PREVENTION AND TREATMENT WITH MEDICINAL PLANTS

DR. LORETTA BOLGAN
Doctor of Pharmaceutical Chemistry and Technology
Ph.D. in Pharmaceutical Sciences
Scientific advisor
loretta.bolgan@gmail.com

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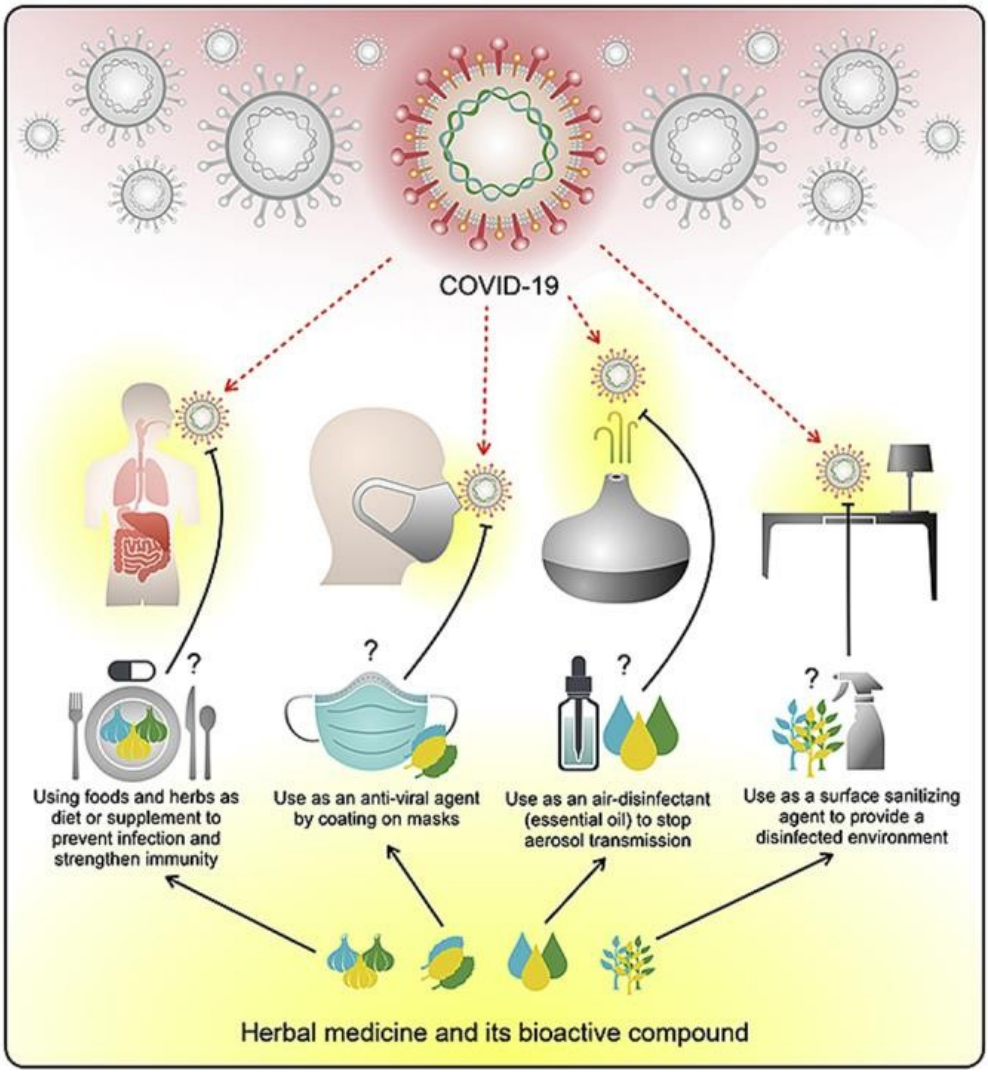


https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7260602/ [1]

[1] Panyod S, Ho CT, Sheen LY.
Dietary therapy and herbal medicine for COVID-19 prevention: A review and perspective.

The prospects of dietary therapy and phytotherapy for the prevention of COVID-19. Diet therapy and phytotherapy could be used against COVID-19 in the following four ways: (1) diet or supplement for infection prevention and immunity enhancement; (2) application as an antiviral agent on masks; (3) air disinfection agent to stop aerosol transmission of the virus; and
(4) surface sanitizing agent to provide a disinfected environment

ESSENTIAL OILS

Essential oils, also called volatile or ethereal oils, are aromatic oily liquids obtained from parts of plants, such as flowers, shoots, seeds, leaves, barks, fruits or roots.
The term "essential oil" was coined in the 16th century by the Swiss physician Paracelsus of Hohenheim, who called "*Quinta essentia*" one of the components of a mixture extracted from a plant.

More than 3,000 plants are sources of essential oils, although only about 300 of these have commercial value. About 30 of the latter plants, often grown on a large scale, produce essential oils whose use as medicines goes back centuries in various cultures around the world, and are described in international and national pharmacopoeias. [2]

Chemical and physical properties [3]

In most cases, essential oils are liquids at ordinary temperature, volatile, oily in consistency, more or less fluid (their density is very often less than that of water), aromatic in smell, generally colorless, but sometimes colored (e.g., in red that of Benzoin and Cinnamon, in blue that of Chamomile, etc.).

J Tradit Complement Med. 2020;10(4):420-427. Published 2020 May 30. doi:10.1016/j.jtcme.2020.05.004
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7260602/

[2] https://scoiattolorampante.wordpress.com/2012/05/27/il-potere-antimicrobico-degli-oli-essenziali-part-i/

https://www.guidaoliessenziali.com/

Sharifi-Rad J, Sureda A, Tenore GC, et al.
Biological Activities of Essential Oils: From Plant Chemoecology to Traditional Healing Systems.
Molecules. 2017;22(1):70. Published 2017 Jan 1. doi:10.3390/molecules22010070
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6155610/

[3] http://www.sienafree.it/salute-e-benessere/fitoterapia/16948-oli-essenziali-in-terapia-seconda-parte- composition-chemistry-and-essences-treated

They are poorly soluble in water, to which, however, they transmit their aroma because they are slightly hydrophilic, while they are soluble in most organic solvents. Due to their pronounced lipophilic characteristics, which make them soluble in skin lipids, all essential oils exhibit high penetration power through the skin.
This property can be exploited to act on organs deep and below the point of application, to convey other active substances or to have systemic effects. In fact, having passed the skin barrier, the essential oil spreads by diffusion into extracellular fluids to reach the blood and lymph.

The effect of essential oils on the respiratory system by inhalation and sanitization of environments[4] , particularly SARS- Cov-2 will be considered here.

Chemical composition [5]

From a chemical point of view, essences are **complex mixtures** of a variety of organic substances that may contain from 20 to 60 constituents, in also very different proportions. They are usually characterized by **2 or 3 main components**, present in high concentration (20 to 70 percent), and generally responsible for biological action, and a variable number of other constituents, often present only in trace amounts.

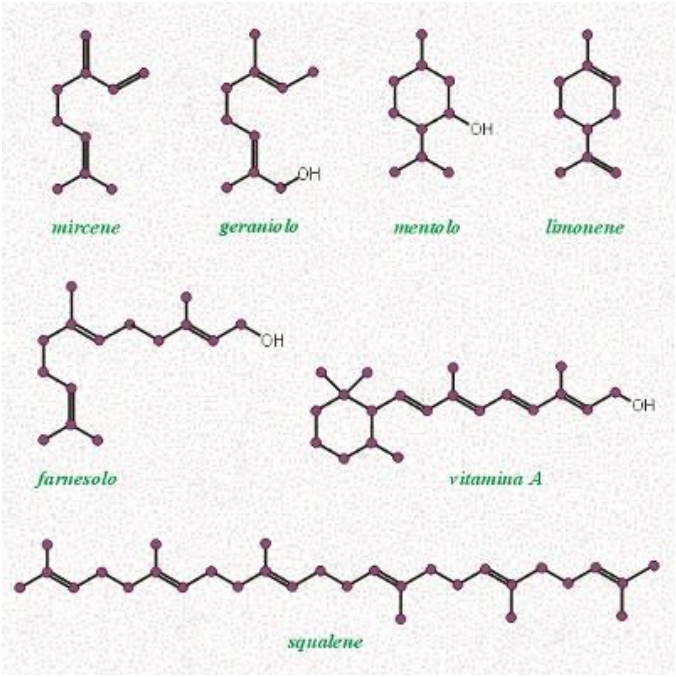
The chemical constituents of essential oils can be included in two groups of hydrocarbons of different biosynthetic origin.
The main group consists of **terpenes** (which are polymers of isoprene) and their derivatives called **terpenoids**.
The other group consists instead of **aromatic and aliphatic** constituents, all of which are characterized by low molecular weight.

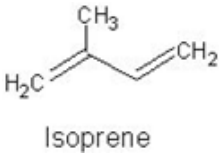
The hydrocarbon moiety facilitates the uptake of molecules by tissues by interaction of the inner phospholipid layer of the cell membrane, while the oxygenated functional group, depending on the active ingredient, determines biological effects on the functioning of both membranes and cellular processes.

[4] PIBIRI, M., GOEL, A., VAHEKENI, N., & ROULET, C. (2006).
Indoor air purification and ventilation systems sanitation with essential oils.
International Journal of Aromatherapy, 16(3-4), 149-153. doi:10.1016/j.ijat.2006.10.002
https://www.researchgate.net/publication/37440987_Indoor_air_purification_and_ventilation_systems_sanitation_with_essential_oils

[5] http://www.guidaoliessenziali.com/composizione-chimica-degli-oli-essenziali/

Consequently, at high concentrations there is a generally irritating effect, due to the changes involved in the essence on membranes, while lower concentrations may result in specific metabolic effects.





Some natural 'terpenes' and 'terpenoids', among which we also find Vitamin A and Squalene

Extraction of essential oils [6]

Essential oils are produced by steam distillation, cold pressure, hyperbaric CO_2 extraction, and solvent extraction. Each method has its advantages and disadvantages and produces a different quality of essential oil.

Steam distillation

Steam distillation is the most common method of extracting essential oils from wood, bark, resin and leaves. Distillation makes use of the capabilities

[6] http://www.guidaoliessenziali.com/come-si-estraggono-gli-oli-essenziali/

https://aromaterapia-scientifica.weebly.com/

extracting steam and sometimes pressure to extract the aromatic part from the herbaceous material.
The plant chosen for extraction is placed on a grid over boiling water, or a stream of superheated steam is channeled so that it passes through the plant. In this way the volatile components are entrained away, condense in a coil, and precipitate as distilled water and volatile components. This mixture is collected and separated in a separating funnel. There are very primitive steam distillation methods that use little heat and require as little as a month to distill a certain amount of essential oil. The advantage of "slow" distillation is that the long time (and patience) allows some of the larger molecules to be gently extracted, thus producing an essence that has a wider variety of aromas.
Modern distillation methods use higher temperatures to extract essential oils very quickly, sometimes within minutes. This method allows very fast, low-cost and effective production, but the bouquet of odors is narrowed, resulting in a loss of some of the possible therapeutic qualities.

Cold pressure

Cold-pressing is the most suitable method for treating citrus peels (lemon, orange, grapefruit, bergamot, and tangerine), which are broken or ground and then pressed to extract the essential oil component in them.
The mechanical nature of this process produces not very pure essential oils that tend to oxidize or lose their properties if they are stored without refrigeration for more than two years. Steam-distilled essential oils, on the other hand, develop a richer aroma over the years and in some cases have an unlimited shelf life.

Extraction with supercritical carbon dioxide [7]

This type of extraction uses pure CO_2 at a pressure of about 22 atmospheres (the same pressure found at an underwater depth of about two hundred meters). At high pressure, the CO_2 becomes liquid and can extract the essential oils from the plant. The liquid is then vented and depressurized, at which point the CO_2 becomes a harmless gas and what remains at the bottom of the vessel is pure essential oil.
This method is especially useful for more volatile aromas such as tuberose and jasmine in which the flowers have very light components that are easily lost. In addition, the essential oil obtained is not affected by heat, the extraction

[7] https://www.avantech.it/tools/processo/

is almost instantaneous and complete, the solvent is inert, and there are no reactions between it and the aromatic substances.
However, the cost of compression equipment is very high, and oils produced by this system are more expensive than those produced by steam distillation.

Solvent extraction

This method is also suitable for flowers with very volatile aromas. The solvent used can be hexane or ether, which is poured over the harvested flowers. Once the solvent has evaporated, a very thick, sticky residue known as "concreta" remains. The concreta can be diluted in alcohol, and the essential oil that remains after evaporation is called "absolute."
This method is the one preferred by perfumers because, by not using heat, pressure or mechanical squeezing, the fragrance of the flowers is not altered. In contrast, for aromatherapy it is the least suitable system, and oils produced in this way are never prescribed for internal use because a small fraction of the hydrocarbon used as a solvent always remains in the essential oil, which can be harmful to the human immune system and cause reactions in sensitive people.

Enfleurage

This traditional method of extraction, now little used, is the method used to extract essential oils from the petals and very tender parts of plants (violet, rose, jasmine), which would otherwise be easily damaged in the presence of heat.
The flowers are placed on slabs covered with purified fat, taking advantage of the ability of fat, to absorb odors. The flowers give up their scent to the fat and are replaced with other flowers until the fat becomes saturated with scent. Then the fat is dissolved with alcohol and then the essential oil is separated.

Essence treatments

The natural, total essential oil almost always proves to be **more active** than its main constituent and, in addition, is able to act on the body with a more comprehensive and balanced biological action.
However, some essential oils **cannot be used raw** because they contain compounds that are unpleasant smelling or irritating to the skin or, in any case, have undesirable properties from a therapeutic point of view. It is then necessary to purify the raw essences from the undesirable constituents, for example, by the technique of fractional distillation, which allows the separation of a well-defined volatile chemical from those with which it forms a mixture.

Some terpene hydrocarbons must **also** often be eliminated; these unsaturated compounds, in fact, are irritating to the skin, oxidize easily at the double bonds, and undergo polymerization processes (resinification) that substantially change the properties, fragrance, and solubility in alcohol of the essential oil.

Purified Essential Oils - Among the various treatments in use today to purify essential oils, the most common is **deterpenation.** This operation consists of the total removal, during distillation, of the head fraction consisting of unscented terpenic hydrocarbons. The main purpose of deterpenation is to obtain an essence that is **30-70 times more fragrant** than the ordinary one; for example, deterpenated lemon essential oil has as much as 10 times more aromatic power than the similar volume of natural essential oil. In addition, so-called "deterpenated" essential oil sees **its bactericidal power activated as** a result of an increased concentration of the fraction of oxygenated compounds, which are more active. Deterpenated **essential oils are more** stable, **more soluble** in water and low-titre alcohol (even 70° and 60°) while they are free of irritating power to the respiratory tract, eyes and mucous membranes in general.

Activated essential oils-Sometimes it may be useful to resort to certain techniques, such as **peroxidation**, which, while leading to a more or less profound change in the original constitution of the essential oil, enhance certain activities, such as **bactericidal activity**, with obvious therapeutic advantages.
Peroxidation involves making **ozone** or ozonized air act under certain conditions of temperature, pressure and partitioning of the essence, resulting in the formation of peroxides in a percentage that is directly proportional to the time and intensity of the oxidant's action.

Conservation

Of utmost importance is the proper storage of essential oils, for which it is best to avoid plastic containers, but to use **darkened glass** containers, tightly closed, as full as possible, stored away from light, humidity and high temperatures.

CHEMISTRY [8]

The essential oil of a plant is defined by its chemotype (ct), that is, its botanical and chemical "profile." In fact, the same plant of the same botanical species **can produce essential oils having a very different chemical composition**.

More specifically, it can have a **different chemotype depending on its culture or growth conditions**: soil composition and nature, orientation relative to the sun, rainfall, temperature.

Common thyme (*Thymus vulgaris*) is a significant example. The thymol chemotype (ct thymol) is the most common. The carvacrol chemotype appears when thyme grows in particularly hot and dry areas, while the tuianol and alpha-terpineol chemotypes are found in wetter areas and the geraniol chemotype in mountainous, harsh-climate areas.

The chemotype is identified by chromatographic and spectrometric analysis that recognizes and identifies molecules. In this case we speak of a chemotyped essential oil "O.E.C.T."

This classification is very important because **it allows essential oils to be selected for targeted use**. In fact, depending on the chemotype, an essential oil has a different use.

For example, **rosemary** essential oil has three chemotypes:

- chemotype cineol (ct cineol) is used for respiratory affections;
- camphor chemotype (ct camphor) is used for t h e muscular system and the painful joints;
- chemotype verbenone (ct verbenone) is a liver and biliary tract stimulant.

Thyme (*Thymus vulgaris*) essential oil has many chemotypes, each of which has different properties:

- Chemotype thymol (ct thymol) has anti-infective properties;
- chemotype linalool (ct linalool) has antibacterial, antifungal (dermatitis, herpes), virucidal, and antiparasitic properties;
- chemotype tujanol (ct tujanol) has neurotonic and antimicrobial properties;
- chemotype cineol (ct cineol) has broncho-pulmonary decongestant, antiviral properties;

[8] http://www.guidaoliessenziali.com/chemiotipo-di-un-olio-essential/#:~:text=The%20essential%20oil%20of%20a,a%20very%20different%20chemical%20composition.

https://herbalfieldschool.files.wordpress.com/2017/11/essential-oil-chemotypes.pdf

https://phytovolatilome.com/essential-oil-chemistry-functional-groups/

- chemotype carvacrol (ct carvacrol) has properties antimicrobial and anti-inflammatory;
- chemotype paracimene (ct paracimene) has antalgic properties, for topical use in rheumatism and arthrosis;
- chemotype geraniol (ct geraniol) has antibacterial, antifungal, and antiviral properties;
- chemotype terpineol (ct terpineol) has antibacterial and antifungal properties.

When a company extracts an oil that has the same name example *Rosmarinus officinalis* but from different areas (countries) it must give an indication of the chemotype or indicate the main constituents.

Humans have been using EOs for thousands of years, not only as ingredients in perfumes or condiments for food flavoring, but also in folk medicine for their many different biological properties, including antimicrobial properties. Given the large number of chemical compounds present in essential oils, it is presumable that their antimicrobial activity is not attributable to a specific mechanism, but rather to a series of actions that combine and are amplified by molecules acting in synergy.

Their antimicrobial qualities are important in managing the rapidly growing problem of drug-resistant microorganisms, and the literature supporting their antiviral and antibacterial activity is very substantial. [9]

[9] Wińska K, Mączka W, Łyczko J, Grabarczyk M, Czubaszek A, Szumny A.
Essential Oils as Antimicrobial Agents-Myth or Real Alternative?
Molecules. 2019;24(11):2130. Published 2019 Jun 5. doi:10.3390/molecules24112130
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6612361/

Reyes-Jurado F, Navarro-Cruz AR, Ochoa-Velasco CE, Palou E, López-Malo A, Ávila-Sosa R.
Essential oils in vapor phase as alternative antimicrobials: A review.
Crit Rev Food Sci Nutr. 2020;60(10):1641-1650. doi: 10.1080/10408398.2019.1586641. Epub 2019 Mar 18. PMID: 30880425.
https://www.tandfonline.com/doi/full/10.1080/10408398.2019.1586641

Tariq S, Wani S, Rasool W, Shafi K, Bhat MA, Prabhakar A, Shalla AH, Rather MA.
A comprehensive review of the antibacterial, antifungal and antiviral potential of essential oils and their chemical constituents against drug-resistant microbial pathogens.
Microb Pathog. 2019 Sep;134:103580. doi: 10.1016/j.micpath.2019.103580. Epub 2019 Jun 11. PMID: 31195112.
https://pubmed.ncbi.nlm.nih.gov/31195112/

Definitions: [10]

The action of an antibiotic can be:

Bacteriostatic: antibiotic blocks the reproduction of bacteria
Bactericidal: antibiotic results in the death of bacteria.

A bactericide is defined as an antibiotic that after 24 h of "in vitro" contact results in a Survival of 0.01% or less.
The bacteriostatic or bactericidal action of an antibiotic depends on the mechanism of action. Bactericidal are those antibiotics that act on structures vital to the bacterial cell such as the wall or nucleic acids.

To assess whether an antibiotic is bacteriostatic or bactericidal, M.I.C. and M.B.C. are determined.

M.I.C. or minimum inhibitory concentration is the lowest concentration of antibiotic that can prevent the development of microorganisms (µg/ml).
M.B.C. or minimum bactericidal concentration is the lowest concentration of antibiotic capable of killing bacterial cells (µg/ml).
If the antibiotic is bactericidal, the MIC and MBC values coincide.
If the antibiotic is bacteriostatic, the MIC and MBC values are different (MBC>MIC)

Among the numerous studies carried out on the action of individual EOs, two researches conducted in the hospital setting are worth mentioning: the first at an Italian hospital (Fondazione "Don Ambrogio Cacciamatta," Iseo) in which a mixture of balsamic essences was used, and a significant reduction in bacterial and fungal contamination was found in clean rooms using standard sanitization alone or in combination with essential oil misting (average decrease of 90% for total count, P <0.01; 90% for yeasts and molds, P < 0.05) and the decrease in antibiotic prescriptions

Burt S. Essential oils: their antibacterial properties and potential applications in foods--a review. Int J Food Microbiol. 2004 Aug 1;94(3):223-53. doi: 10.1016/j.ijfoodmicro.2004.03.022. PMID: 15246235. https://dspace.library.uu.nl/bitstream/handle/1874/24273/full.pdf?sequence=6

[10] http://www.med.unipg.it/ccl/Materiale%20Didattico/Microbiologia%20Clinica/03.ANTIBIOTICI.pdf

(70 percent), mucolytics (100 percent), bronchodilators (100 percent), and steroidal (67 percent) and nonsteroidal (33 percent) anti-inflammatory drugs, with no adverse effects on patients. [11]

The second in an Austrian hospital where the effects of lemon and spruce essences were tested, and it was seen that in the first two hours the average concentration of airborne bacteria and fungi was reduced by about 40% and 30%-60%, respectively. [12]

Antimicrobial activity of essential oils

In medicinal and aromatic plants, chemical components with antimicrobial properties are synthesized to protect them from microbial pathogens.

The antimicrobial properties of essential oils depend on the type of chemical constituents and the amount of major individual compounds. These chemical compounds are secreted through a series of molecular interactions under specific biotic/biotic stress conditions.

Each compound can exhibit a different mechanism of action against microbes.

Overall, the mechanism of antibacterial action is mediated by a series of biochemical reactions in the bacterial cell, which depend on the characteristics of the chemical constituents in the essential oil.[13] In addition, the antibacterial activity of essential oils also differs according to different bacterial architecture, such as Gram-positive and Gram-negative bacteria differing in cell membrane composition.

Below are links to the tables[14] on the:

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[11] Gelmini F, Belotti L, Vecchi S, Testa C, Beretta G. Air dispersed essential oils combined with standard sanitization procedures for environmental microbiota control in nosocomial hospitalization rooms. Complement Ther Med. 2016 Apr;25:113-9. doi: 10.1016/j.ctim.2016.02.004. Epub 2016 Feb 10. PMID: 27062958.
https://air.unimi.it/retrieve/handle/2434/494661/831730/CTIM-S-15-00646%20%281%29.pdf

[12] Lanzerstorfer A, Hackl M, Schlömer M, Rest B, Deutsch-Grasl E, Lanzerstorfer C.
The influence of air-dispersed essential oils from lemon (Citrus limon) and silver fir (Abies alba) on airborne bacteria and fungi in hospital rooms.
J Environ Sci Health A Tox Hazard Subst Environ Eng. 2019;54(3):256-260. doi: 10.1080/10934529.2018.1546498. Epub 2019 Feb 22. PMID: 30795725.
https://www.researchgate.net/publication/331301161_The_influence_of_air-dispersed_essential_oils_from_lemon_Citrus_limon_and_silver_fir_Abies_alba_on_airborne_bacteria_and_fungi_in_hospital_rooms

[13] Nazzaro F, Fratianni F, De Martino L, Coppola R, De Feo V.
Effect of essential oils on pathogenic bacteria.
Pharmaceuticals (Basel). 2013;6(12):1451-1474. Published 2013 Nov 25. doi:10.3390/ph6121451
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3873673/

[14] Swamy MK, Akhtar MS, Sinniah UR.

- Chemical composition and antibacterial activity of EOs.
- Chemical composition and antifungal activity of EOs.
- Chemical composition and antiviral activity of EOs.

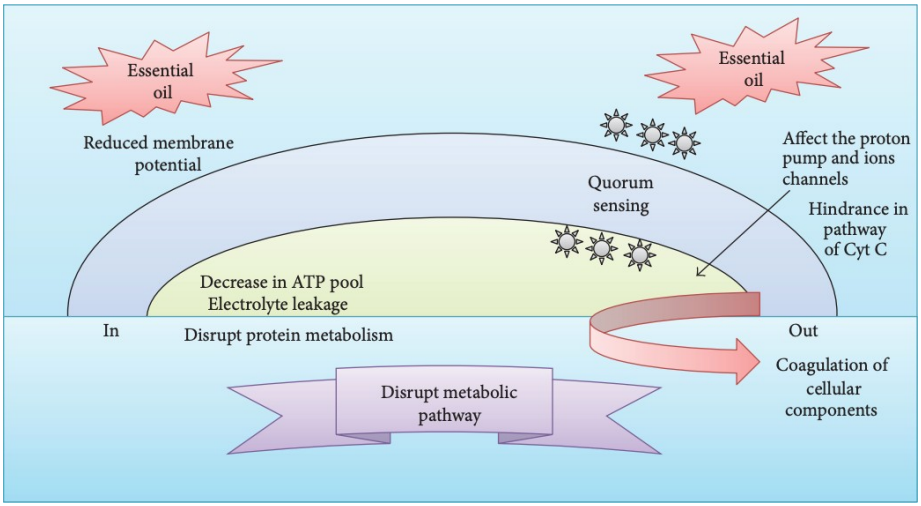
From the point of view of mechanism, the probable actions exerted by compounds in essential oils on bacteria are as follows: [15]

- Cell wall degradation;
- Damage to the cytoplasmic membrane;
- Damage to membrane proteins;
- Spillage of the cell's contents;
- Coagulation of the cytoplasm;
- Depletion of proton-motor force.

The possible antimicrobial actions of essential oils are illustrated in the figure below:

Antimicrobial Properties of Plant Essential Oils against Human Pathogens and Their Mode of Action: An Updated Review.
Evid Based Complement Alternat Med. 2016;2016:3012462. doi:10.1155/2016/3012462
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5206475/

[15] Swamy MK, Akhtar MS, Sinniah UR.
Antimicrobial Properties of Plant Essential Oils against Human Pathogens and Their Mode of Action: An Updated Review.
Evid Based Complement Alternat Med. 2016;2016:3012462. doi:10.1155/2016/3012462
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5206475/



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5206475/

Use of essential oils to treat viral respiratory infections

The inhalation of essential oils to cause a desired therapeutic effect is known as **aromatherapy**, "aroma" associated with smell, and "therapy" associated with treatment. Essential oils can be administered topically, orally, and inhaled to treat respiratory tract infections.

Topical application[16] includes massage or application of diluted essential oils to the surface of the skin. For the treatment of respiratory-related infections, it is recommended to apply essential oils to the chest, back, and soles of the feet.

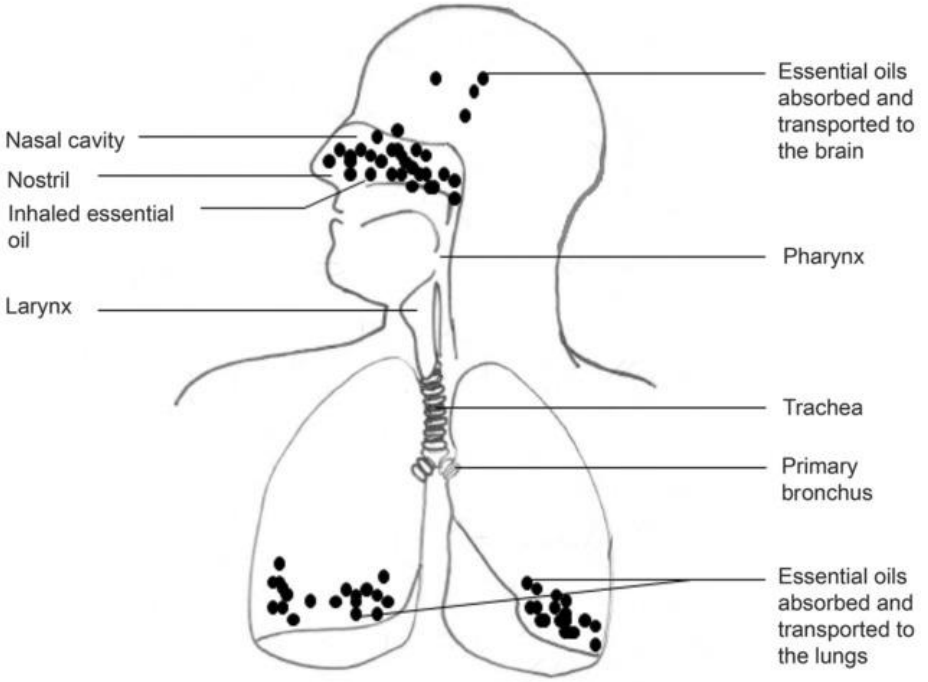
Chest and back applications are indicated for sinus drainage and fluidization of phlegm due to the aromatic effect of the essential oils, while applications on the soles of the feet are indicated for absorption of the essential oil into the bloodstream for a pharmacological effect. Locally applied essential oils have poor absorption, with only 5.0% of the essential oil carried into the bloodstream.

[16] Bahl AS (2020)
Effectiveness of Polyherbal Topical Oil Treatment for Patients either with 'COVID-19 like Symptoms' or 'COVID-19 Positive': A Prospective Study.
Insights Biomed Vol.5 No.4:13 DOI: 10.36648/2572-5610.4.4.77
https://biomedicine.imedpub.com/effectiveness-of-polyherbal-topical-oil-treatment-for-patients-either-with-covid19-like-symptoms-or-covid19-positive-a-prospective.pdf

The second route of essential oil administration is through **ingestion** of essential oils that are usually formulated by encapsulation in gelatin capsules or diluted in water for oral administration. The bioavailability of essential oils is around 95.0 percent through oral ingestion, however due to the potential risk of toxicity administration should only be done under medical supervision.

The preferred means of administering an essential oil for the treatment of respiratory tract infections is **inhalation**. Essential oils are then distributed to the lungs, with an effective bioavailability of 50.0%. [17]

[17] Leigh-de Rapper S, van Vuuren SF.
Odoriferous Therapy: A Review Identifying Essential Oils against Pathogens of the Respiratory Tract. Chem Biodivers. 2020 Jun;17(6):e2000062. doi: 10.1002/cbdv.202000062. Epub 2020 Jun 16. PMID: 32207224.
https://onlinelibrary.wiley.com/doi/full/10.1002/cbdv.202000062



https://onlinelibrary.wiley.com/doi/full/10.1002/cbdv.202000062
A schematic representation of the absorption path followed by essential oils once inhaled.

Essential oils, once inhaled, can reach the smallest spaces within the lungs, and because of their effects on mucociliary clearance, they are able to remain in these spaces for prolonged periods.
Inhalation of essential oils, in addition to acting by dis-inflaming the nasal mucosa, also causes behavioral and mood changes thus allowing the patient to be treated holistically.In fact, about 5.0% of the absorbed essential oils are transported to the brain through olfactory receptors.
Once absorbed through the bloodstream, essential oils are transported to the liver and kidneys for metabolism and excretion, with 70-90.0% of essential oils absorbed and removed in this way.

Commercially available aromatherapy texts report extensively on the use of essential oils for the treatment of respiratory infections, with numerous sources for quick reference for treatment regimens. Within the literature cited

In Leigh-de Rapper's review, (Tab. 9)[18] 55 different essential oils were identified for the treatment of respiratory infections. Essential oils when used in combination are not only blended for potential antimicrobial synergy, but also for a holistic synergistic effect. In fact, essential oils have been shown to have antioxidant (Table 10), anti-inflammatory (Table 11), and antihistamine (Table 12) effects, and thus a combination of essential oils can act on different pathways to treat respiratory infection on various levels.

The antiviral activity of essential oils used for respiratory infections

Because of their lipophilic nature, EOs have the potential to intercalate in the double lipid layer of the viral envelope. Subsequently, the fluidity of the membranes is changed, and at higher concentration, the membranes are even ruptured. [19]
The main mechanisms by which EOs induce antiviral actions are: a direct action on free viruses, inhibition of steps involved in virus binding, penetration, intracellular replication, its release from host cells, and inhibition of vital viral enzymes[20] .

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[18] Leigh-de Rapper S, van Vuuren SF.
Odoriferous Therapy: A Review Identifying Essential Oils against Pathogens of the Respiratory Tract.
Chem Biodivers. 2020 Jun;17(6):e2000062. doi: 10.1002/cbdv.202000062. Epub 2020 Jun 16. PMID: 32207224.
https://onlinelibrary.wiley.com/doi/full/10.1002/cbdv.202000062

Horváth G, Ács K. Essential oils in the treatment of respiratory tract diseases highlighting their role in bacterial infections and their anti-inflammatory action: a review. Flavour Fragr J. 2015 Sep;30(5):331-341. doi: 10.1002/ffj.3252. Epub 2015 May 26. PMID: 32313366; PMCID: PMC7163989.
https://onlinelibrary.wiley.com/doi/full/10.1002/ffj.3252

[19] Wink M.
Potential of DNA intercalating alkaloids and other plant secondary metabolites against SARS-CoV-2 causing COVID-19.
Diversity. 2020;12:175. doi: 10.3390/d12050175.
https://www.mdpi.com/1424-2818/12/5/175/htm

[20] Ma L, Yao L.
Antiviral Effects of Plant-Derived Essential Oils and Their Components: An Updated Review.
Molecules. 2020;25(11):2627. Published 2020 Jun 5. doi:10.3390/molecules25112627
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7321257/.

Swamy MK, Akhtar MS, Sinniah UR.
Antimicrobial Properties of Plant Essential Oils against Human Pathogens and Their Mode of Action: An Updated Review.

Influenza viruses

According to a study conducted by Garozzo et al.[21] essential oil of Melaleuca alternifolia (tea tree) has an inhibitory effect on influenza virus replication at doses below the cytotoxic dose and specifically showed that viral replication was significantly inhibited if tea tree essential oil was added in the early stages of infection (within two hours of infection).

In another study[22] essential oils of Coridothymus capitatus L. (Spanish oregano), Origanum dictamnus L. (dittany) and Salvia fruticosa Mill. (Greek sage) were added to extra virgin olive oil and tested against human influenza virus strains, showing that the combination of essential oils exhibited antiviral activity against influenza A/H1N1, influenza B and human rhinovirus 14 (HRV14) virus strains, while no viral inhibition was found against influenza A/H3N2, respiratory syncytial virus (RSV) and adenovirus 5 .

Finally, Hwa-Jung Choi in his in vitro study found a particular action inhibiting the cytopathic effect of influenza A virus by linalool, an essential oil contained in marjoram, clary sage and anise plants. [23]

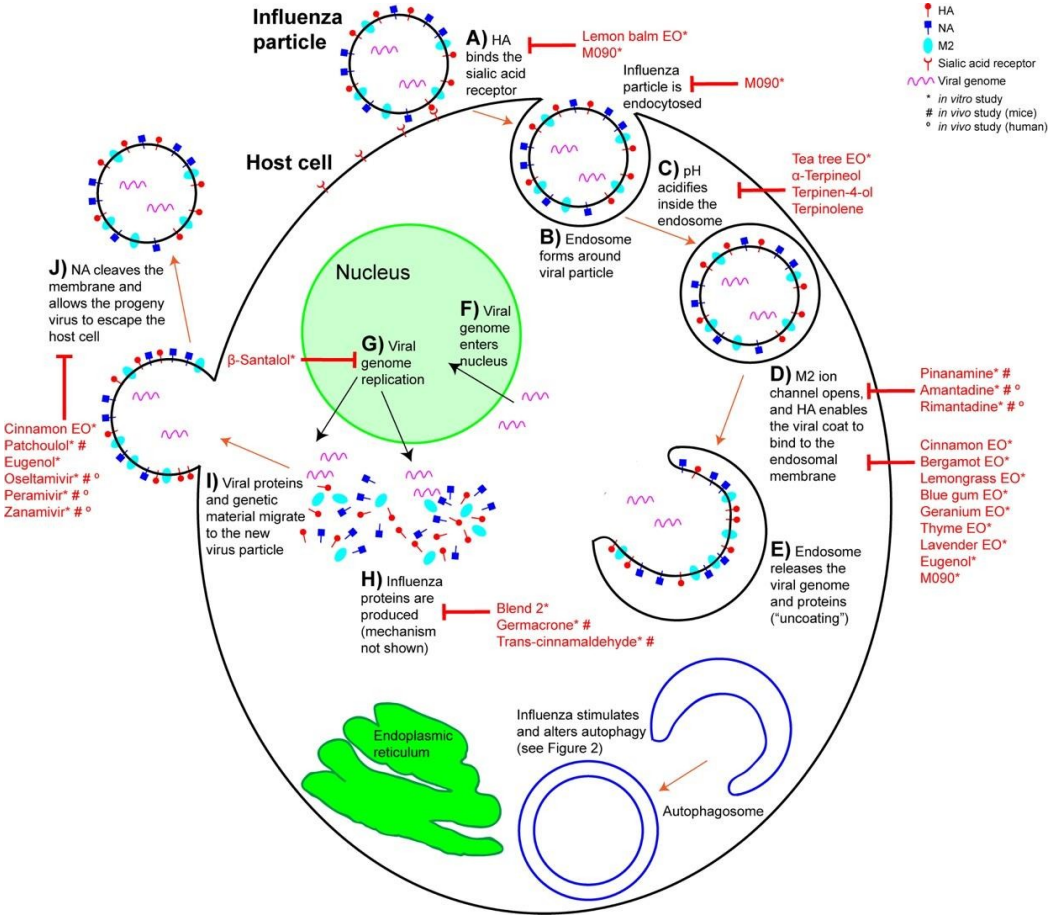
Evid Based Complement Alternat Med. 2016;2016:3012462. doi:10.1155/2016/3012462
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5206475/

[21] Garozzo A, Timpanaro R, Stivala A, Bisignano G, Castro A.
Activity of Melaleuca alternifolia (tea tree) oil on Influenza virus A/PR/8: study on the mechanism of action. Antiviral Res. 2011 Jan;89(1):83-8. doi: 10.1016/j.antiviral.2010.11.010. Epub 2010 Nov 21. PMID: 21095205.
https://pubmed.ncbi.nlm.nih.gov/21095205/

[22] Tseliou, Melpomeni & Pirintsos, Stergios & Lionis, Christos & Castanas, Elias & Sourvinos, George. (2019). Antiviral effect of an essential oil combination derived from three aromatic plants (Coridothymus capitatus (L.) Rchb. f., Origanum dictamnus L. and Salvia fruticosa Mill.) against viruses causing infections of the upper respiratory tract.
Journal of Herbal Medicine. 17-18. 100288. 10.1016/j.hermed.2019.100288.
https://www.researchgate.net/publication/333725513_Antiviral_effect_of_an_essential_oil_combination_derived_from_three_aromatic_plants_Coridothymus_capitatus_L_Rchb_f_Origanum_dictamnus_L_and_Salvia_fruticosa_Mill_against_viruses_causing_infections_of/citation/download

[23] Choi HJ.
Chemical Constituents of Essential Oils Possessing Anti-Influenza A/WS/33 Virus Activity.
Osong Public Health Res Perspect. 2018 Dec;9(6):348-353. doi: 10.24171/j.phrp.2018.9.6.09. PMID: 30584499; PMCID: PMC6296812.
Choi HJ. Chemical Constituents of Essential Oils Possessing Anti-Influenza A/WS/33 Virus Activity. Osong Public Health Res Perspect. 2018;9(6):348-353. doi:10.24171/j.phrp.2018.9.6.09

The following are the sites of action of essential oils in the replication cycle of the influenza virus and their mode of use for air purification and inhalation.



https://tisserandinstitute.org/essential-oils-flu/

Essential oil or blend	Latin name	Use	Directions
Tea tree	*Melaleuca alternifolia*	Kill airborne influenza viruses	Diffuse 30 minutes or nebulize 15 minutes in closed room, wait 15 minutes, then air out room
Blue mallee	*Eucalyptus polybractea*		
Bergamot	*Citrus bergamia*	Kill influenza viruses on surfaces	Diffuse 30 minutes or nebulize 15 minutes in closed room, wait 15 minutes, then air out room. Use in cleaning solution for non-porous surfaces
Blue Gum	*Eucalyptus globulus*		
Geranium	*Pelargonium graveolens*		
Cinnamon leaf	*Cinnamomum zeylanicum*		
Clove bud	*Syzygium aromaticum*		
Cinnamon bark, Clove bud, sweet Orange, Blue Gum, Rosemary	*Cinnamomum zeylanicum, Syzygium aromaticum, Citrus sinensis, Eucalyptus globulus, Rosmarinus officinalis*		
Cassia	*Cinnamomum cassia*	Prevent pneumonia due to influenza	Use in a personal inhaler such as an aromastick
Cinnamon bark	*Cinnamomum zeylanicum*		
Patchouli	*Pogostemon cablin*	Modulate immune response to influenza	

https://tisserandinstitute.org/essential-oils-flu/

The benefits of essential oils toward SARS-Cov-2 infection [24]

Several studies are available that have tested the antiviral effect of a broad-spectrum Of essential oils against SARS-Cov-1, for which we refer to the literature

[24] Patne T, Mahore J and Tokmurke P:
Inhalation of essential oils: could be adjuvant therapeutic strategy for Covid-19.
Int J Pharm Sci & Res 2020; 11(9): 4095-03. doi: 10.13040/IJPSR.0975-8232.11(9).4095-03.https://ijpsr.com/bft-article/inhalation-of-essential-oils-could-be-adjuvant-therapeutic-strategy-for-covid-19/?view=fulltext

Silva JKRD, Figueiredo PLB, Byler KG, Setzer WN.
Essential Oils as Antiviral Agents. Potential of Essential Oils to Treat SARS-CoV-2 Infection: An In-Silico Investigation.
Int J Mol Sci. 2020;21(10):3426. Published 2020 May 12. doi:10.3390/ijms21103426
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7279430/

Emmanuel Onah Ojah
Exploring essential oils as prospective therapy against the ravaging Coronavirus (SARS-CoV-2)
Iberoam J Med, vol.2, n4, p.322-330, 2020 http://dx.doi.org/10.5281/zenodo.3903594

attached, and which could be equally active by inhalation and suffusion for SARS-Cov-2[25] . E.g., the essential oils contained in T. orientalis, J. oxycedrus, L. nobilis, Rosemary, Ravensara, Ravintsara, Tea Tree, Bergamot, Eucalyptus, Lemon Balm, Thyme, Oregano, Fennel, Peppermint, Cinnamon, Clove with active compounds such as β-ocimene, 1,8-cineole, α-pinene and β-pinene, rosmarinic acid, carnosic acid active against SARS-Cov-1 may be useful in preventing Covid-19. [26]

Based on the research conducted for SARS-Cov-2, geranium and lemon essential oils and their main compounds, citronellol, geraniol, limonene, linalool, and neryl acetate, are particularly suggested as they are able to upregulate the expression of ACE2 in epithelial cells, thereby blocking virus entry into host cells and ultimately preventing viral infection. [27]

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http://www.iberoamericanjm.periodikos.com.br/article/10.5281/zenodo.3903594/pdf/iberoamericanjm- 2-4-322.pdf

[25] Wen CC, et al
Specific plant terpenoids and lignoids possess potent antiviral activities against severe acute respiratory syndrome coronavirus.
J Med Chem. 2007 Aug 23;50(17):4087-95. doi: 10.1021/jm070295s. Epub 2007 Jul 31. PMID: 17663539.
https://www.academia.edu/17144711/Specific_Plant_Terpenoids_and_Lignoids_Possess_Potent_Antiviral_Activities_against_Acute_Respiratory_Syndrome_Coronavirus

Boukhatem MN, Setzer WN. Aromatic Herbs, Medicinal Plant-Derived Essential Oils, and Phytochemical Extracts as Potential Therapies for Coronaviruses: Future Perspectives. Plants (Basel). 2020;9(6):800. Published 2020 Jun 26. doi:10.3390/plants9060800
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7356962/

Tshibangu, D. S. T., et al (2020).
Possible Effect of Aromatic Plants and Essential Oils against COVID-19: Review of Their Antiviral Activity.
Journal of Complementary and Alternative Medical Research, 11(1), 10-22.
https://doi.org/10.9734/jocamr/2020/v11i130175
https://www.journaljocamr.com/index.php/JOCAMR/article/view/30175

[26] Patne T, Mahore J and Tokmurke P:
Inhalation of essential oils: could be adjuvant therapeutic strategy for Covid-19.
Int J Pharm Sci & Res 2020; 11(9): 4095-03. doi: 10.13040/IJPSR.0975-8232.11(9).4095-03.
https://ijpsr.com/bft-article/inhalation-of-essential-oils-could-be-adjuvant-therapeutic-strategy-for-covid-19/?view=fulltext

[27] Senthil Kumar KJ, Gokila Vani M, Wang CS, et al.
Geranium and Lemon Essential Oils and Their Active Compounds Downregulate Angiotensin-Converting Enzyme 2 (ACE2), a SARS-CoV-2 Spike Receptor-Binding Domain, in Epithelial Cells.
Plants (Basel). 2020;9(6):770. Published 2020 Jun 19. doi:10.3390/plants9060770
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7355681/

Other essential oils include those contained in eucalyptus *(*Eucalyptus globulus)[28] such as jensenone/ 1,8-cineole (eucalyptol) for potential activity against SARS-Cov-2 proteinase. Various in vitro and ex vivo studies have been conducted to investigate the effects of eucalyptus oils and eucalyptol treatments on monocytes and macrophage recruitment in response to inflammation and lung infection. Data from these studies demonstrate marked immunomodulatory properties of both eucalyptus oil and its active ingredient, namely eucalyptol. Both treatments reduced the release of pro-inflammatory cytokines from monocytes and macrophages without changing their phagocytic properties. Eucalyptol is also known to have mucolytic and bronchodilator properties. Interestingly, eucalyptus oil has also been shown to have disinfectant properties and to inhibit the growth of viruses on various tools and filtering devices. Overall, data from preclinical and clinical studies support the promising therapeutic potential of eucalyptus oil and its active constituent, namely eucalyptol in the prevention and treatment of COVID-19.

Garlic[29] has been used for centuries as a medicine to treat colds, flu and other types of infections. Garlic oil was chemically analyzed by GC- MS method, and 18 compounds were identified, of which allyl disulfide (28.4%), allyl trisulfide (22.8%), allyl (E)-1-propenyl disulfide (8.2%), allyl methyl trisulfide (6.7%) and diallyl tetrasulfide (6.5%) were identified as the main constituents of garlic essential oil. Seventeen compounds were studied for activity against the ACE2 protein and the main viral protease (M^{pro} /6LU7) of SARC-CoV-2. All 17 compounds studied showed interactions with the host protein (ACE2) and viral proteases, indicating that garlic oil has great potential to treat COVID-19 patients. Furthermore, based on in vitro studies, it has been proposed that garlic essential oils and their isolated constituents, particularly allyl disulfide, have the potential to prevent

[28] Dev, Sharma & Kaur, Inderjeet. (2020).
Bioactive molecules from eucalyptus essential oil as potential inhibitors of COVID 19 corona virus infection by molecular docking studies.
Kragujevac Journal of Science. 29-43. 10.5937/KgJSci2042029D.
https://www.researchgate.net/publication/343221952_Bioactive_molecules_from_eucalyptus_essential_oil_as_potential_inhibitors_of_COVID_19_corona_virus_infection_by_molecular_docking_studies.

[29] Thuy BTP, My TTA, Hai NTT, et al. Investigation into SARS-CoV-2 Resistance of Compounds in Garlic Essential Oil [published correction appears in ACS Omega. 2020 Jun 23;5(26):16315]. ACS Omega. 2020;5(14):8312-8320. Published 2020 Mar 31. doi:10.1021/acsomega.0c00772
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7123907/

virus entry into host cells and to activate molecular antioxidant mechanisms that reduce the production of harmful pro-inflammatory cytokines.

Treatment with cinnamaldehyde (active ingredient of cinnamon) was shown to significantly reduce the wet-to-dry lung ratio and pulmonary edema in mice. Cinnamaldehyde also significantly inhibited neutrophils, macrophages and total cell number in bronchoalveolar lavage fluid and reduced the levels of inflammatory cytokines such as TNF-α, IL-6, IL-13 and IL-1β indicating a possible beneficial role in COVID-19.

Eugenol, menthol, and carvacrol were also studied against various SARC-CoV-2 protein targets and revealed binding affinity toward SARC-CoV-2 spike protein, major protease (M^{pro}), RNA-dependent RNA polymerase, and human ACE-2 proteins. Another in silico study evaluated the binding potential of carvacrol against the SARC-CoV-2 major protease (M^{pro}) and showed that it has the potential to inhibit Mpro and thus may arrest viral replication. [30]

Ginger deserves its own note because it can be successfully used for self-care of mild COVID-19 symptoms with suffumigation, as well as for oral use in the form of decoction, for its significant anti-inflammatory, antimicrobial, antioxidant, and bronchodilator effect[31] .

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[30] Asif M, Saleem M, Saadullah M, Yaseen HS, Al Zarzour R.
COVID-19 and therapy with essential oils having antiviral, anti-inflammatory, and immunomodulatory properties.
Inflammopharmacology. 2020;28(5):1153-1161. doi:10.1007/s10787-020-00744-0
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7427755/

Kulkarni SA, Nagarajan SK, Ramesh V, Palaniyandi V, Selvam SP, Madhavan T. Computational evaluation of major components from plant essential oils as potent inhibitors of SARS-CoV-2 spike protein. J Mol Struct. 2020;1221:128823. doi:10.1016/j.molstruc.2020.128823
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7334662/

https://medicinanaturaleolistica.it/oli-essenziali-e-coronavirus-lo-stato-della-scienza/

[31] Wang X, Shen Y, Thakur K, Han J, Zhang JG, Hu F, Wei ZJ.
Antibacterial Activity and Mechanism of Ginger Essential Oil against Escherichia coli and Staphylococcus aureus.
Molecules. 2020 Aug 30;25(17):3955. doi: 10.3390/molecules25173955. PMID: 32872604; PMCID: PMC7504760.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7504760/

Mahboubi, M.

A study carried out in several Italian regions with wide variability in deaths from COVID-19 led to the hypothesis that the lower incidence of mortality in Molise, Calabria, and Basilicata is also related to a protective effect of evergreen vegetation, particularly Laurus nobilis L (laurel), which produces lauruside 5, a potential protease inhibitor of SARS-Cov-2 M^{pro} . [32]

Finally, it is worth mentioning that in China since the beginning of the COVID-19 epidemic, fumigation has been used for air disinfection to prevent the spread of the virus. It has also been shown that in the clinical treatment period, the application of moxibustion[33] plays the role of anti-inflammatory agent, regulates immune function and prevents patients' deterioration. [34]

To summarize, the following is a partial list of aromatic plants and contained essential oils that are useful for the prevention of SARS-Cov-2 infection, most of which can be used for air sanitization, and for

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Zingiber officinale Rosc. essential oil, a review on its composition and bioactivity.
Clin Phytosci 5, 6 (2019). https://doi.org/10.1186/s40816-018-0097-4
https://clinphytoscience.springeropen.com/articles/10.1186/s40816-018-0097-4

Imanishi N, Andoh T, Mantani N, Sakai S, Terasawa K, Shimada Y, Sato M, Katada Y, Ueda K, Ochiai H.
Macrophage-mediated inhibitory effect of Zingiber officinale Rosc, a traditional oriental herbal medicine, on the growth of influenza A/Aichi/2/68 virus.
Am J Chin Med. 2006;34(1):157-69. doi: 10.1142/S0192415X06003722. PMID: 16437748.
https://www.worldscientific.com/doi/abs/10.1142/S0192415X06003722

[32] Roviello V, Roviello GN.
Lower COVID-19 mortality in Italian forested areas suggests immunoprotection by Mediterranean plants [published online ahead of print, 2020 Aug 14]. Environ Chem Lett. 2020;1-12. doi:10.1007/s10311-020-01063-0
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7427271/

[33] Deng H, Shen X.
The mechanism of moxibustion: ancient theory and modern research.
Evid Based Complement Alternat Med. 2013;2013:379291. doi:10.1155/2013/379291
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC3789413/

[34] Zhang XR, Li TN, Ren YY, Zeng YJ, Lv HY, Wang J, Huang QW.
The Important Role of Volatile Components From a Traditional Chinese Medicine Dayuan-Yin Against the COVID-19 Pandemic.
Front Pharmacol. 2020 Sep 25;11:583651. doi: 10.3389/fphar.2020.583651. PMID: 33101037; PMCID: PMC7546797.
https://www.frontiersin.org/articles/10.3389/fphar.2020.583651/full

inhalation and suffumigation. Some of these medicinal plants will be discussed in more detail in the therapy section of COVID-19. [35]

Plant « English Name »	Family	The main components
Quinquina (*Cinchona*)	Rubiaceae	quinidinone; épiquini. dine; épiquinine; quinidine; cinchonine; cinchonidine; quinine; hydroquinidine;
Eucalyptus	Myrtaceae	α-Pinene ; β-Pinene ; α-Thujene ; β-Phellandrene, p-Cymene ; 1,8 cineole
Garlic	Amaryllidaceae	Alliin; Allicin ; E-Ajoene; Z-Ajoene; 2-Vinyl-4H-1,3-dithiin; Diallyl sulfide (DAS); Diallyl disulfide (DADS) ; Diallyl trisulfide (DATS) Allyl methyl sulfide (AMS)
Thyme	Lamiaceae	camphor, camphene, α-pinene, 1,8-cineole, borneol, β-pinene
Cinnamon (*Cinnamomum sp.*)	Lauraceae	Tannins, Flavonoids, Anthocyans, Free quinones, Coumarins, Terpenes, Sterol substances and Alkaloids
Ginger	Zingiberaceae	phenolic, saponin, tannin and flavonoids
Dianthus	Caryophyllaceae	monoterpene hydrocarbons
Mentha	Lamiaceae	monoterpenes and terpenoids
Laurel	Lauraceae	1,8-cineole, terpinyl acetate, sabinene, α- pinene, β-pinene, terpinin-4-ol and 4 -terpineol
Artemisia	Asteraceae	eucalyptol, chrysanthenone, α-thujone, verbenone, cischrysanthenyl acetate, myrtenyl acetate and heptadienal

https://www.jpsr.pharmainfo.in/Documents/Volumes/vol12issue08/jpsr12082017.pdf

The use of essential oils and masks deserves a note:

Masks and essential oils

Essential oils could also be used on face masks, either to prevent the growth of bacteria on the cotton mask or as a personal balm, always however with the precaution of changing the mask often and using them
diluted so as to avoid irritation to mucous membranes.

[35] Rachid FLOUCHI 1,2, and Kawtar FIKRI-BENBRAHIM 1*.
Prevention of COVID 19 by aromatic and medicinal plants: A systematic review
J. Pharm. Sci. & Res. Vol. 12(8), 2020, 1106-1111
https://www.jpsr.pharmainfo.in/Documents/Volumes/vol12issue08/jpsr12082017.pdf

To this end, the Defense Institute of Advanced Technology (DIAT-India) has patented a biodegradable face mask made from nanofibers of Ayurvedic products (neem oil, turmeric, tulsi (holy basil), ajwain (bishop's herb), black pepper, gum arabic, clove, sandalwood and saffron) that acts as a virus neutralizer and resists bacteria and has named it "Pavitrapati" . [36] Equally, masks made of different fabrics impregnated with Chinese antibacterial medicinal herbs have been manufactured with excellent results. [37]

The speakers for the environment [38]

To diffuse the fragrance given off by essential oils, there are several possibilities:

Electric essential oil diffuser (usually ultrasonic)
the oil is not burned but heated gradually and kept at a constant temperature; this ensures perfect diffusion of the essential aroma that retains all its characteristics and properties.
The electric or ultrasonic spray diffuser variant is the only one in which essential oils are mixed together with water. They diffuse the atomized essence and can be electric or ultrasonic. This device turns the essential oils into a mist that falls back more quickly, weighed down by the water. These microdroplets can leave traces on the supporting surface, so it is not recommended to place it on a piece of furniture made of wood or material that is not water-repellent.

Candle essential oil diffuser (essence burner)
Essence burners found on the market can be found in classic 'candle' models, usually made of ceramic, and consist of small to medium-sized vessels with a space at the base where a **lit candle is** placed.
he heat produced by the flame heats the cup containing the essence, and the fumento thus released releases the fragrant aroma into the air.

[36]h ttps://innov.afro.who.int/global-innovation/pavitrapati-2121

[37] Wang, Y.F., Kang, F., You, S.J., Tsai, C.H. and Lin, G.L. (2017).
Preparation and Characteristic of Antibacterial Facemasks with Chinese Herbal Microcapsules.
Aerosol Air Qual. Res. 17: 2119-2128. https://doi.org/10.4209/aaqr.2017.06.0208
https://aaqr.org/articles/aaqr-17-06-oa-0208.pdf

[38] https://www.tuttogreen.it/diffusore-oli-essenziali/

The cost of a candle essence burner is quite affordable (10 euros and up), but the use of this type of essential oil diffuser is not recommended. In fact, the excessive overheating produced by the flame tends to oxidize the oil, and the risk of releasing toxic substances such as benzopyrene, or simply of the essences losing their characteristics, is high.

Thermosiphon humidifiers

During the colder season, however, radiators and heaters are the most immediate and inexpensive way to scent home environments with your favorite natural essences. Scented drops can be added directly to humidifiers or water bowls attached to radiators or to a special cup, bowl or tray placed on the radiator itself.

Perfumer with sticks

To diffuse an essential oil, a glass bottle in which balsa wood sticks are dipped that soak up the oil and slowly release it into the environment may also be fine. They need to be replaced every 2 to 3 months because they become too soaked with oil and no longer absorb it well.

Precautions for use and toxicity of essential oils [39]

Many aromatherapy providers, especially on the Internet, continue to sell dangerous essential oils without adequate warnings. There are also examples of

[39] https://www.rch.org.au/clinicalguide/guideline_index/Essential_Oil_Poisoning/
https://ifaroma.org/en_GB/home/blog/essential-oils-coronavirus-covid19
https://ifaroma.org/application/files/9215/5169/6992/INGESTION __NEAT_APPLICATION_OF_ESSENTIAL_OILS_GUIDANCE.pdf
https://ifaroma.org/en_GB/home/explore_aromatherapy/safety

Eisenhut M.
The toxicity of essential oils.
Int J Infect Dis. 2007 Jul;11(4):365; author reply 365-6. doi: 10.1016/j.ijid.2006.07.004. Epub 2007 Feb 23. PMID: 17321181.
https://www.ijidonline.com/action/showPdf?pii=S1201-9712%2806%2900158-5
Oliviu Vostinaru, Simona Codruta Heghes and Lorena Filip (February 27th 2020). Safety Profile of Essential Oils, Essential Oils - Bioactive Compounds, New Perspectives and Applications, Mozaniel Santana de Oliveira, Wanessa Almeida da Costa and Sebastião Gomes Silva, IntechOpen, DOI: 10.5772/intechopen.91363. https://www.intechopen.com/books/essential-oils-bioactive-compounds-new-perspectives-and- applications/safety-profile-of-essential-oils

National Institute of Health Essential oils for human health and the environment.
Edited by Francesca Mondello, Anna Maria Marella, Maria Grazia Bellardi and Maura Di Vito
2015, ii, 85 p. ISTISAN Reports 15/6 (in Italian).

inadequate labeling regarding sell-by or expiration dates, which should always be provided especially for essential oils from the citrus and pine families, which develop skin-sensitizing chemicals as they age.

Shelf life can be extended with the addition of artificial antioxidants or vitamin E, however, be warned that essential oils without antioxidants should not be used on the skin after about six months, while they can still be used as fragrances, and that storing such oils under optimal conditions, such as in sealed containers in the refrigerator can slow chemical changes in the oil. [40]

Some definitions may help in understanding the toxicology of essential oils.

Essential oil: a volatile oil composed of a mixture of complex hydrocarbons (usually terpenes) and other chemicals extracted from a plant, usually by a distillation method. Essential oils give the plant its characteristic aroma and quickly evaporate from the skin or other surface.
Essence: an essence is a concentrated fragrance, a perfume.

http://old.iss.it/binary/publ/cont/15_6_web.pdf

Aromatherapy Undiluted- Safety and Ethics
https://www.alliance-aromatherapists.org/assets/Undiluted-are%20we%20in%20denial.pdf

Toxicity Myths - the Actual Risks of Essential Oil Use
By Ron Gub
http://www.agoraindex.org/Frag_Dem/toxicitymyths.html
EFEO/IFRA Guidelines on Environmental Assessment of Complex Natural Substances (NCS) - Version. 01. May 26, 2016 -
https://echa.europa.eu/documents/10162/22697263/eco_tox_essential_oil_guidance_ifra_it.pdf/85e47836-d8dc-3bce-4780-a4cebc00ad1e

EFEO/IFRA GUIDELINES ONSUBSTANCE IDENTIFICATION AND USE OF COMPLEX NATURAL SUBSTANCES (NCS) UNDER REACH AND CLP REGULATIONS - - Version of August 5, 2015 -
https://echa.europa.eu/documents/10162/13643/efeo_ifra_guidelines_it.pdf/4f15e052-bbb8-4489-9a80-77267d9f834b

[40] The safety issue in aromatherapy
http://www.pharmpress.com/files/docs/aromascich07.pdf

Fixed oil: a fixed oil is a nonvolatile oil composed of long-chain fatty acids (such as castor oil or safrole).
Carrier oils: essential oils used therapeutically in herbal remedies are too concentrated to be applied directly and must be diluted. Often only a few drops are put into carrier oil (e.g., safflower oil) in a therapeutic application [41]

Essential oils can be used by herbalists in a variety of ways. Topical applications, bathing, inhalation, ingestion, or parenteral use have been documented. Some definitions are helpful in understanding what herbalists mean by prescribing essential oils to a patient.

Aromatherapy: the use of volatile oils from therapeutic use.
Carminative: agent that helps expel gas from the gastrointestinal tract. **Rubefacient**: agent that flushes the skin and causes a localized sensation of heat through skin vasodilation.
Emmenagogue: agent that promotes menstruation and treats problems related to menstrual flow.
Abortive: agent that induces abortion [42]

The link For the Conscious Use of Essential Oils[43] In which the precautions for use and potential risks are found general and in pregnancy, lactation, in infants, children, allergy sufferers and in cases of hormone-dependent diseases.

Regarding **usage warnings,** please note that: [44]

[41] http://www.guidaoliessenziali.com/come-usare-gli-oli-essenziali-gli-oli-vettori/

[42] Woolf A.
Essential oil poisoning.
J Clin Toxicol. 1999;37(6):721-7. doi: 10.1081/clt-100102450. PMID: 10584585.
https://pubmed.ncbi.nlm.nih.gov/10584585/

[43] https://www.consigli-dei-sensi.it/guida-oli-essenziali/#per-un-utilizzo-consapevole-degli-oli-essenziali

Oil By Oil - Specific Safety Precautions
https://gaearoyals.com/safety-precautions-by-essential-oil/

[44] http://freyakosmetik.blogspot.com/2012/07/avvertenze-sulluso-degli-oli-essenziali.html

- Essential oils are substances with very powerful biological effects so they should always be used in small doses and recommended for use by a qualified person and if for oral use under medical supervision
- They should never be used pure on the skin but diluted in vegetable oils, base creams ect... as they are highly concentrated substances.
- Store away from light, in a cool place because essential oils tend to oxidize over time and in contact with light producing toxic derivatives
- To rule out possible allergic reactions, the first time you use an essential oil limit yourself to a small diluted amount (1 drop), regardless of the mode of intake (internal or external).
- Almost all essential oils are contraindicated in pregnancy, and in particular: basil, cypress, sweet fennel, hyssop, marjoram, oregano, rosemary, sage, and thyme.
- Essences of basil, camphor, eucalyptus and sweet fennel should not be given to children.
- The essences of camphor, sweet fennel, hyssop, rosemary, and thyme are contraindicated in cases of epilepsy.
- Essences of orange, basil, bergamot, sweet fennel, lemon, peppermint, oregano, and rosemary can cause sensitization.
- Orange, bergamot, sweet fennel, and lemon essences are photosensitizing: avoid applying them to the skin before sun exposure.
- Essences of chamomile, camphor and peppermint can decrease the effectiveness of homeopathic treatments.
- Essential oils are highly flammable, so they should be kept away from heat sources and tend to damage furniture wood and lacquers, so care should be taken to clean up immediately if they come in contact.

The test to tell if the oil is natural is to drop a drop on a sheet of paper: synthetic oil will make a drop that does not spread and absorbs very slowly; natural oil immediately spreads a lot, evaporating after only one day. Essential oils (e.g., peppermint) can, in their pure state damage furniture or lacquer surfaces, so use glass containers and wipe off any spilled drops!

First aid measures

EYES: rinse thoroughly with water and seek medical attention if severe redness occurs

SKIN: The best way to remove an essential oil is with a cotton ball soaked in jojoba or sweet almond oil. It can also be washed with soap and water. If signs of inflammation occur, a doctor should be consulted
INTERNAL USE: In case of inappropriate ingestion, do not induce vomiting and
Consult the doctor by showing the container or label

Essential oils (more or less) natural [45]

We must first make a clear (and preliminary) distinction between : Adulterations, Sophistications and Technological Interventions

Adulterations: Consist of (partial) modification of the original essential oil (EO).
They are usually implemented for two purposes:
1) Improve chemical, organoleptic and biological properties by adding certain compounds typical of that EO and/or extraneous
2) Increase the amount of EO by the addition of diluting substances.
In both cases it is commercial fraud; sometimes there may be a risk of toxicity (especially with thinners)

ESEMPI DI ADULTERAZIONE

Olio essenziale	Sostanze aggiunte
Camomilla romana	Esteri dell'acido tiglico e angelico
Garofano	Eugenolo….
Lavanda	Acet. di linalile, di nerile; linalolo
Melissa	Dist.to di melissa su o.e. di limone
Neroli	Linalolo, acet. di geranile,…
Rosmarino	1,8-cineolo….

Dilution of different essential oils, by addition of : benzyl alcohol, benzyl benzoate, diethylene glycol, diethyl phthalate, ect

Sophistications: consist of fraudulently declaring as "essential oil of....." an EO of another (sometimes not well known) botanical species. They can pose acute or chronic toxicological risks.
Example:
Juniperus sabina or *J.phoenicea*, instead of *J.communis*
In some cases, sophistication finds only cost motivation Example: EO of *Dracocephalum moldavicum* instead of *Melissa officinalis*

[45] http://www.pianteofficinali.eu/wp-content/uploads/2016/11/Alfonsine-2004-05-O.e.pdf

Technological interventions: They can be legitimate and justified, as long as they are declared and known. They are in fact intended to change the "original" composition of the EO to improve its properties. They require suitable technologies and equipment Examples: rectification, tri-rectification, deterpenation, sesquideterpenation, de- camphoration.

Analytical investigations carried out on many essential oils often reveal problems of adulteration and/or adulteration, and this aspect assumes considerable importance both from an economic point of view (many essential oils have very high costs and therefore the fraudulent addition of different oils of low cost and/or quality or of some components of the essential oil itself obtained by synthesis or isolated from other plant species is not to be underestimated) and from the point of view of safety and possible efficacy.

Methods of applying essential oils to purify environments

Taken from Essential Oils, Coronavirus & COVID19 (International federation of aromatherapists)[46]

Before using essential oils, for yourself or others, be aware that some essential oils have particularly strong, penetrating, pungent and tenacious odors and are not necessarily suitable for children, pregnant women (whose sense of smell is often heightened) or frail people. Click here or here for essential oil uses, potential risks, and application methods.

- **Direct inhalation** using a scent strip or nasal inhaler can improve breathing or help you relax. This method can help relieve upper respiratory tract symptoms such as stuffy nose, sneezing, coughing, sore throat or mild breathing difficulties caused by sinusitis, hay fever or cold. Useful essential oils include **lavender, eucalyptus, peppermint, pine needles, and melaleuca**. Essential oils that have been shown to be effective in reducing stress, anxiety, irritability, mental and physical fatigue, or for general relaxation include **geranium, lavender, tangerine, orange, rose, and vetivert**.

- **Diffusers and sprays** are more suitable not only for maintaining a pleasant environment but also as air purifiers, since many essential oils have antiseptic and antimicrobial properties, e.g., **cinnamon, eucalyptus, peppermint,**

[46] https://ifaroma.org/en_GB/home/blog/essential-oils-coronavirus-covid19

melaleuca. Essential oils that increase mental alertness, improve memory, and enhance autonomic functions are **bergamot, lemon, peppermint, and rosemary**.

- **Topical applications** to enhance immune system and organ action through transdermal absorption of essential oils

Sanitizing against microbes in the air - by using essential oils in a diffuser, spray bottle or aerosol

When an airborne infection is present, it is important to keep the surrounding air as free of infectious organisms as possible. Spraying essential oils into the air helps keep the environment healthier for everyone and can stimulate the immune system. Some useful essential oils for air purification are:

Name of the aromatic plant	Benefits
Bergamot *Citrus bergamia Risso & Poit.*	anti-infective, antiviral, deodorant
Cinnamon leaves *Cinnamomum zeylanicum Nees*	A powerful antimicrobial and air disinfectant.
Eucalyptus (all) *Eucalyptus globulus labill.* *Eucalyptus radiata Seiber ex DC* *Eucalyptus smithii RT Baker*	Antimicrobial that can help prevent further infection, antiviral, immunostimulant
Lavender (flower heads) *Lavendula*	Anti-infective, immunostimulant, mucolytic
May Chang CT Citral - *Litsea cubeba*	Antimicrobial and air freshening
	Antimicrobial, antiviral, purifies the air.

Peppermint *Mintha piperata*	

Immuno-stimulants / Antimicrobials / Antivirals

These are essential oils that can b o o s t immunity or directly fight infectious organisms:

Name of the aromatic plant	Benefits
Bergamot *Citrus bergamia Risso & Poit.*	antimicrobial, antiviral
Cajeput *Melaleuca leucadendron*	Antiviral, antimicrobial, expectorant, immunostimulant
Eucalyptus (all) *Eucalyptus globulus labill.* *Eucalyptus radiata Seiber ex DC* *Eucalyptus smithii RT Baker*	Antiviral, anti-infective, antimicrobial, febrifuge, immunostimulant, expectorant
Lavender *Lavendula latifolia Medik*	Antiviral, antimicrobial, expectorant, anti-infective
Lemongrass *Cymbopogon citratus DC Stapf.*	Antiviral, antifungal, anti-infective
Manuka *Leptospermum scoparium Forst & Forst*	Antiviral, antimicrobial, immunostimulant, antitussive, expectorant
Melissa *Melissa officinalis*	immunostimulant, expectorant, antitussive
Niaouli CT Cineolo *Melaleuca quinquinervia or Viridiflorol*	Antiviral, antimicrobial, expectorant, immunostimulant

Ravintsara *Cinnamomum camphora*	Antiviral, antimicrobial, anti-infective, immunostimulant,
Rosemary CT Cineolo *Rosmarinus officinalis*	antimicrobial, expectorant
Tea-Tree *Melaleuca alternifolia*	Antiviral, antimicrobial, anti-infective, immunostimulant
Thyme CT Thymol *Thymus vulgaris*	Antimicrobial, anti-infective, immunostimulant

Adaptogens and antioxidant essential oils

Adaptogens: some essential oils are classified as adaptogens because they are known to have a "normalizing" effect on bodily processes, hormone release and stress, which means their action can be energizing, stimulating, invigorating or decreasing, calming, sedative depending on what is needed. Adaptogenic essential oils can help regulate stress hormone levels, increase stamina, improve immune response, regularize blood pressure, heart and respiratory rates, reduce inflammation, and contribute to prevention and recovery from illness.

Examples of adaptogenic essential oils: Bergamot, Frankincense, Rose Geranium, Lavender, Lemon, Lemon Balm, Rose, Neroli, Turmeric Root, Ylang-ylang.

Antioxidants maintain balance, help control oxidative stress, help improve immunity and keep the body healthy.
Examples of antioxidant essential oils: - citrus essential oils, black pepper, ginger, hickory, oregano.

Essential oils to soothe a spasmodic cough: the best methods of application are steam inhalation or a chest massage.

Examples of antitussive and respiratory antispasmodic essential oils are Benzoin, Cypress, Chamomile R, Fennel, Phragonia, Inula, Lavender, Myrtle (Green), Manuka, Marjoram.

Note: Benzoin, Chamomile R., Fragonia, Lavender and Manuka essential oils are suitable for children or vulnerable people in a diffuser or in a mixture diluted from 0.5% to 1% and applied to the soles of the feet.

Chest rubs and inhalation in recovery can be helpful up to 6 months after illness:
Respiratory anti-inflammatory and tissue repairing: benzoin, cedarwood, frankincense, niaouli CT Linalool and CT Nerolidol, blue tanacetus, thyme CT linalool.

PHYTOTHERAPY

Primary prevention in SARS-Cov-2 infection is to be recommended in all population groups, but it is of crucial importance in the over-65 age group who are predisposed by multiple diseases and therefore at greater risk of the fatal serious complications.

Because the first phase of infection has very flu-like symptoms and the immune system response is predominantly innate, **all treatments that go to stimulate the nonspecific, tissue repair response are effective**.

Medicinal plants possessing antiviral and antioxidant properties are very **numerous**, as are very consistent clinical studies conducted showing their efficacy even against the SARS virus and SARS-Cov-2

Italian law (L. 99/1931) identifies as officinal plant a heterogeneous group of plant species belonging to three broad categories: medicinal, aromatic and perfume.

The WHO (World Health Organization) defines **medicinal plant** as a plant organism that contains substances that can be used for therapeutic purposes to create pharmacologically active preparations.

Of the medicinal plants[47] certain parts, called **drugs**, are used in which the functional substances, or active ingredients, responsible for the activity of the preparation are present.

HERBECEDAR: List of medicinal plants and herbs - tabs

The set of functional substances contained within a drug is termed **phytocomplex**.

Let us examine the main herbal preparations found in the market, beginning with the distinction of preparations from fresh plant and preparations from dried plant.
Two different preparations are obtained from fresh plant:

– The **juice**, which is obtained by simple squeezing of the drug
– the **mother tincture,** which is obtained by maceration in an appropriate mixture of water and alcohol. Mother tinctures have a concentration of 1:10 expressed according to the dry weight of the drug and have the advantage of having all the functional substances present in the drug, including enzymes; the only drawback is the need to use rather high dosages being low concentration preparations.

Multiple preparations are obtained from dried plant:

– the simplest is the so-called ***tisane*** *cut* with which infusions or decoctions are prepared
– Micronized **powder**: is obtained by fine pulverization of drugs
– **Fluid extract**: is obtained by maceration in water and alcohol of dried drugs, and the solution obtained has a concentration of 1:1

[47] https://www.visioneolistica.it/le-piante-officinali-e-i-benefici-per-ciascun-organo/

– **soft extract**: obtained from the fluid extract by partial evaporation of the solvent to a paste thick enough not to wet a sheet of paper on which it is laid. Having fallen into disuse, soft extracts endure almost exclusively for ginseng. Concentration ratio about 2.5:1.

– **dry extract**: is obtained by total evaporation of the solvent and represents the highest possible concentration obtainable from a drug. With some exceptions, the concentration ratio is 4-5:1.

The main classes of compounds found in drugs are the:

- Essential oils
- Heterosides
- O-heterosides: flavonoids; coumarins; tannins; anthraquinones; hydroquinones; saponins; salicylates; iridoids
- S-heterosides
- Alkaloids
- Fibers: mucilages; pectins; gums
- Oils
- Vitamins and minerals

MEDICINAL PLANTS AND COVID-19

The following is a list of some recent published studies on the antiviral effects of medicinal plants used in traditional herbal medicine, Chinese medicine, and Ayurvedic medicine with reference to the prevention and treatment of mild-to-moderate forms of COVID- 19.

Traditional Chinese Medicine

Xian Y, Zhang J, Bian Z, et al.
Bioactive natural compounds against human coronaviruses: a review and perspective.
Acta Pharm Sin B. 2020;10(7):1163-1174. doi:10.1016/j.apsb.2020.06.002
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7278644/

Historically, TCM (Traditional Chinese Medicine) has developed medical theories and accumulated rich and valuable experience in the prevention and treatment of

lung diseases, particularly pneumonia. Natural products such as Chinese herbs possess various bioactivities and have been widely used to treat diseases of viral origin such as the common cold, influenza, and SARS.
Many studies have reported the anti-inflammatory activities of natural compounds, and inflammation has been considered as the underlying pathogenesis of various medical conditions, including influenza and COVID-19. **Emodin**, a flavonoid isolated from *Rhei Radix et Rhizoma*, is able to block SARS-CoV by interfering with the interaction of protein S and ACE2.
It also showed anti-inflammatory, antiproliferative and anti-carcinogenic properties. Dose-dependent hemodin ameliorated asthmatic airway inflammation by inhibiting activated macrophage polarization and STAT6 phosphorylation.
Scutellarein, another flavonoid derived from the plant, exerted anti-inflammatory action by suppressing the expression of cyclooxygenase-2 and inducible nitric oxide synthase through inhibition of the NF-κB pathway. Flavonoids from *Lonicerae Japonicae Flos*, **glycyrrhizin** and **resveratrol** have also been reported to possess anti-inflammatory effects.

High-profile research published in Science reported that **desaminotyrosine** (DAT), a metabolite produced by a specific human-associated gut microbe, *Clostridium orbiscindens*, was able to protect the host from influenza through suppression of type I interferon signaling and increased lung immunopathology[48] . DAT could be produced by human enteric bacteria from flavonoids and amino acid metabolism. In addition, DAT is also a degradation product of flavonoids in which some Chinese foods and medicinal plants are rich. Therefore, the protective effect of DAT against influenza may be related to the anti-inflammatory effect of flavonoids.

Western medicine used to treat COVID-19 patients usually includes broad-spectrum antibiotics, antivirals, corticosteroids or their combination. These conventional drugs could quickly manage patients' main symptoms but can cause serious side effects, while the TCM treatment modality has the advantage of low toxicity.
A systematic review and meta-analysis revealed that integrated Chinese and Western medicine had better effects and fewer adverse drug reactions on the
COVID-19 patients compared with Western medicine alone. In addition, it has been reported that

[48] Steed AL, Christophi GP, Kaiko GE, et al.
The microbial metabolite desaminotyrosine protects from influenza through type I interferon.
Science. 2017;357(6350):498-502. doi:10.1126/science.aam5336
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5753406/

TCM treatment is able to mitigate the side effects associated with conventional therapies for patients with SARS-CoV.

Below are the active ingredients studied against SARS-Cov and SARS-Cov-2 with related
mechanism o f action.

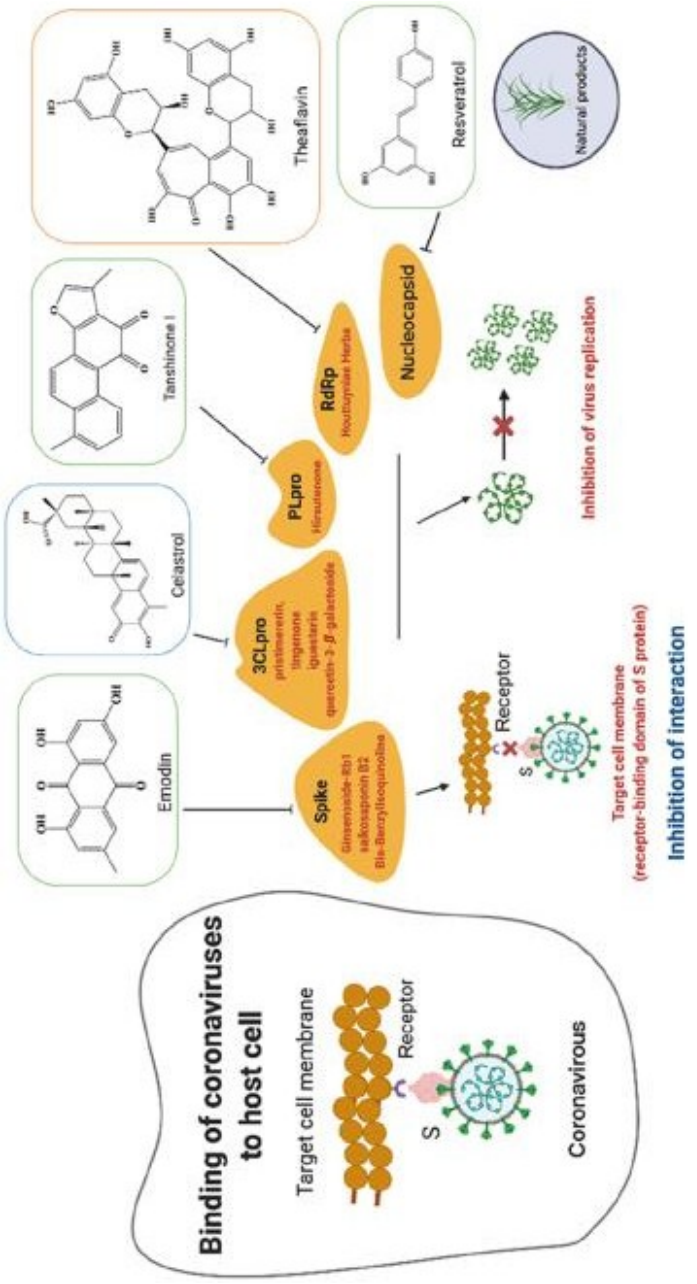

Binding of coronaviruses to host cell
Target cell membrane
Receptor
S
Coronavirous
Inhibition of interaction
Target cell membrane (receptor-binding domain of S protein)
Inhibition of virus replication
Spike
3CLpro
PLpro
RdRp
Nucleocapsid
Emodin
Celastrol
Tanshinone I
Theaflavin
Resveratrol
Natural products

Table 2 Chinese herbal formulae used for the treatment of SARS-CoV and COVID-19.

Type of virus	TCM formulae	Constituent
SARS-CoV COVID-19	*Lian-Hua-Qing-Wen Capsule*	Forsythiae Fructus, Lonicerae Japonicae Flos, Ephedrae Herba, Armeniacae Semen Amarum, Isatidis Radix, Dryopteridis Crassirhizomatis Rhizoma, Houttuyniae Herba, Pogostemonis Herba, Rhei Radix et Rhizoma, Rhodiolae Crenulatae Radix et Rhizoma, Glycyrrhizae Radix et Rhizoma and Gypsum Fibrosum
COVID-19	*Ren-Shen-Bai-Du-San*	Bupleuri Radix, Peucedani Radix, Notopterygii Rhizoma et Radix, Platycodonis Radix, Glycyrrhizae Radix et Rhizoma, Ginseng Radix et Rhizoma, Poria, Chuanxiong Rhizoma, Aurantii Fructus, Angelicae Pubescentis Radix
SARS-CoV	*Qing-Fei-Jie-Du Decoction*	Astragali Radix, Bupleuri Radix, Ephedrae Herba, Armeniacae Semen Amarum, Gypsum Fibrosum, Coicis Semen, Trichosanthis Pericarpium, Platycodonis Radix, Menthae Haplocalycis Herba, Scutellariae Radix, Glycyrrhizae Radix et Rhizoma, Lonicerae Japonicae Flos, and Artemisiae Annuae Herba
SARS-CoV COVID-19	*Jin-Hua-Qing-Gan Granule*	Lonicerae Japonicae Flos, Gypsum Fibrosum, Ephedrae Herba, Armeniacae Semen Amarum, Scutellariae Radix, Forsythiae Fructus, Fritillariae Thunbergii Bulbus, Anemarrhenae Rhizoma, Arctii Fructus, Artemisiae Annuae Herba, Menthae Haplocalycis Herba, Glycyrrhizae Radix et Rhizoma
SARS-CoV COVID-19	*Shu-Feng-Jie-Du Capsule*	Patriniae Herba, Isatidis Radix, Bupleuri Radix, Glycyrrhizae Radix et Rhizoma, Polygoni Cuspidati Rhizoma et Radix, Forsythiae Fructus, Phragmitis Rhizoma, Verbenae Herba
COVID-19	*Xue-Bi-Jing Injection*	Carthami Flos, Paeoniae Radix Rubra, Chuanxiong Rhizoma, Salviae Miltiorrhizae Radix et Rhizoma, Angelicae Sinensis Radix
SARS-CoV	*Ma-Xing-Shi-Gan Decoction*	Ephedrae Herba, Armeniaca Semen Amarum, Gypsum Fibrosum, Glycyrrhizae Radix et Rhizoma
SARS-CoV	*Shuang-Huang-Lian Granule*	Lonicerae Japonicae Flos, Scutellariae Radix, Forsythiae Fructus
SARS-CoV	*Yin-Qiao Powder*	Forsythiae Fructus, Lonicerae Japonicae Flos, Platycodonis Radix, Menthae Haplocalycis Herba, Lophatheri Herba, Glycyrrhizae Radix et Rhizoma, Schizonepetae Spica, Sojae Semen Praeparatum, Arctii Fructus, Phragmitis Rhizoma

Table 1 Summary of the anti-CoVs effects of natural compounds and their possible action mechanisms.

Plant	Compound	Virus acting on	IC_{50} value	Reported antiviral mechanism
Licorice root	Glycyrrhizin	SARS-CoV	300 mg/L	Upregulates nitrous oxide synthase and nitrous oxide production
Polygonum cuspidatum	Resveratrol	MERS-CoV	–	–
Panax ginseng	Ginsenoside-Rb1	SARS-CoV	100 μmol/L	Inhibits glycoprotein activity
Rauvolfia serpentina	Reserpine	SARS-CoV	6.0 μmol/L	–
Aesculus hippocastanum	Aescin	SARS-CoV	3.4 μmol/L	–
Boenninghausenia sessilicarpa	Leptodactylone	SARS-CoV	100 μg/mL	–
Lycoris radiata	Lycorine	SARS-CoV	15.7 ± 1.2 nmol/L	–
Salvia miltiorrhiza	Dihydrotanshinone	MERS-CoV	1 μg/mL	–
Bupleurum chinense	Saikosaponin B_2	HCoV-229E	1.7 ± 0.1 μmol/L	Interferes with events of early viral entry
Stephania tetrandra	Tetrandrine	HCoV-OC43	0.33 ± 0.03 μmol/L	Inhibits p38 MAPK pathway
Stephania japonica	Cepharanthine	SARS-CoV-2	0.98 μmol/L	ACE inhibitor
Rheum palmatum	Emodin	SARS-CoV	200 μmol/L	Blocks the binding of S protein to ACE2
Triterygium regelii	Celastrol	SARS-CoV	10.3 μmol/L	Inhibits SARS-CoV 3CLpro
Triterygium regelii	Pristimererin	SARS-CoV	5.5 μmol/L	Inhibits SARS-CoV 3CLpro
Triterygium regelii	Tingenone	SARS-CoV	9.9 μmol/L	Inhibits SARS-CoV 3CLpro
Triterygium regelii	Iguesterin	SARS-CoV	2.6 μmol/L	Inhibits SARS-CoV 3CLpro
Ginkgo biloba	Quercetin-3-β-galactoside	SARS-CoV	42.79 ± 4.97 μmol/L	Competitively inhibits SARS-CoV 3CLpro
Salvia miltiorrhiz	Tanshinones I–VII	SARS–CoV	0.7–30 μmol/L	Inhibits PLpro activity
Alnus japonica	Hirsutenone	SARS-CoV	4.1 μmol/L	Inhibits PLpro activity
Black tea	Theaflavin	SARS-CoV-2	–	Inhibits RdRp activity
Myrica rubra	Myricetin	SARS-CoV	2.71 ± 0.19 μmol/L	Inhibits ATPase activity
Scutellaria baicalensis	Scutellarein	SARS-CoV	0.86 ± 0.48 μmol/L	Inhibits ATPase activity
Angelica keiskei	Chalcones I–IX	SARS–CoV	11.4–129.8 μmol/L	Competitively inhibits SARS-CoV 3CLpro

–IC_{50} value or the mechanism of antiviral activity of these active compounds is not clear.

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.
Int J Biol Sci. 2020;16(10):1708-1717. Published 2020 Mar 15. doi:10.7150/ijbs.45538
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7098036/

Table 2 TCM herbal formulas used for the treatment of SARS-CoV infection Table 3

TCM herbal extracts or TCM-derived compounds with anti-HCoV activity

To date, the NHC has published 6 editions of Diagnosis and Treatment Guidelines for COVID-19. Since the fourth version, several herbal medicines used in the TCM system have been recommended for the treatment of COVID-19, depending on the stage of the disease and symptom differentiation. According to the latest edition of the guideline, the following Chinese multi-component herbal products are recommended for patients in the medical observation period as a preventive measure: *Huo Xiang Zheng Qi Shui, Lian Hua Qing Wen Capsule, Shu Feng Jie Du Capsule and Jin Hua Qing Gan Granule*. In the clinical treatment period, it is necessary to select *Qing Fei Pai Du Tang, Xi Yan Ping Injection, Xue Bi Jing Injection, Re Du Ning Injection, Tan Re Qing Injection, Xing Nao Jing Injection* and some other Chinese medicine formulas. In addition, for critically ill patients, Shen *Fu Injection, Sheng Mai Injection, Shen Mai Injection, Su He Xiang Pill and An Gong Niu Huang Pill* should be administered.

Khalifa SAM, Yosri N, El-Mallah MF, et al.
Screening for natural and derived bio-active compounds in preclinical and clinical studies: One of the frontlines of fighting the coronaviruses pandemic
[published online ahead of print, 2020 Aug29]. Phytomedicine. 2020;153311. doi:10.1016/j.phymed.2020.153311
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7455571/

Table 2 list of plant extracts used against coronavirus
Table 4 List of patents on the treatment of COVID-19 using traditional Chinese medicine.

Through screening of natural products with antiviral activity against different types of human coronaviruses, extracts of *Lycoris radiata (L'Hér.), Gentiana scabra Bunge, Dioscorea batatas Decne., Cassia tora L., Taxillus chinensis (DC.), Cibotium barometz L.* and *Echinacea purpurea L.* showed promising effect against SARS-CoV.

In addition to the listed compounds, Lycorin, emetin dihydrochloride hydrate, pristimerin, armin, conhexin, berbamine, 4`-hydroxychalcone, papaverin, mycophenolic acid, mycophenolate mofetil, monensin sodium, cycloheximide, oligomycin, and valinomycin show potent activity against human coronaviruses.

Chinsembu KC.
Coronaviruses and Nature's Pharmacy for the Relief of Coronavirus Disease 2019
[published online ahead of print, 2020 Oct 6]. Rev Bras Pharmacogn. 2020;1-19. doi:10.1007/s43450-020- 00104-7
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7537782/

Potential anti-coronavirus therapies can be divided into two categories according to their target:

- Those that affect the human immune system or human cells, and
- Those that interfere with the coronavirus itself.

The need for pharmacologically potent and safe antivirals should be able to be met outside official protocols, and indigenous knowledge of medicinal plants could be the solution against infectious diseases such as COVID-19.
Yang et al. (2020) reported that more than 85% of patients with SARS- CoV-2 infection in China were treated with traditional Chinese medicine and that the mortality rate of COVID-19 patients in China was limited by the use of TCM, and suggest that the use of current medicinal plants and other natural products for the treatment of COVID-19 should become an integral part of the new health care system.

Comparative genomics lends credence to the reuse of anti-SARS natural products for the treatment of SARS-CoV-19. This is because the genome sequence of SARS-CoV is very similar to that of SARS-CoV-2, and this brings an important biomedical perspective: if medicinal plants used against SARS-CoV and MERS-CoV are carefully repurposed, they could also be effective against SARS-CoV-2, and the natural products could become part of the survival kit for COVID-19.
This review discusses medicinal plants active against SARS-Cov according to the mechanism of action: Inhibitors of virus entry; Lectins; Protease inhibitors; Derivatives of anthraquinones; Polyphenols and aromatic compounds; General inhibitors of replication; Chimotrypsin-like protease inhibitors; Virus inactivation and neutralization; Immunomodulatory agents; Sponges and seaweed; Remedies traditional regional (China, Lebanon, Malaysia, Singapore, South Africa)

Traditional Indian medicine

Vellingiri B, et al
COVID-19: A promising cure for the global panic.
Sci Total Environ. 2020 Jul 10;725:138277. doi: 10.1016/j.scitotenv.2020.138277. Epub 2020 Apr 4. PMID: 32278175; PMCID: PMC7128376.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7128376/

Traditional Indian medicinal practices include Ayurveda, Siddha, Unani and Yoga, Naturopathy and Homeopathy, which are successfully practiced for the treatment of various diseases. Since ancient times, Indian herbs have been used as a treatment and preventive strategy for various diseases, including respiratory viral infections. The advantage of using these herbs in viral respiratory infections is that they induce immune-stimulating and inflammation-modulating effects. The holistic approach of AYUSH medicine systems[49] focuses on prevention through improved lifestyle and diet, prophylactic interventions to improve immunity, and the use of simple remedies based on symptom presentation (AYUSH, 2020).

Table 4 Preventive and prophylactic Indian medicinal plants recommended by AYUSH for COVID-19.
Table 5 List of Indian medicinal herbs that could inhibit HCoV and other viruses.

Khanna K, Kohli SK, Kaur R, et al.
Herbal Immune-boosters: Substantial Warriors of Pandemic Covid-19 Battle
[published online ahead of print, 2020 Oct 3]. Phytomedicine. 2020;153361. doi:10.1016/j.phymed.2020.153361
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7532351/

Ayurveda and Siddha practices[50] originated originally in India and are still widely practiced to treat a plethora of infections. It has frequently been

[49] Ministry of Ayush, Government of India Homeopathy for prevention of coronavirus infections. 2020. https://pib.gov.in/PressReleasePage.aspx?PRID=1600895

[50] Srikanth, Narayanam & Sulochana, & Jain, Seema & Tiwari, Vimal & Group, Working. (2014). Evidence Based Ayurvedic Practice (Based on CCRAS R&D Contributions).

indicated that 70-80% of people belonging to developing countries depend directly on herbal medicines for their primary health care compared to modern synthetic drugs. The beneficial impact of medicinal plants lies in the specific secondary metabolites of their bioactive constituent (steroids, alkaloids, aliphatic diterpenes and triterpenes, and glycosides, etc.). Exploration of novel phytochemicals with antiviral bioactivity has often been substandard and inefficient due to adaptive viral resistance accompanied by viral latency and persistent infections in patients with compromised immunity.

Among the proposed Ayurvedic medicines, the **decoction of sunthi** (*Zingiber officinale Roscoe* ginger*),* lavanga (*Syzygium aromaticum* clove), and maricha (*Piper nigrum* black pepper) has been recommended for both healthy and COVID-19-infected persons, as it provides support in humoral and cell-mediated responses and lowers airway hyperreactivity and nasal congestion. Various ayurvedic products and fatty acids in the form of ghee are involved in increasing immune resistance in a pleiotropic manner, and bioactive compounds participate in various processes of adaptive and innate immune responses. Similarly, the bioactive constituent in *Curcuma longa Linn.* i.e., **curcumin**, is able to block the release of cytokines, particularly interleukin-1, interleukin-6, pro-inflammatory cytokines, and tumor necrosis factor-α and is recommended to be consumed with milk. Inhibition of cytokine storm is one of the major clinical developments associated with experimental protocols against influenza and other infectious diseases and has also been compared with COVID-19 where similar cytokine storms play a key role in disease progression. In addition, AYUSH recommended some plants for prevention and prophylaxis of COVID-19 including hot extracts of *Tinospora cordifolia* (recommended for chronic fever), *Andrograhis paniculata* (recommended for fever and cold), *Cydonia oblonga, Zizyphus jujube, and Cordia myxa* (potentiate antioxidant, immunomodulatory, anti-allergic, smooth muscle relaxant, anti-influenza activity) and *Arsenicum album 30* (found effective against SARS-CoV-2, immunomodulatory).

The following secondary metabolites are discussed in the review: terpenoids, polyphenols/flavonoids, dipeptides, sulfated polysaccharides, vitamins A/C/E/D, minerals, nutraceuticals and probiotics (e.g., *Bifidobacterium longum* to enhance immunomodulatory responses and beneficial effects on the gut microbiota in the elderly), PAK-1 blockers (caffeic acid and its esters, propolis, triptolide, ivermectin, artemisinin ect) and antiviral substances against COVID-19.

https://www.researchgate.net/publication/263659349_Evidence_Based_Ayurvedic_Practice_Based_on_CCRAS_RD_Contributions

Table 1 Herbal formulations as possible therapies against COVID-19 infection

Traditional phytotherapy

Orhan IE, Senol Deniz FS.
Natural Products as Potential Leads Against Coronaviruses: Could They be Encouraging Structural Models Against SARS-CoV-2?
Nat Prod Bioprospect. 2020;10(4):171-186. doi:10.1007/s13659-020-00250-4
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7289229/

Table 1 Examples of some promising natural molecules with coronavirus inhibitory activity

Most of the naturally active compounds belong to **polyphenols and flavonoids** (quercetin, luteolin, hesperetin, amentoflavone, tetra-O-gallyl-β-D-glucose, sinigrin, forsythoside A, psoralidin, tomentin B, terrestrimin, broussochalcone, priflavonol A). In addition, some **alkaloids** (lycorin, typhorin, 7-methoxycryptopleurin, jubanin H, nummularin B), **anthraquinones** (aloe-emodin, emodin), **saponins** (glycyrrhizin, escinidin, saikosaponin B2), **acid terpenes** (curcumin, betulinic acid, saviguin, iguestirin, dihydrotanshinone I, cryptotanshinone, 3β-friedelanol, chrysanthemumin B), **coumarins** (leptodactylone, xanthoangelol E), **diarylheptanoids** (hirsutenone) and **lectins** (APA, UDA, HHA, alstotide 1) appear to be effective against SARS.
More recent in silico studies have also revealed that molecules such as myricitrin, methyl rosmarinate, 5,7,3 ', 4'-tetrahydroxy-2 ' - (3,3-dimethylallyl) isoflavone, 3,5,7,3 ', 4 ', 5'-hexahydroxy flavanone-3-O-β-D-glucopyranoside, (2S)-eriodictyol 7-O- (6 ' ' - O-galloyl)
-β-D-glucopyranoside, calceolarioside B, myricetin 3-O -β-D-glucopyranoside, lycoleafol, and amaranthin could be effective anti-SARS-CoV-2.

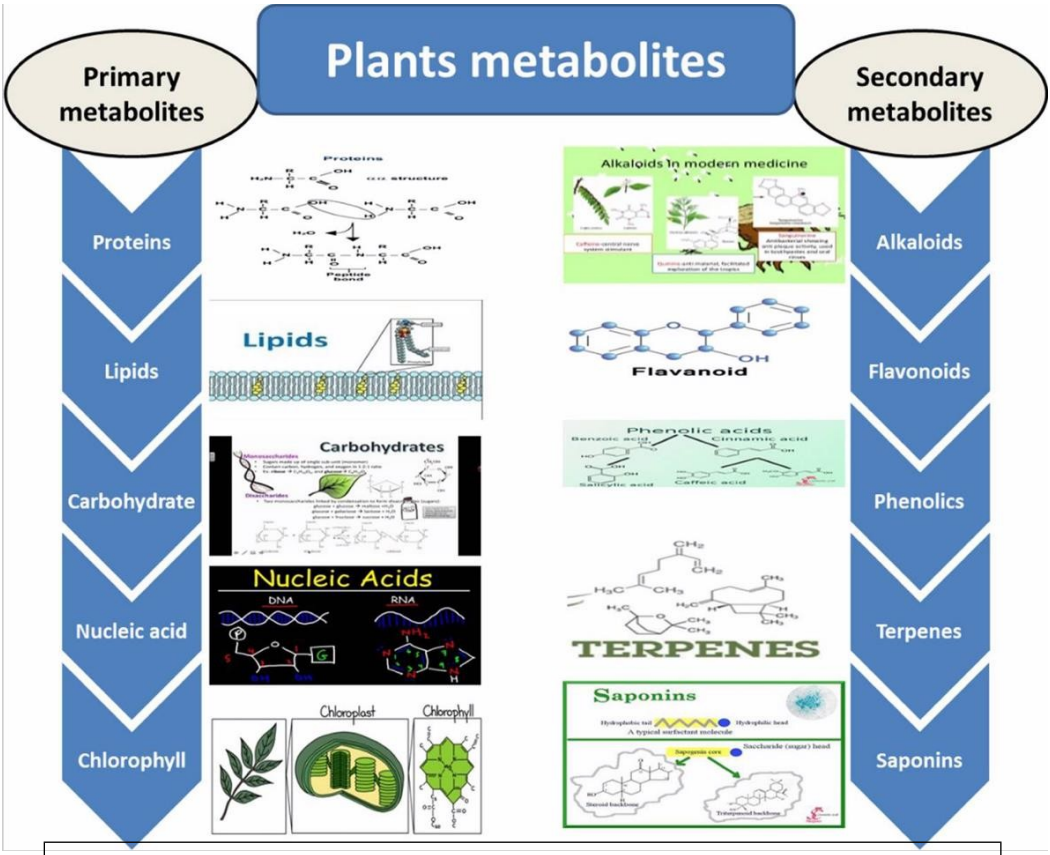
Singh YD, Jena B, Ningthoujam R, et al.
Potential bioactive molecules from natural products to combat against coronavirus
[published online ahead of print, 2020 Sep 15]. Advances in Traditional Medicine. 2020;1-12.
doi:10.1007/s13596-020-00496-w
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7490776/

Medicinal plants contain huge amounts of minerals and vitamins that can be easily assimilated by the human body. According to many scientific studies, vitamins and minerals obtained through chemical synthesis cannot give the same benefits compared to natural products. Natural products have more bioactive molecules because they can have synergistic and complementary action between vitamins, enzymes and minerals. Synthetic drugs have more side effects than medicinal plants, and their interaction with other substances in the body can lead to more harmful effects on humans.

Natural compounds obtained from plants are classified into two main categories.
Primary metabolites such as proteins, fats, sugars, etc., are common to all biological systems, while **secondary metabolites** (alkaloids, terpenes, saponins, flavonoids, phenolic acid, tannins, volatile oils, ect.) are specific to different species and are the direct result of the evolutionary process of a particular phylogenetic group as they play a key role during the processes of plant adaptability and survival (Fig.2).

Included in the secondary metabolites are bioactive molecules that show activity therapeutic, toxicological, and immunostimulatory.

The bioactive molecules discussed in the review obtained from natural products including plants, animals and other microbes as a source of antivirals against covid-19 are shown in Table 2.



Bhuiyan FR, Howlader S, Raihan T, Hasan M.
Plants Metabolites: Possibility of Natural Therapeutics Against the COVID-19 Pandemic.
Front Med (Lausanne). 2020;7:444. Published 2020 Aug 7. doi:10.3389/fmed.2020.00444
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7427128/

Table 3 Probable secondary metabolites of medicinal plants promising against COVID-19.
Supplementary material

Some 219 plants from 83 families have been found to have antiviral activity.
Among them, 149 plants from 71 families were screened for the identification of key plant secondary metabolites (PSMs) that could be effective for this pandemic.

Shahzad F, Anderson D, Najafzadeh M.
The Antiviral, Anti-Inflammatory Effects of Natural Medicinal Herbs and Mushrooms and SARS-CoV-2 Infection.
Nutrients. 2020 Aug 25;12(9):E2573. doi: 10.3390/nu12092573. PMID: 32854262.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7551890/

This review found that naturally occurring triterpene glycosides, known as **saikosaponins,** isolated from medicinal plants *such as Bupleurum spp., Heteromorpha spp. and Scrophularia* showed great antiviral activity against human coronaviruses (Table 1). These naturally occurring compounds were able to effectively prevent the early stages of coronavirus infection by affecting viral binding and cell penetration.

In addition, many natural compounds such as **myricetin, scutellarein**, and phenolic compounds from *Isatis indigotica* and *Torreya nucifera were* identified as natural inhibitors against coronavirus enzymes, including nsP13 helicase and 3CL protease. The aqueous extract of *Houttuynia cordata was* also identified as another natural anti-coronavirus drug, as it was able to both inhibit viral protease 3CL and block viral dependent RNA polymerase activity, thus showing various antiviral mechanisms against SARS-CoV1.

Based on the data presented, this mini-review aims to review the antiviral and anti-inflammatory effects of natural herbs and fungi against viral infections (Table 2), as well as to provide an overview of the possibilities of using natural and effective treatments
versus COVID-19.

Table 1

Antiviral effects of several natural products against coronavirus.

Virus	Natural Product(s) Evaluated	Proposed Mechanism(s)
Coronavirus	Saikosaponins (A, B_2, C, D) against HCoV-22E9	Saikosaponin B_2 inhibits viral attachment and penetration stages unclear
	Lycoris radiata and its active component lycorine. *Artemisia annua*, *pyrrosia lingua*, and *lindera aggregata* against SARS-CoV1.	
	Phenolic compounds of *Isatis indigotica* against SARS-CoV1.	SARS-CoV1 3CL protease inhibitor
	Amentoflavone isolated from *Torreya nucifera* against SARS-CoV1	SARS-CoV1 3CL protease inhibitor
	Myrcetine and scutellarein against SARS-CoV1	SARS-CoV1 helicase inhibitor
	Houttuynia cordata water extract against SARS-CoV1	SARS-CoV1 3CL protease inhibitor; viral polymerase inhibitor

Table 2

The list of introduced medicinal herbs and mushrooms. (+ stands for the level activity, representing mild, moderate, severe and very severe respectively).

Medicinal Herbs and Mushrooms	Antiviral Activity	Anti-Inflammatory Activity	Anticancer Activity
Prunella vulgaris	++	+++	++
Garlic (*Allium sativum*)	++	+	++
Zingiber officinalis	++	+++	+
Lentinus edodes mycelia (shiitake)	+++	+++	-
Grifola frondosa	++	+	++
Ganoderma lucidum aqueous extract (GLE)	+++	+++	-
Chlorella vulgaris ethanolic extract (CVE)	+++	+++	-
Inonotus obliquus	++	++++	++++

Chojnacka K, Witek-Krowiak A, Skrzypczak D, Mikula K, Młynarz P.
Phytochemicals containing biologically active polyphenols as an effective agent against Covid-19-inducing coronavirus.
J Funct Foods. 2020;73:104146. doi:10.1016/j.jff.2020.104146
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7392194/ Table

1 Bioactive compounds and their antiviral activity.

Many natural plant-derived compounds (polyphenols) could provide a starting point for research on the use of plant extracts in the treatment and prevention of coronavirus. **Polyphenolic** antiviral **drugs** can inhibit coronavirus enzymes, which are essential for virus replication and infection. This group of natural substances (betulinic acid, indigo, aloeemodine, luteolin and quinomethyl triterpenoids, quercitin or gallates) is a potential key to designing antiviral therapies to inhibit viral proteases. The known pharmacophore structures of bioactive substances may be useful in the development of new anti-Covid-19 formulations. The advantage of using preparations containing phytochemicals is their high safety for patients and absence of side effects.

Boukhatem MN, Setzer WN.
Aromatic Herbs, Medicinal Plant-Derived Essential Oils, and Phytochemical Extracts as Potential Therapies for Coronaviruses: Future Perspectives.
Plants (Basel). 2020;9(6):800. Published 2020 Jun 26. doi:10.3390/plants9060800
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7356962/

Table 2 List of medicinal plants or isolated active compounds that inhibit Coronaviruses.

Four extracts showed moderate to potent inhibition effects against SARS-CoV: ***Lycoris radiata*** (red spider lily), ***Pyrrosia lingua*** (a fern), ***Artemisia annua*** (sweet wormwood), and ***Lindera aggregata***, an aromatic evergreen shrub that is a member of the laurel family. The antiviral effects of these extracts were dose-dependent and varied from low to high concentrations in the extracts, depending on the herbal extract considered. In particular, ***L. radiata*** showed the most potent antiviral activity against the viral strain.

Islam MT, Sarkar C, El-Kersh DM, Jamaddar S, Uddin SJ, Shilpi JA, Mubarak MS.
Natural products and their derivatives against coronavirus: A review of the non-clinical and pre-clinical data.
Phytother Res. 2020 Apr 4. doi: 10.1002/ptr.6700. Epub ahead of print. PMID: 32248575.
https://onlinelibrary.wiley.com/doi/epdf/10.1002/ptr.6700

The crude extracts are listed in Table 1 and the isolated compounds showing activity against CoV are listed in Table 2.

TABLE 1 List of natural products inhibiting CoV

Extracts or preparations	Test system	Test dose/ concentration	Proposed mechanism	IC_{50} or EC_{50} value
Lycoris radiata	SARS-CoV	10^{-1}–10^{-4} mg/mL	Undefined.	2.4 ± 0.2 μg/mL
Artemisia annua	SARS-CoV	10^{-1}–10^{-4} mg/mL	Undefined.	34.5 ± 2.6 μg/mL
Pyrrosia lingua	SARS-CoV	10^{-1}–10^{-4} mg/mL	Undefined.	43.2 ± 14.1 μg/mL
Lindera aggregata	SARS-CoV	10^{-1}–10^{-4} mg/mL	Undefined.	88.2 ± 7.7 μg/mL
Isatis indigotica	SARS-CoV	1–500 μg/mL	3CL protease inhibition.	—
Extract (*Rheum officinale* Baill., *Polygonum multiflorum* Thunb.)	SARS-CoV spike (S) protein.	0–100 μg/mL	Inhibits the interaction of SARS-CoV S protein and ACE2.	1 to 10 μg/mL
Houttuynia cordata aq. Extract	SARS-CoV	0–400 μg/mL	3CL protease and viral polymerase inhibition.	—
Herbal extracts (*Gentiana scabra*, *Dioscorea batatas*, *Cassia tora*, *Taxillus chinensis*, *Cibotium barometz*)	SARS-CoV	25–200 μg/mL	3CL protease inhibition.	39 μg/mL and 44 μg/mL (two extracts of *Cibotium barometz*)
Anthemis hyalina, *Nigella sativa*, and *Citrus sinensis* extracts	Coronavirus-infected HeLa-epithelial carcinoembryonic antigen-related cell adhesion molecule 1a cells inoculated with MHV-A59 (mouse hepatitis virus–A59)	1/50 and 1/100 dilution of ethanolic extract (100 g/200 mL)	Increased IL-8 level. Significantly changed the expression of *TRPA1*, *TRPC4*, *TRPM6*, *TRPM7*, *TRPM8*, and *TRPV4* genes.	-

In this study, some of the natural products studied have antiviral activity in **nanomolar concentrations** (e.g., lycorine, homoharringtonine, silvestrol, ouabain, tylophorine, 7-methoxycryptopleurine) and thus can be considered antiviral drugs for all intents and purposes, while a good number of natural products with anti-corona virus activity are the main constituents of some common dietary supplements, which can be exploited to improve immunity in the general population.

Hensel A, Bauer R, Heinrich M, Spiegler V, Kayser O, Hempel G, Kraft K.
Challenges at the Time of COVID-19: Opportunities and Innovations in Antivirals from Nature.
Planta Med. 2020 Jul;86(10):659-664. doi: 10.1055/a-1177-4396. Epub 2020 May 20. PMID: 32434254; PMCID: PMC7356065.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7356065/

In the field of natural substances, we know some drugs that contain large amounts of tannins. This very heterogeneous group of natural substances includes.

proanthocyanidins (syn. Condensed tannins), **hydrolyzable tannins** (syn. Gallotannins) and the so-called **Lamiaceae tannins** (depsides).
They all have in common that they interact with proteins and are able to greatly modify or inhibit protein structure and function. Tannins therefore often have nonspecific antimicrobial effects but can also inhibit the functionality of viral envelope proteins. The inhibitory effects of condensed tannins or tannin-containing extracts on influenza virus or RSV are known from several publications.

Of course, these plants cannot be used as a therapeutic agent for viral infections. According to the authors, concentrated tannin extracts could be applied locally in the oral cavity for prophylaxis and as adjuvant therapy (provided there are no risks of interactions). **Sorrel** prepared as lozenges or chewing gum, which contain proanthocyanidins in the highest possible concentration, offers such opportunities. In addition, other pharmaceutical preparations such as gargling solutions and mouthwashes containing such extracts have been used locally.
Lignans also play an important role as potential drug candidates for the development of antiviral compounds. Highly active representatives of this class of natural products are **podophyllotoxin**, a typical lignan from the arylnafatelenes group, and **biclicol**, belonging to the uncommon subclass of dibenzocyclooctenes.

Signer J, Jonsdottir HR, Albrich WC, et al.
In vitro virucidal activity of Echinaforce®, an Echinacea purpurea preparation, against coronaviruses, including common cold coronavirus 229E and SARS-CoV-2.
Virol J. 2020;17(1):136. Published 2020 Sep 9. doi:10.1186/s12985-020-01401-2
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7479405/

In this study, HCoV-229E was found to be irreversibly inactivated when exposed to Echinaforce® at 3.2 µg/mL IC_{50}. Pre-treatment of cell lines, however, did not inhibit HCoV-229E infection, and post-infection treatment had only a marginal effect on virus propagation at 50 µg/mL. However, the authors observed a protective effect in an organotypic respiratory cell culture system by exposing pretreated respiratory epithelium to droplets of HCoV-229E, so as to mimic natural infection. The observed virucidal activity of Echinaforce® was not limited to common cold coronaviruses, as both SARS-
CoV-1 that MERS-CoV were inactivated at comparable concentrations. Finally, even

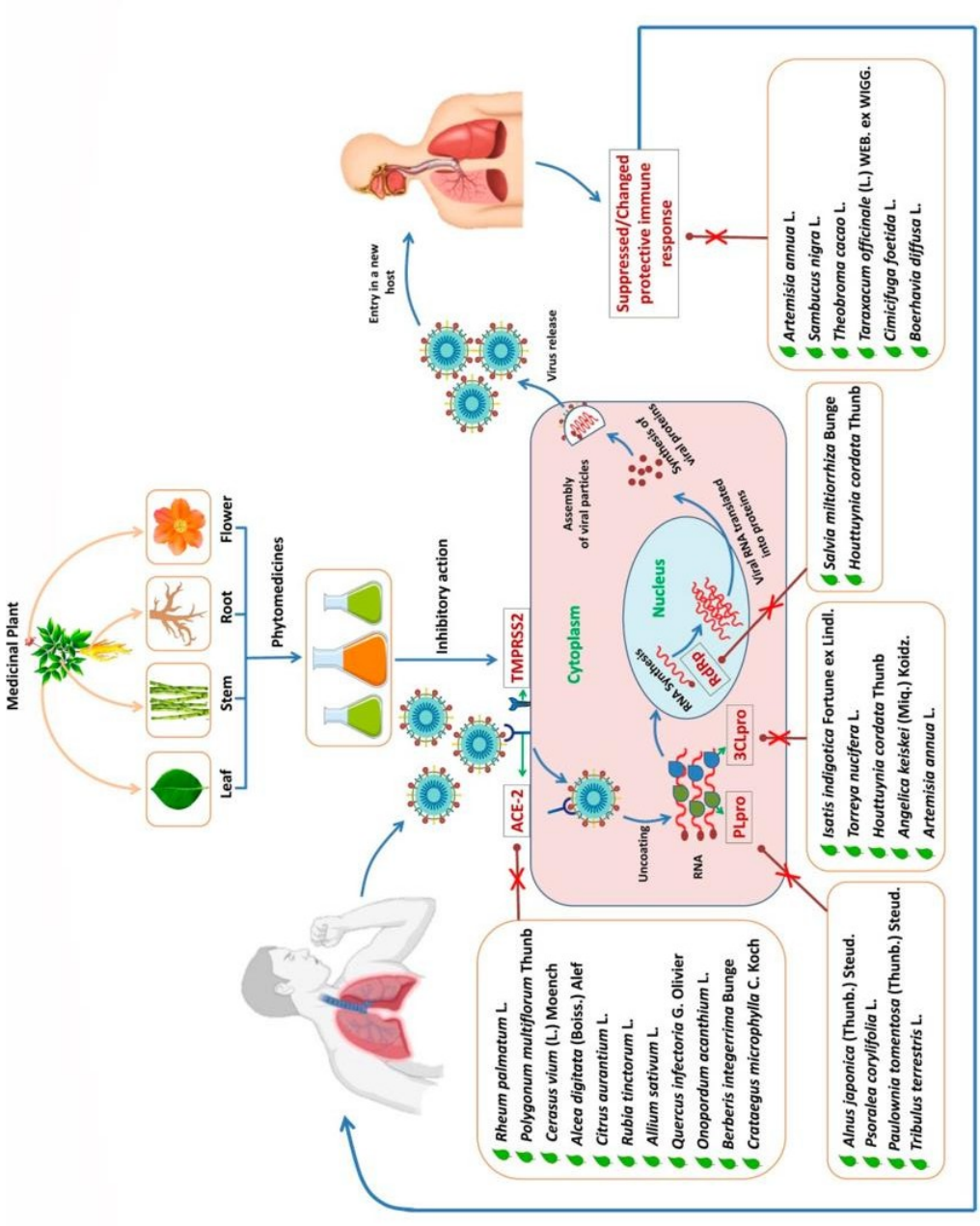
The etiologic agent of COVID-19, SARS-CoV-2, was inactivated during treatment with 50 µg/mL Echinaforce®.

Siddiqui AJ, Danciu C, Ashraf SA, Moin A, Singh R, Alreshidi M, Patel M, Jahan S, Kumar S, Alkhinjar MIM, Badraoui R, Snoussi M, Adnan M.
Plants-Derived Biomolecules as Potent Antiviral Phytomedicines: New Insights on Ethnobotanical Evidences against Coronaviruses.
Plants (Basel). 2020 Sep 21;9(9):E1244. doi: 10.3390/plants9091244. PMID: 32967179.
https://www.mdpi.com/2223-7747/9/9/1244/htm

This review reports data on several medicinal plants and their natural bioactive metabolites with promising antiviral activities against coronaviruses with detailed mode of action/mechanism.
Below is the figure and table summarizing the mechanism of action of various plants medications evaluated.

Figure 1. Schematic representation of various medicinal plants and their possible specific inhibitory sites to act against SARS-CoV-2.

Table 1. List of medicinal plants used to treat MERS-CoV, SARS-CoV-1 and other viral infections with their potent bioactive compounds, biological activities and therapeutic effect against various diseases. These plants may possibly be used to treat SARS-CoV-2.


Medicinal Plant
Leaf
Stem
Root
Flower
Phytomedicines
Inhibitory action
TMPRSS2
ACE-2
Cytoplasm
Uncoating
RNA
PLpro
3CLpro
Nucleus
RNA Synthesis
RdRp
Viral RNA translated into proteins
Synthesis of viral proteins
Assembly of viral particles
Virus release
Entry in a new host
Suppressed/Changed protective immune response
Rheum palmatum L.
Polygonum multiflorum Thunb
Cerasus vium (L.) Moench
Alcea digitata (Boiss.) Alef
Citrus aurantium L.
Rubia tinctorum L.
Allium sativum L.
Quercus infectoria G. Olivier
Onopordum acanthium L.
Berberis integerrima Bunge
Crataegus microphylla C. Koch
Alnus japonica (Thunb.) Steud.
Psoralea corylifolia L.
Paulownia tomentosa (Thunb.) Steud.
Tribulus terrestris L.
Isatis indigotica Fortune ex Lindl.
Torreya nucifera L.
Houttuynia cordata Thunb
Angelica keiskei (Miq.) Koidz.
Artemisia annua L.
Salvia miltiorrhiza Bunge
Houttuynia cordata Thunb
Artemisia annua L.
Sambucus nigra L.
Theobroma cacao L.
Taraxacum officinale (L.) WEB. ex WIGG.
Cimicifuga foetida L.
Boerhavia diffusa L.

Botanical Name and Vegetal Part Use for Medicinal Purpose	Picture	Bioactive Compounds	Biological Activities	Therapeutic Effect against Diseases
		Medicinal Plants Against Coronavirus Related Infections		
Bupleurum species (Root)		SSa, SSb2, SSc and SSd	Antiviral, anti-inflammatory, anti-tumor, neuro-modulation, immune-regulation	CoVs and Influenza virus
Lycoris radiate (L'Hér.) Herb. (Flower and stem cortex)		Lycorine	Antiviral effects, anticancer, anti-malarial, anti-inflammatory, induction of nausea and emesis	SARS-CoV-1, poliovirus, HIV, HSV and coxsackie virus
Artemisia annua L. (Whole plant)		Quercetin, flavonoid, polyphenols, triterpenes, sterols, saponins, polysaccharides, dicaffeoylquinic acid	Anti-malarial, antiviral, anticancer, bronchitis, haemorrhoids	SARS-CoV-1, MERS-CoV, Poliovirus, HIV, RSV, HSV1, hepatitis C, type 2 dengue virus and human cytomegalovirus
Pyrrosia lingua(Thunb.) Farw. (Leaves)		Flavonoids, (mangiferin, isomangiferin, trifolin, astragalin), chlorogenic acid, mangiferin, isomangiferin, astragalin, and trifolin	Antiviral, antioxidant, antibacterial, anticancer	HIV, SARS-CoV-1

Isatis indigotica Fortune ex Lindl. (Leaf and root)		Indigo, indirubin, indican, β-sitosterol, sinigrin, hesperetin, aloe-emodin	Antiviral, antioxidant, antibacterial	SARS-CoV-1 3CLpro, HSV1, Influenza virus, coxsackie virus B3
Torreya nucifera L. (Leaves)		Biflavonoid amentoflavone	Antiviral	SARS-CoV-1 3CLpro, stomachache, hemorrhoids, and rheumatoid arthritis
Houttuynia cordata Thunb. (Leaves)		Volatile oils, organic acids, flavonoids cordarine, kalium sulfuricum, potassium, zinc, iron, copper, amino acid, vitamins and manganese	Antiviral, anti-inflammatory, anti-allergic, anti-oxidant, Immunomodulatory and anticancer	SARS-CoV-1 3CLpro and RdRp, cough, lung abscess, phlegm, dyspnea, pneumonia, refractory hemoptysis
Lindera aggregate (Sims) Kosterm. (Root)		Flavonoids, isoquinoline alkaloids, sesquiterpene lactones and tannins	Antiviral, anti-tumor, anti-inflammatory, antimicrobial and anti-diabetic	SARS-CoV-1, chest pain, inflammation, indigestion, cold hernia
Rheum palmatum L. (Root)		Emodin, physcion, chrysophanol, rhein, and aloe-emodin	Antiviral, anti-pyretic, anti-neoplastic, anti-pasmolytic, antibacterial, laxative, hemostatic, and anti-spasmodic	SARS-CoV-1 ACE2, laxative or astringent, stomachicum, hemorrhoids, liver bile disease or gastroenteritis

Polygonum multiflorum Thunb. (Root)		Polygonumosides A, B, C, and D, resveratrol, chrysophanol, polydatin, emodin-1,6-dimethyl ether, rhaponticoside, emodin, 2-acetylemodin, physcion, rhein, citreorosein, apigenin, fallacinol, tricin, rutin, quercetin, luteolin, kaempferol, iso-orientin, hyperoside, vitexin, quercetin-3-O-arabinoside, polygonflavanol A, hexadecanoic acid ethyl ester, phosphatidylethanolamine, hexanoic acid, copaene, eicosane, squalene, catechin, epicatechin, 3-O-galloyl-procyanidin B2, *β*-sitosterol, gallic acid, methyl gallate, daucosterol, and schizandrin	Anti-CoVs, antioxidant, immunomodulation, anti-hyperlipidemia, anticancer, hepato-protection, anti-inflammation,	SARS-CoV-1 ACE2, rubella, scrofula, waist and knee pain, paralysis, vaginal discharge, hypercholesterolemia (liver and kidney), malaria, neuro-protective
Cerasus avium (L.) Moench (Stem)		Polyphenols, carotenoids, vitamins, minerals	Antioxidant, antimicrobial and antiviral	SARS-CoV-1 ACE2, oxidative stress, tooth aches and mouth diseases
Alcea digitata (Boiss.) Alef (Flower)		Unknown	Antiviral, antioxidant, anti-inflammatory, antimicrobial, anti-tussive, expectorant and laxative	SARS-CoV-1 ACE2, lung respiratory disorder, head and neck cancer and lubrication of throat
Citrus aurantium L. (Fruit)		Phenolics (flavanone glycosides, hydroxycinnamic acids), vitamin C, and carotenoids	Antiviral, antioxidant, anticancer	SARS-CoV-1 ACE2, anxiety, lung related disease, obesity, gastrointestinal disorder and prostate cancer

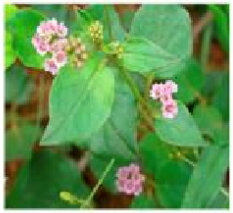
Rubia tinctorum L. (Root)		Anthraquinone, Alizarin and pseudopurpurin	Antiviral, antimicrobial	SARS-CoV-1 ACE2, kidney, bladder stone, menstrual and urinary disorder
Allium sativum L. (Cloves)		Alliin, allicin, ajoenes, vinyldithiins, and flavonoids	Antiviral, antimicrobial, antioxidant, anti-inflammatory, and anticancer	SARS-CoV-1 ACE2, inflammation, cancer and bacterial infection
Quercus infectoria G. Olivier (Gall)		Phenolic compound (*p*-hydroxybenzoic acid, catechol, caffeine, pyrogallol, catechein, e-vanillic acid, 3-hydroxytyrosol cinnamic, *p*-Coumaric, gallic acids and resveratrol), flavonoid compounds	Antiviral, anti-fungal, antibacterial, antioxidant, anti-inflammatory, anti-diabetic, anti-parasitic, anti-venom	SARS-CoV-1 ACE2, diarrhea, menorrhagia, dysentery, gonorrhea, tonsillitis, impetigo and internal hemorrhages
Onopordum acanthium L. (Leaf, flower, stem and root)		Flavonoids, sesquiterpene lactones, lignans, phenylpropanoids, triterpenoids, and sterols	Antiviral, anti-tumor, anti-inflammatory, antioxidant and cardio-tonic agent	SARS-CoV-1 ACE2, cancer, treat nervousness
Berberis integerrim Bunge (Root)		Berbamine, berberuin, palmatine, oxyacanthine, malic acid, ascorbic acid, caffeic acid, ursolic acid, coumarin, beta carotene, and tannin	Antiviral, anti-inflammatory, anti-hyperglycemic, anti-hyperlipidemic, anticancer, antioxidant	SARS-CoV-1 ACE2, alleviate insomnia, bronchial diseases, and liver disorder

Crataegus microphylla C. Koch (Leaves, flower, stem and root)		Phenols, phenolic acids, procyanidins, flavonoids, triterpenes, polysaccharides, catecho-lamines	Antiviral, antioxidant, anti-inflammatory and anti-diabetic	SARS-CoV-1 ACE2, heart muscle cells activation, coronary dilation, regulated blood flow
Alnus japonica (Thunb.) Steud. (Bark)		Hirsutenone, oregonin, rubranoside rubranoside B, rubranol, and hirsutanonol	Antiviral, anticancer, anti-inflammatory, antioxidant and induction of lymphatic and gastroenteric disorders.	SARS-CoV-PLpro fever, cancer, blood and lymphatic disorders, gastroenteric disorders
Psoralea corylifolia L. (Seed)		Neobavaisoflavone, isobavachalcone, Bavachinin, 40 –O-methyl bavachalcone, corylifol A and psoralidin	Antiviral, antioxidant, antibacterial and anti-depressant activities	SARS-CoV-PLpro leukoderma, psoriasis, vitiligo, asthma, ulcers, kidney disorders
Paulownia tomentosa (Thunb.) Steud. (Fruit)		Tomentin A, tomentin B, tomentin C, tomentin D, tomentin E, geranylated flavonones	Antiviral, antioxidant and antibacterial	SARS-CoV-PLpro inflammatory bronchitis, upper respiratory tract infection, asthma, tonsillitis, gonorrhea, traumatic bleeding, enteritis, bacteriological diarrhea, erysipelas, swelling, bronchopneumonia, conjunctivitis, and hemorrhoid
Tribulus terrestris L. (Fruit)		Flavonoid and alkaloids	Antiviral, anti-inflammatory, antioxidant, anti-tumor, anti-diabetic and anti-urolithic	SARS-CoV-PLpro hypertension, premature ejaculation, erectile dysfunction, vitiligo, and kidney

Angelica keiskei (Miq.) Koidz. (Leaves)		Chalcones, flavanones and coumarins, coumarins phenolic, acetylenes, sesquiterpene, diterpene, and triterpenes	Antiviral, antibacterial, anti-diabetic, anticancer, anti-inflammatory, antioxidative, anti-coagulant, anti-obesity, anti-tumor, anti-mutagenic and hepato-protective	SARS-CoV-1 3CLpro, bacterial treatment, cancer and diabetes
		Medicinal Plants against Other Viral Infections		
Sambucus nigra L. (Leaf, flower and fruit)		Flavonoids, lectins, anthocyanin, peptic polysaccharides, polyphenolic compound	Antiviral, Immunomodulatory activity, anti-inflammatory	Common cold, HIV, HSV1, influenza, urinary tract infection, edema, rheumatic
Eleutherococcus senticosus (Rupr. & Maxim.) Maxim. (Leaf and root)		Phenols, lignans, coumarins, phenylpropanoids, flavonoids, hyperin, rutin, afzelin, quercetin, kaempferol, phenolic acids, triterpenic acids, and anthocyanin	Antiviral, anti-diabetic, anticancer, antioxidant	Influenza virus, chronic coughing, fatigue and infection, ischemic heart disease, diabetic, cancer, altitude sickness, neurodegenerative disorder
Salvia miltiorrhiza Bunge (Root)		Lipophilic diterpenoids, flavonoids, triterpenoids and hydrophilic phenolic compound	Antiviral	HIV, enterovirus removing blood stasis, improving blood circulation, atherosclerosis, thrombosis, angina pectoris, cardiovascular disease

Acacia arabica (Lam.) Willd (Leaves)		Methyl 3,4,5 tri hydroxyl benzoate, ferulic acid, p - coumaroylquinic acid, isoferulic acid, *p*-coumaroyl glucoside, epicatechin-3-gallate, ascorbic acid, quercetin, oleic acid, myristic acid, palmitic acid and steroidal sapogenin aglycone	Antiviral, antimicrobial, anti-diabetic, antioxidant	HIV, influenza virus, Newcastle disease, vaccinia virus, bursal disease virus, skin disease
Ocimum sanctum L. (Leaves)		Flavonoids, tannins, saponins, alkaloids, phenols, anthocyanine, triterpenoids,	Antiviral, antimicrobial, anti-cataract, anti-inflammatory, anti-diabetic, anti-hypercholesterolemia, anti-hypertensive, anti-carcinogenic, anti-pyretic, anti-allergic, immunomodulatory, anti-asthmatic, anti-tussive, anti-fertility, anti-ulcer, anti-emetic, anti-spasmodic, anti-arthritic, adaptogenic, anti-leukodermal, anti-coagulant activities	H9N2 influenza disease anxiety, cough, asthma, diarrhea, fever, skin disease, dysentery, arthritis, eye diseases, otalgia, indigestion, hiccups, vomiting, gastric, cardiac and genitourinary disorders, back pain, skin diseases, ringworm, insect, snake and scorpion bites, malaria and antioxidant
Ocimum basilicum L. (Whole plant)		Phenolic compounds, flavonoids and anthocyanins	Antiviral, anti-inflammatory, antioxidant and antibacterial	HIV infection and bacterial infection
Theobroma cacao L. (Seed)		Polyphenol, theobromine and flavonoids (heobromine, lignin, dietary fiber, free fatty acid, minerals, zinc, copper, iron)	Antiviral, antioxidant, anti-inflammatory	Influenza virus

Pelargonium sidoides DC (Root)		Methoxycoumarin, proanthocyanidins, EPs 7639 and prodelphinidins	Antiviral and antioxidant	Influenza virus, tuberculosis, respiratory disease, cough, gastrointestinal infection, viral disease
Taraxacum officinale (L.) WEB. ex WIGG. (Aerial part and root)		Terpenes, flavonoids, phenolic compounds, terpenoids, triterpenoids, steroids, coumarins, phenols, saponins, flavones, flavonols, chalcones, phlobatannins, and cardiac glycosides	Antiviral, antibacterial, choleretic, anti-diabetic, anti-inflammatory, antioxidant, hepato-protective, diuretic and antifungal	HIV, influenza virus, kidney related disease, lung related disease, tumor of breast, diabetic, uterus related infection, digestive system related abnormality
Illicium oligandrum Merr and Chun (Root)		Sesquiterpene lactones, neolignan glycosides, phenolic diglycosides and prenylated compounds	Antiviral	HSV, coxsackie virus and influenza virus, rheumatoid arthritis, neurotoxic and neurotrophic effects.
Glycyrrhiza glabra L. (Root)		Flavonoids, glycyrrhizic acid, triterpenoid, saponins	Antiviral, anti-inflammatory, antimicrobial, antioxidant, anti-tumorigenic and anti-ulcer	CoVs, HIV, influenza virus
Polygala karensium Kurz (Root)		Xanthones	Antiviral, antimicrobial, antioxidant, cytotoxicity activity	Influenza virus, cough, bronchitis, neurasthenia, inflammation and amnesia

Calophyllum brasiliense Cambess (Leaves)		Tricyclic coumarin	Antiviral, antibacterial, anti-protozoal and antifungal	HIV, parasitic diseases, bacterial and fungal disease
Cimicifuga foetida L. (Rhizomes)		Cimicifugin, cycloartane triterpenoids and glycosides	Antiviral, anti-tumor, anti-inflammatory	Respiratory Syncytial Virus, fever, headache, sore throat, toothache, uterine prolapse and inflammation
Boerhavia diffusa L. (Leaf, stem and root)		Flavonoids, triterpenoids, alkaloids, hypoxanthine, steroids, lipids, lignins, ursolic acid, boeravinone, punarnavoside	Antiviral, anti-fibrinolytic, anti-convulsant, antibacterial, anti-hepatotoxic, anti-asthmatic and anti-nematodal activity	Hepatitis C virus, abdominal pain, jaundice, dyspepsia, release the stress, spleen enlargement, liver
Terminalia chebula Retz (Leaf, bark and fruit)		Flavonoids, polyphenols, terpenes, anthocyanins, glycosides, gallic acid, chebulagic acid, punicalagin, chebulanin, corilagin, neochebulinic acid, ellagic acid, chebulinic acid, alkaloids	Antiviral, antioxidant, antibacterial, antifungal, anti-protozoal, anti-carcinogenic, anti-mutagenic, anti-diabetic, reno-protective, anti-inflammatory, anti-arthritic, anti-anaphylactic, anti-caries, anti-allergic, immunomodulatory, anti-ulcer, anti-spasmodic	Human cytomegalovirus, hepatitis C virus, dengue virus, measles virus, respiratory syncytial virus, irregular fevers, urinary diseases, diabetes, skin diseases, heart diseases, constipation, ulcers, vomiting, colic pain, hemorrhoids, digestive diseases
Caesalpinia sappan L. (Root)		Xanthone, sappanchalcone, coumarin, chalcones, flavones, homoisoflavonoids, and brazilin	Antiviral, anti-inflammatory, antioxidant, antibacterial, antifungal, anti-complementary	HIV, Influenza virus, tuberculosis, diarrhea, dysentery, skin infections and anemia

Edible mushrooms and ß-glucans

Recent studies show that innate immune populations may possess a form of memory, called Trained Immunity (TRIM - memory of innate immunity), in which they undergo metabolic, mitochondrial, and epigenetic reprogramming following exposure to an initial stimulus that results in an enhanced immune response when exposed to a secondary, heterologous stimulus.

The finding that memory induction of innate immunity by BCG (tuberculosis vaccine)[51] and β-glucan is able to provide protection against a range of viral infections, allows hypothesizing a potential role for β-glucan in decreasing worldwide morbidity and mortality due to COVID-19. [52]

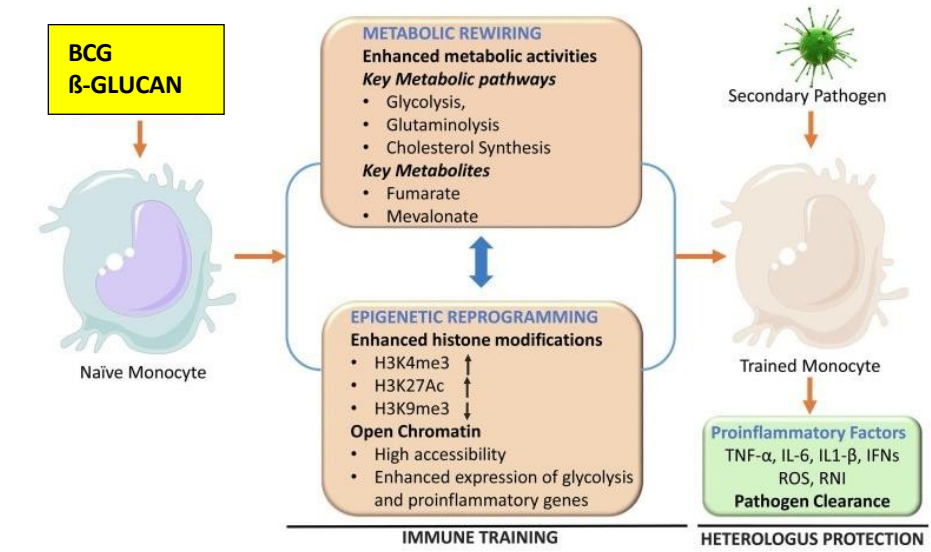
[51] Gupta PK.
New disease old vaccine: Is recombinant BCG vaccine an answer for COVID-19?
Cell Immunol. 2020;356:104187. doi:10.1016/j.cellimm.2020.104187
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7386780/

[52] Geller A, Yan J.
Could the Induction of Trained Immunity by β-Glucan Serve as a Defense Against COVID-19?
Front Immunol. 2020;11:1782. Published 2020 Jul 14. doi:10.3389/fimmu.2020.01782
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7372085/

Rao KS, Suryaprakash V, Senthilkumar R, et al. Role of Immune Dysregulation in Increased Mortality Among a Specific Subset of COVID-19 Patients and Immune-Enhancement Strategies for Combatting Through Nutritional Supplements. Front Immunol. 2020;11:1548. Published 2020 Jul 9. doi:10.3389/fimmu.2020.01548.
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7363949/

Jawhara, S.
How to boost the immune defense prior to respiratory virus infections with the special focus on coronavirus infections.
Gut Pathog 12, 47 (2020). https://doi.org/10.1186/s13099-020-00385-2
https://gutpathogens.biomedcentral.com/articles/10.1186/s13099-020-00385-2

Jawhara, S. How to boost the immune defense prior to respiratory virus infections with the special focus on coronavirus infections. Gut Pathog 12, 47 (2020). https://doi.org/10.1186/s13099-020-00385-2
https://gutpathogens.biomedcentral.com/articles/10.1186/s13099-020-00385-2



Adapted from https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7386780/
Trained immunity and mechanism below.

BCG Vaccine and COVID-19

Several studies have been rapidly initiated to test whether TRIM induction, through BCG vaccine administration, can help protect against COVID-19. On March 30, 2020, the BRACE trial was initiated in Australia, which aimed to administer BCG vaccine to up to 4,170 health care workers in order to determine whether BCG vaccination can reduce the incidence and severity of COVID-19 during the 2020 pandemic. Because of the enthusiasm and promise of this trial, on May 3, 2020, the Bill and Melinda Gates Foundation awarded a $10 million grant to expand this study to 10,000 health care workers. In support of this study, an epidemiological survey by Miller et al., showed a correlation between the BCG universal vaccination policy and reduced morbidity and mortality due to COVID-19. [53]

[53] Correlation between universal BCG vaccination policy and reduced mortality for COVID-19
Aaron Miller, Mac Josh Reandelar, Kimberly Fasciglione, Violeta Roumenova, Yan Li, Gonzalo H Otazu
medRxiv 2020.03.24.20042937; doi: https://doi.org/10.1101/2020.03.24.20042937
https://www.medrxiv.org/content/10.1101/2020.03.24.20042937v2.full.pdf

Although the BCG vaccine has gained the most commercial attention as a known inducer of TRIM, β-glucan has numerous advantages over the vaccine (for which serious adverse effects are known to include, but are not limited to, abscess formation at the injection site, lymphadenitis, severe local reactions, and even death) in that it can be administered orally, has an extremely high safety profile, does not require access to health care to receive treatment, and is known to act similarly to the BCG vaccine in terms of boosting innate immune responses, and thus there is a strong debate in favor of using β-glucan for prophylaxis against COVID-19. [54]

β-glucans are natural polysaccharides obtained from a variety of sources such as oats, barley, bacteria, yeasts, algae, and fungi[55] and have variations in their structure responsible for their specific biological properties. To date there are about 12,000 scientific publications reporting the immunomodulatory effects of these substances.
It is known that humans have always encountered β-glucans as part of their diet or as pathogens as they are components of the cell wall of plant cells, yeasts, fungi and bacteria.
Bioactive β-glucans consist of D-glucose monomers linked via bonds
β-glycosides with a β- (1 → 3), β- (1 → 6) or β- (1 → 4) configuration[56] .

In Table 1, β-glucans that are most commonly used in immune modulation studies are listed, and in Figure 1 they are exemplified schematically

[54] Geller A, Yan J.
Could the Induction of Trained Immunity by β-Glucan Serve as a Defense Against COVID-19?
Front Immunol. 2020;11:1782. Published 2020 Jul 14. doi:10.3389/fimmu.2020.01782
https://www.frontiersin.org/articles/10.3389/fimmu.2020.01782/full

[55] https://www.yumpu.com/it/document/read/27958905/i-beta-glucani-dei-funghi-erboristeria-rainbow

Beta-glucans: uses, side effects, interactions, dosage and warning - Vitamins - Supplements - 2020
https://it.medicineh.com/77-beta-glucans-63043

[56] Du B, Meenu M, Liu H, Xu B.
A Concise Review on the Molecular Structure and Function Relationship of β-Glucan.
Int J Mol Sci. 2019;20(16):4032. Published 2019 Aug 18. doi:10.3390/ijms20164032
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC6720260/

structural features and variation in branching, which are considered to be critical for the biological activities of β-glucans.[57] .

Several studies comparing the immunologic properties of commercially available β-glucans in terms of their effects on phagocytosis, IL- 2 production, antibody secretion, superoxide production, IFNγ production, and inhibition in experimental models of cancer have been published, and it has been shown that glucans in general have strong stimulatory effects on most functions of the immune system. However, there are significant differences among the glucans tested: highly purified and highly active glucans have potent, pleotropic effects and stimulate all aspects of immunological reactions, whereas poorly defined glucans have only medium biological effects (if any). [58]

It has been reported that β-glucans such as pleuran from the mushroom *Pleurotus ostreatus*,[59] and lentinan extracted from the edible mushroom *Lentinus edodes*[60] reduce the production

[57] de Graaff P, Govers C, Wichers HJ, Debets R.
Consumption of β-glucans to spice up T cell treatment of tumors: a review.
Expert Opin Biol Ther. 2018 Oct;18(10):1023-1040. doi: 10.1080/14712598.2018.1523392. PMID: 30221551.
https://www.tandfonline.com/doi/full/10.1080/14712598.2018.1523392

[58] Jawhara, S.
How to boost the immune defense prior to respiratory virus infections with the special focus on coronavirus infections.
Gut Pathog 12, 47 (2020). https://doi.org/10.1186/s13099-020-00385-2
https://gutpathogens.biomedcentral.com/articles/10.1186/s13099-020-00385-2

[59] Bobovčák M, Kuniaková R, Gabrižˇ J, Majtán J.
Effect of Pleuran (β-glucan from Pleurotus ostreatus) supplementation on cellular immune response after intensive exercise in elite athletes.
Appl Physiol Nutr Metab. 2010 Dec;35(6):755-62. doi: 10.1139/H10-070. PMID: 21164546.
https://pubmed.ncbi.nlm.nih.gov/21164546/

[60] Murphy EJ, Masterson C, Rezoagli E, et al.
β-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.
Sci Total Environ. 2020;732:139330. doi:10.1016/j.scitotenv.2020.139330
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7211630/

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 Gastroenterol Dietol. 2020 Jun;66(2):172-176. doi: 10.23736/S1121-421X.20.02697-5. Epub 2020 Mar 12. PMID: 32162896.

of proinflammatory cytokines and oxidative stress and consequently are able to reduce the incidence of symptoms associated with upper respiratory tract (URTI) and lung infections. Therefore, β-glucans could be vital tools to combat COVID-19 through the immune system.

In a recent study, the potential usefulness of β-glucans in the treatment of complications from COVID-19 was further demonstrated: it is known that the active ingredients of *Basidiomycota Agaricus blazei Murill* (AbM), *Hericium erinaceus* (HE) and *Grifola frondosa* (GF) exert antimicrobial activity against viral agents, Gram - positive and Gram - negative bacteria and parasites in vitro and in vivo. Since the mechanism is immunomodulatory and not antibiotic, the fungi should also be active against multidrug-resistant microbes. In addition, because these Basidiomycetes also have anti-inflammatory properties, they may be suitable for the treatment of the severe pulmonary inflammation that often follows COVID-19 infection. In particular, an AbM-based mushroom extract (Andosan ™), also containing HE and GF, was found to significantly reduce bacteremia, increase survival in mice with pneumococcal sepsis, and improve symptoms and quality of life in patients with IBD through an anti-inflammatory effect. Therefore, these mushroom extracts could have a prophylactic or therapeutic effect against pulmonary superinfection and severe lung inflammation that often complicates COVID-19 infection. [61]

https://www.minervamedica.it/it/riviste/gastroenterologica-dietologica/articolo.php?cod=R08Y2020N02A0172

[61] Hetland G, Johnson E, Bernardshaw SV, Grinde B.
Can medicinal mushrooms have prophylactic or therapeutic effect against COVID-19 and its pneumonic superinfection and complicating inflammation?
[published online ahead of print, 2020 Jul 13]. Scand J Immunol. 2020;e12937. doi:10.1111/sji.12937
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7404338/

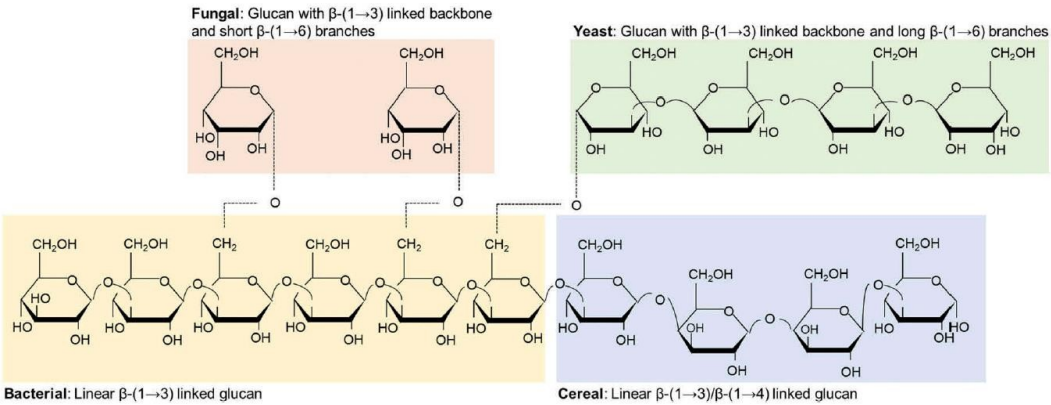


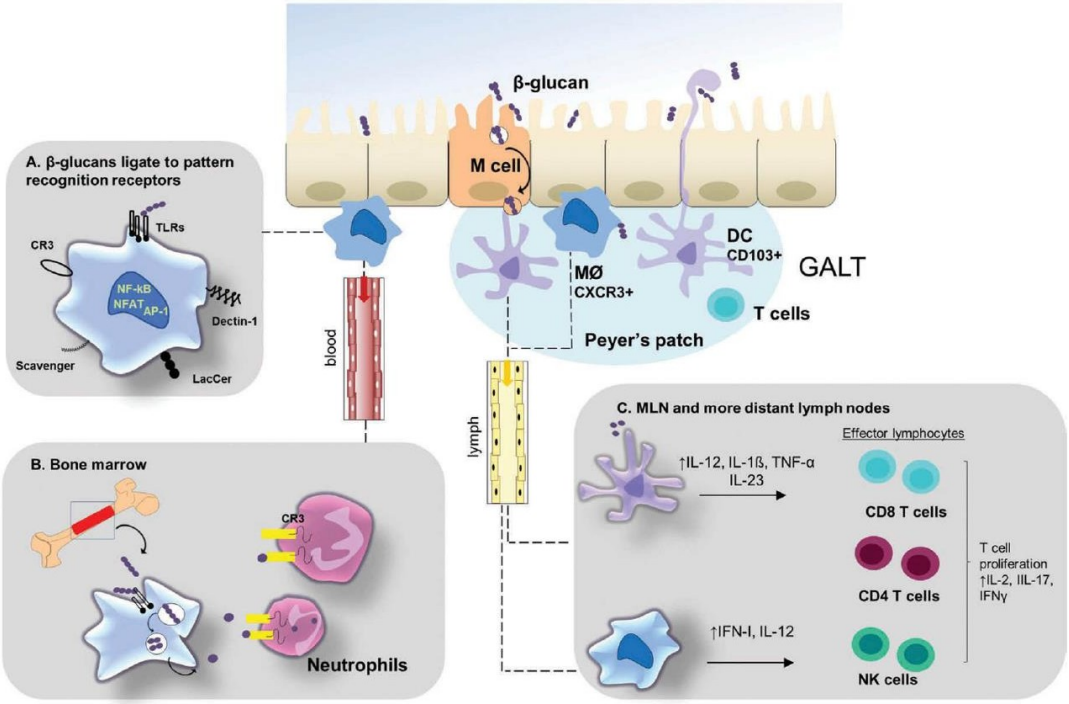
Figure 1 Glucans and their chemical structures. Examples and configurations of β-glucans derived from bacteria, fungi, yeasts and cereals.

Table 1. Source and chemical properties of most commonly reported β-glucans.[a]

	β-glucan	Organism/species	Glycosidic linkages
Algae	Laminarin	*Laminaria digitata*	β-(1➞3, 1➞6)
Bacteria	Curdlan	*Alcaligenes faecali*	β-(1➞3)
Fungi	Maitake	*Grifola frondosa*	β-(1➞3, 1➞6)
	Lentinan	*Lentinula edodes*	β-(1➞3, 1➞6)
	Pachyman	*Poria cocos*	β-(1➞3, 1➞6)
	PGG	*Saccharomyces cerevisiae*	β-(1➞3, 1➞6)
	Pleuran	*Pleurotus ostreatus*	β-(1➞3, 1➞6)
	PSK	*Trametes versicolor*	β-(1➞3, 1➞4)
	Schizophyllan	*Schizophyllum commune*	β-(1➞3, 1➞6)
	Scleroglucan	*Sclerotium rolfsii*	β-(1➞3, 1➞6)
	SSG	*Sclerotinia sclerotiorum*	β-(1 ➞ 3)
	WGP	*Saccharomyces cerevisiae*	β-(1➞3, 1➞6)
	Yeast	*Saccharomyces cerevisiae*	β-(1➞3, 1➞6)
	Zymosan	*Saccharomyces cerevisiae*	β-(1➞3, 1➞6)
Higher plants	Barley	*Hordeum vulgare*	β-(1➞3, 1➞4)
	Oat	*Avena sativa*	β-(1➞3, 1➞4)

https://www.tandfonline.com/doi/full/10.1080/14712598.2018.1523392

[a]N/A: Not determined; PGG: poly-glucopyranosyl-glucopyranose; PSK: polysaccharide-K; SSG: sclerotinan; WGP: whole glucan particles.



https://www.tandfonline.com/doi/full/10.1080/14712598.2018.1523392
Absorption, trafficking and immune activation of β-glucans. β-glucans enter the proximal small intestine through intestinal epithelial cells or M cells in Peyer's plaques, where they are captured by CXCR3 macrophages or CD103 DCs. Exposure to β-glucans induces these cells to migrate through the bloodstream to the bone marrow or through the lymphatic system to mesenteric lymph nodes or more distant lymph nodes.

The following table shows some effects of β-glucans on immune cells

Table 2. Effects of β-glucans toward immune cells.[a]

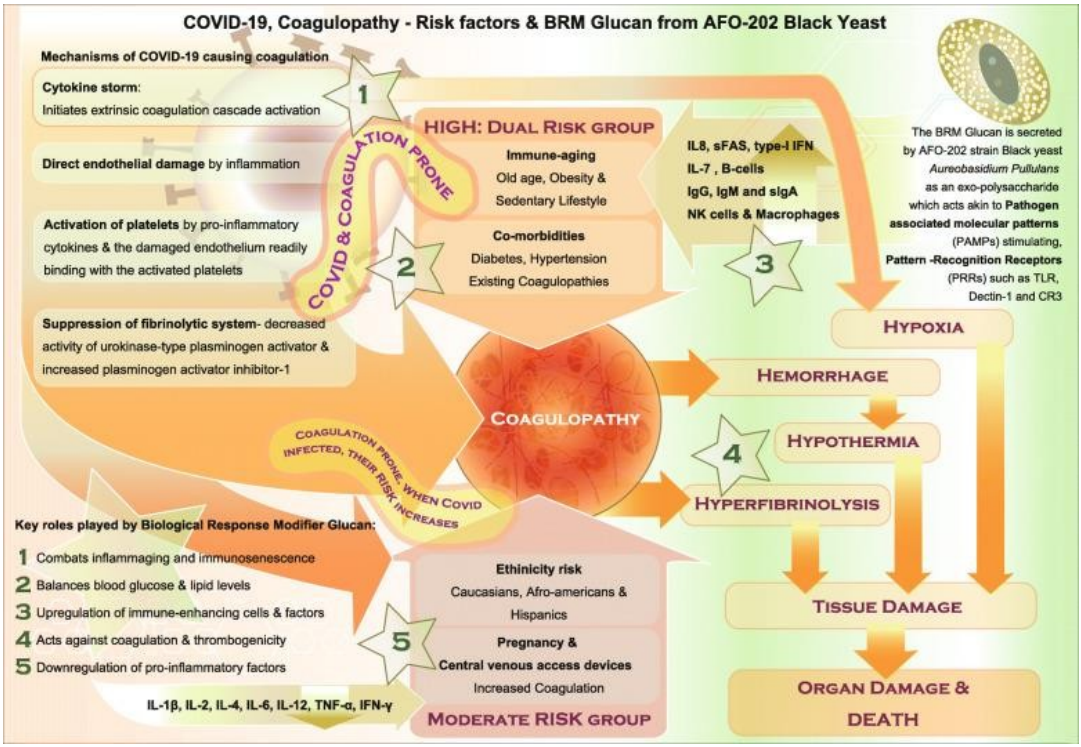
Immune cell type[b]	β-glucan	Potentiation of:	Attenuation of:
Neutrophils	β-(1→6)-glucan (from *Candida albicans*)[c] PGG[c]	• Gene expression of heat shock proteins • Production of ROS • Phagocytosis • Complement cascade and opsonization by C3b and further degradation in iC3b and C3dg	
Macrophages	Barley, Oat, Lentinan[c] Wellmune Soluble, Lentinan[c]	• Gene expression of IL-1β, IL-8 and IL-10 • Gene expression of C-type lectin receptors • Skewing macrophages toward an alternative, M1-like gene expression profile	
Dendritic cells	WGP[c] Curdlan[c]	• Gene expression of IL-6, IL-12, IL-2, TNF-α and IFN-γ • Surface expression of CD11c, HLA-DR, CD86 and CD40 • Production of IFN- γ, IL-2 and IL12p40 • Gene expression and protein secretion of IL-1β, IL-6, and IL-23	
B lymphocytes	Curdlan, Zymosan[c]	• Production of TNF-α, IL-6 and IL-8	• IgM production and B-cell proliferation
Myeloid-derived suppressor cells	Curdlan[d]	• Gene expression of IL-12p35 • Surface expression of CD11c, CD40, CD86, MHCII and CD80	• Arginase activity and nitrites in spleen

https://www.tandfonline.com/doi/full/10.1080/14712598.2018.1523392
[a]iC3b: inactivated C3b; IFN-γ: interferon gamma; IgM: immunoglobulin M; MHCII: major complex of histocompatibility II; ROS: reactive oxygen species; TNF-α: tumor necrosis factor-alpha.
[b] For unlisted immune cell types (such as T lymphocytes), β- glucans have not (yet) been reported to induce direct effects[c] Primary cells and human cell lines[d] mouse study

Another important effect of β-glucans concerns their beneficial action in reducing the risk of coagulopathy in predisposed patients (due to COVID-19 infection and due to the presence of co-pathologies such as hypertension, diabetes mellitus, dyslipidemia, and obesity).
It has been reported by various studies that β-glucans have direct antiplatelet, antioxidant, anticoagulant, and antithrombotic actions, further supporting their beneficial effects as a supplement to prevent COVID-19-associated coagulopathy. [62]

[62] Ikewaki N, Rao KS, Archibold AD, et al.
Coagulopathy associated with COVID-19 - Perspectives & Preventive strategies using a biological response modifier Glucan.
Thromb J. 2020;18:27. Published 2020 Oct 16. doi:10.1186/s12959-020-00239-6
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7563912/

Ikewaki N, Iwasaki M, Abraham SJK.
Biological response modifier glucan through balancing of blood glucose may have a prophylactic potential in COVID-19 patients
[published online ahead of print, 2020 Oct 21]. J Diabetes Metab Disord. 2020;1-4. doi:10.1007/s40200-020- 00664-4
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7575334/



https://www.ncbi.nlm.nih.gov/pmc/articles/PMC7563912/
A schematic illustration of the implications of the COVID-19 coagulopathy cascade and the stepwise mechanism leading to organ damage. Various risk factors modulated by the glucan biological response modifier (BRM) at various steps of this cascade are listed and classified

Medicinal plant regulations

Taken from the website of the Italian Society of Phytotherapy

From a regulatory point of view, herbal medicines have many different placements, depending on the purpose of use, the way they are registered and placed on the market; consequently, herbal products can follow either the drug regulation (2001/83/EC), or the food supplement regulation (2002/46/EC).

Medicines

Herbal products that have the status of a medicine in Italy can be classified into: medicinal specialties registered with AIC, products in one or more pharmacopoeias of the European Union, traditional herbal medicines, and herbal products prescribed by prescription.
In the European Pharmacopoeia, the Italian Pharmacopoeia, and those of other European Community member states, there are entire chapters devoted to herbal products.
The F.U.I. 12th edition, currently in force, is one of the pharmacopoeias that best characterizes herbal products and indicates specific assays and quality requirements. F.U.I. also contains a number of monographs on individual plant extracts and preparations.
Traditional herbal medicines are an option offered to companies by the European Medicines Agency (EMA) to be able to register certain products following a simplified regulation (2004/24/EC), without performing large-scale clinical and toxicological trials. Products that qualify for registration as traditional herbal medicines are all reviewed by EMA's specific committee dealing with herbal products.

Drug regulatory agencies are therefore responsible for the authorization and monitoring of medicinal plants as well. To this end, we would like to point out the dedicated section on the EMA's website on phytotherapy regulations and the monographs of the various substances authorized or under evaluation[63] and the WHO's collection of monographs[64] .

Dietary supplements

Most of the botanical species known for their health-promoting properties do not have reference products for medicinal use, and for this reason they can only be used for the purpose of maintaining good health, preventing possible disease states, and supplementing nutritional deficiency states. The regulatory apparatus that governs these products is that of dietary supplements,

[63] https://www.ema.europa.eu/en/human-regulatory/herbal-medicinal-products
https://www.ema.europa.eu/en/human-regulatory/herbal-products/european-union-monographs-list-entries
https://www.ema.europa.eu/sites/default/files/Medicines_output_herbal_medicines.xlsx
https://www.ema.europa.eu/en/documents/other/inventory-herbal-substances-assessment_en.pdf

[64] World Health Organization, WHO Consultation on Selected Medicinal Plants, WHO Consultation on Selected Medicinal Plants (2nd : 1999 : Ravello-Salerno, Italy), WHO Consultation on Selected Medicinal Plants (3rd : 2001 : Ottawa, Ont.) & WHO Consultation on Selected Medicinal Plants (4th : 2005 : Salerno-Paestum, Italy). (2006). WHO monographs on selected medicinal plants.
World Health Organization. https://apps.who.int/iris/handle/10665/42052

regulated in detail in Italy by the 2002/46/EC standard. The Ministry of Health in Italy and EFSA in Europe impose a number of requirements for ingredients that can be used, starting with safety of use. Herbal products placed on the market as food supplements may carry health claims, which are authorized by EFSA.
The safety of herbal products in Italy is monitored through a phytovigilance service that updates and collects and reports adverse events derived from the use of herbal medicines.

How to use medicinal plants [65]

Preparation and doses

All phytotherapy traditions insist on the importance of how medicinal plants are administered and recognize that their effectiveness depends largely on the prescription. The following information has been drawn from the most consistent sources of natural medicine that have come down to us over the years: ayurveda and Chinese medicine. The recommended doses are obviously generalized, so you should evaluate according to your own reactions and also refer to the recommended doses for each specific plant, after checking that it is not toxic.

Types of preparations

Below are the different types of preparations, according to the intended use and the part Of plant used.

The Juice

It is normally made from fresh plants, from which the pulp is squeezed and then filtered through a natural fiber cloth. The most common juices are those of parsley, garlic, onion, and of course fruit juices. Dried plant juice is less effective than fresh plant juice. If dried plants are used, they should be soaked for 24 hours in an amount of water equal to twice their weight, after which the liquid is extracted.

The Pasta

It is made from chopped and blended fresh plants; a little water can be added
In case dried plants are used.
It can be given alone or mixed with honey, oil or clarified butter, usually in double the amount.

[65] https://www.projectindia.blog/2017/07/25/fitoterapia-tipologie-di-preparato/

If no water is added, the pastes will keep almost indefinitely, preferably in the refrigerator. Pastes can be used as an elutuary (mixture of plant powder or pesto with honey or syrup), and then eaten with a spoon, or incorporated into decoctions. Externally, they can form the basis of poultices and poultices.

The Decoction

Heavier roots and barks, as well as substances whose volatile oils are not essential to therapy, are administered in decoction form. Therefore, it is not correct to prepare a decoction of aromatic plants such as lies, because the volatile oils would evaporate. In the West, the average amount used for most plants is equivalent to one ounce (or about 28.35 grams) per about half a liter of water. A practical way to approach the required amount is to fill the palm of one hand with the heavier roots and barks, while lighter substances may require a large handful.

The decoction is prepared by bringing the water to a boil, adding the plants and covering; it is continued by simmering for twenty to thirty minutes. Ayurvedic medicine uses the following basic recipe: boil one part dried plants to sixteen parts water, or approximately 1/2 ounce of plants to 8 ounces of water. Simmer until reduced to 1/4 of the original amount, or half for a lighter decoction.

Both Western and Eastern traditions distinguish between single, double, and even narrower decoctions, depending on the level of boiling, and thus extraction of the various components. At a first level the most sensitive volatiles are extracted, at the next level the other biochemical elements, and finally the mineral substances. The problem is that if the first decoction is not set aside, prolonged boiling tends to dissipate the previously extracted elements.

The Hot Infusion

It is obtained by soaking one ounce of plants in half a liter of boiling water, and letting it sit, covered, for a minimum of 10 to 20 minutes, up to several hours. This method does not require the use of fire, which allows the aromatic principles of the plants to be preserved intact. Since, however, many recipes combine aromatic plants with heavier roots and barks, a good compromise in such cases is to boil the roots for about 20 minutes to an hour, at the end of cooking turn off and add the lighter herbs.

The Cold Infusion

It is obtained by letting the plants rest in cold water for at least an hour. Some people let the infusion sit in the sun, while others prefer to let it sit overnight. The cold infusion method is also used when it is necessary to preserve plants rich in volatile oils, as in the case of mint, lemongrass (citronella), lemon balm, hibiscus, and sandalwood, which by nature play a refreshing role.
In cold infusion, the powders are mainly used, since since they are already partially decomposed, it is easier to extract their active ingredients by simply mixing them in water.
It should also be kept in mind that some substances are thermolabile, so in contact with heat they would be damaged, as in the case of amygdalin contained in apricot seeds or cherry bark.

The Powders

They are obtained by grinding through a mortar of dried plants. Powders are a practical and effective means because they allow for a homogeneous mixture where the active ingredients are easily extracted with maximum efficiency, as less is needed compared to whole plants.
The powders can be administered in a variety of ways: incorporating them into gelatin capsules, mixing them into a liquid such as water, milk, or broth (in the dose of a tablespoon or two per glass).
Ayurvedic medicine mixes the powders with clarified butter, oil, honey or brown sugar, as these ingredients for their properties are considered excellent carriers or "*anupana.*"
It should be kept in mind, however, that the powders should be used within a period of about two to three months, after which they tend to oxidize, thus losing their effectiveness.

Pills or Tablets

for convenience of intake, it is used to cook the plants until they settle to the bottom like a paste, or by mixing the powdered plants with a little water, syrup or honey. Pills of the desired size are then made from the resulting paste.

The Wines

They are made by dissolving about 3 to 4 pounds (about 1.5 kg) of honey or whole-grain sugar in 2-3 liters of herbal tea. As soon as the mixture reaches 20°C, add an appropriate amount of live ferments. Allow it to ferment in a partially covered container so that the carbon dioxide that will be formed can disperse. When fermentation is almost complete, strain and store in a vacuum container to prevent fermentation from continuing any longer than necessary.

Wines are excellent as tonics, some plants such as Siberian ginseng or hawthorn berries make excellent wine, however in case of treatment of acute situations tinctures should be preferred.

The Tinctures

They are made by combining 1 to 4 ounces of powdered, or otherwise well ground, plants to 8 to 12 ounces of alcohol.
Add water to make a 50% mixture. Alternatively, pour 30% (60 proof) vodka over the powder. The amount of liquid should exceed what the plants are able to absorb, so add as needed. Shake and let stand for 2 weeks in a dry, warm place, taking care to stir once a day. Finally strain and store in dark bottles. You administer 1 to 30 drops depending on the type of plant used.
Glycerin tinctures exert a lighter, calming effect on the digestive system, and they contain no alcohol. Their main disadvantage is that glycerin cannot dissolve the resinous and oily components as effectively as alcohol. Preparation is done by mixing one part vegetable glycerin with four parts hot water. Then add the powdered plants and let it sit for two weeks in a warm place.

The Liniments

They are prepared like tinctures, but because they are intended exclusively for external applications they can be prepared with the cheaper isopropyl alcohol sold in pharmacies. For sprains, bruises, muscle and joint pain, calorific plants stimulating circulation are used, for example, cayenne pepper, ginger, myrrh, angelica, cloves, caraway seeds, or bay leaves. The resulting liquid is used to rub the affected area.

Syrups

Useful for throat and lung disorders, as it can soothe and protect the throat. The basic syrup is made by boiling 3 pounds of raw sugar in about half a liter of herbal tea until the proper consistency is reached. Or add the alcoholic extracts of the plants while cooking, this way the alcohol will evaporate letting the active ingredients settle. You can substitute honey for sugar; they are great for children.

Cataplasms and Poultices

Poultice is made by chopping fresh plants and applying them directly into the part to be treated, eliminates pain and promotes healing of wounds, cuts and fractures.

A common poultice is made from comfrey root and plantain, combined with cayenne pepper, which activates their potential.
Poultice is made by spreading a thin layer of honey on a muslin cloth, and sprinkling the powder of the stimulating plants on it. Applied to the affected part, the poultice acts as a revulsive, eliminating pain and congestion.
The compress is made by soaking the muslin cloth in the plant decoction, and applying it as hot as possible to the affected part. The most common are the ginger or turmeric compress, made by boiling the respective grated roots in water. Ginger is used against muscle and joint pain, such as arthritis and back pain, as well as stiff neck, menstrual pain, strains and sprains.
Tear poultice is useful for extracting splinters embedded in the skin. It is made by combining comfrey root (fresh or powdered), plantain, and a small amount of cayenne pepper.

Medicinal Oils or Oleolites

Widely used in Ayurvedic medicine because they are considered *anupana,* or transporters within the body of the vata principle, or nervous system. Base oils can be varied, depending on the use to be made of them, for example, olive oil, sesame oil, safflower oil, coconut oil, and castor oil. It is recommended to use those with high antioxidant value, so that if they are to be stored for a long time they will not go rancid. If they are used for external use, 1% alpha-tocopherol, or vitamin E, can be added to prevent oxidation.
The basic Ayurvedic recipe calls for: 1 part plants, 16 parts water, 4 parts oil, cook everything until the water evaporates completely. Since it is difficult to strain the cooked plants into the oil a good expedient is to prepare the decoction separately, strain it and then proceed as above.
As already noted plants rich in volatile oils such as mint, camphor and rose lose their active ingredients when exposed to high temperatures. In this case the correct way to prepare them is to macerate the powder of the dried plants directly in the oil. You let it sit for twenty days, stirring occasionally, strain and bottle in dark containers for use. Another way is to finely crush the whole plant (fresh as in the case of ginger garlic or onion, dried as in the case of lavender flowers, which should be removed from their stems), and then proceed as just described. Garlic oil for example is administered to treat earache in children.
Medicinal oils are mainly used as external massage, as ointments, balms for wounds, ulcers, burns, or as a base for enemas, irrigations, or in inhalations. Some oils can be administered internally in small doses.

The Medicinal Clarified Butter

Similar to medicinal oils, clarified butter or Ghee is a specific vehicle related to pitta (fire); being cooling, it is therefore suitable for treating gastrointestinal inflammation, fevers and ulcers.
Clarified butter is made by heating unsalted raw butter over medium heat until the saturated fats condense separating from the unsaturated pure oils. By Ayurvedic medicine it is considered on par with the yin -tones of Chinese medicine, believed to strengthen fluids, and vital tissues, such as blood, muscle, fat, reproductive secretions, and ojas, the essential life force residing in the heart.

The Alchemical and Spargyric Tinctures

Many herbalists believe that tinctures do not present a complete balance of all the therapeutic elements of plants. The alternative method involves the use of a standard alcohol extract, the resulting solid residue that is normally discarded in this case is burned to a white ash, which in turn is stirred to the filtered liquid extract. The whole is carefully redistilled, leaving the ash residue at the bottom.

The choice of which type of preparation is preferable to relieve a condition is based on various criteria. Generally, herbal teas are good in most cases; powders are perfect for digestive problems; pills are more suitable when bitter plants have to be taken with prolonged administrations and in very small doses; elutuaries, herbal and honey mixtures are suitable for tonic and nourishing action; and medicinal oils are suitable for the treatment of neurological problems, and for external applications.

Dr. Loretta Bolgan

Ph.D. in Pharmaceutical Chemistry and Technology Ph.D. in Pharmaceutical Sciences
Scientific Advisor