The trends on plants in the prevention and treatment of the COVID-19

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The use of natural products is growing everyday around the world. Herbal phytoconstituents have been effective in the past reducing infectious conditions for many years, before antibiotics were introduced. Herbal medicinal products appear to be an alternative for the manufacturing of novel antivirals, antibodies, vaccines, growth factors and cytokines[1].

Identifying the antiviral mechanisms, of these herbal medicinal products has elucidated on how and where they interact or interrupt with the viral life cycle. This includes viral input, replication, assembly and release, as well as virus-specific interactions[1-3].

The greatest advantage of using products that originate from plants to produce vaccines is the inability they have to replicate human pathogens, because these products can diminishing the risk of contamination and making the purification process less strident. In otherwise they can be produced in massive quantities by molecular farming in plants, reducing the cust of production[2,3].

Phytonutrients in the diet (originating from fruits and vegetables) generally promote immune responses, due to the presence of antioxidants and anti-inflammatory compounds. These include phenolic compounds, flavonoids, carotenoids and vitamins of complex B, C, D and E, in addition to iron, selenium and zinc. The strategy of providing a diet with anti-inflammatory compounds has proven to be a viable option for managing COVID-19. The insufficiency of micronutrients and others nutritional aspects, have been shown to affect the clinical course of the disease[4].

Flavonoids belong to a group of secondary metabolites by plants with a polyphenolic structure, which is widely found in fruits and vegetables. They have a biochemical and antioxidant effect in some diseases. The effects are as antioxidants, anti-inflammatory, anti-mutagens, anti-cancer-causing and antiviral activity, associated with the ability to control major cell enzyme functions. Specifically, apigenin, luteolin, quercetin, amentoflavone, puerarin, epigallocatechin, epigallocatechin gallate, gallocatechin gallate and kaempferol, these show the ability to inhibit the proteolytic activity of SARS-CoV 3CLpro[5].
Occasionally Chinese medicinal herbs have been used in the treatment of viral epidemics in some countries. China and South Korea have produced a protocol that considers the use of these components in the treatment of COVID-19. The SARS-CoV2 (similar to SARS-CoV) uses the ACE-2 receiver as the gateway to the cell. Some compounds can inhibit infection because they have the same virus receptor, so the compound blocks the receptor and blocks the virus from accessing the cell. Thus, herbal compounds that have this binding capability with the ACE-2 receptor have been used in China and Korea in the treatment of COVID-19, such as, *Glycyrrhiza uralensis*.[6]

Furthermore, some herbal products of Traditional Chinese Medicine, may have potentially immunosuppressive effect, this can reduce inflammatory markers (TNF-α, IL-1β, IL-6, IL-8, IL-10), resulting in decreased lung inflammation or acute lung disease. Other formulas showed significant inhibition of SARS-CoV-2 replication and reduced pro inflammatory cytokines (TNF-α, IL-6, CCL2/MCP-1, and CXCL10/IP-10) produced at the mRNA level.[6]

Considering the evidence, there are many studies being produced, these aim to focus on the use of plant products in the treatment and prevention of viral infections, especially COVID-19. Find on the TABLE 1 some species that have shown promising results in several studies.

**TABLE 1:** Potential antiviral strategies from plants against Coronavirus.

| Plant specie | Biological action | Active compound | EC50 or IC50 (SD) |
|--------------|-------------------|-----------------|-------------------|
| *Allium porrum* J. Gay Alliaceae | Action of lecithins in inhibition of viral action | Agglutinin | 0.45 (0.00) μg[6,8] |
| *Allium sativum* | Secondary metabolites that inhibit the action of the virus | Quercetin | ND[6,8,9] |
| *Angelica keiskei* (Ashitaba) | 3CLpro inhibitor | Chalcones | 11.40-129.80 μg[2,13] |
| *Camellia sinensis* | 3CLpro Inhibitor | Tannic acid | 3.00 μg[7,9,10] |
| *Camellia sinensis* | 3CLpro Inhibitor | 3-isotheaflavin urtiga3-gallate | 7.00 μg[7,8] |
| *Camellia sinensis* | Binding to RNA-dependent RNA polymerase | Theaflavin | ND[6,7] |
| *Camellia sinensis* | Replication & 3CLpro | Betulinic acid | ND[6,7] |
| *Camellia sinensis* | PLpro & 3CLpro | Coumaroyltyramine | ND[6,7] |
| *Camellia sinensis* | PLpro & 3CLpro | Cryptotanshinone | ND[6,7] |
| *Camellia sinensis* | Replication, 3CLpro & entry | Desmethoxyreserpine | ND[6,7] |
| *Camellia sinensis* | Entry & spike protein | Dihydrotanshinone | ND[6,7] |
| *Camellia sinensis* | PLpro & 3CLpro | Kaempferol | ND[6,7] |
| *Camellia sinensis* | Replication & 3CLpro | Lignan | ND[6,7] |
| *Camellia sinensis* | PLpro | Moupinamide | ND[6,7] |
| *Camellia sinensis* | PLpro & 3CLpro | N-cis-feruloyltyramine | ND[6,7] |
| *Camellia sinensis* | PLpro & 3CLpro | Quercetin | ND[6,7] |
| *Camellia sinensis* | Replication & 3CLpro | Sugiol | ND[6,7] |
| *Camellia sinensis* | PLpro & 3CLpro | Tanshinone IIa | ND[6,7] |
| *Cinnamomi sp.* | Early stage inhibition of viral entry (clathrin-dependent endocytosis pathway) | Procyanidin A2 | 10.70 (0.40) μg/mL (EtOH fraction) - Water extraction followed by phase extraction[6,8] |
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| Plant                        | Inhibitory Activity                                      | Plant Extract          | Concentration (μg/ml) |
|-----------------------------|----------------------------------------------------------|------------------------|-----------------------|
| **Dioscoreae Rhizoma**      | Viral growth inhibitor                                    | Plant extract          | 200.00 μg/ml          |
| **Galla chinensis**         | ACE2 receptor inhibitor                                   | Tetra-O-galloylβ-d-glucose | 4.50-24.00 μg (from 85% ethanol extract) |
|                             |                                                          |                        | 1.70 (0.30) μg (Isolated compounds) |
| **Galla chinensis**         | ACE2 receptor inhibitor                                   | Tetra-O-galloylβ-d-glucose | 4.50-24.00 μg (from 85% ethanol extract) |
|                             |                                                          |                        | 1.70 (0.3) (Isolated compounds) |
| **Glycyrrhiza glabra and Glycyrrhiza uralensis (Licorice)** | Viral growth inhibitor of SARS-CoV | Glicirrizina | 30.00 μg/ml |
|                             |                                                          | Glycyrrhizin           | 365.00 (12.00) μg/ml (Chemical standards) |
|                             |                                                          |                        | 18β-glycyrrhetinic acid | > 20.00 μg/ml |
| **Houttuynia cordata**      | 3CLpro Inhibitor and RNA dependent RNA polymerase (RdRp) Inhibitor. May inhibit pivotal enzymes and trigger negative feedback control in immune systems. | Plant extract          | >200.00 μg/ml          |
|                             |                                                          | Boiled water extract   | 50.00 μg/ml           |
|                             |                                                          |                        | ~ 1000.00 μg/mL (Essential oil) |
| **Isatis indigotica**       | 3CLpro inhibitor                                          | Hesperetin             | 8.30 μg               |
|                             |                                                          | Sinigrin                | 2170.00 μg            |
| **Laurus nobilis**          | Viral Growth inhibitor                                    | Plant Extract          | 120.00 μg/mL          |
|                             | Inhibition of viral replication                           | L. nobilis: β-ocimene, 1,8-cineole, αpinene, β-pinene | 120.00 (1.20) μg/mL (Essential oil) |
| **Nicotiana tabacum**       | Plant bioreactors that can be used in the development of oral vaccines | Antígeno Viral S1 Antígeno Viral N | 1.60 (0.50) μg |
| **Nicotiana benthamiana**   | Viral growth inhibitor. Studying its use for creating a vaccin. | NICTABA Lectin         | ND³                   |
| **Psoralea corylifolia**    | Mixed inhibitor of SARS-CoV PLpro (isobavachalcone and psoralidin also reversible) | Ethanol extract of seeds | 15.00 μg/mL |
|                             |                                                          | Bavachinin             | 38.40 (2.40) μg       |
|                             |                                                          | Neobavaisoflavone      | 18.30 (1.10) μg       |
|                             |                                                          | Isobavachalcone        | 7.30 (0.80) μg        |
|                             |                                                          | 4′-O-methylbavachalcone| 10.10 (1.20) μg       |
|                             |                                                          | Psoralidin             | 4.20 (1.00) μg        |
|                             |                                                          | Corylifol A            | 32.30 (3.20) (rest in μM) |
| **Rheum palatum**           | Inhibition of 3CLpro                                      | Plant extract in 75 % etanol. Possibly anthraquinones | 13.76 (0.03) μg/mL |
| **Rheum officinale**        | Viral spike protein and human ACE2 receptors inhibitor    | Emodin Water extracts (at 40°C) of roots | ~5.00 μg/mL |
|                             | Inhibited binding of S protein to ACE2                    | Emodin                  | 1.00-10.00 μg/mL       |
| **Salvia miltiorrhiza**     | Non-competitive enzyme inhibition of protease (except for rosmariquinone which exhibits simple reversible slow-binding inhibition). Isolated compounds from ethanol extract | Tanshinones             | 0.80-30.00 μg |
|                             |                                                          | Tanshinone IIA         | 89.10 (5.20) μg       |
|                             |                                                          | Tanshinone IIB         | 24.80 (0.80) μg       |
|                             |                                                          | Methyl tanshinonate    | 21.10 (0.80) μg       |
|                             |                                                          | Cryptotanshinone       | 226.70 (6.20) μg      |
|                             |                                                          | Tanshinone I           | 38.70 (8.20) μg       |
|                             |                                                          | Dihydrotanshinone I    | 14.40 (0.70) μg       |
|                             |                                                          | Rosmariquinone         | 21.10 (0.80) μg       |
|                             |                                                          | Tingenone              | 9.90 μg               |
|                             |                                                          | Iguesterin             | 9.90 μg               |
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| Toona sinensis Roem | Inhibit the cellular entry of SARS-CoV | Quercetin | 30.00–43.00 μg/mL Boiled water extract of leaves |
|---------------------|--------------------------------------|-----------|-----------------------------------------------|

Legend: CLpro = chymotrypsin-like protease; n/a = not applicable to this study; ND = no data; PLpro = papain-like proteases; RNA = ribonucleic acid; EC50 = effective concentration, IC50 = inhibitory concentration, ACE2 = angiotensin-converting enzyme; SARS –CoV = Severe Acute Respiratory Syndrome CoV.

The species of Camellia sinensis, Glycyrhiza glabra, Glycyrrhiza uralensis, Nicotiana tabacum and Nicotiana benthamiana are being widely studied and have brought great promises to the prevention and treatment of the coronavirus, especially COVID-19 kind. The use of isolated plants or compounds has shown the ability to act from the moment the virus enters the cell, until the inhibition of its replication. Thus, the development of a plant-based vaccine is a real possibility and it is already in testing phase. However, further studies are needed to establish how effective, safe to use, individual dose and possible side effects expected from these compounds.

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