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RESEARCH

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In vitro antiviral effect of cinnamon oil, *Moringa oleifera* extract, Manuka honey, and *Nigella sativa* oil against SARS-CoV-2 compared to remdesivir

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Abstract

Background Severe acute respiratory syndrome *coronavirus 2* (*SARS-CoV-2*) is of a public health importance as it is continually evolving due to random mutations. New mutations can potentially affect the degree of infectiousness, virulence, and can increase the virus' capability to evade adaptive immune responses of the body. Immunity is one of the key factors determining the extent of severity of *SARS-CoV-2* patients. Therefore, thinking about natural remedies is the way to boost immunity, keep the body protected, and able to fight the *SARS-CoV-2* virus. We aimed to make progress in the field of anti-*SARS-CoV-2* nutraceuticals, thus providing a safe and natural alternative to traditional chemically manufactured medications.

Methods The cytotoxic activity (CC_{50}) of the natural products was tested experimentally in vitro on the VERO-E6 cells using a crystal violet assay. The cells were then treated with different concentrations of the natural products of *Moringa oleifera* leaves extract, cinnamon bark oil extract, Manuka honey, and *Nigella sativa* oil. The inhibitory concentration 50 (IC_{50}) value and the CC_{50} value were calculated in order to measure the antiviral effect of on *SARS-CoV-2* virus compared to antiviral Remdesivir drug.

Results The tested natural products of honey and extracts exhibited pronounced virucidal effect against one of the most challenging viruses worldwide which is the *SARS-CoV-2* virus. The results showed that the highest selectivity index was the Manuka honey + 20 UMF with SI of 10.23. The second sample following Manuka honey regarding its efficiency was the mixture of the three extracts with the honey (SI = 7.12), then followed by Remdesivir antiviral drug (SI = 3.3), then *Moringa oleifera* leaves extract (SI = 2.1). The last two products showing the least SI were *Nigella sativa* oil (SI = 1.6) and cinnamon bark oil (SI = 1.08), respectively.

Conclusions Manuka honey + 20 UMF alone or combined with other three extracts of *Moringa oleifera*, *Nigella sativa*, and cinnamon bark oil have a much stronger in vitro antiviral effect on *SARS-CoV-2* virus than the traditional antiviral drug Remdesivir. Further research will be needed to test the effectiveness of these natural products in vivo as an antiviral remedy against *SARS-CoV-2* virus.

Keywords *Moringa oleifera*, Cinnamon oil, Anti-*SARS-CoV-2* virus, Manuka honey

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Background

The *SARS-CoV-2* pandemic has spread globally since cases were reported in China. In 2022, cases exceeded 500 million, causing more than six million deaths. Individuals of all ages are at risk for infection with the *SARS-CoV-2* virus as well as developing severe complications. However, it is higher among people aged 60 years, suffering from chronic medical conditions, and living in a nursing home or any care facility (SARS-CoV-2 Treatment Guidelines Panel 2023).

The SARS-CoV-2 is continually evolving due to random mutations, while new mutations can potentially affect the degree of infectiousness as well as the degree of virulence of the virus. It can also increase the virus' capability to evade adaptive immune responses from previous *SARS-CoV-2* infection or previous vaccination. This evolutional characteristic of the *SARS-CoV-2* virus may increase the risk of reinfection or decrease the efficacy of *SARS-CoV-2*-targeted vaccines (SARS-CoV-2 Treatment Guidelines Panel 2023).

A variety of medicinal plants have been used for many centuries either as dietary supplements or as traditional treatments for many ailments (Wood 1997). The Moringa tree (*Moringa oleifera)* has been known as a miracle tree many years ago and has also been used in treating for many diseases. Nowadays, as a result of increased attention to natural products, various therapeutic effects of *Moringa oleifera* such as antimicrobial, antioxidant, antidiabetic, anti-inflammatory, and anticancer effects have been tested (Jung 2014).

Moringa oleifera also exhibited antiviral activity toward influenza A virus subtype H1N1. It was observed and indicated that *Moringa oleifera* can be a promising medicinal remedy for the prophylaxis and treatment of influenza virus infection. One of the key roles of *Moringa oleifera* in suppressing infection with *SARS-CoV-2* virus was as an immune booster. This is very crucial because immunity is one of the important factors determining the degree of severity of *SARS-CoV-2*-infected patients. Individuals who have good immunity can survive attacks by the *SARS-CoV-2* virus (Xiong et al. 2021).

Cinnamaldehyde which is found in cinnamon oil is an important natural flavonoid. It is known that flavonoids are powerful natural anticancer compounds that function through the inhibition of histone deacetylase that can induce apoptosis and programed cell death in many cancer cell types. Therefore, it is considered a powerful anticancer agent that can restore programmed cell death in malignant cells (Kim 2022; Kim and Bae 2011).

Honey has high nutritional and therapeutic values. There are many published works referring to the antimicrobial effects of honey, and that the honey can be beneficial for cases of *SARS-CoV-2* viral infection which is caused by a potent enveloped virus *SARS-CoV-2* through boosting the host immune system, as well as improving other comorbid conditions. This can be done by several major mechanisms including direct virucidal properties, improving comorbid conditions, and boosting host immune signaling pathways. Moreover, honey may act as a preventive agent against increased or diffuse inflammation caused by *SARS-CoV-2* virus. Manuka honey showed higher total phenols content than most other types of honey cited in the literature. There is a strong correlation between the total phenolic content, and antioxidant power, as well as the Unique Manuka Factor (UMF) rating for Manuka honey (Portokalakis et al. 2016). Manuka honey has a virucidal effect as it contains methylglyoxal (GMO), a bioactive component, and has in vitro antiviral activity. Methylglyoxal can modify arginine residues found in the functional domains of viral spike and nucleocapsid proteins, causing protein misfolding and inactivation (Elbashir et al. 2021).

Nigella sativa seeds were proven to be a safe and potent adjuvant therapeutic agent against *SARS-CoV-2* infection. It decreases complications and prevents deaths. So, it may lower the overall burden on healthcare systems significantly. Al-Haidari et al. (2021) found that *SARS-CoV-2*-infected patients who were treated with black seeds at a dose of 40 mg/kg orally, once daily for two weeks in addition to the standard protocol of treatment, were significantly lower in the severity of infection than the control group and there were not any deaths in black seeds group. Therefore, the authors concluded that black seed might be very effective in decreasing the degree of severity of *SARS-CoV-2* infection and preventing death among infected patients (Al-Haidari et al. 2021).

Finally, the aim of the study was to assess the in vitro antiviral effect of *Moringa oleifera* extract, cinnamon oil, Manuka honey, and *N. sativa* oil on the *SARS-CoV-2* virus compared to the antiviral Remdesivir drug. The main goal of this study was to make progress in the field of anti-*SARS-CoV-2* nutraceutical research by investigating a safe and natural alternative to traditional chemically manufactured medications as well as decreasing the risk of reinfections due to frequent mutations of this virus. The percent of inhibition of the tested virus when treated with *Moringa oleifera* leaves extract, cinnamon bark oil extract, Manuka honey, and *N. sativa* oil was calculated using the cytotoxicity (CC_{50}), inhibitory concentration 50 (IC_{50}), and selectivity index (SI).

Material and methods

Study setting and design

An experimental study was conducted at the High Institute of Public Health Central Laboratory and the National Research Center Virology Laboratory. The

target virus was SARS-CoV2 virus isolates cultured on the experimental tissue culture plates.

Extracts and products processing

Cinnamon bark oil extract preparation

Cinnamon bark (*Cinnamomum verum*) was accurately weighed (100 g) and remaceration and Soxhletation each with 96% ethanol 1000 mL. The solution was stored for 24 h and then filtered using a filter paper (11 cm, 102 medium). After that the extracted liquid was dried by a rotary evaporator device by which the liquid filtrate was poured into a large flask and then put in a water bath at a temperature of 70 °C at a speed of 50 rpm for one and a half hours to obtain cinnamon oil extract. The extracted cinnamon oil extract was analyzed to determine the level of cinnamaldehyde using both gas chromatography-mass spectrometry and high-performance liquid chromatography (HPLC) (Wardatun et al. 2017).

Moringa oleifera leaves extract

The dried *M. oleifera* leaves weighed 150 mg (obtained from Siwa Oasis, Western Egypt) were suspended in one mL of cold water at 4 °C, then vigorously vortexed for thirty seconds, and refrigerated for five minutes to 24 h. The suspension was repeatedly vortexed vigorously for one minute at room temperature. The water-insoluble parts of the suspension were removed by centrifuging it twice (12,000 rpm) for 10 min each, and the supernatants were collected by membrane filtration of 0.2-mm filter paper. The resulting *M. oleifera* leaves extracts were lyophilized and stored at − 20 °C for further analysis (Jung 2014).

Manuka honey

A 100% pure New Zealand Manuka honey harvested from the remote and pristine hills and coastal areas in New Zealand with UMF +20. The color was golden brown with a heavy thick consistency. The pH ranges from 3.5 to 4.5. It was tested in 2022 by the Hill Laboratories in Hamilton, New Zealand, and the results showed that dihydroxyacetone (DHA) was 1182 mg/kg, leptosperin was 760 mg/kg, methylglyoxal was 831 mg/kg, hydroxymethylfurfural was (HMF) 27.80 mg/kg (Unique Manuka Factor (UMF) 2022). The honey was kept at a cold room temperature of 10–20 °C in a dark place (not the fridge), and it was prepared freshly before use, at different concentrations (1.25–20%) for 24 to 48 h (Portokalakis et al. 2016).

Nigella sativa oil

A 100% natural organic cold-pressed *Nigella sativa* oil extract was obtained from Imtinan Health shop, Egypt. It was kept at room temperature and then dissolved at concentrations of 0.6 and 1.25% (v/v) for 24 h (Alsanosi and Sheikh 2022).

In vitro laboratory methods

Cytotoxicity (CC_{50}) determination

The natural products of Manuka honey and extracts of *Moringa oleifera and Nigella sativa* were dissolved in 10% dimethyl sulfoxide solvent (DMSO, Sigma-Aldrich), while the extract of cinnamon bark oil was dissolved double-distilled water (ddH2O) at tested concentrations. Cytotoxic activity of the products was tested in VERO-E6 cells using a crystal violet assay (Feoktistova et al. 2016) with minor modifications. In brief, the cells were seeded in 96-well plates (100 µl/well at a density of 3×105 cells/ml) and then incubated for 24 h at 37 °C in 5% carbon dioxide (CO_2). After 24 h, the cells were treated with different concentrations of the honey and extracts in triplicate. At 27 h post-treatment, the supernatant was removed and discarded, while the cell monolayers were fixed with 10% formaldehyde for one hour at room temperature. The fixed monolayers were further dried thoroughly and stained with 50 µl of 0.1% crystal violet for twenty min at room temperature on a bench rocker. The monolayers were then washed, and left to dry overnight, and the crystal violet dye in each well was dissolved in 200 µl methanol for twenty minutes on a bench rocker at room temperature. The absorbance of the crystal violet solutions was measured at a maximum wavelength (λmax) of 570 nm as a reference wavelength using a multi-well plate reader. The CC_{50} value was calculated using the software (GraphPad Prism software version 5.01) and analyzed by the nonlinear regression analysis by plotting log concentrations of the tested honey and extracts compared to normalized response (variable slope) (Mosmann 1983).

$$\text{cytotoxicity percentage \%} = \frac{\text{absorbnce of cells with no treatment} - \text{absorbance of cells with treatment}}{\text{absorbance of cells with no treatment}} X100$$

The concentration that displayed 50% cytotoxicity (CC_{50}) was calculated using a plot of percent cytotoxicity in opposition to sample concentration (Mosmann 1983).

Inhibitory concentration 50 (IC_{50}) determination

The IC_{50} values for natural products of Manuka honey and *Moringa oleifera*, *Nigella sativa*, and cinnamon bark were all analyzed by the nonlinear regression analysis of GraphPad Prism software (version 5.01) through plotting log inhibitor against normalized response (variable

slope) (Mostafa et al. 2020). The 2.4×10^4 Vero-E6 cells were placed in each well of 96-well tissue culture plates and then cultured overnight at a temperature of 37 °C in a humidified 5% CO_2 incubator. Afterward, the cell monolayers were rinsed once in 1 × phosphate-buffered saline (PBS) (Kandeil et al. 2020).

An aliquot of the *SARS-CoV-2* "NRC-03-nhCoV" virus containing 100 $TCID_{50}$ was prepared and incubated with serially diluted concentrations of the tested products of honey and extracts which were kept at a temperature of 37 °C for one hour. Moreover, another set of Vero-E6 cells was treated with a virus/products mix and co-incubated at a temperature of 37 °C in a total volume of 200 µl per well. The untreated cells infected with the *SARS-CoV-2* virus represent virus control; on the other hand, untreated cells that have not been infected represent cell control. The cells were fixed with 100 µl of 10% paraformaldehyde for twenty minutes and stained with 0.5% crystal violet in distilled water for fifteen minutes at room temperature after being incubated for seventy-two hours at a temperature of 37 °C in a 5% carbon dioxide incubator. Afterward, 100 µl of absolute methanol per well was added to liquefy the crystal violet dye and the optical density of the color was measured at 570 nm using the plate reader Anthos Zenyth 200rt. The IC_{50} of the tested natural products was needed to reduce the virus-induced cytopathic effect (CPE) by 50%, relative to the virus control (Kandeil et al. 2020).

Statistical analysis

The IC_{50} value and the CC_{50} value were calculated by GraphPad Prism software version 5.0 using the nonlinear regression analysis; this was done by plotting log concentrations of the tested natural products of honey and extracts against normalized response on a variable slope curve. The selectivity index was calculated by dividing the CC_{50} value by the IC_{50} value (Mosmann 1983; Mostafa et al. 2020).

Results

Figure 1 describes the dose–inhibition curves for anti-*SARS-CoV-2* "NRC-03-nhCoV" virus and the inhibitory concentration 50 (IC_{50}), and cytotoxicity CC_{50} values for all tested products of honey and extracts. Cinnamon oil extract showed CC_{50} 1.06 µg/ml and IC_{50} 0.98 µg/ml, while *Moringa oleifera extract showed* CC_{50}111.54 µg/ml and IC_{50} was 52.79µg/ml. Manuka honey showed CC_{50} 11.135 µg/ml and IC_{50} 1.08 µg/ml, while *N. sativa* oil showed CC_{50} 6.05 µg/ml and IC_{50} 3.71. The mixture of honey and the above extracts showed CC_{50} 7.883 µg/ml and IC_{50} 1.10 µg/ml µg/ml, while *Remdesivir* showed CC_{50} 201.5 µg/ml and IC_{50} 60.74 µg/ml.

Table 1 describes the antiviral activity and selectivity index of all tested products of Manuka honey and extracts of *M. oleifera*, *N. sativa*, and cinnamon bark oil against *SARS-CoV-2* "NRC-03-nhCoV" virus. Manuka honey showed the highest selectivity index of 10.23, followed by a mixture of cinnamon bark oil, *M. Oleifera*, Manuka honey, *and N. sativa* oil with a SI of 7.12. The third highest SI was Remdesivir (3.3), then *M. oleifera leaves extract* (2.1), then *N. sativa oil* (1.6), and cinnamon bark oil extract (1.08), respectively.

Identification of compounds in cinnamon bark oil extract

GC-Mass spectrometry

The results showed that the compound with the highest peak was cinnamaldehyde with a peak area of 68.89% at a retention time of 12.24 min.

High-performance liquid chromatography

The cinnamaldehyde 98% chemical reference substance (LOBA Chemie laboratory reagents and fine chemicals, India) was dissolved in acetonitrile and then injected into the HPLC. The highest peak of the standard chemical was 3.477 retention time, and the cinnamon oil extract showed the highest peak at 3.261 retention time. The cinnamaldehyde concentration was calculated to be equal to 72.1 µg/gm of the sample.

Discussion

A combination of the four natural products, *Moringa oleifera*, *Nigella sativa*, and cinnamon bark oil, and Manuka honey, was studied for the first time compared to the antiviral drug Remdesivir. However, each of them (Manuka honey and extracts) was tested alone in previous studies either experimentally in the laboratory or clinically on humans.

Obtained results shown in Fig. 1 and Table 1 are in line with El Bashir, et al., that was carried out in 2021 on Manuka honey which concluded that Manuka honey has potent antiviral activity against *SARS-CoV-2* when put and incubated with the virus in cell-free media at no greater than 40-fold dilutions of 250 + grade. This is attributed to the methylglyoxal content of Manuka honey which mediated the antiviral effect. However, in our study, the tested Manuka honey was 20 + UMF which is equal to 829 + MGO (methylglyoxal) which is much more powerful than that used by authors in 2021 (Elbashir et al. 2021).

The antiviral effect of *Moringa oleifera* leaves extract on the *SARS-CoV-2* virus can be explained by Siddiqui S, et al., in 2022 which concluded that bioactive compounds of *M. oleifera* leaves extract showed a very powerful binding affinity with *SARS-CoV-2* spike glycoprotein. The

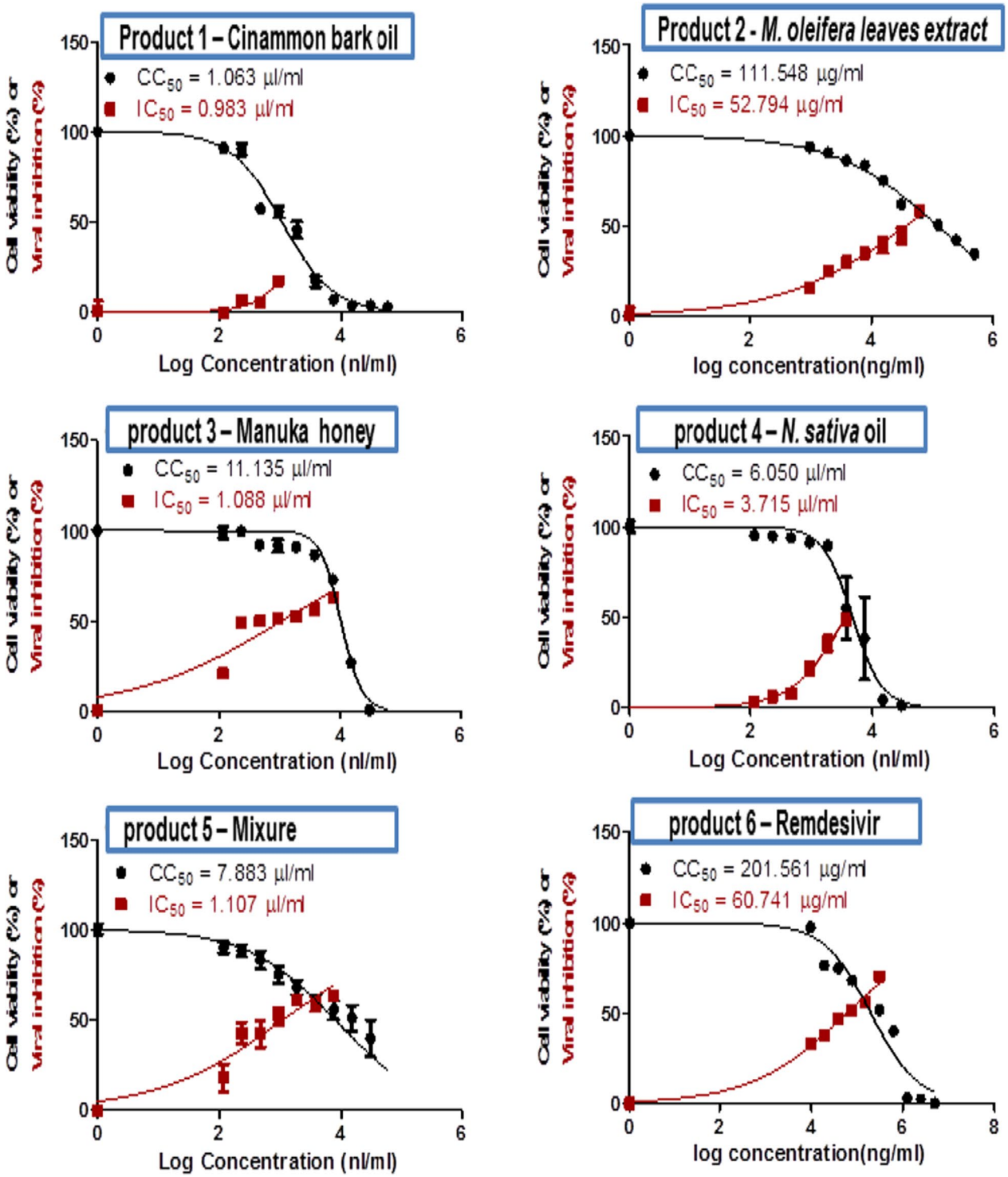

Fig. 1 Dose–inhibition curves for anti-*SARS-CoV-2* "NRC-03-nhCoV" virus and the inhibitory concentration 50 (IC_{50}) and cytotoxicity CC_{50} values for product 1 (cinnamon extract), product 2 (*M. oleifera* leaves extract), product 3 (Manuka honey), product 4 (*N. sativa* oil), product 5 (mixture of the first 4 products), and product 6 (Remdesivir)

Table 1 The antiviral activity and selectivity index of all tested products of Manuka honey and extracts of *M. oleifera*, *N. sativa*, and cinnamon bark oil against *SARS-CoV-2* "NRC-03-nhCoV" virus:

Product's no	CC_{50}	IC_{50}	SI (selectivity index)
1. Cinnamon bark oil	1.063	0.983	1.08
2. *M. oleifera* leaves extract	111.548	52.794	2.11
3. Manuka honey UMF 20+	11.135	1.088	10.23
4. *N. sativa* oil	6.050	3.715	1.60
5. Mixture of the above (cinnamon bark oil, *M. Oleifera*, Manuka honey, *N. sativa* oil)	7.883	1.107	7.12
6. Remdesivir 100 mg	201.561	60.741	3.30

best were β-tocopherol and β-sitosterol showed good stability. Interestingly, most of the phytoconstituents of *M. oleifera* displayed drug-likeness with no toxicity (Siddiqui et al. 2022).

The data presented in Fig. 1 and Table 1 showed that cinnamon oil has an antiviral effect against the *SARS-CoV-2* virus. This can be explained by Zareie A, et al. that the active ingredients in cinnamon such as cinnamaldehyde and trans-cinnamic acid can decrease the production of inflammatory cytokines by suppressing the inflammatory pathways. Thus, it is possible that the beneficial effects of cinnamon on suppressing inflammation may help in controlling and preventing *SARS-CoV-2* complications (Zareie et al. 2021).

Although our data showed that *Nigella sativa* oil was of lower selectivity and lower antiviral effect than other tested products of honey and extracts, when it was tested on humans it gave good results according to Al-Haidari, et al., on *SARS-CoV-2*-infected patients given *Nigella sativa* seeds (40 mg/kg dose orally) daily for two weeks in addition to the standard medications given to those patients. It was found that there was a significant decline in the degree of severity of infection with *SARS-CoV-2* compared to the control group. The improvement might be attributed to the presence of an active compound called Thymoquinone in *N. sativa* seeds. This compound has the ability to reduce oxidative stress and influences the immune modulators, thus helping in reducing the cytokine storm chances and mortalities (Al-Haidari et al. 2021).

Generally, in our research, there were some limitations such as having difficulty in avoiding all possible errors and having full control of the research variables; we had to repeat some work to reach the ultimate results which was time-consuming as well. Also, it cannot be generalized at the population level and should be tested on real-life *SARS-CoV-2*-infected patients to determine its potency and efficiency.

Conclusions

This study highlighted that Manuka honey + 20 UMF alone or combined with other three extracts of *Moringa oleifera* leaves extract, *Nigella sativa*, and cinnamon oil were found to have a much more potent antiviral effect on *SARS-CoV-2* than the traditional antiviral drug Remdesivir. This can be useful and important for providing a natural immune-boosting antiviral remedy for patients with *SARS-CoV-2* infection or those at risk of *SARS-CoV-2* infection. Further research will be needed for in vivo testing and determining the effective dose of those extracts and honey as a potential treatment for *SARS-CoV-2* disease.

Abbreviations

SARS-CoV-2	Severe acute respiratory syndrome *coronavirus 2*
UMF	Unique Manuka Factor
HPLC	High-performance liquid chromatography
CC_{50}	Cytotoxicity
IC_{50}	Inhibitory concentration 50
SI	Selectivity index
DMSO	Dimethyl sulfoxide
ddH_2O	Double-distilled water
CO_2	Carbon dioxide
Rt	Room temperature
λ max	Maximum wavelength
$TCID_{50}$	The median tissue culture infectious dose
CPE	Virus-induced cytopathic effect
GMO	Methylglyoxal
M. oleifera	*Moringa oleifera*
N. sativa	*Nigella sativa*

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Author contributions

All authors contributed equally to this research work. WM was responsible for the extraction of the tested natural products and writing of the manuscript. FK was responsible for analyzing the data of the study. SM was responsible for the statistical interpretation of the results after testing of natural compounds on the virus. MA was responsible for all the virology testing and tissue culture processes in the laboratory at the NRC. All authors read and approved the final manuscript.

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Availability of data and materials

All data generated and analyzed during this study are included in this article. Also, the related datasets are available from the corresponding author upon reasonable request.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable.

Competing interests
No conflict of interest.

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