A Possible Synergistic Herbal Solution for COVID-19

Ephraim Shmaya Lansky

1 Laboratory of Applied Metabolomics and Pharmacognosy (LAMP), Institute of Evolution, University of Haifa, 3498838 Haifa, Israel
*Correspondence: elansky@research.haifa.ac.il (Ephraim Shmaya Lansky)

Abstract

The COVID-19 pandemic has provided an opportunity for repurposing of drugs, including complex, natural drugs, to meet the global need for safe and effective antiviral medicines which do not promote multidrug resistance nor inflate medical costs. The author herein describes his own repurposing of herbal tinctures, previously prepared for oncology, into a possibly synergistic, anti-COVID 41 “herb” formula of extracts derived from 36 different plants and medicinal mushrooms. A method of multi-sample in vitro testing in green monkey kidney vero cells is proposed for testing the Hypothesis that even in such a large combination, antiviral potency may be preserved, along with therapeutic synergy, smoothness, and complexity. The possibility that the formula’s potency may improve with age is considered, along with a suitable method for testing it. Collaborative research inquiries are welcome.

Keywords: botanical; harmine; licorice; medicinal mushroom; Peganum harmala; synergen; virus; virucidal

1. Background

When the reality of the pandemic really hit home in March 2020 at the time of our first national “lockdown”, I had, stashed away in my subterranean laboratory numerous containers of medicinal herbs and their concentrated tinctures that I had prepared over the previous year for use with oncology patients. I began to wonder if any of that could be “repurposed” as antivirals against COVID-19. But when two totally unrelated friends from vastly different places, times, and contexts independently contacted me, a physician-pharmacognosist, around the same time asking if I had any herbal solution for COVID, I went down to the lab to see what I could do with what I had. Upstairs, I also had the computer to search the Internet and literature of the world.

I discovered, for example, that among COVID-19 patients in Wuhan, China, 91% had received Chinese herbal medicines as part of their hospital therapeutic programs [1].

Redundancy, required for synergy, may benefit medical interventions just as it may benefit viruses [2,3].

In phytotherapy, synergy may be “pharmacodynamic” affecting multiple targets; “pharmacokinetic” by improving drug transport, permeation, and bioavailability; diminishing side effects; or deactivating drug resistance [4]. Plant drugs may inhibit target-modifying and drug-degrading enzymes, or inactivate cellular efflux pumps [5].

Harmine, from the methanolic extract of Peganum harmala (Fig. 1) seeds, synergized with the conventional antiviral agent acyclovir against human Herpes simplex virus Type 2 in vitro. The P. harmala extract alone, though not cytoprotective, was virucidal both during the entry of viruses and during release of newly formed virions [6]. Similarly, an alkalized aqueous extract of the leaves of Sasa senanensis synergized in vitro with acyclovir against herpes simplex virus, while alone, S. senanensis suppressed human immuno-virus (HIV) [7].

Different natural products from a single plant or medicinal mushroom may also synergize with each other. Berberine (Fig. 2) an alkaloid prominent in the yellow roots of Coptis chinensis and goldenseal, Hydrastis canadensis, is typically regarded as the “active” in these plants, but when the complex H. canadensis extract, or its isolated novel flavonoid, 3,3’-dihydroxy-5,7,4’-trimethoxy-6,8-C-dimethylflavone, itself without antibiotic activity is combined with berberine, the effective antibiotic dose (IC50) of berberine dropped from 132 to 92 µM [8]. Also, the H. canadensis flavonoids sideroxylin, 8-desmethyl-sideroxylin, and 6-desmethyl-sideroxylin are identified as “synergens”, not antibiotic alone, but combined with berberine, enhanced berberine’s antibiotic potency by inhibiting an efflux pump [9], as did 5’-methoxyhydnocarpin, another H. canadensis non-antibiotic “synergen” [10].

Synergy may occur in phytochemical interactions within and between different foods to improve or weaken their medicinal potency and utilization [11,12]. Improvement of solubility of a complex often improves its absorption and so augments synergies [13].

To measure synergy within a super-complex mixture of three complex mixtures all derived from the same pomegranate fruits (Punica granatum), we used a simplified method. Extracts from pomegranate seeds (pressed oil), peels (aqueous extract), and juice (fermented, concentrated, and extracted with ethyl acetate) were tested individually and in combinations for their ability to inhibit invasion of human PC-3 human prostate cancer cells in vitro.
Harmine and berberine are common alkaloids with antiviral properties. The other four compounds are synergens, not antiviral in themselves, but increasing the antiviral potency of true antiviral compounds.

vitro. We fixed a dry weight dosage of each component to 1 mg/1 mL medium. This 1 mg was constant whether 1 component, 2 components, or 3 components were tested, which were equal in % dry weight to each other. Using this assessment, each component, used alone, effected an approximately 60% inhibition of invasion. When oil and peel, or oil and fermented juice components were combined in a 1:1 ratio totaling 1 mg/mL, we observed a 90% inhibition. When we combined equally all three components, oil, peel extract, and fermented juice extract to total 1 mg/mL, we found >99% inhibition. We showed the results to be significant by the Kruskal-Wallis non-parametric H test through a double blinded protocol involving researchers from two continents. Significance for inhibiting invasion was $p < 0.01$ [14]. We similarly applied the Kruskal-Wallis nonparametric test to prove synergistic inhibition of invasion with pure compounds representative of the different pomegranate fractions, i.e., punicic acid for oil, caffeic acid for peel, and luteolin for fermented juice [15].

Pure compounds can be quantified with molarity, but complex botanical extracts can only be measured by dry weight. In the above example, an isobologram assessment for the fermented juice and peel fractions is feasible since their largely overlapping chemistry is aimed at common targets. However, because the oil’s chemistry is so different, and likely involves different mechanisms and targets for its physiological effects than peel or juice, isobologram assessment was unsuitable for measuring the combination effect between the pomegranate’s lipid and aqueous compartments [16]. In general, synergy involves different sites of actions, while simple addism serves same sites of action [17].

Herbal synergy may describe synergistic interactions between phytochemicals within a single herb, and/or synergistic effects between different herbs in a single formula [18]. Prescribing different drugs together to achieve syner-
gistic benefits is common practice with antimycotics [19]. In nutrition, synergy among fruits and vegetables, which may be intensified or modulated during intestinal absorption, improves or impairs their overall clinical effectiveness [20]. Further, synergistic mixtures require lower levels of use with superior efficacy [21]. The concept of synergy, i.e., a whole or partially purified extract of a plant being better than a single isolated ingredient, underlies the philosophy of herbal medicine [22].

1.1 Synergy in Antiviral Therapeutics

Similar to the pomegranate synergy described above, three different fractions, namely alkaloids, lignans, and organic acids of the roots of Isatis tinctoria were evaluated for antiviral activity against respiratory syncytial virus in a mouse model. Each fraction exhibited antiviral properties, the strongest effect was when all three fractions were combined [23].

In the past, combination treatments for influenza were favored if they did not contribute to the emergence of drug resistant strains of virus or result in increased costs of treatment. If they did not prolong the virus’s eclipse phase, they were required to be used in combination with antiviral drugs that did [24].

The plant alkaloids emetine, from Psychotria ipecacuanha and homoharringtonine, from Cephalotaxus fortunei synergized with the broad spectrum antiviral, Remdesivir, or the anti-HIV retroviral, Lopinavir, against SARS-CoV-2 [25]. Synergy was observed between hydroxychloroquine and azithromycin as probable competitive inhibitors to the SARS-CoV-2 virus at the host’s cell membranes [26]. Synergy was also central to a proposal for testing various deoxynucleosides with 5-fluorouracil which had become ineffective when used alone due to coronavirus recognition [27]. Recent three dimensional methods have been advanced to quantify synergy between different modern antiviral drugs, which could be as high as 180 fold when stimulated by a synergist [28,29].

1.2 Phytotherapy and COVID-19

Many papers were published over the past two years regarding herbal treatments or potential treatments for COVID-19 [30,31]. A sampling of this research, presented according to plant name, is presented in Table 1.

1.3 Chemistry of Complexity

When a wine or fine spirit ages, its chemistry becomes more complex, or alternatively, its complexity increases. Aggregates of polyphenols increase during aging, and are associated with increased pharmaceutical potency [32,33]. One bottle of Pinot Noir recovered from a French wine cellar and estimated to be between 200 and 300 years old was reported to have a higher amount of such aggregates, with its resveratrol also preserved [34]. Although during viniﬁcation a maximum phenolic concentration is achieved in about nine days, the antioxidant properties can continue to increase for many years, presumably related to the formation of such aggregation of polyphenols [35] and additional changes in flavanols and anthocyanins with the subjective sense being being mellow and smooth [36]. In one recent study, aging in wine resulted in increased inhibition of topoisomerase-2 [37], an enzyme required for viral replication [38].

Complexity may also occur in pharmaceuticals when many, even thousands, of compounds constitute the drug. Such “complex drugs” have some advantages, such as being able to impact multiple targets at once, and being less likely to cause drug resistance [39].

When I made a pilot mixture of ethanolic extracts from the tissues of 34 different herbs and two mushrooms for preventing or treating COVID-19 two years ago, I was guided by several constraints. Initially, the first constraint was whether I had the herb or foodstuff in my possession, and later, whether I could obtain it during increasing COVID-19 restrictions. Second, was that the material must be legal. Use of certain herbs may be prohibited by law. Third, the herb should not be too toxic. And finally, if possible, the solution should taste good, or at least, not taste too bad.

In herbal therapeutics, herbs of specific “temperament” such as being hot or cold, are used to balance or correct their opposites in the “temperament” of a patient. However, when designing a formula aimed to suit all for a specific task (preventing or treating COVID-19), it should have “round edges” and be well tolerated by persons regardless of their individual “temperaments”. So it was in this spirit that I combined the mostly certified organic, and if not organic, then usually wildcrafted herbs in the original formulation. Those herbs, extracted and concentrated to fit in a 1 liter laboratory bottle, have now aged for almost two years. In their present form, they might offer a point of departure for further studies.

2. Hypothesis

I hypothesize that the combination of 41 herbal extracts which I have designated as “Core-Own-A” (Table 2) will be more effective in preventing or diminishing COVID-19 viral infection than any single one of its components, or even of smaller combinations of its components. Furthermore, I hypothesize that the efficacy and synergy within the combination will be enhanced during its aging.

The testing will:
1. Be able to ascertain the relative anti-SARS-CoV-2 effect (while not killing the host cell) of each of the 41 herbs from Table 2.
2. Show at which point in the complexity (i.e., higher N of herbs) either the synergism or dilution of the anti-SARS-CoV-2 effect is first noted. If it diminished, was it the increased increment of complexity, or the specific herb added at that time? Findings would point the way to further studies for more precise definition.
Table 1. Selected herbs cited by PubMed for COVID-19 prevention/therapy.

| Number | Latin name of the source of the crude drug | Reference(s) |
|--------|------------------------------------------|--------------|
| i      | Acanthopanacis gracilistylus            | [41]         |
| ii     | Aconitum lateralis                      | [42]         |
| iii    | Adenophora stricta                      | [43]         |
| iv     | Agastache rugosa                        | [43]         |
| v      | Aglaia sp.                              | [41]         |
| vi     | Alhagi pseudalhagi                       | [41]         |
| vii    | Allium porrum                            | [41]         |
| viii   | Allium ursinum                           | [41]         |
| ix     | Alstonia scholaris                       | [41]         |
| x      | Amelanchier alnifolia                    | [41]         |
| xi     | Ammi visnaga                             | [45]         |
| xii    | Anemarrhena asphodeloides               | [46]         |
| xiii   | Angelica sinensis                        | [41,47,51]   |
| xiv    | Anthemis hyaline                         | [41]         |
| xv     | Arctium sp.                              | [48]         |
| xvi    | Ardisia japonica                         | [46]         |
| xvii   | Armenia caramara                         | [49]         |
| xviii  | Aster tataricus                          | [41]         |
| xix    | Artemisia apiacum                        | [50]         |
| xx     | Astragalus membranaceus                  | [50,51]      |
| xxi    | Atractylodes sp.                         | [50]         |
| xxi    | Bambusa sp.                              | [50]         |
| xxii   | Benincasa hispida                        | [50]         |
| xxiii  | Boenninghausenia sessilicarpa            | [41]         |
| xxiv   | Broussonetia papyrifera                  | [41]         |
| xxv    | Bupleurum chinense                       | [41,50,52]   |
| xxvii  | Camellia sinensis                        | [41]         |
| xxviii | Cassia fistula                           | [41]         |
| xxix   | Cassia tora                              | [41]         |
| xxx    | Chrysanthemum sp.                        | [46,50]      |
| xxxi   | Cibotium barometz                        | [41]         |
| xxxii  | Cibotium barometz                        | [41]         |
| xxxiii | Cimicifuga racemosa                      | [41]         |
| xxxiv  | Cistanche sp.                            | [41]         |
| xxxv   | Citrus sinensis                          | [41]         |
| xxxvi  | Cladastis lutea                          | [41]         |
| xxxvii | Codonopsis pilosula                      | [47]         |
| xxxviii| Coix lacryma-jobi                        | [50]         |
| xxxix  | Corydalis bungeana                       | [53]         |
| xl     | Crocus sativus                           | [44,45]      |
| xli    | Cymbidium sp.                            | [41]         |
| xlii   | Cyrtomium fortunei                       | [43]         |
| xliii  | Dendrobium nobile                        | [43]         |
| xliiv  | Desmodium canadense                      | [41]         |
| xlv    | Dianthus sp.                             | [41]         |
| xlvii  | Dioscorea batatas                        | [41]         |
| xlviii | Dryopteris crass                         | [42,54,61]   |
| xlix   | Ephedra sinica                           | [41,46,50,54,61] |
| l      | Epipactis helleborine                     | [41]         |
| li     | Eriogonum breviscapum                    | [46]         |
| lii    | Eriobotrya japonica                      | [46]         |
| liii   | Eupatorium sp.                           | [43]         |
| liii   | Euphorbia helioscopica                   | [46]         |
| Number | Latin name of the source of the crude drug | Reference(s) |
|--------|------------------------------------------|---------------|
| liv    | *Fagopyrum cymosum*                     | [46]          |
| lv     | *Tussilago farfara*                     | [64]          |
| lvi    | *Foeniculum vulgare*                    | [45]          |
| lvii   | *Forsythia suspensa*                    | [41,45,54,56,61] |
| lviii  | *Fortunes bossfern*                     | [46]          |
| lix    | *Fritillaria verticillata*              | [41]          |
| lx     | *Galanthus nivalis*                     | [41]          |
| lxi    | *Gentiana scabra*                       | [41]          |
| lxii   | *Ginkgo biloba*                         | [41,51]       |
| lxi     | *Gleditsia spina*                       | [62]          |
| lxiv   | *Glycyrrhiza sp.*                       | [41,46,50,54,56,61,69] |
| lxv    | *Griffithia*                            | [41]          |
| lxvi   | *Gypurm Fibrosum*                       | [41,45,46,63] |
| lxvii  | *Hedysarum multijugum*                  | [46]          |
| lxviii | *Heteromorpha sp.*                      | [41,43]       |
| lxix   | *Hippeastrum sp.*                       | [41]          |
| lxx    | *Houttuynia cordata*                    | [41,45,52,54,55] |
| lxxi   | *Hovenia dulcis*                        | [46]          |
| lxxii  | *Hymenaea verrucosa*                    | [45]          |
| lxxiii | *Inula sp.*                             | [46]          |
| lxxiv  | *Isatis indigotica*                     | [52,53]       |
| lxxv   | *Isatis tinctoria*                      | [54,61]       |
| lxxvi  | *Laurus nobilis*                        | [45]          |
| lxxvii | *Lavandula stoechas*                    | [45]          |
| lxxviii| *Ledebouriella multiflora*              | [46,56]       |
| lxix   | *Lepidium sativum*                      | [56]          |
| lxx    | *Ligusticum striatum*                   | [51]          |
| lxxi   | *Lindera aggregata*                     | [52]          |
| lxxii  | *Loniceria japonica*                    | [41,46,51,54,56,61] |
| lxxiii | *Lycoris radiata*                       | [41,52]       |
| lxxiv  | *Magnolia officinalis*                  | [63]          |
| lxxv   | *Mela sp.*                              | [41]          |
| lxxvi  | *Mentha haplocalyx*                     | [41]          |
| lxxvii | *Mentha piperita*                       | [41]          |
| lxxviii| *Morus nigra*                           | [41]          |
| lxxix  | *Myrtus communis*                       | [45]          |
| xe     | *Narcissus pseudonarcissus*             | [41]          |
| xci    | *Nepeta cataria*                        | [46,48]       |
| xcii   | * Nerium oleander*                      | [46]          |
| xciii  | *Nicotiana tabacum*                     | [41]          |
| xciv   | *Nigella sativa*                        | [41,52]       |
| xcv    | *Notopterygium forbesii*                | [51]          |
| xcvii  | *Ophiopogon sp.*                        | [63]          |
| xcviii | *Paeonia alba*                          | [41,57]       |
| xcix   | *Panax ginseng*                         | [56]          |
| e      | *Panax notoginseng*                     | [43]          |
| ei     | *Panax quinquefolius*                   | [63]          |
| eii    | *Paris polyphylla*                      | [42]          |
| eiii   | *Paulownia tomentosa*                   | [41]          |
| eiv    | *Pelargonium sidoides*                  | [41,52]       |
| eiv    | *Paeucedanum sp.*                       | [46]          |
| Number | Latin name of the source of the crude drug | Reference(s) |
|--------|------------------------------------------|--------------|
| cv     | *Phellodendron* sp.                      | [41]         |
| cvi    | *Phragmites* sp.                        | [43]         |
| cvii   | *Pinellia* sp.                          | [42]         |
| cviii  | *Platycodon grandiflorus*               | [48,50]      |
| cix    | *Pogostemon cablin*                     | [48,54,61,63]|
| ex     | *Polygonatum multiflorum*               | [41]         |
| xi     | *Prunus armeniaca*                      | [47,50,56,63]|
| xii    | *Prunus serrulata*                      | [41]         |
| xiii   | *Pogostemon cablin*                     | [41,51]      |
| xiv    | *Punica granatum*                       | [41,45]      |
| xv     | *Pyrrosia lingua*                       | [52]         |
| xvi    | *Rehmannia glutinosa*                   | [48]         |
| xvii   | *Rheum australe*                        | [45]         |
| xviii  | *Rheum officinale*                      | [41,54,55,61]|
| xix    | *Rheum palmatum*                        | [41]         |
| xx     | *Rhodiola crenulata*                    | [54,61]      |
| xxi    | *Rosa nutkana*                          | [41]         |
| xxi    | *Salvia miltiorrhiza*                   | [41]         |
| xxi    | *Sambucus formosana*                    | [41]         |
| xxiv   | *Sambucus nigra*                        | [41]         |
| xxv    | *Sauge officinale*                      | [45]         |
| xxvi   | *Schizonepeta tenuifolia*               | [56]         |
| xxvii  | *Scrophularia scorodonia*               | [41,43,48,52,56]|
| xxviii | *Scutellaria baicalensis*               | [41,44,48,53]|
| xxix   | *Sophora flavescens*                    | [41,51]      |
| xxx    | *Sophora subprostrata*                  | [41]         |
| xxxi   | *Stephania tetrandra*                   | [41]         |
| xxxii  | *Stroblanthes cusii*                    | [41]         |
| xxxiii | *Tamariscis cacumen*                    | [46]         |
| xxxiv  | *Tamarindus indica*                     | [45]         |
| xxxv   | *Taraxacum mongolicum*                  | [53]         |
| xxxvi  | *Thuja orientalis*                      | [41]         |
| xxxvii | *Thymus vulgaris*                       | [41]         |
| xxxviii| *Toona sinensis*                        | [41,64]      |
| xxxix  | *Torilis* sp.                           | [41]         |
| xl     | *Torreyja nucifera*                     | [41,52]      |
| xli    | *Trichosanthes* sp.                     | [47]         |
| xlii   | *Tripterygium regelii*                  | [41]         |
| xliiv  | *Tripterygium wilfordii*                | [65,66]      |
| xlv    | *Tulipa* sp.                            | [41]         |
| xlvii  | *Urtica dioica*                         | [41]         |
| xlviii | *Veratrum sabadilla*                    | [41]         |
| xlix   | *Zingiber officinale*                   | [41,44,52]   |
| cxx    | *Ziziphus jujuba*                       | [41]         |
Table 2. Components of Core-Own A.

(Roman Numeral Rankings in the second column are for building the progressive formulae for testing as described in the text.)

| Source | Crude part | % | Action | Reference(s) |
|--------|------------|---|--------|--------------|
| Acorus calamus | Dried rhizome | 1 | inhibition of early stage Dengue viral RNA replication in vitro | [67] |
| Angelica sinensis | Dried root | 3 | Inhibited murine leukemia virus replication in vivo and enhanced CD4(+)CD8(+) ratio | [68] |
| Astragalus membranaceus | Dried root | 15 | Inhibited influenza virus growth in vitro | [69] |
| Atractylodes macrocephala | Dried rhizome, atractylon | 3 | Alleviated influenza virus induced pulmonary injury; suppression of H3N2 growth | [70,71,77] |
| Angelica sinensis | Dried root | 3 | Inhibited murine leukemia virus replication in vivo and enhanced CD4(+)CD8(+) ratio | [72] |
| Astragalus membranaceus | Dried root | 15 | Inhibited influenza virus growth in vitro | [73,74] |
| Cinnamomum cassia | Dried stem | 1 | non-toxic inhibition of H7N3 bird flu virus in vitro | [75,77] |
| Citrus reticulata | Dried pericarp | 6 | impaired respiratory syncytial virus replication and entry into human epithelial cells | [78,79] |
| Commiphora myrrha | Dried stem gum | 1 | virucidal for enveloped respiratory syncytial virus B | [79,80] |
| Cordyceps militaris | Dried fruiting body | 1 | Benefits mouse H1N1 2009 influenza survival, clinical COVID-19 convalescence | [81–85] |
| Curcuma longa | Dried rhizome | 0.2 | Higher affinity to SARS-CoV-2 “catalytic core” than standard antiretroviral Lopinavir | [86] |
| Eriobotrya japonica | Dried leaf | 2 | increasing cytokines and activating interferon gamma host antiviral defense | [89,90] |
| Forsythia suspensa | Dried fruits | 4 | improved outcome and less inflammation in influenza A infected mice | [87,88] |
| Ginkgo biloba | Dried leaf | 2 | inhibiting H3N2 influenza A 1968 pandemic virus, via inhibition of reverse transcriptase | [95–98] |
| Glycyrrhiza glabra | Dried roots | 4 | inhibition of SARS-associated coronavirus isolates main viral protease inhibition; blocks viral cell attachment | [99–100,110,116] |
| Humulus lupulus | Dried flowers | 1 | suppression of 5 H1N1 and H7N1 influenza A strains via redox disruptions | [111,112] |
| Hypericum perforatum | Dried rhiome | 1 | inhibition of SARS-CoV-3C-like protease and RNA polymerase in vitro | [113–115] |
| Isatis tinctoria | Dried aerial parts | 3 | Blocks angiotensin-converting enzyme type 2 receptor, key entry of SARS-CoV-2, dose dependently inhibited its replication | [96–117,119] |
| Lentinula edodes | Dried fruiting body | 0.5 | reduced phagocytic index in vitro, possible preventive of Covid-19 cytokine storm | [120–124] |
| Mentha piperita | Dried leaf | 2 | Reduced inflammatory response to RSV in vitro, anti HIV, good taste, promotes patient compliance | [130–132] |
| Musa acuminata | Dried peels | 3 | Anti HIV lectins, sweet taste | [133,134] |
| Olea europaea | Dried leaf | 2 | Anti HSV, anti EBV, anti HSV, anti influenza in vitro | [135–139] |
| Oldenlandia diffusa | Dried leaf | 1 | Contains cyclotides with anti HIV | [140] |
| Panax ginseng | Dried root | 1 | Prevents viral respiratory infections, possibly also COVID cytokine storm, anti HSV, reduces viral virulence | [59,141–147] |
| Peganum harmala | Seeds | 0.1 | Anti influenza virus, anti HSV2, possible role in COVID | [148–154] |
| Source       | Crude part | % | Action                                                                 | Reference(s)       |
|-------------|------------|---|------------------------------------------------------------------------|--------------------|
| **Pueraria lobata** | Dried root | 4 | Inhibits influenza virus neuraminidase, *in silico* targeting of COVID-19 targets, suppression of HIV attachment | [155–157]          |
| **Punica granatum** | Dried pericarps | 1 | Inhibits SARS-CoV-2 spike binding to human ACE2 receptor (*in vitro*), virucidal to many viruses | [158–169]          |
| **Punica granatum** | Dried flowers | 1 | Rich source of oleanolic and ursolic acids, inhibitors of COVID-19 main protease, SARS-CoV-2 entry and associated inflammation | [168–175]          |
| **Sambucus nigra** | Dried fruits | 4 | Widely used, safe antiviral, studies in COVID warranted, pleasant taste | [160,174–177]      |
| **Sambucus nigra** | Dried flowers | 1 | Inhibits SARS-CoV-2 S1 protein receptor binding domain, safe, wide use as antiviral, reduces inflammation | [178,196]          |
| **Schisandra sinensis** | Dried fruits | 2 | Contains lignans with anti-HIV activity | [179,180]          |
| **Scutellaria baicalensis** | Dried roots | 4 | Acts on multiple signaling pathways to reduce COVID-19 related organ damage, inhibition of SARS-CoV-2 3C-like protease | [61,181–186]       |
| **Taraxacum officinale** | Dried roots | 2 | Inhibition of replication of dengue, HCV, HBV, HIV, influenza viruses; benefits oxidative stress in liver and kidney, possible interference with SARS-CoV-2 attachment | [61,187–192]       |
| **Tripterygium wilfordii** | Dried root | 0.1 | Potential for anti-SARS-CoV-2 Rx | [65,66]            |
| **Tripterygium wilfordii** | Dried stem | 0.1 | Similar to root | [193,194]          |
| **Urtica dioica** | Dried leaves | 1 | Novel inhibitors of angiotensin-converting enzyme 2 (ACE-2) receptor; adjunct rx for COVID-19 | [195,197]          |
| **Zingiber officinalis** | Fresh rhizome | 8 | Extremely safe, most loved spice/herb worldwide, anti-viral, anti-influenza, stomachic, COVID-19 drug lead studies ongoing | [49,118,197–202]   |
2.1 Evaluation of the Hypothesis

I propose a rapid screen of in vitro antiviral activity in standard SARS-CoV-2 infected green monkey kidney vero cells. In addition to controls which will be infected but not treated, these infected cells will be subjected to 83 different herbal interventions aimed at preventing or inhibiting the progression of the infection. The first 41 interventions will be simply the same dry weight dose of each of the 96% food grade ethanolic extracts of each of the 41 different “herbs” listed in Table 2. The first of the next 41 interventions will be extracted from the single herb, Glycyrrhiza glabra (licorice). The second intervention will be licorice plus a second herb, according to the priority shown by Roman Numeral in Column 1 of Table 2, such that their total dry weight is equivalent to the dry weight of licorice only in the first intervention. Similarly, the third intervention will be licorice plus the next two more herbs according to the herb’s priority by Roman Numeral as indicated in the first column of Table 2. Successive interventions will include the herbs from the previous intervention plus one more, until in the 41st intervention, all 41 herbs will be present. The quantities of each herb in each intervention will be mathematically “weighted” to reflect their percentages in the complete 41 herb formula. Finally, a second 41 herb formula intervention, namely the aged, not the freshly made formula. So, the first intervention will include one herb, the second intervention, two herbs, the third, three herbs, until the 41st intervention, all 41 herbs has been achieved. Starting with licorice, Glycyrrhiza, in the first experiment, additional single “herbs” will be added at each trial, one at a time, according to the Roman Numerals in Column 1 of Table 2. A 42nd intervention will employ the aged, not the fresh, 41 “herb” combination.

2.2 Implications of the Hypothesis

The hypothesis challenges the classical wisdom that “you can’t have your synergy and efficacy too” [40], as one author put it, because as you continue to add new herbs to the mix, you dilute the amounts of each herb, pushing the individual herbs into sub-effective doses. In other words, more is less, that is, more herbs means less of each. In the alternative and complementary view, more is more, because even though the amount of each herb will be less, the sum of all the herbs results in a greater, i.e., a synergistic effect.

The question of the impact of aging on the formula’s antiviral potency also goes against conventional wisdom which believes that the fresher the drug, i.e., that the closer it is to its date of production, the better, and the more potent it will be. The hypothesis that aging could improve the product may seem counterintuitive.

However, in either case, that of increasing the N, the number of herbs in a formula, or its aging, what number of herbs, or how long an aging, is optimum? When does synergy start, when does it peak, and when does it decline, and finally when does it become extinguished? These are all questions which the results of the proposed trial will possibly begin to answer, while illuminating pathways for further investigations. Practical applications for a safe and effective combination of herbal tinctures would include both internal and external uses, the latter for sterilizing sprays and for impregnating face masks.

Author Contributions

ESL is solely responsible for all the work leading to and resulting in this paper, including researching and writing the paper, editing the paper, wildcrafting or purchasing the herbs, extracting the herbs and medicinal mushrooms, combining the extracts.

Ethics Approval and Consent to Participate

Not applicable.

Acknowledgment

The author acknowledges the help of Shelly Shen-Aridor of the University of Haifa Library for her expert, tireless, and generous assistance in locating and obtaining obscure references. Zipora Lansky drew, in pen and ink, the original artwork in Fig. 1.

Funding

This research received no external funding.

Conflict of Interest

The author will provide the composition gratis to fellow researchers via academic collaborations for furthering experimental in vitro or in vivo investigations. The author declares no legal, financial, or institutional conflicts of interest.

References

[1] Wan S, Xiang Y, Fang W, Zhang Y, Li B, Hu Y, et al. Clinical features and treatment of COVID-19 patients in northeast Chongqing. Journal of Medical Virology. 2020; 92: 797–806.
[2] Ambrós S, de la Iglesia F, Rosario SM, Butkovič A, Elena SF. Engineered Functional Redundancy relaxes Selective Constraints upon Endogenous Genes in Viral RNA Genomes. Genome Biology and Evolution. 2018; 10: 1823–1836.
[3] Maginnis MS. Virus–Receptor Interactions: The Key to Cellular Invasion. Journal of Molecular Biology. 2018; 430: 2590–2611.
[4] Caesar LK, Cech NB. Synergy and antagonism in natural product extracts: when 1 + 1 does not equal 2. Natural Product Reports. 2019; 36: 869–888.
[5] Ayaz M, Ullah F, Sadiq A, Ullah F, Ovais M, Ahmed J, et al. Synergistic interactions of phytochemicals with antimicrobial agents: Potential strategy to counteract drug resistance. Chemico-Biological Interactions. 2019; 308: 294–303.
[6] Benzekri R, Bouslama L, Papetti A, Hammami M, Smaoui A, Limam F. Anti HSV-2 activity of Peganum harmala (L.) and
isolation of the active compound. Microbial Pathogenesis. 2018; 114: 291–298.
[7] Sakagami H, Fukuchi K, Kanamoto T, Terakubo S, Nakashima H, Natori T, et al. Synergism of alkaline extract of the leaves of Sasa senanensis Rehder and antiviral agents. In Vivo. 2016; 30: 421–426.
[8] Britton ER, Kellogg JJ, Kvalheim OM, Cech NB. Biochemometrics to identify synergists and additives from botanical medicines: A case study with Hydrastis canadensis (Goldenseal). Journal of Natural Products. 2018; 81: 484–493.
[9] Junio HA, Sy-Cordero AA, Ettefagh KA, Burns JT, Micko KT, Graf TN, et al. Synergy-directed fractionation of botanical medicines: a case study with goldenseal (Hydrastis canadensis). Journal of Natural Products. 2011; 74: 1621–1629.
[10] Stermitz FR, Lorenz P, Tawara JN, Zenewicz LA, Lewis K. Synergy in a medicinal plant: Antimicrobial action of berberine potentiated by 5′-methoxyhydnocarpin, a multidrug pump inhibitor. Proceedings of the National Academy of Sciences. 2000; 97: 1433–1437.
[11] Jacobs DR, Gross MD, Tapsell LC. Food synergy: an operational concept for understanding nutrition. The American Journal of Clinical Nutrition. 2009; 89: 1543S–1548S.
[12] Nair KM, Augustine LF. Food synergies for improving bioavailability of micronutrients from plant foods. Food Chemistry. 2018; 238: 180–185.
[13] Wang S, Zhu F. Dietary antioxidant synergy in chemical and biological systems. Critical Reviews in Food Science and Nutrition. 2017; 57: 2343–2357.
[14] Lansky EP, Jiang W, Mo H, Bravo L, Froom P, Yu W, et al. Possible synergistic prostate cancer suppression by anatomically discrete pomegranate fractions. Investigational New Drugs. 2005; 23: 681–690.
[15] Lansky EP, Harrison G, Froom P, Jiang WG. Pomegranate (Punica granatum) pure chemicals show possible synergistic inhibition of human PC-3 prostate cancer cell invasion across Matrigel. Investigational New Drugs. 2005; 23: 121–122.
[16] Doern CD. When does 2 Plus 2 Equal 5? A Review of Anesthetic Interactions Producing Hypnosis and Immobility. Anesthesia & Analgesia. 2008; 107: 494–506.
[17] Malongane F, McGaw LJ, Mudau FN. The synergistic potential of various teas, herbs and therapeutic drugs in health improvement: a review. Journal of the Science of Food and Agriculture. 2017; 97: 4679–4689.
[18] Musol R, Mrozek-Wilczkiewicz A, Polanski J. Synergy against Fungal Pathogens: Working together is Better than Working alone. Current Medicinal Chemistry. 2014; 21: 870–893.
[19] Phan MAT, Paterson J, Bucknall M, Aroot J. Interactions between phytochemicals from fruits and vegetables: Effects on bioactivities and bioavailability. Critical Reviews in Food Science and Nutrition. 2018; 58: 1310–1329.
[20] Reyes MM, Gravina SA, Hayes JE. Evaluation of Sweetener Synergy in Humans by Isobole Analyses. Chemical Senses. 2005; 29: 601–602.
[21] Williamson E. Synergy and other interactions in phytotherapies. Phytomedicine. 2001; 8: 401–409.
[22] Xue H, He L, Chen J, Hou X, Fan F, Wu H, et al. Different types of effective fractions from Radix Isatidis reveal a multiple-target synergy effect against respiratory syncytial virus through RIG-I and MDAS signaling pathways, a pilot study to testify the theory of superposition of traditional Chinese Medicine efficacy. Journal of Ethnopharmacology. 2019; 239: 111901.
[23] Melville K, Rodriguez T, Dobrovolsky HM. Investigating different mechanisms of action in combination therapy for influenza.
[24] Frontiers in Pharmacology. 2018; 9: 1207.
[25] Choy K, Wong AY, Kaewpreedee P, Sia SF, Chen D, Hui KPY, et al. Remdesivir, lopinavir, emetine, and homoharringtonine inhibit SARS-CoV-2 replication in vitro. Antiviral Research. 2020; 178: 104786.
[26] Fantini J, Chahinian H, Yahia N. Synergistic antiviral effect of hydroxychloroquine and azithromycin in combination against SARS-CoV-2: what molecular dynamics studies of virus-host interactions reveal. International Journal of Antimicrobial Agents. 2020; 56: 106020.
[27] Ahmad SI. 5-Fluorouracil in combination with deoxyribonucleosides and deoxyribose as possible therapeutic options for the Coronavirus, COVID-19 infection. Medical Hypotheses. 2020; 142: 109754.
[28] Prichard MN, Prichard LE, Shipman C. Strategic design and three-dimensional analysis of antiviral drug combinations. Antimicrobial Agents and Chemotherapy. 1993; 37: 540–545.
[29] Smeek DM, Prichard MN. Comparison of three dimensional synergistic analyses of percentage versus logarithmic data in antiviral studies. Antiviral Research. 2017; 145: 1–5.
[30] Ling C. Traditional Chinese medicine is a resource for drug discovery against 2019 novel coronavirus (SARS-CoV-2). Journal of Integrative Medicine. 2020; 18: 87–88.
[31] Zhang H, Huang M, Liu X, Zheng X, Li X, Chen G, et al. Evaluation of the Adjuvant Efficacy of Natural Herbal Medicine on COVID-19: a Retrospective Matched Case-Control Study. The American Journal of Chinese Medicine. 2020; 48: 779–792.
[32] Lansky EP, Von Hoff DD. Complex and simple. Leukemia Research. 2005; 29: 601–602.
[33] Wagner H, Ulrich-Merzenich G. Synergy research: Approaching a new generation of phytopharmaceuticals. Phytomedicine. 2009; 16: 97–110.
[34] Roullet-Gall C, Heinzmann SS, Garcia J, Schmitt-Kopplin P, Gougeon RD. Chemical messages from an ancient buried bottle: metabolomics for wine archeochemistry. Npj Science of Food. 2017; 1: 1.
[35] Burns J, Gardner PT, Matthews D, Duthie GG, Lean J, Crozier A. Extraction of Phenolics and Changes in Antioxidant Activity of Red Wines during Vinification. Journal of Agricultural and Food Chemistry. 2001; 49: 5797–5808.
[36] Cheynier V. Polyphenols in foods are more complex than often thought. The American Journal of Clinical Nutrition. 2005; 81: 2238–2298.
[37] Quideau S, Jourdes M, Lefevre D, Montaudon D, Saucier C, Glories Y, et al. The Chemistry of Wine Polyphenolic-C-Glycosidic Ellagitannins Targeting Human Topoisomerase II. Chemistry. 2005; 11: 6503–6513.
[38] Schröder HC, Kelve M, Schäcke H, Pleifereder W, Charubala R, Suhadolnik RJ, et al. Inhibition of DNA topoisomerase i activity by 2′,5′-oligoadenylates and mismatched double-stranded RNA in uninfected and HIV-1-infected H9 cells. Chemico-Biological Interactions. 1994; 90: 169–183.
[39] Zimmermann Gr, Lehár J, Keith Ct. Multi-target therapeutics: when the whole is greater than the sum of the parts. Drug Discovery Today. 2007; 12: 34–42.
[40] Sen P, Saha A, Dixit NM. You cannot have your Synergy and Efficacy too. Trends in Pharmacological Sciences. 2019; 40: 811–817.
[41] Mani JS, Johnson JB, Steel JC, Broszczak DA, Neilsen PM, Walsh KB, et al. Natural product-derived phytochemicals as potential agents against coronaviruses: a review. Virus Research. 2020; 284: 197989.
[42] Gu M, Liu J, Shi NN, Li XD, Huang ZD, Wu JY, et al. Analysis of property and efficacy of Traditional Chinese Medicine in staging, prevention, and treatment of coronavirus disease 2019. Zhongguo Zhongyao Zazhi. 2020; 45: 1253–1258. (In Chinese)
[43] Yang Y, Islam MS, Wang J, Li Y, Chen X. Traditional Chinese Medicine in the Treatment of Patients Infected with 2019-New Coronavirus (SARS-CoV-2): a Review and Perspective. International Journal of Biological Sciences. 2020; 16: 1708–1717.

[44] Gautam S, Gautam A, Chhetri S, Blhattarai U. Immunity against COVID-19: Potential role of Ayush Kwath. Journal of Ayurveda and integrative medicine. 2020; 100050.

[45] Chang KW, Lin TY, Fu SL, Ping YH, Chen FP, Kung YY. A Houttuynia Cordata-based Chinese herbal formula improved symptoms of allergic rhinitis during the COVID-19 pandemic. Journal of the Chinese Medical Association. 10: 1097.

[46] Ahmad A, Rehman MU, Alkharfy KM. An alternative approach to minimize the risk of coronavirus (COVID-19) and similar infections. European Review for Medical and Pharmacological Sciences. 2020; 24: 4030–4034.

[47] Yang T, Jia M, Zhou S, Pan F, Mei Q. Antivirus and immune enhancement activities of sulfated polysaccharide from Angelica sinensis. International Journal of Biological Macromolecules. 2012; 50: 768–72.

[48] Ma J, Huo XQ, Chen X, Zhu WX, Yao MC, Qiao YJ, et al. Study on screening potential Traditional Chinese Medicines against 2019-nCoV Based on Mpro and PLP. Zhongguo Zhongyao Za-zhi. 2020; 45: 1219–1224. (In Chinese)

[49] Zrig A. The Effect of Phytochemicals of Medicinal Plants on Coronavirus (2019-NCOV) Infection. Pharmaceutical chemistry journal. 2022; 31: 1–5.

[50] Xu J, Zhang Y. Traditional Chinese Medicine treatment of COVID-19. Complementary Therapies in Clinical Practice. 2020; 39: 101165.

[51] Zhang D, Wu K, Zhang X, Deng S, Peng B. In silico screening of Chinese herbal medicines with the potential to directly inhibit 2019 novel coronavirus. Journal of Integrative Medicine. 2020; 18: 152–158.

[52] Chen F, Chan KH, Jiang Y, Kao RYT, Lu HT, Fan KW, et al. In vitro susceptibility of 10 clinical isolates of SARS coronavirus to selected antiviral compounds. Journal of Clinical Virology. 2004; 31: 69–75.

[53] Aanouz I, Belhassan A, El-Khatibi K, Lakhlifi T, El-Idrissi M, Bouachrine M. Moroccan Medicinal plants as inhibitors against SARS-CoV-2 main protease: Computational investigations. Journal of Biomolecular Structure and Dynamics. 2021; 39: 2971–2979.

[54] Nikhat S, Fazil M. Overview of Covid-19: its prevention and management in the light of Unani medicine. Science of the Total Environment. 2020; 728: 138859.

[55] Ho TY, Wu SL, Chen JC, Li CC, Hsiang CY. Emodin blocks the SARS coronavirus spike protein and angiotensin-converting enzyme 2 interaction. Antiviral Research. 2007; 74: 92–101.

[56] Ye M, Luo G, Ye D, She M, Sun N, Lu YJ, et al. Network pharmacology, molecular docking integrated surface plasmon resonance technology reveals the mechanism of Toujie Quwen Granules against coronavirus disease 2019 pneumonia. Phytomedicine. 2021; 85: 153401.

[57] Han Y, Yang Z, Fang S, Zhang M, Xie Z, Fan Y, et al. Data-mining-based of ancient traditional Chinese medicine records from 475 BC to 1949 to potentially treat COVID-19. The Anatomical Record. 2022.

[58] Fan T, Chen Y, Bai Y, Ma F, Wang H, Yang Y, et al. Analysis of medication characteristics of Traditional Chinese Medicine in treating COVID-19 based on data mining. Zhejiang Da Xue Xue Bao Yi Xue Ban. 2020; 49: 260–269. (In Chinese)

[59] Zhang Z, Wu W, Hou J, Zhang L, Li F, Gao L, et al. Active constituents and mechanisms of Respiratory Detox Shot, a traditional Chinese medicine prescription, for COVID-19 control and prevention: Network-molecular docking-LC–MSE analysis. Journal of Integrative Medicine. 2020; 18: 229–241.

[60] Zhou Z, Zhu CS, Zhang B. Study on medication Regularity of Traditional Chinese Medicine in treatment of COVID-19 based on data mining. Zhongguo Zhong Yao Za Zhi. 2020; 45: 1248–1252. (In Chinese)

[61] Deng W, Xu Y, Kong Q, Xue J, Yu P, Liu J, et al. Therapeutic efficacy of Padilan XiaoYan Oral Liquid (PDL) for COVID-19 in vitro and in vivo. Signal Transduction and Targeted Therapy. 2020; 5: 66.

[62] Jia W, Wang C, Wang Y, Pan G, Jiang M, Li Z, et al. Qualitative and Quantitative Analysis of the Major Constituents in Chinese Medicine Preparation Lianhua-Qingwen Capsule by UPLC-DAD-QTOF-MS. The Scientific World Journal. 2015; 2015: 731765.

[63] Runfeng L, Yunlong H, Jicheng H, Weiqi P, Qinhai M, Yongxia S, et al. Lianhuaqingwen exerts anti-viral and anti-inflammatory activity against novel coronavirus (SARS-CoV-2). Pharmacological Research. 2020; 156: 104761.

[64] Chen C, Michaelis M, Hsu H, Tsai C, Yang KD, Wu Y, et al. Toona sinensis Roem tender leaf extract inhibits SARS coronavirus replication. Journal of Ethnopharmacology. 2008; 120: 108–111.

[65] Caruso F, Singh M, Belli S, Bernino M, Rossi M. Interrealted mechanism by which the methide quinone celastrol, obtained from the roots of Tripterygium wilfordii, Inhibits main protease 3CLpro of COVID-19 and acts as superoxide radical scavenger. International Journal of Molecular Sciences. 2020; 21: 9266.

[66] Merarchi M, Dudha N, Das BC, Garg M. Natural products and phytochemicals as potential anti-SARS-CoV-2 drugs. Phytotherapy Research. 2021; 35: 5384–5396.

[67] Yao X, Ling Y, Guo S, Wu W, He S, Zhang Q, et al. Tatanan a from the Acorus calamus L. root inhibited dengue virus proliferation and infections. Phytomedicine. 2018; 42: 258–267.

[68] Yang T, Jia M, Zhou S, Pan F, Mei Q. Antivirus and immune enhancement activities of sulfated polysaccharide from Angelica sinensis. International Journal of Biological Macromolecules. 2012; 50: 768–772.

[69] Khan HM, Raza SM, Anjum AA, Ali MA. Antiviral, embryo toxic and cytotoxic activities of Atragrurus membranaceus root extracts. Pakistan Journal of Pharmaceutical Sciences. 2019; 32: 137–142.

[70] Cheng Y, Mai J, Hou T, Ping J, Chen J. Antiviral activities of attractylin from Atractylodis Rhizoma. Molecular Medicine Reports. 2016; 14: 3704–3710.

[71] Gu S, Li L, Huang H, Wang B, Zhang T. Antitumor, antiviral, and anti-Inflammatory efficacy of essential oils from Atractylodes macrocephala Koidz. produced with different processing methods. Molecules. 2019; 24: 2956.

[72] Lee W, Lan K, Liao S, Huang Y, Hou M, Lan K. Antiviral effect of saikosaponin B2 in combination with daclatasvir on NS5a resistance-associated substitutions of hepatitis C virus. Journal of the Chinese Medical Association. 2019; 82: 368–374.

[73] Roscoe CW, Hall NA. A preliminary study of the alkaloidal principles of Ceanothus americanus and Ceanothus velutinus. Journal of the American Pharmacists Association. 1960; 49: 108–112.

[74] Buhner SH. Herbal Antivirals: Natural Remedies for Emerging & Resistant Viral Infections (pp. 480). 2nd edn. Storey Publishing: North Adams, Massachusetts, USA. 2021.

[75] Fatima M, Zaidi NS, Amraiz D, Afzal F. In Vitro Antiviral Activity of Cinnaumomum cassia and its Nanoparticles against H7N3 Influenza a Virus. Journal of Microbiology and Biotechnology. 2016; 26: 151–159.

[76] Zareie A, Soleimani D, Askari G, Jamialahmadi T, Guest PC, Bagherniya M, et al. Cinnamon: a Promising Natural Product against COVID-19. Advances in Experimental Medicine and Biology. 2021; 1327: 191–195.
Antiviral effect of Cordycepin: a bioactive metabolite of Cordyceps militaris and polyadenylation inhibitor with therapeutic potential against COVID-19. Journal of Biomolecular Structure and Dynamics. 2020; 45: 753–768.

Molecular Medicine. 2020; 42: 2776–2792.

Eleutheroside B1 mediates its anti-influenza activity through regulating innate signaling pathways. ACS Omega. 2021; 6: 1505–1515.

Li RF, Zhou XB, Zhou HY, Yang ZF, Jiang HM, Wu X, et al. Novel fatty acid in Cordyceps suppresses influenza A (H1N1) virus-induced proinflammatory response through regulating innate signaling pathways. ACS Omega. 2021; 6: 1505–1515.

Li RF, Zhou XB, Zhou HY, Yang ZF, Jiang HM, Wu X, et al. Novel fatty acid in Cordyceps suppresses influenza A (H1N1) virus-induced proinflammatory response through regulating innate signaling pathways. ACS Omega. 2021; 6: 1505–1515.

Li RF, Zhou XB, Zhou HY, Yang ZF, Jiang HM, Wu X, et al. Novel fatty acid in Cordyceps suppresses influenza A (H1N1) virus-induced proinflammatory response through regulating innate signaling pathways. ACS Omega. 2021; 6: 1505–1515.

Forsythoside A from Forsythia suspensa (Thunb.) Vahl fruit induces interferon-gamma production mainly by the JAK-STAT pathway. Molecules. 2016; 21: 722.

Law AH, Yang CL, Lau AS, Chan GC. Antiviral effect of forsythoside A from Forsythia suspensa (Thunb.) Vahl fruit induces interferon-gamma production mainly by the JAK-STAT pathway. Molecules. 2016; 21: 722.

Law AH, Yang CL, Lau AS, Chan GC. Antiviral effect of forsythoside A from Forsythia suspensa (Thunb.) Vahl fruit induces interferon-gamma production mainly by the JAK-STAT pathway. Molecules. 2016; 21: 722.

Law AH, Yang CL, Lau AS, Chan GC. Antiviral effect of forsythoside A from Forsythia suspensa (Thunb.) Vahl fruit induces interferon-gamma production mainly by the JAK-STAT pathway. Molecules. 2016; 21: 722.

Law AH, Yang CL, Lau AS, Chan GC. Antiviral effect of forsythoside A from Forsythia suspensa (Thunb.) Vahl fruit induces interferon-gamma production mainly by the JAK-STAT pathway. Molecules. 2016; 21: 722.

Law AH, Yang CL, Lau AS, Chan GC. Antiviral effect of forsythoside A from Forsythia suspensa (Thunb.) Vahl fruit induces interferon-gamma production mainly by the JAK-STAT pathway. Molecules. 2016; 21: 722.

Law AH, Yang CL, Lau AS, Chan GC. Antiviral effect of forsythoside A from Forsythia suspensa (Thunb.) Vahl fruit induces interferon-gamma production mainly by the JAK-STAT pathway. Molecules. 2016; 21: 722.

Law AH, Yang CL, Lau AS, Chan GC. Antiviral effect of forsythoside A from Forsythia suspensa (Thunb.) Vahl fruit induces interferon-gamma production mainly by the JAK-STAT pathway. Molecules. 2016; 21: 722.

Law AH, Yang CL, Lau AS, Chan GC. Antiviral effect of forsythoside A from Forsythia suspensa (Thunb.) Vahl fruit induces interferon-gamma production mainly by the JAK-STAT pathway. Molecules. 2016; 21: 722.

Law AH, Yang CL, Lau AS, Chan GC. Antiviral effect of forsythoside A from Forsythia suspensa (Thunb.) Vahl fruit induces interferon-gamma production mainly by the JAK-STAT pathway. Molecules. 2016; 21: 722.

Law AH, Yang CL, Lau AS, Chan GC. Antiviral effect of forsythoside A from Forsythia suspensa (Thunb.) Vahl fruit induces interferon-gamma production mainly by the JAK-STAT pathway. Molecules. 2016; 21: 722.

Law AH, Yang CL, Lau AS, Chan GC. Antiviral effect of forsythoside A from Forsythia suspensa (Thunb.) Vahl fruit induces interferon-gamma production mainly by the JAK-STAT pathway. Molecules. 2016; 21: 722.

Law AH, Yang CL, Lau AS, Chan GC. Antiviral effect of forsythoside A from Forsythia suspensa (Thunb.) Vahl fruit induces interferon-gamma production mainly by the JAK-STAT pathway. Molecules. 2016; 21: 722.

Law AH, Yang CL, Lau AS, Chan GC. Antiviral effect of forsythoside A from Forsythia suspensa (Thunb.) Vahl fruit induces interferon-gamma production mainly by the JAK-STAT pathway. Molecules. 2016; 21: 722.

Law AH, Yang CL, Lau AS, Chan GC. Antiviral effect of forsythoside A from Forsythia suspensa (Thunb.) Vahl fruit induces interferon-gamma production mainly by the JAK-STAT pathway. Molecules. 2016; 21: 722.

Law AH, Yang CL, Lau AS, Chan GC. Antiviral effect of forsythoside A from Forsythia suspensa (Thunb.) Vahl fruit induces interferon-gamma production mainly by the JAK-STAT pathway. Molecules. 2016; 21: 722.
Di Sotto A, Checconi P,Celesti O,Locatelli M,Cardissimi S,De Angelis M,et al. Antiviral and antioxidant activity of a hydroalcoholic extract from Humulus lupulus L. Oxidative Medicine and Cellular Longevity. 2018; 2018:5919237.

Buckwold V, Wilson R, Nalca A, Beer B, Voss T, Turpin J, et al. Antiviral activity of hop constituents against a series of DNA and RNA viruses. Antiviral Research. 2004; 61: 57–62.

Bahadur Gurung A, Ajmal Ali M, Lee J, Abul Farah M, Mashay Al-Anazi K, Al-Hemaid F. Identification of SARS-CoV-2 inhibitors from extracts of Houttuynia cordata Thumb. Saudi Journal of Biological Sciences. 2021; 28: 7517–7527.

Lau K, Lee K, Koon C, Cheung CS, Lau C, Ho H, et al. Immunomodulatory and anti-SARS activities of Houttuynia cordata data. Journal of Ethnopharmacology. 2008; 118: 79–85.

Das SK, Mahanta S, Tanti B, Tag H, Hui PK. Identification of phytochemicals from Houttuynia cordata Thumb. as potential inhibitors for SARS-CoV-2 replication proteins through GC–MS/MS LC–MS characterization, molecular docking and molecular dynamics simulation. Molecular Diversity. 2022; 26: 365–388.

Yalçın S, Yalçınkaya S, Ercan F. Determination of Potential Drug Candidate Molecules of the Hypericum perforatum for COVID-19 Treatment. Current Pharmacology Reports. 2021; 1–7.

Masiello P, Novelli M, Belfy P, Menegazzi M. Can Hypericum perforatum (SJW) prevent cytokine storm in COVID-19 patients? Phytotherapy Research. 2020; 34: 1417–1473.

Boozari M, Hosseinzadkh H. Natural products for COVID-19 prevention and treatment regarding to previous coronavirus infections and novel studies. Phytotherapy Research. 2021; 35: 864–876.

Matos ADR, Caetano BC, de Almeida Filho JO, Martins JSCC, de Oliveira MGP, Sousa TDC, et al. Identification of hypericin as a candidate repurposed therapeutic agent for COVID-19 and its potential anti-SARS-CoV-2 activity. Frontiers in Microbiology. 2022; 13: 828984.

Mandal A, Jha AK, Hazra B. Plant products as inhibitors of coronavirus 3CLprotease. Frontiers in Pharmacology. 2021; 12: 583387.

Cai C, Xu L, Fan J, Dai Z, Wu Q, Liu X, et al. In silico prediction and bioactivity evaluation of chemical ingredients against influenza A virus from Isatis tinctoria L. Frontiers in Pharmacology. 2021; 12: 755396.

Wang T, Wang X, Zhou Y, Si C, Yang L, Meng L, et al. Antiviral activity of polysaccharide from Radix Isatidis (Isatis indigotica Fortune) against hepatitis B virus (HBV) in vitro via activation of JAK/STAT signal pathway. Journal of Ethnopharmacology. 2020; 257: 112782.

Adhikari B, Marasini BP, Rayamanjhe B, Bhattarai BR, Lamichhane G, Khadayat K, et al. Potential roles of medicinal plants for the treatment of viral diseases focusing on COVID-19: A review. Phytotherapy Research. 2021; 35: 1298–1312.

Luo H, Tang Q, Shang Y, Liang S, Yang M, Robinson N, et al. Can Chinese Medicine be used for Prevention of Corona Virus Disease 2019 (COVID-19)? A Review of Historical Classics, Research Evidence and Current Prevention Programs. Chinese Journal of Integrative Medicine. 2020; 26: 243–250.

Murphy EJ, Masterson C, Rezaoglu E, O'Toole D, Major I, Stack GD, et al. B-Glucan extracts from the same edible shiitake mushroom Lentinus edodes produce differential in-vitro immunomodulatory and pulmonary cytoprotective effects - Implications for coronavirus disease (COVID-19) immunotherapies. Science of the Total Environment. 2020; 732: 139330.

Di Pierro F, Bertuccioli A, Cavecchia I. Possible therapeutic role of a highly standardized mixture of active compounds derived from cultured Lentinula edodes mycelia (AHCC) in patients infected with 2019 novel coronavirus. Minerva Gastroenterologica. 2020; 66: 172–176.

Oesch F, Oesch-Bartlomowicz B, Effert H. Toxicity as prime selection criterion among SARS-active herbal medications. Phytotherapy. 2021; 85: 153476.

Ge L, Xie Q, Jiang Y, Xiao L, Wan H, Zhou B, et al. Genus Lonicera: New drug discovery from traditional usage to modern chemical and pharmacological research. Phytotherapy. 2022; 96: 153889.

Zhao H, Zeng S, Chen L, Sun Q, Liu M, Yang H, et al. Updated pharmacological effects of Lonicerae japonicae flos, with a focus on its potential efficacy on coronavirus disease–2019 (COVID-19). Current Opinion in Pharmacology. 2021; 60: 200–207.

Li Y, Liu Y, Ma A, Bao Y, Wang M, Sun Z. In vitro antiviral, anti-inflammatory, and antioxidant activities of the ethanolic extract of Mentha piperita L. Food Science and Biotechnology. 2017; 26: 1675–1683.

Herrmann EC Jr, Kucera LS. Antiviral substances in plants of the mint family (labiatae). 3. Peppermint (Mentha piperita) and other mint plants. Proceedings of the Society for Experimental Biology and Medicine. 1967; 124: 874–878.

Demeke CA, Woldeyohanehans AE, Kifile ZD. Herbal medicine use for the management of COVID-19: a review article. Metabolism Open. 2021; 12: 100141.

Swanson MD, Winter HC, Goldstein IJ, Markovitz DM. A Lectin Isolated from Bananas is a Potent Inhibitor of HIV Replication. Journal of Biological Chemistry. 2010; 285: 8646–8655.

Akkouh O, Ng TB, Singh SS, Yin C, Dan X, Chan YS, et al. Lectins with anti-HIV activity: a review. Molecules. 2015; 20: 648–668.

Ben-Amor I, Musarra-Pizzo M, Smeriglio A, D’Arrigo M, Pennisi R, Attia H, et al. Phytochemical characterization of Olea europaea leaf extracts and assessment of their anti-microbial and anti-HSV-1 activity. Viruses. 2021; 13: 1085.

Ben-Amor I, Gargouri B, Attia H, Tili K, Kallel I, Musarra-Pizzo M, et al. In vitro anti-Epstein Barr virus activity of Olea europaea L. leaf extracts. Plants. 2021; 10: 2445.

Salamanca A, Almodóvar P, Jarama I, González-Hedström D, Prodanov M, Inaréjos-García AM. Anti-influenza virus activity of the elenolic acid rich olive leaf (Olea europaea L.) extract Isenolic®. Antiviral Chemistry and Chemotherapy. 2021; 29: 2040206621003391.

Altindir M, Aksan FG, Uzuner H, Uñal H, Köroğlu M, Kulaç S, et al. Comparison of antiviral effect of olive leaf Extract and propolis with acyclovir on Herpes simplex virus Type 1. Microbiologiyi Bulenti 2020; 54: 79–94.

Micol V, Caturla N, Pérez-Fons L, Más V, Pérez L, Estepa A. The olive leaf extract exhibits antiviral activity against viral haemorrhagic septicemia rhadorivirus (VHSV). Antiviral Research. 2005; 66: 129–136.

Ireland DC, Wang CKL, Wilson JA, Gustafson KR, Craik DJ. Cyclotides as natural anti-HIV agents. Biopolymers. 2008; 90: 57–62.

Panossian A, Brendler T. The role of adaptogens in prophylaxis and treatment of viral respiratory infections. Pharmaceuticals. 2020; 13: 236.

Choi JH, Lee YH, Kwon TW, Ko S, Nah S, Cho I. Can Panax ginseng help control cytokine storm in COVID-19? Journal of Ginseng Research. 2022. (in press)

Lee JS, Ko EJ, Hwang HS, Lee YN, Kwon YM, Kim MC, et al. Antiviral activity of ginseng extract against respiratory syncytial virus infection. International Journal of Molecular Medicine. 2014; 34: 183–190.

Alsayari A, Muhsinah AB, Almaghahalah D, Annadurai S, Wahab S. Pharmacological efficacy of ginseng against respiratory
ttract infections. Molecules. 2021; 26: 4095.

[145] Lee YY, Quah Y, Shin J, Kwon H, Lee D, Han JE, et al. COVID-19 and Panax ginseng: Targeting platelet aggregation, thrombosis and the coagulation pathway. Journal of Ginseng Research. 2022; 46: 175–182.

[146] Shi H, Xia Y, Gu R, Yu S. Ginseng adjuvant therapy on COVID-19: A protocol for systematic review and meta-analysis. Medicine. 2021; 100: e27586.

[147] Kushtwaha PP, Singh AK, Prajapati KS, Shuaib M, Gupta S, Kumar S. Phytochemicals present in Indian ginseng possess potential to inhibit SARS-CoV-2 virulence: a molecular docking and MD simulation study. Microbial Pathogenesis. 2021; 157: 104954.

[148] Tuzun B, Nasibova T, Garage F, Sayin K, Ataseven H. Could Peganum harmala be effective in the treatment of COVID-19? Bratislava Medical Journal. 2021; 122: 670–679.

[149] Moradi M, Karimi A, Rafieian-Kopaei M, Fotouhi F. In vitro antiviral effects of Peganum harmala seed extract and its total alkaloids against Influenza virus. Microbial Pathogenesis. 2017; 110: 42–49.

[150] Wu ZN, Chen NH, Tang Q, Chen S, Zhan ZC, Zhang YB, et al. β-Carboline alkaloids from the seeds of Peganum harmala and their anti-HSV-2 virus activities. Organic Letters. 2020; 22: 7310–7314.

[151] Lansky ES, Lansky S, Paavilainen HP. Harmal: The Genus Peganum. CRC Press: Boca Raton, Florida, USA. 2017.

[152] Zhang L, Li D, Yu S. Pharmacological effects of harmine and its derivatives: a review. Archives of Pharmacal Research. 2020; 43: 1259–1275.

[153] Moradi MT, Karimi A, Fotouhi F, Kheiri S, Torabi A. In vitro and in vivo effects of Peganum harmala L. seeds extract against influenza A virus. Avicenna Journal of Phytomedicine. 2017; 7: 519–530.

[154] Sharifi-Rad J, Quispe C, Herrera-Bravo J, Semwal P, Painuli Moslemifard M, Gorji N, Ghadimi R, Kamalinejad M, Shirafkan H, Mozaffarpur SA. Pomegranate (Punica granatum) purified polyphenol extract inhibits influenza virus and has a synergistic effect with oseltamivir. Phytomedicine. 2009; 16: 1127-1136.

[155] Moslemifard M, Gorji N, Ghadimi R, Kamalinejad M, Shirafkan H. Pomegranate (Punica granatum) purified polyphenol extract inhibits influenza virus and has a synergistic effect with oseltamivir. Phytomedicine. 2009; 16: 1127-1136.

[156] Moradi MT, Karimi A, Rafieian-Kopaei M, Rabiei-Faradonbeh M, Montaz H. Pomegranate peel extract inhibits internalization and replication of the influenza virus: An in vitro study. Avicenna Journal of Phytomedicine. 2020; 10: 143–151.

[157] Zhang J, Zhan B, Yao X, Gao Y, Shong J. Antiviral activity of tannin from the pericarp of Punica granatum L. against genital Herpes virus in vitro. Zhongguo Zhong Yao Za Zhi. 1995; 20: 556–558, 576, inside back cover. (In Chinese)

[158] Reddy BU, Mullick R, Kumar A, Sadha G, Srinivasan N, Das S. Small molecule inhibitors of HCV replication from Pomegranate. Scientific Reports. 2014; 4: 5411.

[159] Kumar A, Choudhur G, Shukla SK, Sharma M, Tyagi P, Bhushan A, et al. Identification of phytochemical inhibitors against main protease of COVID-19 using molecular modeling approaches. Journal of Biomolecular Structure and Dynamics. 2021; 39: 3760–3770.

[160] Pawelczyn A, Zaprutko L. Anti-COVID drugs: repurposing existing drugs or search for new complex entities, strategies and perspectives. Future Medical Chemistry. 2020; 12: 1743–1757.

[161] Wang YX, Yan FL, Wang X. Chemical constituents from Punica granatum flowers. Zhong Yao Cai. 2014; 37: 804–807. (In Chinese)

[162] Katz SR, Newman RA, Lansky EP. Punica granatum: heuristitc treatment for diabetes mellitus. Journal of Medicinal Food. 2007; 10: 213–217.

[163] Sharifyan F, Mirjalili SA, Fazilati M, Poorazizi E, Habibollahi S. Variation of ursolic acid content in flowers of ten Iranian pomegranate (Punica granatum L.) cultivars. BMC Chemistry. 2019; 13: 80.

[164] Al-kuraishy HM, Al-Gareeb AI, El-Saber Batiha G. The possible role of ursolic acid in Covid-19: a real game changer. Clinical Nutrition ESPEN. 2022; 47: 414–417.

[165] Ali S, Alam M, Khattoo F, Fatima U, Elasbali AM, Adnan M, et al. Natural products can be used in therapeutic management of COVID-19: Probable mechanistic insights. Biomedicine & Pharmacotherapy. 2022; 147: 112658.

[166] Hamlett J, Oakes K, Cariot J, Leach M, Brown D, Cramer H, et al. The effects of Sambucus nigra berry on acute respiratory viral infections: a rapid review of clinical studies. Advances in Integrative Medicine. 2020; 7: 240–246.

[167] Kim H, Calderón AI. Rational and safe use of the top two botanical dietary supplements to enhance the immune system. Combinatorial Chemistry and High Throughput Screening. 2022. (in press)

[168] Boroudske A, Jekabsons K, Riekstina U, Muceniece R, Roschts N, Nakurte I. Wild Sambucus nigra L. from north-east edge of the species range: a valuable germplasm with inhibitory capacity against SARS-CoV-2 S-protein RBD and hACE2 binding
in vitro. Industrial Crops and Products. 2021; 165: 113438.

Santin JR, Benvenutti L, Broering MF, Nunes R, Goldoni FC, Patel YBK, et al. Sambucus nigra: a traditional medicine effective in reducing inflammation in mice. Journal of Ethnopharmacology. 2022; 283: 114736.

Li XN, Pu JX, Du X, Yang LM, An HM, Lei C, et al. Lignans with anti-HIV activity from Schisandra propinqua var. sinensis. Journal of Natural Products. 2009; 72: 1133–1141.

Li X, Lei C, Yang L, Li H, Huang S, Du X, et al. Three new arylnaphthalene lignans from Schisandra propinqua var. sinensis. Fitoterapia. 2012; 83: 249-252.

Liu H, Ye F, Sun Q, Liang H, Li C, Li S, et al. Scutellaria baicalensis extract and baicalein inhibit replication of SARS-CoV-2 and its 3C-like protease in vitro. Journal of Enzyme Inhibition and Medicinal Chemistry. 2021; 36: 497–503.

Song J, Long J, Xie L, Zhang L, Xie Q, Chen H, et al. Applications, phytochemistry, pharmacological effects, pharmacokinetics, toxicity of Scutellaria baicalensis Georgi. And its probably potential therapeutic effects on COVID-19: a review. Chinese Medicine. 2020; 15: 102.

Song J, Zhang L, Xu Y, Yang D, Zhang L, Yang S, et al. The comprehensive study on the therapeutic effects of baicalein for the treatment of COVID-19 in vivo and in vitro. Biochemical Pharmacology. 2021; 183: 114302.

Pei T, Yan M, Huang Y, Wei Y, Martin C, Zhao Q. Specific flavonoids and their biosynthetic pathway in Scutellaria baicalensis. Frontiers in Plant Science. 2022; 13: 866282.

Ayele AG, Enyew EF, Kifle ZD. Roles of existing drug and drug targets for COVID-19 management. Metabolism Open. 2021; 11: 100103.

Zhu D, Su H, Ke C, Tang C, Witt M, Quinn RJ, et al. Efficient discovery of potential inhibitors for SARS-CoV-2 3C-like protease from herbal extracts using a native MS-based affinity-selection method. Journal of Pharmaceutical and Biomedical Analysis. 2022; 209: 114538.

Tran HTT, Gigl M, Le NPK, Dawid C, Lamy E. In vitro effect of Taraxacum officinale leaf aqueous extract on the interaction between ACE2 cell surface receptor and SARS-CoV-2 spike protein D614 and four mutants. Pharmaceuticals. 2021; 14: 1055.

Flores-Ocelotl MR, Rosas-Murrieta NH, Moreno DA, Vallejo-Ruiz V, Reyes-Leyva J, Domínguez F, et al. Taraxacum officinale and Urtica dioica extracts inhibit dengue virus serotype 2 replication in vitro. BMC Complementary and Alternative Medicine. 2018; 18: 95.

Jia YY, Guan RF, Wu YH, Yu XP, Lin WY, Zhang YY, et al. Taraxacum mongolicum extract exhibits a protective effect on hepatocytes and an antiviral effect against hepatitis B virus in animal and human cells. Molecular Medicine Reports. 2014; 9: 1381–1387.

Yang Y, Ying G, Wu S, Wu F, Chen Z. In vitro inhibition effects of hepatitis B virus by dandelion and taraxasterol. Infectious Agents and Cancer. 2020; 15: 44.

Eshrat R, Jafari M, Gudarzi S, Nazari A, Samizadeh E, Ghafourian Hesami M. Comparison of ameliorative effects of Taraxacum syriacum and N-acetylcysteine against acetaminophen-induced oxidative stress in rat liver and kidney. Biochemical Journal. 2021; 169: 337–350.

He W, Han H, Wang W, Gao B. Anti-influenza virus effect of aqueous extracts from dandelion. Virology Journal. 2011; 8: 538.

Fan D, Parhira S, Zhu G, Jiang Z, Bai L. Triterpenoids from Polygonum multiflorum and with a potential antiviral activity against SARS-CoV-2. Journal of Medicinal Plants Research. 2020; 14: 1055.

Martin BR, Richardson J. An Exploratory Review of Potential Adjunct Therapies for the Treatment of Coronavirus Infections. Journal of Chiropractic Medicine. 2021; 20: 199–217.

Safa O, Hassaniazad M, Farashahinejad M, Davoodian P, Dadvand H, Hassanipour S, et al. Effects of Ginger on clinical manifestations and parasitical features of patients with Severe Acute Respiratory Syndrome due to COVID-19: a structured summary of a study protocol for a randomized controlled trial. Trials. 2020; 21: 841.

Zahair MS, Maulana S, Widodo A, Pitopang R, Arba M, Hariono M. GC-MS, LC-MS/MS, Docking and molecular dynamics approaches to identify potential Roscoce. Molecules. 2021; 26: 5230.

Unuofin JO, Masuku NP, Paimo OK, Lebelo SL. Ginger from farmyard to town: nutritional and pharmacological applications. Frontiers in Pharmacology. 2021; 12: 779352.

Orisakwe OE, Orish CN, Nwanaforo EO. Coronavirus disease (COVID-19) and Africa: Acclaimed home remedies. Scientific African. 2020; 10: e00620.

Villena-Tejada M, Vera-Ferchau I, Cardona-Rivero A, Zamalloa-Concejo R, Quipe-Florez M, Frisano-Triveño Z, et al. Use of medicinal plants for COVID-19 prevention and respiratory symptom treatment during the pandemic in Cusco, Peru: A cross-sectional survey. PLoS ONE. 2021; 16: e0257165.

Nallusamy S, Mannu J, Ravikumar C, Angamuthu K, Nathan M, Ethrington J, et al. Exploring phytochemicals of traditional medicinal plants exhibiting inhibitory activity against main protease, spike glycoprotein, RNA-dependent RNA polymerase and non-structural proteins of SARS-CoV-2 through virtual screening. Frontiers in Pharmacology. 2021; 12: 667704.