



## Antioxidant composition Twendee X may improve long COVID symptoms

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### Abstract

As the SARS-CoV-2 pandemic rages, long-lasting sequelae (long COVID) are a problem in many countries around the world. At present, there is no effective and evidence-based treatment. COVID-19 has been shown to cause oxidative stress in the body, which is responsible for the amplification and persistence of cytokine storms and blood coagulation abnormalities in the causative SARS-CoV-2 infection. Therefore, it was hypothesized that the administration of an antioxidant supplement would provide symptomatic relief. TIMA Tokyo Ltd. conducted a web-based survey of people suffering from long COVID and participants were provided with the antioxidant composition supplement Twendee X free of charge. The survey asked participants to self-report the severity of the eight typical adverse reactions (fatigue, breathing difficulty, chest pain, smell and taste disorders, headache, brain fog, joint pain, and dizziness) on a six-point scale at the time of participation and one month after taking Twendee X. In this interim report, severity scores for all symptoms except joint pain were significantly reduced. In particular, when the scores of the relatively severe participants who responded with scores 3-5 were averaged, the scores were less than half of the pre-taking scores in all cases. The results suggest that the symptoms of long COVID are caused by elevated systemic oxidative stress, and that antioxidants may help prevent or treat the reduction.

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**Abbreviations:** COVID-19, coronavirus disease 2019; LNP, lipid nanoparticle; TwX, Twendee X.

**Key words:** long COVID, COVID-19, Twendee X, antioxidant composition, web-based survey

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## Introduction

As the SARS-CoV-2 epidemic rages on, the increase in severe cases and mortality due to SARS-CoV-2 infection is a major concern worldwide. Over the past two years, SARS-CoV-2 has mutated rapidly, and the newer strains tend to have milder symptoms and lower mortality rates, but COVID-19 has a problem with long-lasting sequelae (long COVID) even after symptoms improve. At present, the disease is being treated symptomatically and there is no known therapeutic agent that have been proven effective against long COVID. As such, even in former COVID-19 patients who have been cleared of the virus, symptoms from long-lasting sequelae can be an issue.

COVID-19 is the result of SARS-CoV-2 infection; it induces oxidative stress in the body, which amplifies and prolongs cytokine storm and abnormal blood coagulation in patients [1]. From the outset, the relative risk of developing severe COVID-19 is higher in older age groups and in individuals with an underlying disease. This is consistent with the tendency for such individuals to have increased oxidative stress. SARS-CoV-2 infection causes systemic inflammation by the spike proteins, and residual post-infection oxidative stress can be expected even in patients who no longer have the virus.

Addressing residual oxidative stress in long COVID patients may help to reduce the incidence and severity of sequelae. In this paper, we will report the results of a questionnaire survey conducted by TIMA Tokyo, Inc. on symptoms before and after taking a one-month supply of Twendee X, an antioxidant composition supplements, to patients suffering from long COVID.

## Materials and Methods

### *Antioxidant Formula: Twendee X*

Twendee X is an antioxidant composition, manufactured and distributed by TIMA Tokyo Co., Ltd. It contains eight active ingredients: vitamin C, L-glutamine, cystine, coenzyme Q10, fumaric acid, succinic acid, niacin, and vitamin B2 [2,3]. Twendee X has independently certified to have no side serious effects and the formula has passed the safety tests required for medicinal products: preliminary toxicity test (Ina Research Test No. GL43080), chromosome aberration test (Ina Research Test No. BV07158), toxicity test (Ina Research Test No. BV07156), mutation test (Ina Research Test No. BV07352), side effects in human clinical trials (Ina Research Test No. NRP 07-

001).

In experiments using cultured cells, Twendee X reduced cellular and mitochondrial oxidative stress by 45-63% and raised SOD by 60-147%. Twendee X is also proven to be three times more potent than vitamin C and 2.5 times more effective than vitamin E, both of which is a commonly used antioxidant, at scavenging hydrogen peroxide, a reactive oxygen species at similar concentrations (0.23 mg/ml). The Japanese Society for Dementia Prevention led a multicenter, double-blinded, placebo-controlled, prospective, interventional clinical trial of Twendee X in Japanese aged 65-85 years with mild cognitive impairment. The results showed that as a dietary supplement, Twendee X is effective at lowering the risk of dementia [4]. The Twendee X used in this study was kindly donated by TIMA Tokyo Ltd. The patent and trademark for Twendee X, and the data used in this report are the property of TIMA establishment (Liechtenstein). The data in this report was obtained from website and is being used with permission from TIMA establishment.

Table 1: Questions asked in the questionnaire

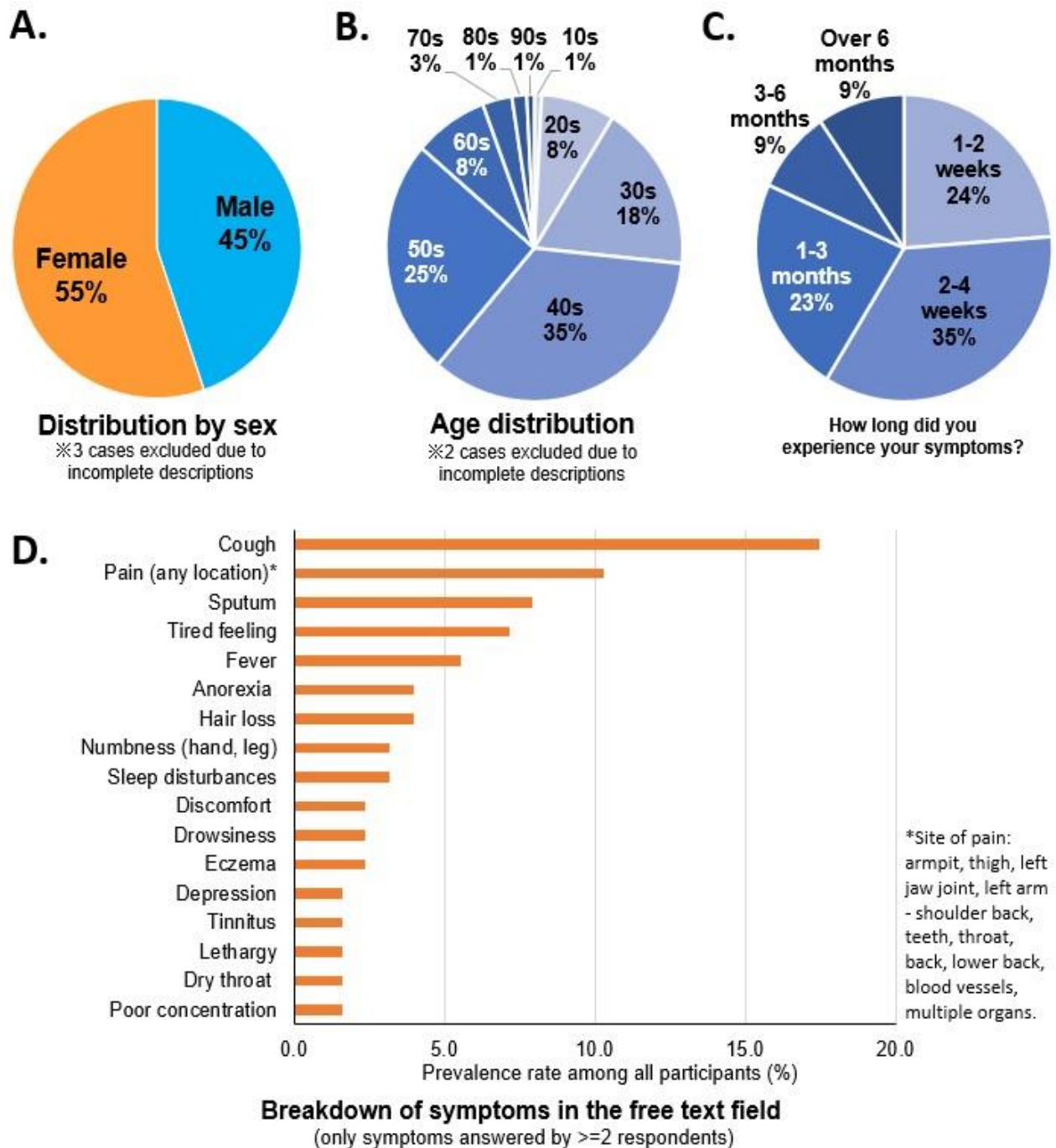
Questions	Options
How long did you experience your symptoms?	1-2 weeks, 2-4 weeks, 1-3 months, 3-6 months, over 6 months.
What was the severity of the following symptoms?	
1. Fatigue	0 (None), 1, 2, 3, 4, 5 (Severe)
2. Breathing difficulty	0 (None), 1, 2, 3, 4, 5 (Severe)
3. Chest pain	0 (None), 1, 2, 3, 4, 5 (Severe)
4. Smell & taste disorders	0 (None), 1, 2, 3, 4, 5 (Severe)
5. Headache	0 (None), 1, 2, 3, 4, 5 (Severe)
6. Brain fog	0 (None), 1, 2, 3, 4, 5 (Severe)
7. Joint pain	0 (None), 1, 2, 3, 4, 5 (Severe)
8. Dizziness	0 (None), 1, 2, 3, 4, 5 (Severe)

### *Web-based survey and questionnaire*

TIMA Tokyo Co., Ltd. enrolled participants with long COVID via the company's website. At the time of enrollment, participants were asked to self-report the duration and severity of their symptoms on a 6-point scale from no symptoms (0) to severe symptoms (5) (Table 1). Furthermore, any symptoms of concern other than those listed in Table 1 could be freely described. Patients were given complimentary samples of Twendee X and instructed to take 3 tablets /one time/one day for 1 month. After one month of taking Twendee X, the participants were asked to self-report the severity of each major symptom again on the 6-point scale. At the time of the post-treatment report, participants' responses to the pre-treatment questionnaire were not disclosed in order to avoid any bias. The results are presented as mean, and we used Student's t test unless otherwise indicated. Differences

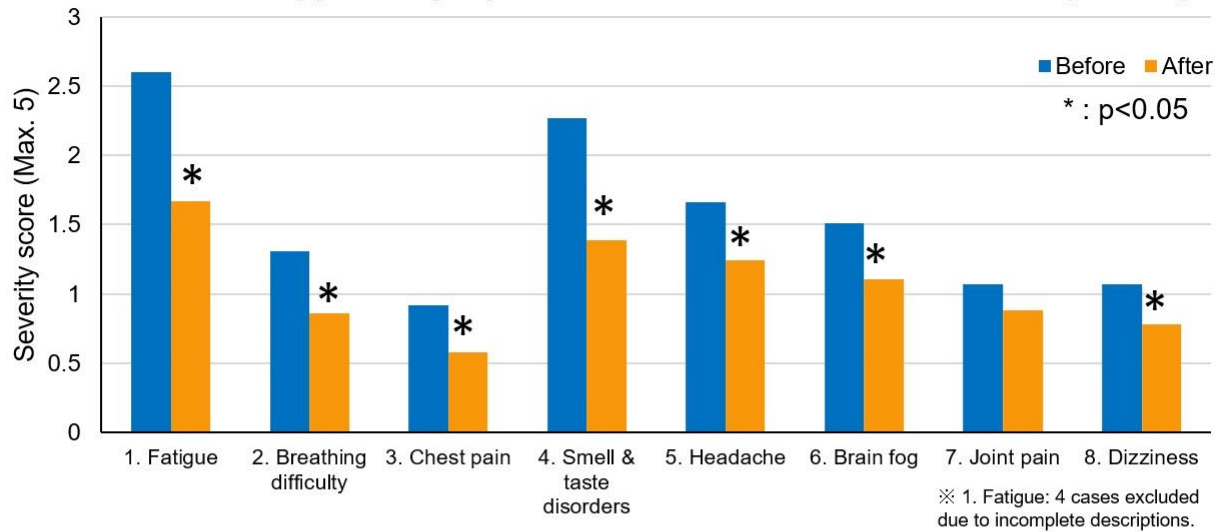
with a probability value of  $p < 0.05$  were considered to be statistically significant. The data were collected and made available on the internet by TIMA establishment

with participants' consent (URL: <https://www.twendee.com/long-covid-and-twendee-x>). The data in this report is being used with permission from TIMA establishment.

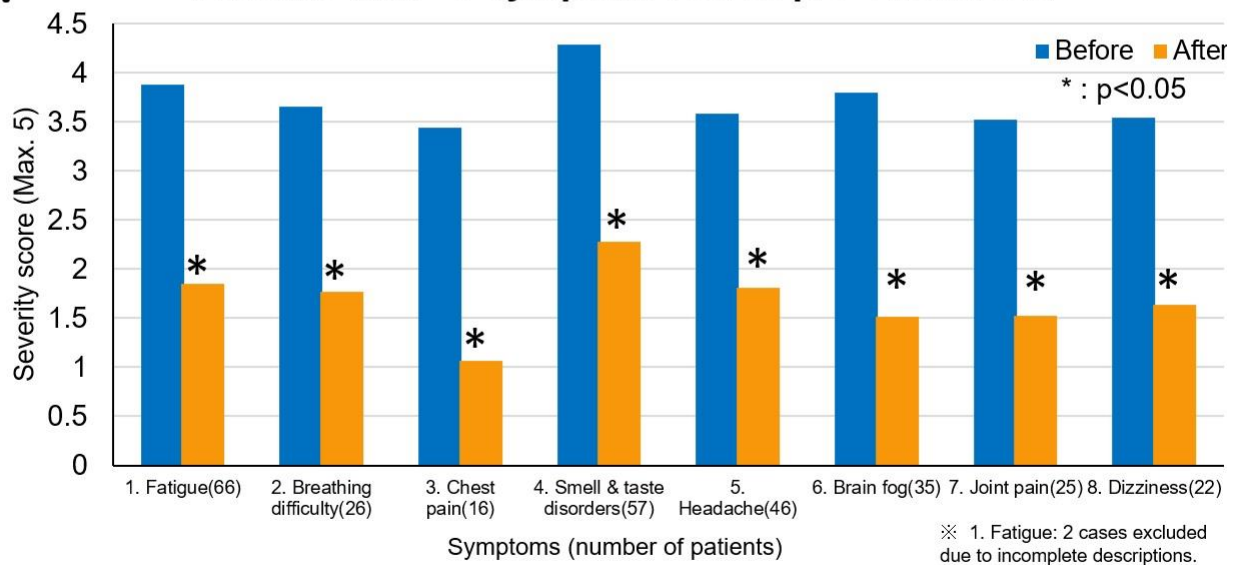


**Fig. 1: Patient Characteristics & Symptom Distribution**

### A. Scores of typical symptoms before & after Twendee X (n=126)



### B. Patients with >3 symptom scores pre-Twendee X



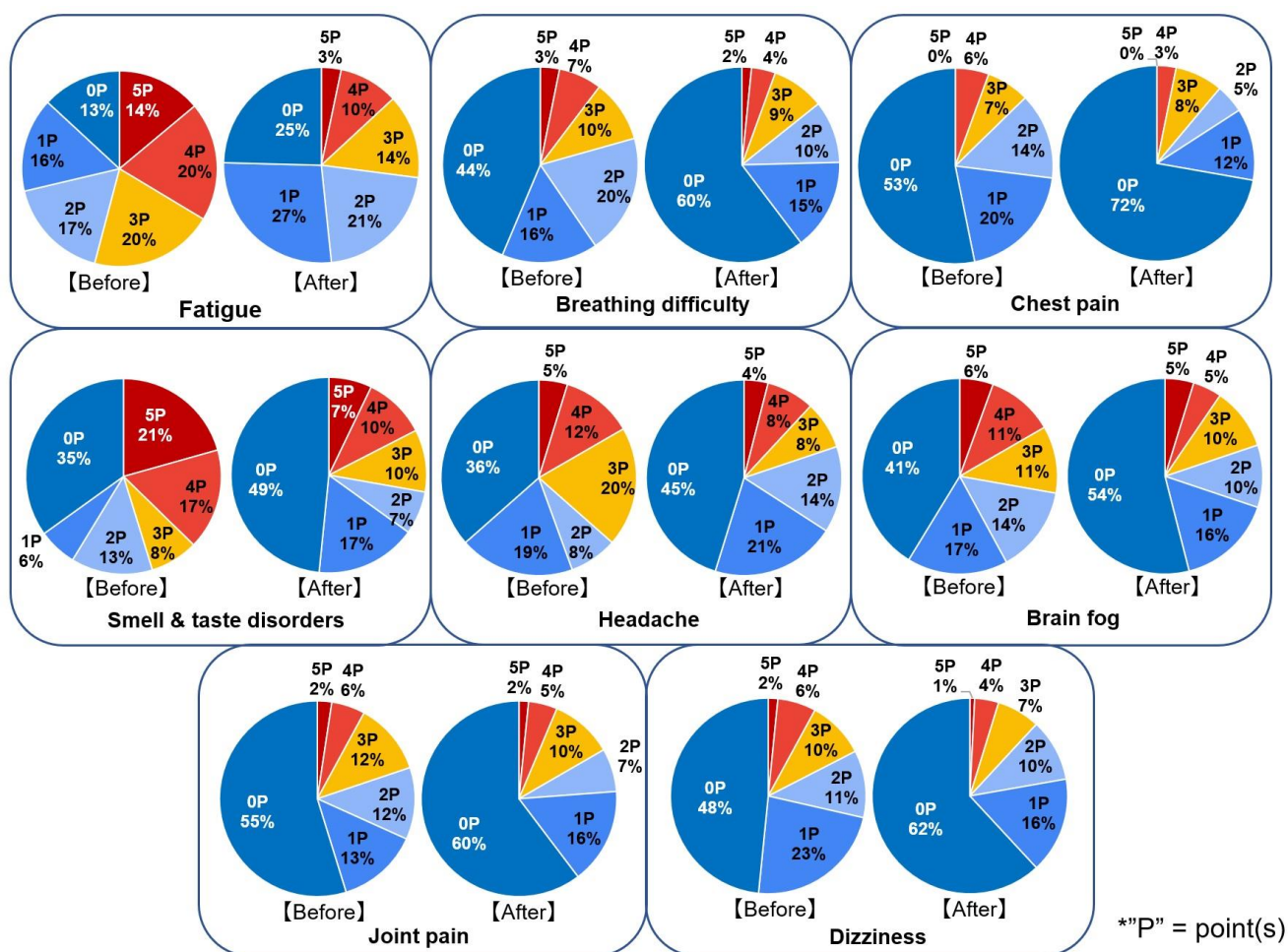
**Fig. 2: Symptom Severity Scores Before and After Twendee X**

## Results

In the interim report (compiled between September 2 and 28, 2021), 126 valid responses were received. Nearly half of the respondents were women (Fig. 1A). The majority of respondents were in their 40s (35%), while those in their 30s (18%) and 50s (25%) accounted for almost 80% of the total (Fig. 1B, Average:47.2, SD:12.9). The most common duration of

symptoms before taking Twendee X was 2 to 4 weeks (35%), followed by 1 to 2 weeks (24%) and 1 to 3 months (23%) (Fig. 1B).

The main sequelae according to the questionnaire were fatigue, breathing difficulty, chest pain, smell and taste disorder, headache, brain fog, joint pain and dizziness (Table 1), and the results of the symptom scores before and after taking Twendee X were tabulated by symptom. The most common complaint before taking the Twendee X was fatigue,



**Fig. 3: Distribution of symptom Severity Scores Before and After Twendee X**

followed by smell and taste disorder, headache, brain fog, breathing difficulty, joint pain, dizziness and chest pain. Other symptoms reported included cough, body aches, tired feeling, fever, anorexia, hair loss and sleep disturbances (Fig. 1D). Symptom scores showed a significant decrease after the first month of treatment with Twendee X, except for joint pain (Fig. 2A). In particular, the mean score for severely ill participants (those with 3 or higher symptoms severity scores), was less than half of the pre-treatment score in all cases ( $p < 0.05$ ) (Fig. 2B). A comparison of the distribution of all symptom scores before and after treatment showed that all symptoms reduced after patients took Twendee X for 30 days (Fig. 3).

## Discussion

The questionnaire revealed that long COVID can present multiple symptoms at the same time, in a

range of severity. The most common complaint was fatigue, but abnormal taste or smell, and respiratory problems attributed to the SARS-CoV-2 route of infection such as cough and sputum were relatively common. These symptoms persisted for a relatively long period of time, and other common symptoms such as mild fever, fatigue and hair loss were also reported by many individuals. Regardless of the symptom and its duration, participants experienced significant improvements after 30 days of taking the antioxidant supplement Twendee X. Arthralgia, which did not show much improvement, could potentially be improved if the participants took Twendee X for a more extended period.

Oxidative stress is known to play a major role in COVID-19 infection, and the results of this study suggest that oxidative stress may be a factor in the symptoms of sequelae. It can be assumed that oxidative stress and pro-inflammatory cytokines, which are elevated by SARS-CoV-2 infection, promote each other,

and that prolonged elevation of these two factors may result in sequelae. Based on this logic, lowering oxidative stress, in this case with antioxidants, may have lower inflammation, leading to an improvement in symptoms.

Since this study is based on questionnaires, the results cannot be considered conclusive. In addition, the nature of the questionnaire does not allow for a placebo group, making it impossible to determine whether the improvement in symptoms is due to Twendee X or over time. However, the results have led us to believe that lowering oxidative stress may help

prevent or alleviate symptoms of long COVID and therefore means to do so should be further investigated. We propose clinical trials that are randomized, double-blind, placebo-controlled interventions that can reliably conclude the role of concentrated anti-oxidants in positively affected long COVID.

### **Conflicts of interests**

The authors disclose no potential conflicts of interest.

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