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# Beekeepers who tolerate bee stings are not protected against SARS-CoV-2 infections

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ABSTRACT

A survey on 5115 beekeepers and 121 patients treated with bee venom by an apitherapy clinic in the Hubei province, the epicenter of COVID-19 in China, reported that none of the beekeepers developed symptoms associated with COVID-19, the new and devastating pandemic. The hypothesis that immunity to bee venom could have a preventive effect was expressed and the authors of the Chinese survey suggested that the next step should be animal experiments on monkeys.

We believed that before starting such studies, a second independent survey should verify the findings and define the hypothesis more clearly. Thus we asked all German beekeepers to complete an assessment form which would summarize their experiences with COVID-19. In contrast to the Chinese study we found that two beekeepers had died from a SARS-CoV-2 infection and forty-five were affected. The reaction to bee stings (none; mild swelling; severe swelling) correlated with the perceived severity of the SARS-CoV-2-infection-associated symptoms - exhaustion and sore throat. Beekeepers comorbidity correlated with problems with breathing at rest, fever, and diarrhea.

Our results did not confirm the findings of the Chinese study. However, since the antiviral effects of bee venom have been found in several studies, we cannot exclude that there could be a direct preventive or alleviating effect when bee venom is administered during the infection.

## 1. Introduction

COVID-19, the new and devastating pandemic, has strained healthcare systems around the world to and beyond their limits. Although most affected individuals do not require hospitalization, some COVID-19 patients do and for some, a critical illness develops that even warrants mechanical ventilation. For some patients, especially those that are older or with predisposing risk factors, the disease can be deadly. Treatment concepts for COVID-19 are still developing. Possible options include antiviral drugs (e. g. remdesivir, ritonavir or lopinavir) which were developed to disrupt the replication mechanism of other viruses, immunomodulators (interferons, biologicals, corticosteroids) and other medication for infectious diseases, e.g. the malaria drugs (hydroxychloroquine and chloroquine). However, there are some concerns against the use of hydroxychloroquine, chloroquine and corticosteroids (Cortegiani et al., 2020; Theoharides and Conti, 2020).

The development of specific substances against SARS-CoV-2 appears to be extremely interesting. Possible targets include the transmembrane angiotensin-converting enzyme 2 (ACE 2), the transmembrane protease, serine 2 (TMPRSS2) and several others. Currently the development of a vaccine against the virus is considered to be the most important step against the pandemic. However, it remains unclear if and how soon such a vaccine will generally be available.

Therefore, the search for other effective and potentially life-saving treatments is also underway. Two reports suggest that bee venom could play a role regarding the prevention and treatment of COVID-19 (Yang et al., 2020; Block, 2020). Yang et al. (2020) report on a survey of 5115 beekeepers in the Hubei province, the epicenter of COVID-19 in China, which showed that none of the beekeepers developed symptoms associated with COVID-19. The paper also reports on 121 patients of an apitherapy clinic treated with bee venom who also did not develop symptoms associated with COVID-19. Yang et al. (2020) believe that bee venom's influence on the body's immune system and the enhancement of the differentiation of human regulatory T cells could play an important role in control of SARS-CoV-2. Block (2020) argues that the anti-inflammatory and antimicrobial properties of bee venom

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derivatives might be useful in the prevention of long-term fibrotic destruction of the lung.

Yang et al. (2020) suggest that the next step should be animal experiments on monkeys. These monkeys should be raised in the same environment and contaminated by SARS-CoV-2; however, a subgroup would have been made tolerant to bee venom after a period of daily bee stings, while the other subgroup would have received no such intervention.

Before starting such studies, a second independent survey may help to determine the trustworthiness of the former data and define the hypotheses more clearly.

## 2. Material and methods

### 2.1. Assessment form

We developed an assessment form in which the beekeepers were asked to report on 6 items:

1. Demographic data (age, gender, presence of chronic diseases, how long they had been a beekeeper)
2. Estimated total number of received bee stings, number of bee stings received in 2020 and reaction to bee stings/tolerance of bee stings.
3. Symptoms in case the beekeeper was affected by COVID-19. The assessment was based on the "Triage-Fragebogen grippaler Infekt/Influenza/Corona" which was developed by Dielmann-von Berg, Scherer and Mühlenfeld (https://www.degam.de/files/Inhalte/Degam-Inhalte/Aktuelles/2020/Benefits/Coronavirus_MFA-Fragebogen.pdf; assessed 28.06.2020).
4. Contact to COVID-19 affected patients (confirmed contact with the COVID-19 disease or probable contact with the COVID-19 disease).
5. Other measures taken by the beekeeper against COVID-19 disease.
6. Knowledge of any beekeeper who died from COVID-19.

Beekeepers who had come into contact with COVID-19 were asked to complete the assessment form and return it.

### 2.2. Ethics

The study was acknowledged by the ethics committee of the University of Jena on May 19th, 2020 (registration number 2020-1786-Bef).

### 2.3. Data collection

In order to get information on beekeepers in contact with the COVID-19 disease we contacted various beekeeper associations and beekeeping journals in Germany. The *Deutsche Imkerbund* (German Beekeepers Association) and its associated federal beekeeping associations in the various states of the German Federal Republic provided non-monetary support. We figured that the presidents of local beekeeper associations would be the best source for potentially affected beekeepers because many of these local beekeeper associations would have agreed to help affected beekeepers by taking care of the hives. The addresses of these local beekeeper associations were identified via the homepage of the German Beekeepers Association (https://deutscherimkerbund.de/171-Die_Imker_Landesverbaende; assessed 28.06.2020) and its associated federal beekeeping associations in the various states of the German Federal Republic. We also asked the major beekeeping journals to inform beekeepers about our project (https://www.bienenundnatur.de/; https://www.bienenjournal.de; https://www.lvwi.de/verband/bienenpflege; assessed 28.06.2020). All this was done in order to get in contact with as many beekeepers as possible. According to the most recent statistics there are about 150.000 beekeepers in Germany; 125.000 are members of the German Beekeepers Association (https://deutscherimkerbund.de/161-Imkerei_in_Deutschland_Zahlen_Daten_Fakten; assessed 28.06.2020).

From May 20th, 2020 to August 15th, 2020 we contacted beekeepers using the institutions and media described above.

### 2.4. Statistics

Returned assessment forms were analyzed after data were transferred into the computer program PSPP, a free replacement for the proprietary program SPSS for calculating frequencies and correlation analyses.

## 3. Results

All in all, 342 assessment forms were returned. Unfortunately, many of them (n = 108) could not be evaluated as many participants did not clearly state whether they had been exposed to SARS-CoV-2 patients. Some of them sent in assessment forms clearly stating that they were sure that they had not had contact with SARS-CoV-2-infected people. After excluding these forms from further analyses, 234 evaluable forms were left. Most of them were returned by E-Mail (n = 145; 62.0%), followed by fax (n = 51; 21.8%) and mail (n = 38; 16.2%). The characteristics of the entire group as well as the subsets of beekeepers who had suffered from the SARS-CoV-2-infection, who had had close contact with people with the SARS-CoV-2-infection and those who possibly had contact with people with a SARS-CoV-2-infection are summarized in Table 1. Comorbidities in the various groups are summarized in Table 2.

### 3.1. Beekeepers who died during COVID-19

We received notice of 2 beekeepers who had died due to or from complications due to COVID-19. We were informed by one president of a beekeeping club that one member (male) died from the coronavirus. Unfortunately, we were unable to obtain any further information with respect to the beekeeper's exposure to bee stings; however, it can be assumed that the beekeeper would have had experiences with bee stings. In the second case a beekeeper's brother provided some information. The patient had been a beekeeper for 10 years, did not suffer from any chronic diseases and had developed a level of tolerance to the effects of bee stings.

### 3.2. Beekeepers who were affected during COVID-19

All in all, 45 beekeepers reported that they were affected by the virus SARS-CoV-2. The symptoms of these beekeepers are summarized in Fig. 1. There are no significant differences between the groups with respect to age, to how long they had been a beekeeper, total number of bee stings received, and number of bee stings received in 2020, and reaction to bee stings between beekeepers who were affected during COVID-19 and those who had close contact with people affected by COVID-19. The Beekeepers who were affected during COVID-19 differed significantly between with respect to how long they had been a beekeeper ($F_{ANOVA} = 19.6$; $p < 0.001$) and total number of bee stings received ($F_{ANOVA} = 8.2$; $p = 0.005$).

By correlation analyses we found that the reaction to bee stings (none; mild swelling; severe swelling) correlates with the perceived severity of the SARS-CoV-2-infection-associated symptoms (exhaustion ($r = 0.476$; $p = 0.001$) and sore throat ($r = 0.347$; $p = 0.023$)). The total number of bee stings, the number of bee stings received in 2020, possible signs of bee venom allergy, and comorbidity showed no influence on the perceived severity of the symptoms associated with the SARS-CoV-2-infection.

### 3.3. Beekeepers who had close contact with people affected by COVID-19 or who had contact with people possibly affected by COVID-19

Ninety-nine beekeepers reported that they had not been affected by SARS-CoV-2, despite being in close contact with affected spouses or

**Table 1**
Characteristics of beekeepers in the various groups.

| | Entire group (n = 234) | Beekeepers infected by SARS-CoV-2 (n = 45) | Beekeepers in contact with SARS-CoV-2 infected people (n = 99) | Beekeepers in contact with possibly SARS-CoV-2 infected people (n = 90) |
|---|---|---|---|---|
| Age [years] (mean; (SD)) | 54.6 (13.3) | 52.0 (14.4) | 55.0 (12.6) | 55.4 (13.4) |
| Gender [N (%)] | | | | |
| Female | 54 (23.1) | 7 (15.6) | 31 (31.3) | 16 (17.8) |
| Male | 179 (76.5) | 38 (84.4) | 68 (68.7) | 73 (81.1) |
| missing | 1 (.4) | – | – | 1 (1.1) |
| Beekeepers with comorbidity [N (%)] | 66 (28.2) | 14 (31.1) | 30 (30.3) | 22 (22.4) |
| Time being a beekeeper [years] (mean; (SD)) | 14.1 (14.3) | 12.0 (10.1) | 12.6 (12.9) | 16.6 (17.1) |
| Estimated total number of bee stings [N] (mean; (SD)) | 567 (1619) | 297 (495) | 450 (1300) | 835 (2188) |
| Number of bee stings in 2020 [N] (mean; (SD)) | 28 (114) | 14 (24) | 20 (30) | 44 (182) |
| Reaction to bee stings [N (%)] | | | | |
| None | 35 (15.0) | 4 (8.9) | 14 (14.1) | 17 (18.9) |
| mild swelling | 138 (59.0) | 33 (73.3) | 57 (57.6) | 48 (53.3) |
| severe swelling | 58 (24.8) | 8 (17,8) | 28 (28.3) | 22 (24.4) |
| missing | 3 (1.3) | – | – | 3 (3.3) |
| Signs of allergy on bee sting [N (%)] | | | | |
| none | 156 (66.7) | 29 (64.4) | 59 (59.6) | 68 (75.6) |
| itching | 66 (28.2) | 15 (33.3) | 31 (31.3) | 20 (22.2) |
| rash | 11 (4.7) | 1 (2.2) | 8 (8.1) | 2 (2.2) |
| Shortness of breath/drop in blood pressure | 1 (.4) | – | 1 (1.0) | – |

**Table 2**
Comorbidities in the various groups.

| | Entire group (n = 234) | Beekeepers infected by SARS-CoV-2 (n = 45) | Beekeepers in contact with SARS-CoV-2 infected people (n = 99) | Beekeepers in contact with possibly SARS-CoV-2 infected people (n = 90) |
|---|---|---|---|---|
| Beekeepers with comorbidity [N (%)] | 66 (28.2) | 14 (31.1) | 30 (30.3) | 22 (22.4) |
| Hypertension | 9 (3.8) | 1 (2.2) | 3 (3.0) | 5 (5.6) |
| Asthma | 7 (3.0) | 1 (2.2) | 4 (4.0) | 2 (2.2) |
| Bronchitis, COPD | 5 (2.1) | – | 2 (2.0) | 3 (3.3) |
| Diabetes | 4 (1.7) | 1 (2.2) | 2 (2.0) | 1 (1.1) |
| Hay fever | 4 (1.7) | 1 (2.2) | 1 (1.0) | 2 (2.2) |
| Rheumatism/arthrosis | 5 (2.1) | 2 (4.4) | 2 (2.0) | 1 (1.1) |
| Bee venom allergy | 3 (1.3) | 1 (2.2) | 2 (2.0) | – |
| Hypertension and diabetes | 3 (1.3) | – | 2 (2.0) | 1 (1.1) |
| Hypothyroidism | 3 (1.3) | 1 (2.2) | 2 (2.0) | – |
| Cardiac insufficiency | 2 (.9) | – | 1 (1.0) | 1 (1.1) |
| Coronary heart disease | 2 (.9) | 1 (2.6) | 1 (1.0) | – |
| Asthma, bee venom allergy | 1 (.4) | – | 1 (1.0) | – |
| Asthma, ulcerative colitis and bee venom allergy | 1 (.4) | 1 (2.2) | – | – |
| Atopic dermatitis | 1 (.4) | – | 1 (1.0) | – |
| Atrial fibrillation | 1 (.1) | – | – | 1 (1.1) |
| Breast cancer | 1 (.4) | – | – | 1 (1.1) |
| Herpes zoster | 1 (.4) | – | – | 1 (1.1) |
| Hypertension and migraine | 1 (.4) | – | – | 1 (1.1) |
| Hypertension and bee venom allergy | 1 (.4) | – | – | 1 (1.1) |
| Hay fever and asthma | 1 (.4) | – | 1 (1.0) | – |
| Hypercholesterolemia and reflux esophagitis | 1 (.4) | – | 1 (1.0) | – |
| Heart valve replacement | 1 (.4) | – | 1 (1.0) | – |
| Kidney dysfunction | 1 (.4) | 1 (2.2) | – | – |
| Migraine | 1 (.4) | 1 (2.2) | – | – |
| Multiple sclerosis | 1 (.4) | – | 1 (1.0) | – |
| Multiple sclerosis and epilepsy | 1 (.4) | – | 1 (1.0) | – |
| Sarcoidosis | 1 (.4) | 1 (2.2) | – | – |
| Ulcerative colitis | 1 (.4) | 1 (2.2) | – | – |
| Missing | 2 (.9) | – | 1 (1.0) | 1 (1.1) |

children, a comment many of them had added to the assessment form. Ninety beekeepers reported not to be affected by SARS-CoV-2 despite having had contact with people possibly affected by COVID-19. There are no significant differences between the groups with respect to age, to how long they had been a beekeeper, total number of bee stings received, and number of bee stings received in 2020, and reaction to bee stings. However, there are differences regarding allergic reactions to bee venom ($F_{ANOVA} = 3.8$; $p = 0.023$).

### 3.4. Measures of beekeepers taken against a SARS-CoV-2-infection

Both the beekeepers who had close contact with people affected by COVID-19 and those who had contact with people possibly affected by COVID-19 were asked to write down the measures they had taken to prevent an infection or contracting the disease. The data are summarized in Table 3. As shown, propolis, diets and the combination of propolis with various other bee hive products (apitherapy) were the methods mainly used in addition to the general measures taken against COVID-19.

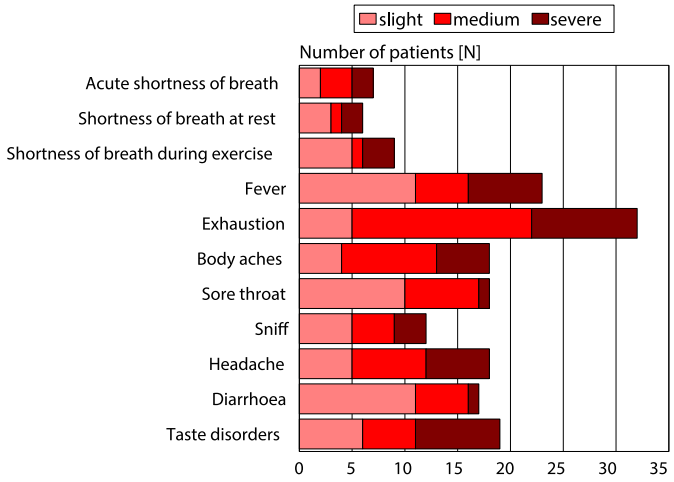


**Fig. 1.** Severity of symptoms in beekeepers affected with SARS-CoV-2 as assessed by the Triage-Fragebogen grippaler Infekt/Influenza/Corona" by Dielmann-von Berg, Scherer and Mühlenfeld (n = 45).

**Table 3**
Additional measures taken against COVID-19.

| | Beekeepers in contact with SARS-CoV-2 infected people (n = 99) | Beekeepers in contact with possibly SARS-CoV-2 infected people (n = 90) |
|---|---|---|
| Number of beekeepers who used preventive measures [N (%)] | 29 (29.3) | 25 (27.8) |
| Propolis [N] | 9 | 9 |
| Diet [N] | 5 | 2 |
| Propolis in combination with honey and/or royal jelly and/or pollen [N] | 1 | 4 |
| Exercise [N] | 0 | 5 |
| Diet and exercise [N] | 3 | – |
| Diet and vitamin C [N] | 2 | – |
| Honey [N] | 2 | 0 |
| Vitamin C and exercise [N] | 0 | 2 |
| Propolis and vitamin C [N] | – | 1 |
| Propolis and diet [N] | 1 | 0 |
| Propolis and zinc [N] | 1 | 0 |
| Vitamin C [N] | 1 | 0 |
| Vitamin C, Vitamin D, selenium [N] | 1 | 1 |
| Vitamin D [N] | 1 | 1 |
| Homoeopathy [N] | 1 | 0 |
| Sauna [N] | 1 | 0 |

## 4. Discussion

The study shows that beekeepers are not immune to infections caused by the novel coronavirus SARS-CoV-2. Especially, our data do not support the hypothesis that beekeepers are not affected by SARS-CoV-2 due to their exposure to bee stings and the associated immunity. The severity of the disease was not influenced by various variables like how long they had been a beekeeper, total number of bee stings received, number of bee stings received in the year 2020 and potentially allergic reactions to bee stings. However, the reaction to a bee sting (none versus mild swelling versus strong swelling) influenced the severity of two of the symptoms of a SARS-CoV-2 infection, namely exhaustion and sore throat pain, all of which were more pronounced in beekeepers who reported being more sensitive to bee stings. Beekeepers with less or a minimal reaction to bee stings were less likely to suffer from severe symptoms.

Although we know that there are about 150,000 beekeepers in Germany, we do not know how many were in contact with people with the COVID-19 disease and how many were reached by our study call. Upon closure of this analysis (August 15th, 2020) we chose to use the data from July 31st, 2020 for calculations regarding the suspected prevalence in beekeepers since we figured that beekeepers still affected from COVID-19 disease will not respond immediately (https://www.worldometers.info/coronavirus/country/germany/; accessed August 1st, 2020). At that time, 210,665 Coronavirus cases had been registered and 9224 Coronavirus associated deaths. Considering the population of Germany (82.3 million) and the percentage of beekeepers, we could expect a total of 539 beekeepers to have been infected by SARS-CoV-2 virus. However, there are some reasons why beekeepers might have had lower infection rates. This may be concluded from a study on a beekeeper's personality which showed that beekeepers tend to spend time alone with their thoughts (https://www.careerexplorer.com/careers/beekeeper/personality/; accessed July 31st, 2020). People who like to spend time alone are probably less likely to come into contact with the virus. Considering these data we assume that reached a substantial percentage of German beekeepers.

We did not assess this systematically but many beekeepers who suffered from SARS-CoV-2 infections provided details on their infection, for example some worked in the health care system and took care of infected people. It seems that there are more retired people in the other two groups, and because they are not active in the employment sector, there would be less chance of coming into contact with the virus, thereby lowering the likelihood of being infected. (Average age of German beekeepers is 57 years.) Unfortunately, the study by Yang et al. (2020) does not provide any information on the beekeepers' demographic characteristics and presents only a summary of the results.

Yang et al. (2020) believed that tolerance to bee stings was the underlying reason for the beekeepers' immunity. Actually, a discriminant analysis of our collective showed that none of the parameters with respect to beekeeping and bee venom seemed to have influenced the likelihood of developing the corona virus infection. Also, Yang's hypothesis is not in general accordance with the apitherapist concept that bee venom could be a potential prophylactic for the COVID-19 disease. Apitherapists consider a direct working mechanism of bee venom. An analysis of the literature shows that bee venom is active against the Influenza A virus (PR8), Vesicular Stomatitis Virus (VSV), Respiratory Syncytial Virus (RSV), and the Herpes Simplex Virus (HSV) but also the replication of non-enveloped viruses such as the Enterovirus-71 (EV-71) and Coxsackie Virus (H3) (Uddin et al., 2016). While the coronavirus belongs to the order of nidovirales, the other viruses do not. Furthermore, melittin, a component of bee venom, was found to inhibit the feline immunodeficiency virus in cats (Hartmann et al., 2016). A recent review summarizes the various working mechanisms of bee venom (El-Seedi et al., 2020). Inhibition of the virus replication, mRNA expression, virus adsorption and penetration as well as lytic and fusogenic properties seem to be of great importance (El-Seedi et al., 2020). However, most interesting with respect to SARS-CoV-2 are findings on the porcine reproductive and respiratory syndrome viruses (PRRSV) which also belongs to the order of nidovirales. It was shown that bee venom and its constituent melittin can induce the immunity via a significant up-regulation of Th1 cytokines (IFN-γ and IL-12) and several types of immune cells, including $CD3^{+}CD8^{+}$, $CD4^{+}CD8^{+}$, and γδ T cells, which not only led to a reduction of the viral load but also decreased the severity of interstitial pneumonia in PRRSV-infected pigs (Lee et al., 2015). However, this effect, which could be very important with respect to the SARS-CoV-2 associated pneumonia, was only achieved when bee venom was administered via a nasal or rectal route (Lee et al., 2015). If bee venom should be a potentially active substance with respect to prevention or treatment of COVID-19 disease, it would be important that the beekeepers were stung during the infection, preferably at the start.

The finding that beekeepers with a more sensitive response to bee stings show a more severe reaction to a SARS-CoV-2 infection should not be causally linked to immunity to SARS-CoV-2, but seen as a sign of the level of responsiveness of the immune system. The fact that the reaction of the immune system plays a significant role is also underlined by current concepts using immunomodulating drugs (Martinez, 2020; Mehta et al., 2020) and that other immunoreactive diseases are associated with SARS-CoV-2, e. g. the Multi-System Inflammatory Syndrome in Children (MIS-C) (Nakra et al., 2020).

The question why 121 patients of an apitherapy clinic treated with bee venom did not develop symptoms associated with COVID-19 cannot be answered by our study (Yang et al., 2020). There could be a direct preventive or alleviating effect when bee venom is administered during the infection. In retrospect it would have been interesting to assess the time intervals between string exposure, onset of disease symptoms or contact to infected people.

Our study has several limitations. A lot are due to the fact that many aspects of the COVID-19 disease are still not known and that the appropriate methods for detecting the disease have not always been available, especially at the beginning of the pandemic. This could mean that beekeepers who had the SARS-CoV-2 infection and exhibited few symptoms or an inapparent infection may have been missed. There are also reports on false negative and false positive tests (Yates et al., 2020). The next problem may be associated with the method of contacting the beekeepers. We used various ways to contact them – via beekeeper associations throughout Germany, beekeeping magazines and internet.

Unfortunately, the beekeepers who were not members of a beekeeping organization may not have been reached. However, our survey attracted a lot of attention and was reported on by several newspapers and radio stations.

Interest in apitherapy could be another bias factor. In fact, prior to our study, various apitherapists had published ideas on treating COVID-19 disease by propolis, royal jelly, honey, pollen, and bee venom acupuncture or propolis tincture in combination with many other measures or propolis vapor and bee hive air (Lima et al., 2020; https://apitherapie.de/wp-content/uploads/2020/03/COVID-19-Empfehlungen-aus-Apitherapeutsicher-Sicht.pdf; https://praxis-kunth.de/medizinische-strategien-gegen-das-corona-virus/; https://www.bienen-zur-gesundheit.de/krankheiten/coronagrippe/; https://www.beecurasystem.de/2020/03/21/propolis-gegen-corona/; accessed 07.04.2020). Recently, stingless bee honey was suggested to reduce the severity of pulmonary manifestations in COVID-19 infections; however, this hypothesis was clearly rejected by other researchers (Mustafa et al., 2020; Ch'ng & Tang, 2020). Other researchers consider propolis to be a potentially preventive substance (Bachevski et al., 2020; Berretta et al., 2020; Scorza et al., 2020). Beekeepers with a stronger belief in apitherapy might have been more interested in completing our assessment form in cases where they hadn't been infected, while those with an infection might have refrained. As shown in Table 3, many beekeepers used products from the beehive for the prevention of COVID-19 disease.

Finally, we did not assess cofactors which might have contributed to the development and severity of the disease such as obesity (Rebello et al., 2020). We also did not assess the ABO blood-group system, which also seems to influence the severity of the disease (Ellinghaus et al., 2020).

In summary, our study fails to support the hypothesis of Yang et al. (2020). Unfortunately, there is no such simple solution to the extraordinarily complex problem of a SARS-CoV-2 infection. However, we cannot exclude that bee venom could have a protective or alleviating effect on a SARS-CoV-2 infection when directly applied during the infection that further and more elaborated studies would be necessary to determine this.

## Author statement

Heidrun Männle: Conceptualization, Methodology, Validation, Writing - Review & Editing, Formal analysis, Jutta Hübner: Conceptualization, Resources, Writing - Review & Editing, Supervision, Resources, Karsten Münstedt: Conceptualization, Methodology, Validation, Writing - Original Draft, Funding acquisition, Formal analysis.

## 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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