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Extract from Cistus × Incanus L. Pandalis also Effective Against "British" Alpha (B.1.1.7) and "South African" Beta (B.1.351) SARS-CoV-2 Variants

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Abstract: *Background:* In previous studies, a special extract from *Cistus* × *incanus* L. Pandalis (Cystus Pandalis® extract) has already proven to be effective against SARS-CoV-2 in vitro. We assume that an effect was also likely against the new SARS-CoV-2 variants, like the "British" alpha variant (B.1.1.7) as well as against the "South African" beta variant (B.1.351). *Methods:* To verify this, we investigated the inhibition of the cytopathic effect (CPE) of the coronaviruses by the Cystus Pandalis® extract in a cell model with human intestinal cells (Caco-2). We inoculated viral pre-treated cells with the herbal extract (A), and we mixed pre-treated viruses with the herbal extract in the cell cultures (B). *Result:* We observed an almost complete inhibition of virus growth by Cystus Pandalis® extract at concentrations of more than 100 µg/ml. The calculated IC50 (mean inhibitory concentration) for the "British" alpha variant (B.1.1.7) as well as for the "South African" beta variant (B.1.351) is below 50 µg/ml. There was no significant difference in the results in the two different ways of treatment. *Conclusion:* Extract from Cistus × incanus L. Pandalis (Cystus Pandalis® extract) can prevent in in-vitro cell cultures infections with SARS-CoV-2. Due to the high in vitro activity against the new variants, it also appears reasonable in the future to use Cystus Pandalis® as prophylaxis against infections with SARS-CoV-2. A development of resistance is unlikely. People tolerate the extract very well. It has no significant side effects.

Keywords: Cystus Pandalis®, Virus Infection, SARS-CoV-2, Variants, Cistus Incanus

1. Introduction

There are still hardly any therapeutic approaches against COVID-19. Even though vaccination campaigns are slowly starting, at least in some industrialized countries, many people are currently still without a vaccination offer or do not want to accept it for various reasons. The fact that SARS-CoV-2 is mutation-friendly and mutation-tolerant complicated the situation. In recent months, several variants have emerged that have altered surface properties and virulence. [1] In Europe and Germany, the alpha (B.1.1.7 also called "British") and beta (B.1.351 also called "South African") SARS-CoV-2 variants are particularly noteworthy, which have almost completely displaced the original wild type since the beginning of the year. [2] From today's perspective, it is therefore possible that the currently approved vaccines will lose their effectiveness over time and would have to be adapted. [3] Natural substances offer an abundance of effective compounds here, which interact with many surface structures of viruses, whereby a development of resistance cannot been expected even in the long term. [5, 9]

Cystus Pandalis® extract is an herbal preparation based on the variety of the Hoary rockrose *Cistus* × *incanus* L. Pandalis, which grows only in a limited area of northern Greece. People used *Cistus* × *incanus* L. in traditional folk medicine since the 4th century BC for its anti-inflammatory, anti-ulcerogenic, antimicrobial and wound-healing properties. [4] A special feature of *Cistus* × *incanus* L. Pandalis is its high content of high-polymer polyphenols, while monomeric polyphenols account for less than 2%. [5] In addition to the quantity of polyphenols, the specific polyphenolic pattern seems to be decisive for its antiviral properties.

Investigations of Cystus Pandalis® extract showed its antiviral potential for years with consistently positive results.

In in-vitro-studies, this efficacy has never been limited to certain virus families or specific subtypes, but has so far applied to all viruses studied. These are the following so far:

a. Influenza A (including H5N1, H7N1, H1N1) [5-7],
b. Human rhinoviruses (HRV14) [5],
c. adenoviruses [8],
d. HIV viruses (HIV-1 and HIV-2) [9],
e. Ebola viruses [9],
f. Marburg viruses [9]
g. SARS-CoV-2 [13]

A placebo-controlled clinical study examined the Cystus Pandalis® extract under practical conditions. Participants suffering from an acute respiratory tract infection took 6 x 2 Cystus Pandalis® lozenges daily. Both the subjective symptoms of the disease and the CRP value (inflammation value in the serum) decreased significantly faster in the verum group, indicating a shortened duration of infection. [10] As early as 2002, a controlled observational study with 53 participants with tonsillopharyngitis showed an improvement through the use with a decoction from *Cistus* × *incanus* L. Pandalis. [14] According to the authors of both studies, endemic coronaviruses were already included as a typical trigger at that time. [15]

In a recent retrolective study investigating the association between the use of Cystus Pandalis® extract and the occurrence of COVID-19, 125 volunteers used Cystus Pandalis® extract in lozenge form (3 x 2 daily) for at least 6 weeks. By the end of the study, none of the participants showed an infection with SARS-CoV-2. Of particular note was the fact that family members living in the home of nine participants developed COVID-19, but the participants themselves showed no infection when using Cystus Pandalis® extract. [11]

Recently showed an in-vitro-trial that the Cystus Pandalis® extract is also effective against SARS-CoV-2 (wild type). [13] As a logical consequence, we now investigated the efficacy of Cystus Pandalis® extract for the alpha (B.1.1.7) and beta (B.1.351) SARS-CoV-2 variants.

2. Material & Methods

To analyze the antiviral activity of a plant extract against SARS-CoV-2, we used a cell culture-based infection model. The Institute for Medical Virology at the Goethe University Frankfurt am Main carried out the investigations.

The tested (Cystus Pandalis®) extract is an aqueous dry extract of the cistus variety *Cistus x incanus* L. Pandalis and was provided by the company Dr. Pandalis Urheimische Medizin GmbH & Co. KG. We used Caco-2 cells in a cell line for the infection model. This cell line derives from human colon carcinoma cells (Caco-2). This human cell line is often used to study SARS-CoV-2 due to its high permissiveness to coronavirus infection. We used Clinical SARS-CoV-2 isolates from nasopharyngeal swabs of COVID-19 patients in the experiments. The strains SARS-CoV-2/B.1.1.7 (alpha variant) and SARS-CoV-2/B.1.351 (beta variant) were present in the swabs. Two experimental set-ups performed an infection with SARS-CoV-2.

A ("British" alpha variant): Caco-2 cells were pre-incubated with *Cistus x incanus* L. Pandalis extract and then infected with SARS-CoV-2/B.1.1.7.

B ("South African" beta variant): SARS-CoV-2/B.1.351 was pre-incubated with *Cistus x incanus* L. Pandalis extract and the mixture was then added to Caco-2 cells.

We used a multiplicity of infection (MOI) of 0.01 for both virus variants. 48 h after infection, we evaluated visually the cytopathogenic effect (CPE) by two independent technicians. In addition, cell viability was measured by MTT assay. The IC50 and CC50 were evaluated using Graph Pad Prism 6 and the results are expressed as mean ± standard deviation.

3. Results

In order to investigate at which concentration of Cystus Pandalis® extract an antiviral activity against the "British" alpha (B.1.1.7) and "South African" beta (B.1.351) SARS-CoV-2 variants can be observed, it was determined to what extent the virus-related cytopathic effect (CPE) was absent at the different test concentrations.

An antiviral effect of the Cystus Pandalis® extract against the "British" alpha (B.1.1.7) and "South African" beta (B.1.351) variants was shown. Depending on the concentration used, both experimental set-ups suppressed CPE (Figure 1). In addition, the MTT assay showed that the Cystus Pandalis® extract had no negative effect on cell viability at the effective test concentrations and far beyond.

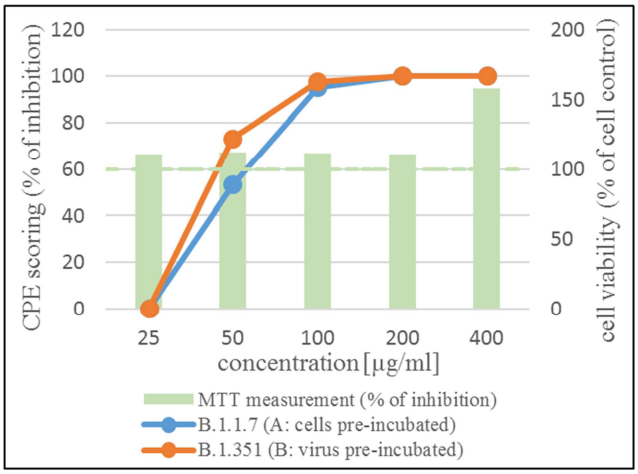

Figure 1. *Concentration-dependent antiviral effects of Cystus Pandalis® extract on SARS-CoV-2-induced cytopathic effect (CPE), determined 48 hours after infection in Caco2 cells infected with the alpha (B.1.1.7) and beta (B.1.351) SARS-CoV-2 variants at a multiplicity of infection (MOI) of 0.01. Cystus Pandalis® extract showed to prevent cell infection in both variants and showed no negative effects on cell viability in MTT assay (green).*

Based on these results, the IC50 value (the mean inhibitory concentration) for inhibition of virus growth by Cystus Pandalis® extract was determined. The IC50 is 48.9 µg/ml for the "British" alpha variant (B.1.1.7) and 45.2 µg/ml for the "South African" beta variant (B.1.351). Both experimental arrangements (A: pre-treat cells with extract, B: pre-treat

viruses with extract) showed a comparable antiviral effect, with the effects being slightly, but not significantly, stronger in experimental arrangement B.

4. Discussion

The results of this study show that Cystus Pandalis® extract inhibits viral replication of the "British" alpha and "South African" beta SARS-CoV-2 variants in a cell culture model with an IC50 of 48.9 µg/ml and 45.2 µg/ml, respectively. In a previous study, an EC50 (mean effective concentration) of 1.94 µg/ml had been determined in a different cell model using a SARS-CoV-2 wild type. [13] The small differences in effectiveness between the previous and the current studies are probably due to the completely different experimental set-up and cell system. The advantage of the current study is to use the Caco-2 cell line, a model with human cells that is closer to reality. Since these investigations with a different model, a different experimental set-up at a different institute led to comparable results to the last one [13], this increases the significance of the antiviral properties. We state therefore that the Cystus Pandalis® extract effectively prevents infection with SARS-CoV-2 regardless of the variant. In view of the antiviral mode of action of the extract, this is also understandable. Based on previous studies, the extract appears to prevent viral replication in the very first step and probably acts as an entry inhibitor, with the components interacting primarily with viruses rather than cells (Figure 2). [5, 8, 13] The current study supports this assumption, as the antiviral effects were more pronounced when the viruses were pre-treated with the extract (Figure 1).

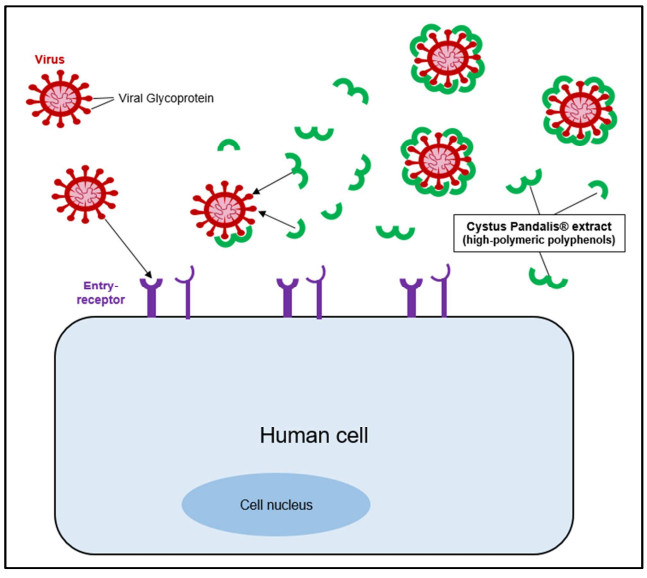

Figure 2. *Possible mechanism of action of Cystus Pandalis® extract against SARS-CoV-2. The high polymer polyphenols in CPE (green) interact with certain viral epitopes of SARS-CoV-2 (red), enveloping the virus and thereby preventing its attachment to cellular receptors (blue/purple), thus preventing infection of the cell (light blue).*

It is still unclear which of the viral proteins is the preferred target for the Cystus Pandalis® extract - the S protein (spike, membrane protein), the E protein (envelope, membrane protein), the M protein (membrane protein) or the N protein (nucleocapsid protein). Since the extract is a multi-substance mixture, it is conceivable that the various high-polymer polyphenols interact with several structures at the same time, which could be a great advantage of this herbal preparation. Recent studies have shown that different polyphenols such as epigallocatechin gallate (EGCG), myricetin and quercetin interact with other surface proteins of SARS-CoV-2 in addition to the S protein. [12] Since these polyphenols are also contained in the Cystus Pandalis® extract, this mechanism is plausible. [16]

The extract also proved effective with cells pre-incubated and the viruses adding later. This is also important for practical application. Through topical application in the form of a lozenge for the mouth and throat, the extract can develop its antiviral potential directly at the point of entry of infections.

Corresponding products with the extract from the variety *Cistus* × *incanus* L. Pandalis have been on the market for years, have been sold and used for a long time and are directly available to everyone. Taking into account these and previous studies on this extract, it makes sense to use Cystus Pandalis® as prophylaxis against infections with SARS-CoV-2. [10, 11, 13] Furthermore, this herbal preparation offers not only optimal tolerability but also safe use without side effects. We showed in this investigation the fact that the Cystus Pandalis® extract even increases cell viability in effective test concentrations. In the MTT assay, this was as high as 158% at 400 µg/ml compared to the untreated control cells (Figure 1). We assume therefore also that there are possible cell-protective effects. It should also be borne in mind that many people cannot or do not want to be vaccinated for health, religious or personal reasons. In addition, there is currently no approved vaccine for younger children. The use of Cystus Pandalis® extract could provide these people with an alternative, which is also a future-proof and effective option with regard to the mutations that are constantly occurring.

5. Conclusion

We tested the Cystus Pandalis® extract against the wild type SARS-CoV-2 in a preliminary study. It has showed an excellent effect on the cell cultures, used in this experiment.

According to these in vitro experiments, it showed also effective against the mutants that are currently mainly spread in Europe ("British" alpha variant [B.1.1.7] and "South African" beta variant [B.1.351]). Prophylactically one can recommend Cystus-Pandalis® lozenges in prevention of infections with SARS-CoV-2, as long as not all eligible people haven't been fully vaccinated against the corona virus and the mutants of this virus.

Conflict of Interest

The author declares that there are no conflicts of interest.

Declaration

The in vitro studies were carried out at the Institute of Medical Virology, Goethe University, Frankfurt am Main, Germany.

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