, etc.

2.3. Statistical Analysis

Data analysis were performed using the SPSS ver.21 statistical program (IBM). The normal distribution of continuous variables was verified by Kolmogorov–Smirnov test. For continuous variables mean $\pm$ standard deviation or median and range were reported while categorical variables were expressed as frequency counts. Correlations were assessed by Pearson's correlation coefficient (for normally distributed data) or Spearman's rank test (in case of non-Gaussian distribution), while Pearson's chi-square test for independence was used to verify the existence of significant correlations between categorical variables. Mean differences were investigated by ANOVA in case the normal distribution of the data occurs, or through Wilcoxon Signed Rank test, for data not normally distributed. The results are considered statistically significant with $p < 0.05$.

3. Results

The hospitalization rate, i.e., the percentage of hospitalized patients compared to the total number of COVID-19 positive patients, found in our sample was 1.6%. None of the patients recruited in this study were admitted to the intensive care units. Three patients were admitted to ordinary pulmonology wards.

Furthermore, results from our sample of 240 patients evidenced the following:

- 161 patients were treated with PTP alone, occasionally combining NSAIDs or paracetamol as needed; all are monitored at home;
- 27 patients were also treated with symptomatic drugs, such as decongestant nasal spray or sedative cough syrup;
- 2 patients were also treated with monoclonal antibodies; both recovered at home and with no documented pulmonary outcomes;
- 9 patients were also treated with enoxaparin, because they were bedridden or half-allied or carriers of high thrombo-embolic risk, at a dosage of 4000–6000 IU/day, in relation to body weight and the degree of thrombo-embolic risk; of these patients, n. 2 were hospitalized, and the other 7 were monitored at home;
- 27 patients were also treated with antibiotics, in the presence of suspected or confirmed bacterial over-infection, (azithromycin, at a dosage of 500 mg/day $\times$ 3–6 days or amoxicillin/clavulanic $\times$ 7 days); of these 27 patients, n. 2 were hospitalized, and the other 25 were healed at home;
- 14 patients were also treated with corticosteroids, for a short period, according to the indications provided during the pandemic period by the WHO and the NHS, for patients with clinically advanced COVID-19 disease or with indications for hospitalization and/or oxygen therapy (See Table 2); of these 14 patients treated with corticosteroids, n. 2 were hospitalized, and the other 12 healed at home;
- Of the 3 hospitalized patients, two were hospitalized in ordinary internal medicine wards and one in pre-intensive care ward. None of them underwent invasive assisted ventilation, but only oxygen therapy with a mask or helmet. The patients were 23, 47 and 48 years old, respectively. The average length of hospitalization of these 3 patients was 7 days, and the longest hospitalization was 12 days.

Table 2. Treatments taken by patients. Abbreviation: PTP, Phytotherapeutic Preparation.

	Number of Cases
Treated with PTP only	161
PTP+ Symptomatic drugs	27
PTP + Antibiotics	27
PTP + Monoclonal Antibody	2
PTP + Heparin	9
PTP + Corticosteroids	14

Moreover, the lethality rate, that is the number of deaths compared to the number of infected people, represents one of the main indicators of the severity of the disease. In our small sample, the lethality rate was 0% in all age groups observed, including the over 80 age group. The average duration of the disease, in terms of symptoms of the acute phase (excluding symptoms such as anosmia/hyposmia, ageusia/dysgeusia and asthenia, because, although characteristic of COVID-19 disease, they are not recognized by the scientific community as acute-phase symptoms) was 10 ± 7 days, with a range of 2–36 days. The mean duration of molecular swab positivity (microbiological disease) was 18 ± 8 days, with a range of 2–49 days. For each patient, the lowest values of O_2 saturation found throughout the clinical course of the acute phase were recorded. The mean value of O_2 saturation found was $96 \pm 2\%$. The lowest saturation value found was 90%. Maximum body temperature values were recorded for each patient; the average of these values was equal to $37.4\ ^{\circ}C \pm 1\ ^{\circ}C$, the maximum temperature recorded during the disease was 40 °C (See Table 1). As reported in Figure 1 the prevailing symptoms in the acute phase were: rhinitis, fever, cough, osteo-muscular pains. Among the symptoms not considered to be of the acute phase, the most frequent were: hyposmia/anosmia, hypogeusia/ageusia, asthenia.

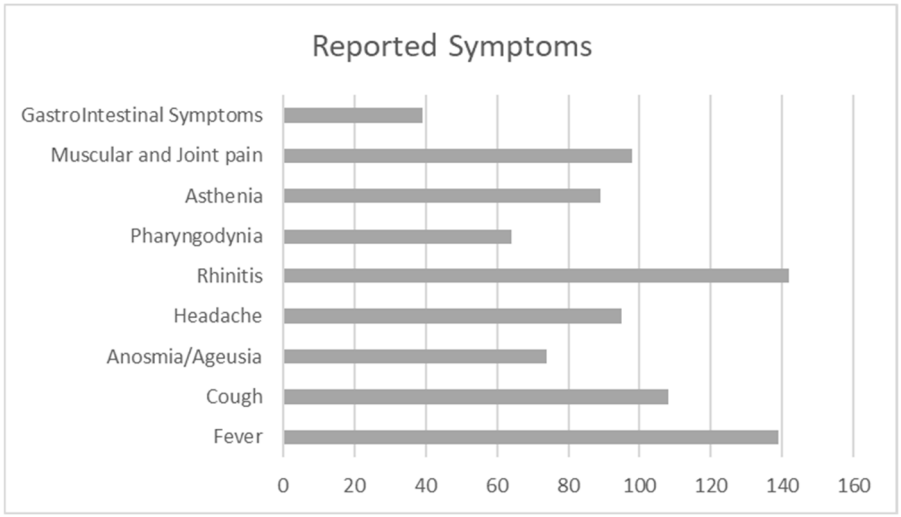

Figure 1. Symptoms reported by subjects during infection.

For the entire course of observation, neither in the acute phase nor in the course of convalescence nor at a distance, no patient showed cardiological, vascular, renal, neurological complications or other complications among those recognized in this disease affecting other organs and systems, apart from the aforementioned pulmonary complications, such as interstitial pneumonia and other manifestations on a predominantly microthromboembolic basis.

The ways in which the infection occurred were also recorded (Figure 2). The area of most frequent transmission of the infection was the family, and this was independent of the age of the subjects.

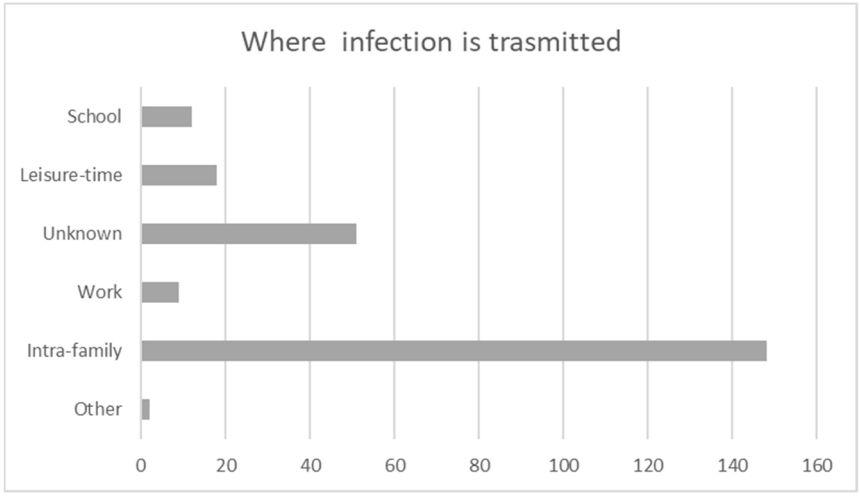

Figure 2. Area of infection transmission.

Moreover, the presence of one or more comorbidities among the patients considered for this study was analyzed. In particular, the coexistence of other pathologies (such as diabetes, hypertension, gastro-intestinal disease) was recorded in 74 out of 240 subjects. On the other hand, 69% of the population analyzed was free from further pathologies. As expected, the older population was the one with the higher number of comorbidities, but no statistically significant correlation was found between the presence of this comorbidity and the duration of microbiologic disease (see Table 3).

Table 3. Duration of microbiologic disease in young and adult patients Abbreviation: y, years old.

	Young (<38 y)	Adult (>38 y)
25% Percentile	11	12
50% Percentile	16	17
75% Percentile	21	23
Min Duration of Disease (days)	2	2
Max Duration of Disease (days)	49	44
Mean Duration of Disease (days)	17.2	18.6

Lastly, a statistically significant correlation between the duration of the disease (microbiological) and the age of the patients was not found; similarly, no correlation was found between the duration of the microbiological disease and the dosage of supplement therapy (two or three times a day). No statistically significant differences were found in the type of symptoms manifested based on age.

4. Discussion

In light of the data reported by the literature [17–19] and given the lack of studies, of the availability of drugs and home therapy protocols that are certainly effective, without side effects [20], during the COVID-19 pandemic, we evaluated the use of a phytotherapeutic formula called Immuno Complex (PTP) with immunomodulating, antiviral and antioxidant properties. This formulation, based on quercetin [21,22], polyphenols of green tea [23], red wine and vitamin C, was inspired by molecular docking studies, which highlighted the binding sites present in SARS-CoV-2 and on the cell guest [24–26]. As was reported by Mhatre et al., epigallocatechin gallate (EGCG) and theoflavins showed a significant interaction with the 3CLpro protease, the Spike protein (S), the RdRp polymerase and the GRP78 receptor [27]. The protective effects of quercetin can be associated with blocking the activation of inflammatory pathways related to cell apoptosis [28,29]. Quercetin seems also to act as a SARS-CoV-2 inhibitor by binding to the active sites of the 3CLpro protease and the cellular ACE-2 receptor, thereby suppressing the coronavirus life cycle [30].

It is known that one of the main problems with polyphenols is their low bioavailability and rapid metabolism [31–33]; nevertheless, most polyphenols have demonstrated significant biological effects that have brought to attention the low bioavailability/high bioactivity paradox [34]. The composition of the meal is able to influence the bioavailability of these substances; for example, the simultaneous intake of dietary fats is able to increase the bioavailability of quercetin [35]. One of the solutions to the problem of low bioavailability is the use of mixtures of various polyphenols that bring synergistic effects causing a lowering of the required therapeutic dose and a biological action towards multiple targets [36]; for example, the simultaneous intake of quercetin and total polyphenols of Camellia sinensis increases the cellular absorption of epigallocatechin gallate by 4 times [37]. So, we propose the intake of a mixture of polyphenols to overcome the problem of low bioavailability of active ingredients to reach a valid effect.

The decision to test immune-phytotherapeutic preparation in COVID-19 disease was dictated by the following considerations shown:

Why administrate phytotherapeutic preparation in subjects affected by COVID-19?

- The presence of a clinically relevant disease, responsible for a large number of deaths and hospitalizations [38,39];
- The lack of a certainly effective drug therapy for the treatment at home of the COVID-19 disease;
- The absence of alternative drugs, tested, and with certain efficacy for the COVID-19 disease that can be administered by mouth and without side effects [40,41];
- The pressing request of therapies to be performed at home from patients diagnosed with COVID-19 disease;
- The absence of side effects of phytotherapy at the dosages used, compared to other drugs used in the same period, such as hydroxychloroquine and azithromycin, regardless of dubious efficacy, except for special situations [42–46];
- The need to slow the clinical progression of the COVID-19 disease and to reduce hospitalizations and the workload in intensive care units due to a disease that is significantly impacting public health, in terms of both morbidity and mortality, as well as on the economic health level;
- The modest cost of phytotherapy compared to other pharmacological therapies used in different protocols (The cost of Immuno Complex 60 tablets Pharma.co Srl Roma Italy is 34 euro for 60 tablets);
- The possibility of starting treatment at a very early stage of the disease, at the patient's home, at the first clinical suspicion, even before a molecular buffer response;
- The simple oral administration, accessible to all patients, starting from 8 years of age;
- The negligible possible drug interactions between phytotherapy and conventional therapies [47];
- The possibility to take phytotherapy and drug therapy at the same time with a possible synergistic effect [48];
- The potential preventive as well as curative effect of this therapy, compared to the intra-family contagiousness and the extent of the viral load transmitted between contacts.

As reported in the results, in the sample studied, we observed the rate of hospitalization and lethality using PTP at home in the early phase. Out of a total of 240 patients, 74 of them had at least 1 comorbidity, in addition to COVID-19 disease. In our sample, the percentage of hospitalized patients compared to the total number of COVID-19 positive patients was found to be 1.6%. Patients who were completely asymptomatic for the entire course of the disease and pediatric patients under the age of 8 were excluded from our sample, as they usually have a very low hospitalization rate.

This non-controlled and non-randomized observational clinical study does not allow us to generalize the results because it was carried out in an emergency period, there is not a control group and it was conducted on small sample size. However, it highlighted the importance of PTP unconventional therapies capable of supporting the innate immune response and counteracting the viral load in an early stage of the COVID-19 disease. Innate

immune response is always accompanied by adaptive immunity, which is the most specific line of defense to which antibodies and T cells belong [49], but it is important to underline that the active ingredients of the phytotherapeutic preparation we used showed positive modulation effects mostly on innate immunity, as reported by other studies [50–53].

5. Conclusions

Based on the preliminary results of this study, the use of the PTP, which has no side effects and which can also be used in association with other pharmacological therapies, can represent a valid weapon against COVID-19 and, more generally, against viral diseases, especially when they appear with new pathogens, capable of causing clinically relevant and potentially fatal clinical pictures. It seems that these results, obtained in an emergency situation, considering all the limitations mentioned above, still deserve to be subjected to the attention and evaluation of the scientific community. Indeed, this pilot observational study should be integrated by experimental clinical evaluations on larger populations and with more rigorous scientific criteria, with the aim to understand, in a clearer and more definitive way, the role of PTP, not only on SARS-CoV-2 disease and all its numerous variants, but also to many other viral diseases, whose prognosis can be serious and disabling.

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Informed Consent Statement: Verbal informed consent was obtained from all subjects involved in the study.

Data Availability Statement: Not applicable.

Conflicts of Interest: The authors declare no conflict of interest.

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