Trop J Nat Prod Res, July 2021; 5(7):1208-1214

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Tropical Journal of Natural Product Research

Available online at https://www.tjnpr.org

Original Research Article

Phytotherapeutic Approaches and Ethnopharmacological Responses Against COVID-19

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ARTICLE INFO

Article history:
Received 08 March 2021
Revised 03 July 2021
Accepted 12 July 2021
Published online 02 August 2021

ABSTRACT

The coronavirus disease 2019 (COVID-19) pandemic, the most important public health problem in 2020, poses severe health and socioeconomic impact. Many people turn to herbal therapy to prevent infection with the virus or alleviate the symptoms caused by it. This study evaluates the patterns of phytotherapy-based product utilization in the prevention against SARS-COV-2 and their reported effectiveness. This cross-sectional survey used a convenience sample of 287 adults who had used any form of phytotherapeutics to help fight and/or treat COVID-19 infection. The majority (n = 194, 67.6%) of participants had used plants from the *Rutaceae* family (like lemon and oranges), followed by those of *Amaryllidaceous* (namely, Garlic and Onion). Participants said that physicians and pharmacists were the primary sources of information about phytotherapy (n=107, 37.3%), and their decision was driven by their positive attitude towards herbal medicine or plant-based products (n=133, 46.3%). Many participants did not notice any side effects of these remedies (n=270, 94%) and believed they were effective (n = 184, 64%). This study provides an overview of the many phytotherapeutic remedies used in the era of COVID-19 by Jordanian society, which could prompt the conduction of interventional trials to assess the effectiveness and safety of this modality of therapy, either as a stand-alone or adjuvant treatment.

Keywords: Phytotherapy, Medicinal plants, Natural products, COVID-19.

Introduction

Medicinal plants are still considering as promising alternatives to prevent or treat numerous diseases.[1,2] Coronavirus disease-19 (COVID-19) is a novel enveloped viruses of the family Coronaviridae disease caused by SARS-CoV-2.[3] They have a single-strand, positive-sense RNA genome that is approximately 26–32 Kb in size.[4] The genome of SARS-CoV-2 contains at least ten open reading frames (ORFs), which is like the number of ORFs present on the genome of other CoVs. Of pathogenic importance, the ORFs at the 3' end of the genome code for several structural proteins that facilitate the pathogenicity of SARS-CoV-2, and they are: spike (S), envelope (E), nucleocapsid (N), and membrane (M) proteins.[5] The spike glycoprotein was found to have an essential role in CoVs cell entry in general and SARS-CoV-2 by binding to the ACE2 receptor to enter the cell. Once SARS-CoV-2 enters the cells, antigen-presenting cells (APCs) in the body present peptide antigen of SARS-CoV-2 on its surface, initiating an immune response.[5] SARS-CoV-2 triggers both humoral and cellular immune responses, and several pro-inflammatory mediators and cytokines are elevated in SARS-COV-2 patients, most notably: IL-1, IL-6, and TNF-α. These cytokines and other components of the immune system lead to the development of symptoms of SARS-COV-2. Furthermore, one of the most common causes of mortality in SARS-COV-2 patients with ARDS is a cytokine storm with numerous pro-inflammatory cytokines, including: IL-1β, IL-6, IL-8, MCP-1, GCS-F, IP-10, CCL1-3, IL-12, IL-17, IL-18, IL-33, IFN-γ, TNF-α, etc.[6] Many complications arising from SARs CoV-2 infections are related to inflammatory response; thus, suppression of inflammation and the use of antivirals have a potential role in the management of COVID-19 patients. Therefore, various therapeutic options were suggested and experimented with in clinical trials, but they're no definitive cure has been identified yet amongst the first medication proposed, the antimalarial agent hydroxychloroquine. However, there is no evidence of its efficacy according to the published literature.[7,8] albeit a significant decrease in viral load amongst infected individuals treated with Hydroxychloroquine has been reported.[9] Antiviral drugs, such as Remdisiver, Lopinavir, and Ritonavir are used in the management of patients of SARS-COV-2, with relative benefit amongst milder cases showing a shortened time to clinical improvement.[10] While severe cases treated with antivirals did not see significant improvement over standard care.[11,12] Several studies investigating the benefits of Phytomedicines have been conducted to explore additional options in SARS-COV-2 therapy. Phytomedicines are used in the treatment of a multitude of illnesses and have an effective therapeutic role alongside traditional pharmacologic treatments.[13,14] The immune-modulating capabilities of phytotherapy make it an effective tool in the management of viral illnesses, through direct antiviral actions as well as symptomatic relief.[15] This makes phytotherapy a promising therapeutic approach to SARS-COV-2. Anti-inflammatory compounds which are extracted from numerous plant species have shown to directly reduce

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Citation: Al-Samydai A, Hajleh MA, Akour A, Alabdallah N, Yousef M, Baqa'in G, Al-saadi A, Al-Halaseh LK, Aburjai T. Phytotherapeutic Approaches and Ethnopharmacological Responses Against COVID-19. Trop J Nat Prod Res. 2021; 5(7):1208-1214. doi.org/10.26538/tjnpr/v5i7.7

Official Journal of Natural Product Research Group, Faculty of Pharmacy, University of Benin, Benin City, Nigeria.

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

inflammation, protect against Acute Lung Injury (ALI),[11] and even reduce fibrotic remodeling of the lungs in rat models.[16]
There are potential candidates from traditional medicinal herbs that can be considered as a part of the complementary and alternative medicine (CAM) therapy of SARS-COV-2, but = the evidence from literature about their efficacy is scarce. Hence, further research is warranted to identify agents with direct benefit in patients with SARS-COV-2 infection.[17] Therefore, the objection of this study is to evaluate the patterns of use of phytotherapy-based products in the protection against SARS-COV-2.

Materials and Methods

Study design and participants
This was a cross-sectional survey conducted between September and October 2020, utilizing an online self-administered questionnaire with close-ended questions. The targeted sample included adults more than 18 years from the Jordanian population. The survey was developed using Google Form, then the link was distributed on social media platforms such as WhatsApp® and Facebook®, as paper questionnaires were not a choice due to the Pandemic. Participants were filled out the questionnaire with integrity after fulfilling the suitability criteria, consenting on voluntary participation, and filling it only once. No form of return was paid to the members upon their involvement in the study.

Study tool
The online questionnaire was created using Google Forms provided by Google® TM and was constructed in modern Arabic. An ethnopharmacological survey has been developed and validated by face validity. To measure the questionnaire statements for clarifying and providing a coherent research questionnaire, a macro review covers academic reviewers who performed all the research constructs from Jordanian universities specialized in phytomedicine, phytochemistry, and marketing management (customer behavior). Some questions were added based on their appreciated recommendations. Some others were reformulated to become more accurate, which is therefore expected to enhance the research instrument. To find the most frequently used medicinal plants for SARS-COV-2 protection on the opinion of the Jordanian population, and questions were built on extensive literature review. The questionnaire was divided into five sections. The first one was about demographics: age, sex.
The second section was concerned with the most frequently used plants in the opinion of the Jordanian population for the protection against SARS-COV-2 from July 2020 to October 2020. The third one was about the relatively known usage of this plant, and finally, the source of information that has been adopted for the use of this plant for the protection against SARS-COV-2 and the outcome of using it.

Statistical analyses
The study aimed to find the most frequently used medicinal plant for the protection against SARS-COV-2 on the opinion of the Jordanian population.[52] Therefore, descriptive statistics (frequencies, percentages) were used to summarize the responses of participants to each question, SPSS® software v.21 was used.

Results and Discussion

Responses from 287 participants were collected. Descriptive statistics are presented in Table 1. The most predominant age category among respondents was 18-30-year-old, with 37% (n=107) of total responses. Most respondents had a college degree, with 67% (n=185) having a bachelor's degree. Considering the SARS-COV-2 global pandemic, we surveyed people from all governorates of Jordan to note the prominence of ethnobotanical use of local plants in the prevention of SARS-COV-2 and to note any predilections towards specific families of plants**.** Table 2 shows the plant families surveyed and the number of individuals that used plants from each family and their frequency of use. The most used families of plants in descending order were: *Rutaceae* (*Citrus limon* commonly known as lemon), (*Citrus sinensis*; orange); *Amaryllidaceous* (*Allium sativum*; Garlic), and (*Allium cepa*; Onion); *Theaceae* (*Camellia sinensis*; Tea (Black and green Tea); *Punicaceae* (Punica granatum; Punica); *Zingiberaceae (Zingiber officinale*; Ginger) and (*Curcuma longa*; Curcumin); Lauraceae (Cinnamomum verum; cinnamon); Apiaceae *(Pimpinella anisum*; aniseed), (*Foeniculum vulgare*; Fennel) and (*Petroselinum crispum*; Parsley); *Asteraceae (Matricaria chamomilla*; chamomile), *Lamiaceae (Teucrium chamaedrys*; Germander), (*Mentha spicata*; garden mint), (*Thymus vulgaris L.*;thyme), (*Salvia officinalis*; sage), (*Melissa officinalis*; Lemon balm); *Malvaceae (Hibiscus sabdariffa*,; Roselle), *Myrtaceae (Syzygium aromaticum*; Cloves), (*Psidium guajava*; Psidium); and *Fabaceae (Glycyrrhiza glabra*; Liquorice) (Figure 1).
The inflammatory process associated with SARS-CoV-2 infections is initiated with the virus entering the cell by binding to ACE-2 as its receptor, followed by the presentation of SARS-CoV-2 antigens on the exterior of Antigen Presenting Cells (APC), initiating the immune response.[5] For initiation chemotaxis IL-6, TNF-α, IL-1β, and type-1 interferons (innate immune system) released as acute-phase response cytokines. In severe cases, cytokine release syndrome (CRS) manifests as a hyper-inflammatory state in which cytokines MCP-1, TNF-α, IL-6, GCS-FCCL1-3, IP-10, IL-8, IL-17, IL1-β, and IFNγ play a pivotal role.[6] The study investigated the anti-inflammatory effect of traditionally used plants among Jordanians to predict their potential to suppress cytokines and inflammatory pathways involved in SARS-COV-2. *Apiaceae* is a large family of mostly aromatic flowering plants that contains over 3700 species, [includes parsley (*Petroselinum crispum*), Aniseed (*Pimpinella anisum*), and Fennel (*Foeniculum vulgare)*, which were the *Apiaceae* species surveyed in this study], are rich in essential oils which contribute to many medicinal properties. Aniseed essential oil was found to reduce inflammation in LPS-induced bronchitis in mice, as mediated by the suppression of IL-1*β* and IL-8, while stimulating mucin secretion.[18] *P. crispum* contains a number of biologically active compounds that have various effects including antioxidant, antimicrobial, and anti-inflammatory effects amongst others. Numerous compounds which were isolated from *P. crispum* have been shown to have anti-inflammatory effects.

Table 1: Demographics of participants (n = 287)

	N(%)
Gender	
Male	128 (44.6%)
Female	159 (55.4%)
Age	
<18	33 (11.5%)
18-30	107 (37.3%)
31-40	41 (14.3%)
41-50	49 (17.1%)
51-60	48 (16.7%)
>60	9 (3.1%)
Social Status	
Single	143 (49.8%)
Married	136 (47.4%)
Other	8 (2.8%)
Education	
School education	48 (16.7%)
Diploma	23 (8%)
Bachelor's degree	185 (64.5%)
Masters or PHD	31 (10.8%)

Apiin, a natural flavonoid found in parsley and celery, was found to inhibit NO release and iNOS expression *in vitro* when administered one hour prior to LPS stimulation.[19] Kulkarni and colleagues studied *in silico* evaluation of Anethole (Volatile Oils) efficacy, from anise fruits (*Anisi fructus) P. anisum L.*, showed inhibition activity against S1 subunit of spike (S) proteins of SAR-CoV-2 which involved in the interaction with host ACE2 receptors.[20]

Allium which includes many plants such as onion *(A. cepa L.),* chives *(A. schoenoprasum L.), and leek (A. porrum L.)* but also the medicinal plant garlic *(A. sativum L.).*[21] *Onion (A. cepa)* and Garlic *(Allium sativum)* were the two *Allium genus* listed in our survey. These two species have been used for centuries in ethnopharmacology within the region, for their antimicrobial and anti-inflammatory effects. The literature at present supports these practices, as Allium genus is mainly familiar with sulphur-containing compounds, particularly Alliin and Allicin, are the main compounds responsible to antiviral activity of garlic against large number of viruses like influenza B, coxsackievirus species, vesicular stomatitis virus, HIV (type 1), herpes simplex virus (types 1 and 2), and gammaretro virus was previous confirmed.[22] furthermore, Alliin showed the best binding efficacy with target protein 6LU7 Insilico.[23] Lately, scientists have understood the structure of the main protease of SARS-CoV-2, the infection rate might be significantly reduced by delaying the cleavage of the viral polyprotein". [22] Diallyl disulfide (DADS), an organosulfur compound derived from A. sativum, has been exposed to display anti-inflammatory activity via the suppression of TNF-α and the NF-κB inflammatory pathway. [23] Amaryllidaceae alkaloids, such as lycorine and lycoricidinol, have also been shown to reduce inflammation by inhibiting TNF-*α,* IL-6, IL-8, and PGE2.[24]

Asteraceae, the largest family[25] in our work Lychnophora passerina is the most used plant from Asteraceae. The *Lychnophora passerina*, known to people as "arnica," have a wide variety of biological activities, where It used in a folk medicine to treat infections, rheumatism, bruises, pest bites and analgesic agents.[26] Triterpenoids, Sesquiterpenoids, Diterpenoids, Steroids and Flavonoids are the major compounds that occur in the Lychnophora genus.[26,27] The ethanolic extract from aerial parts of the *L. passerina* are rich with quercetin and kaempferol. [27] where each of quercetin or kaempferol modulated iNOS, COX-2, and CRP, via mechanisms possible to include blockade of NF-κB activation and the resultant up-regulation of the pro-inflammatory genes so presented an anti-inflammatory activity.[28] *In silico* studies show that quercetin and kaempferol can be potential inhibitors of SARS-COV-2, where it was shown that these compounds share a similar pharmacophore as nelfinavir.[31]

Extracts of Glycyrrhiza glabra have been shown to inhibit the COX-1 and CoX-2 inflammatory pathways, with ethyl acetate extracts inhibiting both, while methanolic extracts appearing to selectively inhibit the COX-2 pathway.[29] Crude extracts of another Fabacae species, M. frondosus, were studied to determine the anti-inflammatory activity of its chemical constituents. The crude extract had a chemical profile that included isoflavononones, including biochanin A and formononetin. They found the crude extract was able to reduce overall inflammation by inhibiting pro-inflammatory mediators such as MPO, NOx, TNF-α, and IL-6, and preventing neutrophil migration.[30]

The Lamiaceae, family which yielding a large number of medicinal taxa, due to their high amounts of essential oil.[31] where *Stachys lavandulifolia* Vahl was the common used plant in this study. *Stachys lavandulifolia* Vahl (Lamiaceae) is a medicinal plant usually used in Turkey and Iranian popular medicine due to its analgesic and anti-inflammatory things, but slight is well-known about its essential oil. The anti-inflammation activity of *S. lavandulifolia* is related mainly to inhibition production of COX-2 products.[31] due to present of bisabolol essential oil**.** COX2 is a serious evolutionary enzyme in many physiologic and pathologic procedures. It has a vital role in regulates expression levels of numerous serum proteins and viral infections,[35] where Baghaki and his research team mention that COX2 inhibition could be a valuable assistant to continues to evolve treatment strategies of SARS-COV-2. Additonally, *α*-bisabolol have immune boosting properties to prevent SARS-COV-2 infection.[32]

The Lauraceae species we have included in the study is Cinnamon (*Cinnamomum verum)*. Cinnamon contains cinnamaldehyde, a potent anti-inflammatory compound and antioxidant. Its effects on inflammatory reactions in the setting of lung injury has been investigated in the literature. Submicron emulsions of cinnamaldehyde (SME-CA) were found to reduce the number of neutrophils and alveolar macrophages in the bronchoalveolar lavage fluid (BALF), as well as suppressing the production of cytokines including IL-1β and TNF-α.[33] Reactive Oxygen Species (ROS) were also decreased when SME-CA was administered. Neolitsea hiiranensis, another species of Lauraceae, has prominent anti-inflammatory effects. Crude extracts from N. hiiranensis were able to reduce the production of IL-12, IFN-γ, and IL-2 when administered to the mice. An in-silico study conducted by Kulkarni and colleagues shown there was an effect of Cinnamaldehyde, in blocking the S1 subunit of spike (S) proteins.[34]

Hibiscus sabdariffa L. (roselle), which is rich with phytochemicals like polyphenols especially anthocyanins, and shows many pharmacological activities.[35] Additionally, anthocyanins are familiar antioxidants that reduce reactive oxygen species (ROS). Numerous studies have demonstrated the anti-inflammatory effects of anthocyanins, through the inhibition of NF-κB goings-on via mitogen activated protein kinase (MAPK) pathways, and inhibited cyclooxygenase enzyme activities, which in turn have been shown to reduce lung inflammation.[36] Furthermore, an *in silico* study showed that anthocyanins could bind with the receptor binding site and catalytic dyad (Cys145 and His41) of 2019-nCoV-3CLpro, which might serve as potential anti-2019-nCoV leading molecules for further.[37]

Psidium guineense Sw. (Myrtaceae) is a native shrub or small tree, the leaves of which have been used in the treatment of inflammation as it mainly contains α- Spathulenol, ϒ-Terpineol and 1,8-cineole. *P. acutangulum* extract inhibits the secretion of the pro-inflammatory cytokines, TNF*α*, IL-1*β*, IL-6, IL-8 and NO. The essential oils from *P. guajava* leaves are potentially useful in the treatment of inflammatory diseases by mechanisms that include the inhibition of eosinophil migration.[30] *In silico* studies show that Spathulenol could bind to angiotensin-converting enzyme 2 (ACE2) receptors by which SARS-CoV-2 gains access into the host cell, which is expected to interfere with host-viral interaction.[38] *Eugenia umbelliflora,* which is frequently identified as Brazilian cherry, shows anti-inflammatory action by reducing the influx of PMN to the inflamed tissue, as well as reducing the cytokine IL-1*β* levels. This anti-inflammatory activity was also accompanied by significant anti-hypersensitive effect. These effects by *E. umbelliflora* does not seem to be correlated with its antioxidant activity,[39] but mainly contributed by its constituents, Catechin, Epicatechin and Ellagic acid pentoside.[40] Indeed, the epigallocatechin-3-gallate (EGCG) and epicatechin gallate (ECG), significantly reduced, in a concentration-dependent manner, the expression of IL-6 and IL-8. This could make this plant a good candidate for the alleviation of the inflammatory response experienced by severe cases of COVID-19, who have increased levels inflammatory cytokines IL-6 and IL-8.[41]

Pomegranate (*Punica granatum)* and Socotran pomegranate (*Punica protopunica*) species, of the genus *punica*, used to be classified in a family of their own (Punicaceae), but after modern phylogenic testing, they now belong to the *Lythraceae* family. Polyphenolic extracts from pomegranates have been shown to attenuate the expression of IL-6 and chemoattractant protein (MCP)-1 in *in vitro* models of human intestinal epithelium.[41] Ethyl acetate fraction obtained from the pomegranate leaf hydroalcoholic extract (EAFPg) decreased the gene expression of TNF-*α*, IL1-*β*, and IL-6 in lung tissue of mice with LPS-induced ALI, and reduced the levels of TNF-*α* protein.[42]

Rutaceae family which includes genus Citrus (like: orange, lemon, lime, mandarin, grapefruit, etc.[43] Essential oil is common in many taxa (Citrus, Ruta). Alkaloids are also commonly present, particularly benzyl tetrahydroisoquinoline, acridone and imidazole.[44] *Rutaceae* species, particularly Lemon (*Citrus Lemon)* and orange (*Citrus sinensis)* fruits, were the species of plants most reported by Jordanians to be used in the prevention of SARS-COV-2 infections. The *Rutaceae* species contain potent compounds with anti-inflammatory and protective effects against ALI in mice.

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

Table 2: Frequency of use of plant families to combat against SARS-COV-2

Plant family	*Frequency of use*						
	Once a day	**Twice a day**	**Three times a day**	**Once a week**	**Twice a week**	**Three times a week**	**Total # Of users**
Asteraceae [a]	43	11	8	42	5	6	115
Apiaceae	47	15	8	40	3	3	115
Lamiaceae	44	10	9	38	5	3	108
Myrtaceae	33	10	5	32	7	2	88
Zingiberaceae	54	16	10	41	5	4	130
Theaceae	58	14	18	30	6	6	131
Rutaceae	84	28	33	40	7	8	194
Fabaceae	28	3	5	33	7	2	77
Amaryllidaceae	80	20	17	37	10	10	174
Malvaceae [a]	36	1	12	31	6	3	89
Punicaceae [a]	56	15	14	33	6	7	131
Lauraceae [a]	40	10	11	44	8	5	118

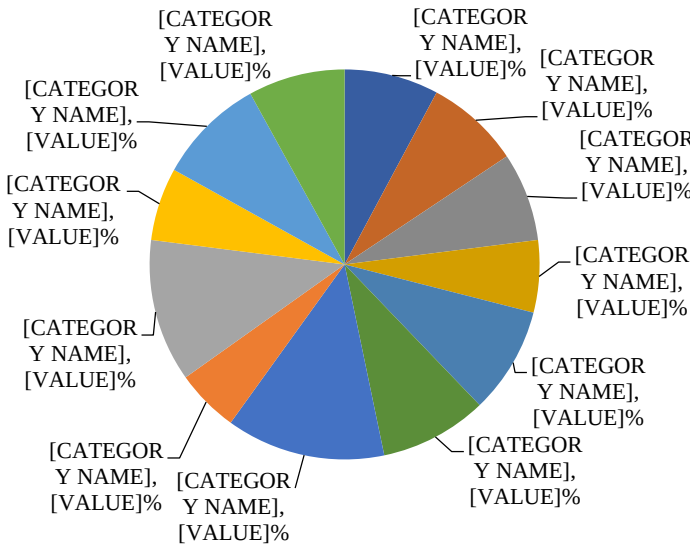

Figure 1: Most used traditional medicinal plant families in the prevention of SARS-COV-2

Table 3: Source of information and factors that affect decision

Source of information regarding plant benefits for SARS-COV-2 as N (%)	
Random posts on social media	33 (11.9%)
A physician or a pharmacist	107 (38.5%)
Text messages from family and friends	41 (14.7%)
Family advice	49 (17.7%)
Other	48 (17.2%)
Effect on decision regarding using the plant for SARS-COV-2 prevention	
Family traditions	61 (21.3%)
Positive aspects associated with herbal medicine	133 (46.3%)
Dissatisfaction with conventional treatment	93 (32.4%)

Hesperetin, a bioflavinoid found in *Rutaceae* species, was found to significantly suppress the levels of IL-6 and tNF-*α*, reduce lung injury, and suppress nuclear factor-kappa B (NF-κB) activation in lung tissue in mice with LPS-induced ALI.[45] P-synephrine, another alkaloid in citrus fruits, was found to inhibit the NF-κB signaling pathway in ALI.[10] Recent *in silico* study evaluated the efficacy of Hesperetin in blocking the S1 subunit of spike (S) proteins of SAR-CoV-2.[46] Additionally, Hesperetin showed dose-dependent inhibition of SARS Mpro in a recent *in vitro* study. Hesperitin glycoside, showed the potential to inhibit many proteins related to SARS-CoV-2 by interfering with their viral cycle. These results underline the importance of initiating further studies to evaluate this molecule and its industrial extraction process from citrus peel.[22] The *Theaceae* family consists of flowering plants such as the well-known tea plant. About 45% of respondents to our survey used Black tea or Green tee (*Camellia Sinensis)* for the health benefits of their extracts, which are well documented in the literature.

Of interest are the anti-inflammatory properties of these species, which arise from the many active compounds in their extracts such as: catechins, theaflavins and theasinensins. These compounds have been shown to have an inhibitory effect on many pro-inflammatory mediators including: COX-2, IL-6, IL-1*β*, and TNF-*α*.[30] They have also shown to increase the release of the anti-inflammatory cytokine IL-10,[47,48] all of which results in the suppression of the inflammatory process and protection of the tissue from injury.

Zingiberaceae family (Monocotyledons), which is rich in essential oil with terpenes such as cineole, borneol, and camphor (monoterpenes, oxygen-containing), camphene, pinene (monoterpenes) and zingiberene (a sesquiterpene), in addition to phenylpropanoids (cinnamic acid derivatives). One such molecule is Zerumbone, a sesquiterpene compound isolated from *Zingiber zerumbet*. It was found to significantly suppress the production of IL-1*β*, IL-6, and TNF-*α*, but did not affect IL-10 levels in blood plasma.[49] Turmuric (*Curcuma longa)* contains curcumin, which is a well-known anti-inflammatory compound

ISSN 2616-0684 (Print)
ISSN 2616-0692 (Electronic)

through targeting multiple inflammatory pathways including the down regulation of NF-κB by inhibition of IκBα kinase and AKT. Curcumin also acts on macrophages, suppressing the release of pro-inflammatory mediators such as IL1, IL-6, and TNF-*α*, and upregulating IL-10 release. Of huge importance in the case of SARS-CoV-2 pulmonary infections and ARDS, curcumin has also shown to have an anti-fibrotic effect on the lungs tissue. This anti-fibrotic effect is the result of its down regulation of metalloproteinase (MMP)-9 and MMP-2, upregulation of tissue inhibitor of matrix metalloproteinases (TIMPs), and its ability to increase the levels of cathepsin K and L, collagenase, and elastase.[16] *In silico* investigations of curcumin binding on the proteins surface which mediating cellular entry of virus and other enzymes essential for viral replications, as SARS-CoV-2 MPro and RdRp.[50] This is not only relevant for active SARS-COV-2 cases but also for its potential to decrease patients' morbidity in the long term.

This study is the first in Jordan to provide an insight into the patterns of herbal medicine used to combat COVID-19 in an adequate number of participants. Nevertheless, there are some limitations to this study: 1) The cross-sectional nature of the study prevents us from establishing any cause-effect or temporal relationship, 2) Most participants were residing in Amman, so we cannot generalize findings to other provinces, 3) There is a chance for selection bias considering the method of sampling (for example those who have no internet connection or technologically-inept could have been missed).

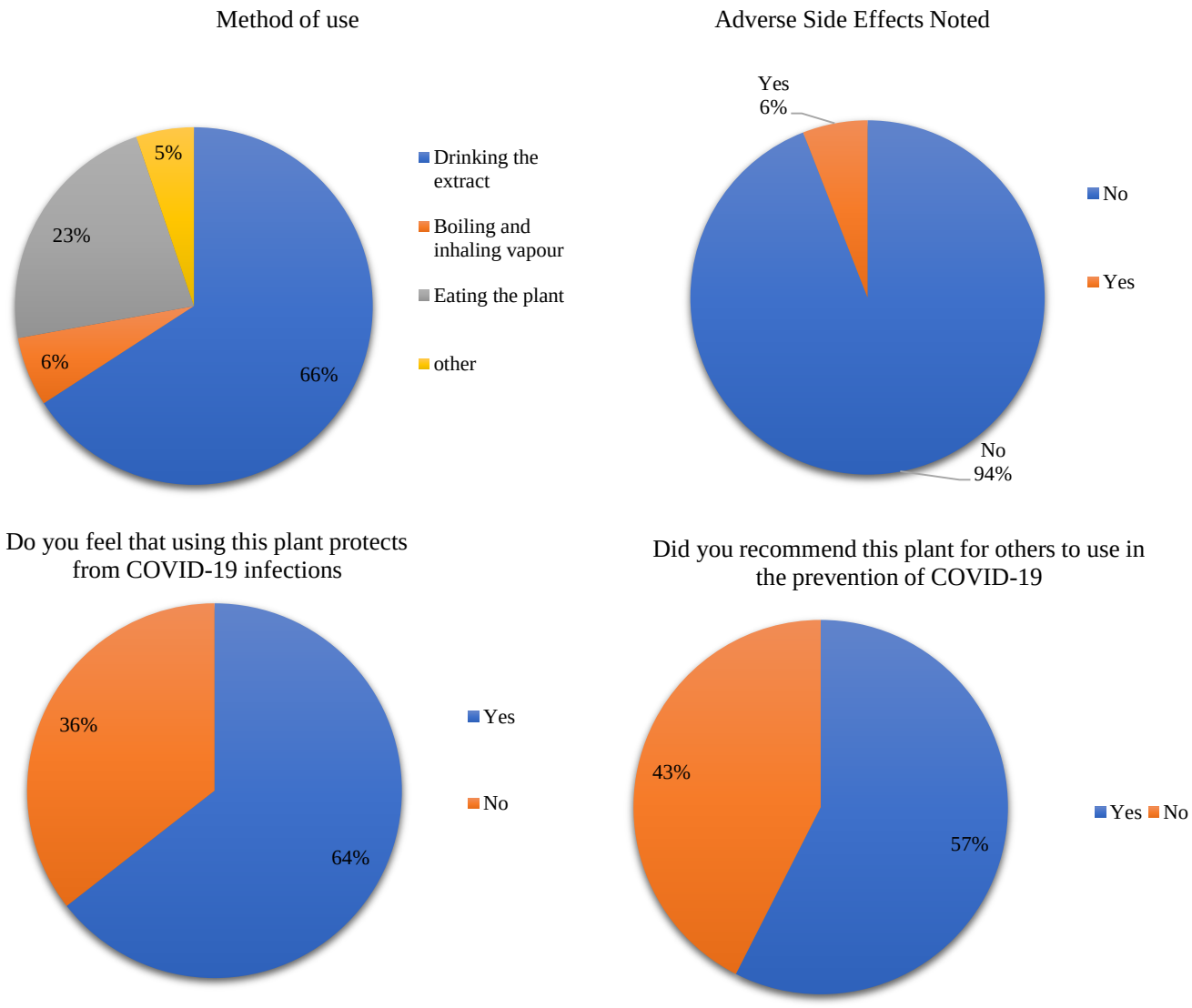

Figure 2: Subjective experience of respondents with the plant used

Conclusion

Natural products discovered from medicinal plants have provided many clinically used medicinally against many diseases. This study could provide more detailed information about the possibility of using natural products in treating SARS-COV-2 infection. The Rutaceae family (like lemon and oranges) and the Amaryllidaceous family (like garlic and onion) were the most helpful family plants from our sample; these plants could use alone or in combination as alternative medicines to treat/prevent SARS-COV-2 infection by offering clues for the development of anti-SARS-COV-2 drugs. Also, evaluating the synergism interaction between these plant extracts and antiviral drugs could help develop a pharmacological agent to treat SARS-COV-2 through increased efficiency, reduction of undesirable effects, and increase in the stability or bioavailability of available antiviral agents. Furthermore, many experimental investigations *in vitro* and *in vivo* studies are needed to see how these natural products will work against the SARS-COV-2 virus.

Conflict of interest

The authors declare no conflict of interest.

Authors' Declaration

The authors hereby declare that the work presented in this article is original and that any liability for claims relating to the content of this article will be borne by them.

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