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Volatile Oils: A Plethora of New Molecular Entities with Diverse Antiviral Activity

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Abstract

Volatile oils are low molecular weight compounds produced by plants which are attributed several biological properties including antibacterial, antifungal and antiviral activities. The specific mixture of terpens and phenylpropanoid compounds might be responsible for these properties. An overview of volatile oil compounds having antiviral activity against important viral strains was described and discussed. This is the foundation for the treatment of viral pathologies in the clinical, veterinary and agricultural fields to further research and develop synthetic drugs. Antiviral activity data were collected from mainly *in vitro* studies conducted on volatile oils and their components published in the last 15 years. Databases such as Scopus, PubMed, CNKI and Google scholar were employed. Phrases such as "volatile oil", "antiviral activity", "phytochemical", "*in vitro*" and their combination were used as keywords. Several types of essential oils obtained from plants have shown antiviral activity against Herpes simplex type-1 and type-2, influenza virus, coronavirus (SARS-CoV2), the human immunodeficiency virus, Hepatitis A, B and C viruses, Noroviruses, Coxsackie virus, Poliovirus, Newcastle disease virus, Yellow fever virus, Japanese encephalitis virus, Junin virus, Dengue virus, phytoviruses and zoonotic viruses. The essential oil might act on one or several steps of the viral replication cycle. Some oils are active on either DNA or RNA viruses, whereas others are active only in enveloped viruses. These oils could serve as a complementary antiviral treatment since they prevent the emergence of resistance mechanisms. There is a plethora of volatile oils that showed potential antiviral activity mainly acting in a key step of the viral replication cycle. Some compounds are effective in several types of viruses independent of their genome type. Although the *in vitro* results support the efficacy of these substances, their clinical use remains a concern due to the unknown side effects. However, this review provides the groundwork for upcoming clinical studies, especially in pandemic times.

Keywords: *Essential oils, Antiviral activity, In-vitro, Virus pandemics*

INTRODUCTION

Historically, viral illnesses have been the main concern for human health for thousands of years. A virus is a nanosize (20-300 nm) infectious unit composed of genes wrapped in a protein or lipid envelope. There are several families of viruses which attacks human, animal or plant hosts causing extraordinary human and economic losses each year. Viruses are classified according to (i) the type of genetic material they use (DNA, RNA or reverse transcribing virus), (ii) the method they use to replicate within the cell and (iii) their structural features. Viruses differ from virusoids, viroids, and prions. Virusoids are nucleic acids that depend on cells and helper viruses for packaging their nucleic acids into virus-like particles. Viroids are naked, and mostly double-strand RNAs that appear to be restricted to plants, spread from cell to cell, and are replicated by cellular RNA polymerase II. Prions are abnormal proteins that propagate and cause disease by altering the structure of a normal cell protein. Prions cause neurodegenerative diseases such as Gerstmann-Straüssler disease, Creutzfeldt-Jakob disease, kuru, and mad cow disease. Viral genomes may consist of single- or double-strand DNA, single- or double-strand RNA, single-strand or segmented antisense RNA, or double-strand segmented RNA. Viral nucleic acids and nucleoproteins are almost always enclosed in a protein capsid where tegument proteins fill the space between the nucleus and the outer envelope of the virus. Enveloped viruses are usually sensitive to detergents or lipid solvents or that can dissolve the envelope, whereas viruses with protein capsid may be somewhat detergent resistant [1].

Viruses can replicate only within cells because their nucleic acid does not encode many enzymes necessary for the metabolism of proteins, carbohydrates and lipids or for the generation of high-energy phosphates. Typically, viral nucleic acids encode messenger RNA (mRNA) and proteins necessary for replicating, packaging, and releasing progeny virus from infected cells. Thus, a virus invades and penetrates the host cell and releases the genetic material taking control of the metabolic pathway of the host cell for its continuous replication. The common steps of the cycle includes attachment and entry to the host cell (whether or not have a lipidic membrane), transcription of viral mRNA, replication of viral genome, assembly into new virus particles, regardless of different genetic materials (RNA or DNA). Ideally, antiviral agents that target multiple stages in the viral replication cycle having little toxicity are desirable. Thereby, some compounds are able to inhibit viral attachment, replication, or production of the viral genome. Interestingly, viruses with an RNA genome (i.e, HIV, HCV, and influenza) lack from the proofreading mechanism (i.e., reverse transcriptase or RNA-dependent polymerase) leading to the rapid development of drug-resistant viruses. Most antiviral commercial drugs target a single viral enzyme, which is crucial in viral replication making them safer. Conversely, antiviral drugs which target cellular molecules exhibit a broader antiviral activity spectrum and less chance of developing virus resistance, but could be more lethal to the host cell. This toxicity is related to prolong treatment periods leading to environmental hazard potential and adverse and carcinogenic effects [2].

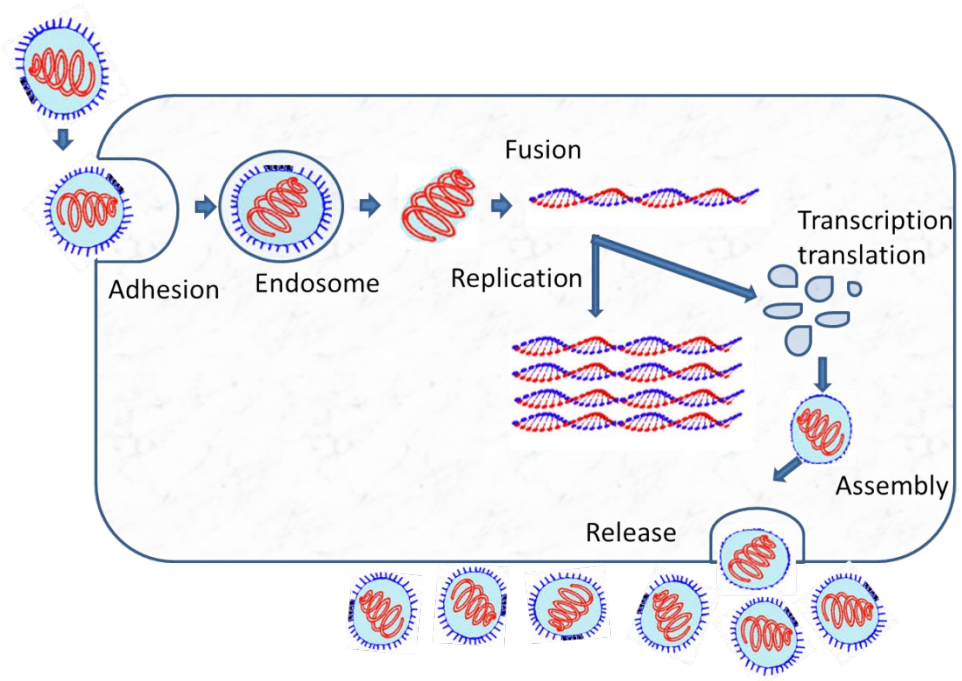

Figure 1: General schematics of the stages of the viral (enveloped) replication cycle

Essential oils (EOs) also known as volatile oils represent a good alternative to synthetic antivirals since they are composed by a mixture of lipidic and volatile substances such as terpenes and phenylpropanoids. In turn, terpenoids could be classified into monoterpenes (C_{10}), sesquiterpenes (C_{15}), and diterpenes (C_{20}). The vast majority of EOs are composed of monoterpenes. The lipophilic nature of EOs enables them to interact with lipids present in the capsid or host nuclei rendering more permeability, and disrupting structural macromolecules, or growth proteins needed in the viral replication cycle. Each compound may exhibit a different mechanism of antiviral action, which in turn is mediated by a series of biochemical reactions. Unfortunately, EOs do not specifically target viruses since they could also affect eukaryotic cells in a reversible or irreversible manner. In extreme cases, EO cytotoxicity may lead to apoptosis and necrosis [3].

Most antiviral activity studies have been focused on Herpex simplex virus type 1 (HSV-1), influenza virus, Coxsackie virus B1, HIV, Hepatitis virus, Polio virus, dengue virus, tobacco mosaic virus, Yellow fever virus and Junin virus. Usually, the antiviral activity of EO is performed in one of several stages of viral cycle into the host. The antiviral screening studies include one or several complementary techniques such as (i) visual microscopic analysis of cytopathic effects, (ii) colorimetric assays (MTT, crystal violet, and neutral red) or (iii) fluorometric assays (Bisbenzidine, AlamarBlue®, Rhodamine). Typically, the antiviral activity is assessed by (i) pretreatment of the host cells with the EO, (ii) pretreatment of the virus with the EO, (iii) treatment of the cells with the virus with concomitant application of the oil and (iv) treatment of the cell already infected (replicative phase) with the oil. Most of these EOs possess a moderate cytotoxicity (100 µg/mL < CC_{50} < 1000 µg/mL). Further, oils having an IC_{50} <30 µg/mL are considered to have a good antiviral activity. Moreover, the therapeutic index or selectivity index is another criterion to evaluate their safety. Any value lower than 4 is considered as cytotoxic for the host cells. The description and discussion of the most relevant studies of EO antiviral activity is denoted in the following sections.

Herpes simplex virus type- 1 (HSV-1) and type-2 (HSV-2)

The herpes simplex virus (HSV) is an enveloped virus which possesses a linear double-stranded DNA belonging to the *Herpesviridae* family. It includes at least eight human pathogenic strains, the neurotropic herpes simplex virus 1 (HSV-1) and herpes simplex virus 2 (HSV-2), varicella zoster virus (HSV-3), lymphotropic human cytomegarovirus (HCMV), HSV-4, EBV (HSV-5), HHV-6, HHV-7, and HHV-8. HSV-1 causes orolabial dermatitis, whereas HSV-2 is related more frequently with genital infections and probably cervical cancer. HSV-1 and HSV-2 viruses establish dormant infections in sensory neurons and periodic lesions around the point of entry into the body. Many synthetic drugs such as acyclovir, ganciclovir, valacyclovir, famciclovir, penciclovir, and cidofovirare have been employed to treat these infections. These drugs are nucleoside analogues functioning as DNA chain terminators preventing its completion. Therefore, the antiherpetic mechanism of these drugs is the inactivation of virus thymidine kinase or DNA polymerase enzyme. Table 1 summarizes several studies on effective HSV-1 and HSV-2 inactivation by several EOs. Eugenol is an important compound found in *E. caryophyllus*, cinnamon and basil EOs and it is proved to inactivate the virus directly. This activity may be due to the damaging effect of lipidic viral envelope and might also interfere with the expression of HSV-1-glycoprotein B needed in the very late stages of viral maturation and release [4]. Eugenol

also induces glutathione S-transferase in rat liver in vivo affecting the acid-soluble sulphydryl levels [5].

The EO from *A. arborecens* exhibits virucidal activity by direct virion inactivation [6], [7]; Likewise, the EOs from *Mintostachys mollis* exerts the inhibitory activity by disruption of viral envelope, inactivating the viral particle before cell entry. However, it is unknown if the inhibitory effect of oil is due to binding of the EOs to viral proteins involved in host cell adsorption and entry, or inactivation of the viral envelope, decreasing the ability to infect host cells [8]. Thyme oil also causes abnormalities in the structure and function of proteins in the Vero cells membranes or HSV-1 envelope, which subsequently inhibit the attachment and penetration of the virus [9]. The *Carum copticum* EO contains thymol, terpinolene and o-cymene which are responsible for directly inactivate virions preventing absorption into the host cells [10]. Likewise, *Moringa peregrina* contains fatty acids with known anti HSV-1 activity. Likewise, the EO from *M. officinalis* and *Salvia fruticosa* possibly bind to viral proteins involved in host cell adsorption and penetration and perhaps directly damaging the virion envelope and glycoproteins [11]. Likewise, inhibition of HSV by anise oil, dwarf-pine oil and chamomile oil occur before, or during, adsorption but not after penetration of the virus particles [12]. It is known that some monoterpenes directly inactivate Herpes virus by interfering with virion envelope structures and masking viral structures which are necessary for penetration into host cells. Thus inhibition of HSV appears to occur before adsorption but not after penetration of the virus into the cell. The antiviral activity of single monoterpenes does not contribute equally to the antiviral activity of the EO [13]. Thus, monotherpenes such as isoborneol, inhibits glycosylation of viral HSV-1 polypeptides [14], whereas, 1,8-cineole and borneol (an isoborneol stereoisomer) are unable to inhibit glycosylation and inhibited viral replication, without affecting viral adsorption [15]. Further, the application of cineole protected mice against infection with HSV-2.

On the other hand, the EO of *S. insularis* prevents adsorption of virion to host cells, and prevent cell-to-cell virus spread in HSV-1 and HSV-2 infected cells. Further, flavonoids such as quercetin and quercitrin in *S. insularis* inactivate HSV-1 by elevating the level of intracellular cyclic AMP [16]. The encapsulation of EO compounds such as camphor, thujon and azulene have shown better antiviral activity than the free EO of *A. arborescens* [17]. The EO of *Santolina insularis* improved viral inactivation by pre-incubation with the EO before viral adsorption, indicating an intracellular mechanism. Small unilamellar liposomes always showed better stability, but were less effective than multilamellar liposomes due to an enhancement of EO availability rendering a more unstable bilayer [18], [19].

Tea tree possessed antiviral activity against HSV-1, but lemongrass showed stronger antiviral activity than tea tree [20]. Further, pretreatment of virus with manuka, eucalyptus and leptuspermum oil prior was twice effective than when the oil was added during the adsorption or post-adsorption phase. The inhibitory effect might occur by binding of the oil to viral proteins involved in host adsorption and penetration or due to damage to the envelops impairing their ability to infect host cells [21]. Peppermint oil having cineole and limonene has virucidal effect prior to viral infection of host cells. Since peppermint oil is able to inhibit an acyclovir-resistant HSV-1 strain, the mechanism of interaction between peppermint oil and acyclovir with HSV is different. Acyclovir inhibits virus replication by interference with the DNA polymerase inside the cell, whereas peppermint oil probably inactivates HSV before it enters the cell [22]. The EO of *M. officinalis*, inhibits the replication of HSV-2 due to the presence of citral and citronellal. Likewise, lemongrass EO inhibited viral replication [23]. The EOs from *Glecon spathulata* and *G. marifollia* were only effective in reducing HSV-1 infectivity at the attachment and viral replicative phases, whereas the oil of thyme, ginger, chamomile, sandalwood, anise, hyssop interferes with viral capsid of HSV-2 [24].

Table 1: Antiviral activity of EOs against Herpes virus (HSV-1, HSV-2)

Reference	**EO source**	**Main components**	**Citotoxic dose CC50 (µg/mL)**	**Efective dose ED50 (**µg/mL)
[6]	*Artemisia arborescens*	4',6,7-trihydroxy-3',5'-dimethoxyflavone and 5',5-dihydroxy-3',4',8-trimethoxyflavone, exiguaflavone A and B, artemetin, bonanzin, eupalitin and chrysosplenetin	Vero cells:132	2.4 (HSV-1) 4.1 (HSV-2)
[17]	*Artemisia arborescens*	Camphor (36%), b-thujon (24%) and azulene derivatives (8%)	Vero cells:100	P90H MLV: 18.3
[25]	*Chrysanthemum trifurcatum*	Limonene (20.9%), g-terpinene (19.1%), 1,8-cineole (10.6%), b-pinene (8.8%), a-pinene (5.3%), 2-hexenal (4.9%), 4-terpenyl acetate (3.4%), b-myrcene (2.3%), germacrene-B (2.0%), b-spathulenol (1.6%), longifolene (1.4%), a-cadinol (1.4%), a-thujene (1.2%) and b-bourbobene (1.06%).	Vero cells: 735.9	>1000 (HSV-1)
[15]	*Cedrus libani* wood	Wood EO: himachalol (22.5%), β-himachalene (21.9%), and α-himachalene (10.5%)	Vero cells: 880	440 (HSV-1)
[26]	*Drimys angustifolia, Drimys brasiliensis*	*D.a*: bicyclogermacrene (19.7%), sabinene (9.7%) and terpinen-4-ol (6.4%) *D.b*: cyclocolorenone (18.3%), terpinen-4-ol (8.4%) and myristicin (6.6%)	Vero cells: *D.A*: 156.3 µg/mL *D.B:* 625 µg/mL	D.A. Log_{10}: 0.75 D.B. Log_{10}: 1

Reference	EO source	Main components	Citotoxic dose CC50 (μg/mL)	Efective dose ED50 (μg/mL)
[4]	*E. caryophyllus*	Eugenyl acetate: 16.5-100% Eugenol: 10.7-27.0%	Vero cells: 112.74 (oil) 218.2 (eugenol)	72.8 (HSV-1) 74.4 (HSV-2) Eugenol inactivate HSV-1 immediately and HSV-2 within 3 h
[27]	*E. caryophyllus*	Eugenol	Vero cells:250	25.6 (HSV-1) 16.2 (HSV-2)
[14]	Eucalyptus, tea tree and thyme	Eucalyptus oil, tea tree oil, thyme oil (p-cymene, thymol), citral and 1.8-cineole Tea tree oil: terpinen-4-ol (40%), α-terpinene (10%) and γ-terpinene (20%).	RC-37 cells: Eucalyptus: 290 Tea tree: 120 Thyme: 70 Terpinene: 38 Pinene: 80 Cymene: 65 Terpineol: 400 Thymol: 85 Citral: 45	Eucalyptus: 55 tea tree: 2 thyme: 11 Terpinene: 7 Pinene: 4.5 Cymene: 16 Terpineol: 22 Thymol: 30 Citral: 3.5
[24]	*Glechon spathulata Glechon marifolia*	*G. spathulata and G. marifolia*: sesquiterpene hydrocarbons (40.1% and 84.5%, respectively. b-caryophyllene (14.2% and 32.2%, respectively) and bicyclogermacrene (17.1% and 16.5%, respectively). *Glechon marifolia* : a-humulene (23.3%). *G. spathulata* oil: 8.5% of b-pinene and 6.9%of a-pinene, G. marifolia oil.	Vero cells: G. spathulata: 95 and G.marifolia:39	HSV-1 Log_{10} reduction G. spathulata: 2.2 and G. marifolia:2.3
[21]	*Leptospermonum scoparium*	Leptospermone (14.5%), calamene (16%), cadinene (6.1%), flavesone (4.5%)	RC-37 cells (green monkey kidney cells) Oil: 38.4 Leptospermone: 105 Flavesone: 1100	Oil pretreatment: HSV-1: 0.96 HSV-2: 0.58
[23]	*Melisa officinalis (lemon balm)*	B cubebene (15.4%), b-caryophyllene (14.2%), sesquiterpene alcohol (7.4), a- cadinol (7.2%), geranial (6.6%)	HEp-2 cell (human laryngeal cancer): 100	NR
[11]	*Melissa officinalis*	Citral a: 20.1% Caryophyllene: 17.3% Citral b: 13.6 % Citronellal: 3.9 % b-Cubebene: 3.8 %	RC-37 cells: 30	4 (HSV-1) 8 (HSV-2)
[28]	*Melaleuca spp*	*M. ericifolia*: methyl eugenol (96.8%); M. leucadendron: 1,8-cineole (64.3%) α-terpineol (11%); *M. armillaris:* 1,8-cineole (33.9%), terpinene (10.4%), terpinen-4-ol (19%); *M. styphelioides*: caryophyllene oxide (43.8%), (-) spathulenol (9.7%).	Vero cells:	HSV-1 Log_{10} reduction : 92-99%
[22]	Peppermint oil	Menthol (42.8%), menthone (14.6%), isomenthone (5.9%), menthyl acetate (4.4%), cineole (3.8%), limonene (1.2%) and carvone (0.6%)	RC-37: 140	20 HSV-1 80 HSV-2
[19]	*Salvia cedronella*	1,8-cineole (13.3%), α-pinene (10.1%), caryophyllene oxide (9.8%) and sabinene	MDCK and MDBK cells 3000 (H7N7) 3000 (HSV-1)	H7N7: 300 HSV-1: 600
[16]	*Santolina insularis*	3,3,6-trimethyl-1,5-heptadien-4-one (21.2%), camphene (8.5%), cineole (9%), bornyl acetate (6.4%), borneol (4.2%) and azulene derivative (12.7%)	Vero cells:112 mg/mL	Pretreatment: 0.88 mg/ml, (HSV-1) and 0.7 (HSV-2)
[18]	*Santolina insularis*	3,3,6-trimethyl-1,5-heptadien-4-one (21.2%), camphene (8.5%), cineole (9%), bornyl acetate (6.4%), borneol (4.2%) and CMDA (azulene derivative, 12.7%)	Vero cells:112 μg/ml (for all)	Cells preincubated with EO. Free oil: 10 UV:13.5 MLV:26
[5]	*Allium cepa, Allium sativum, Cuminum cyminum, Coriandrum sativum, Petroselinum sativum, Ocimum basilicum*	Cumin [cuminaldehyde (60%)], Linalool (coriander 70%), basil (linalool 56%, 1,8- cineole 12%). Onion oil (diisopropyl trisulfide 20.7%). Garlic (di-2-propenyl disulfide 25.2%, methyl-2-propenyl trisulfide 23.8% and di-2- propenyl trisulfide 21.1%). Parsley (myristicin 25% and apiol 18.2%).	Vero cells: 1000	Allium cepa: 1060 Allium sativum: 320 Cumin: 400 Coriander: 341 Basil: 615 Parsley:386 Linalool:10.5

Reference	EO source	Main components	Citotoxic dose CC50 (μg/mL)	Efective dose ED50 (μg/mL)
[12]	Anise dwarf-pine, chamomile	Dwarf pine: α-pinene, β-pinene, l-limonene, dipentene, l-phellandrene Chamomile: azulene-7-ethyl-1,4-dimethyl, limonene, bisabolol oxides A and B, bisabolone oxide	Vero cells: Anise: 160 dwarf-pine: 40 chamomile:30	Anise: 40 dwarf-pine: 7 chamomile: 0.3 effective in pretreatment & replication
[7]	*Anethum graveolens, Foeniculum vulgare Mentha piperita, Mentha spicata, Lavandula officinalis, Ocimum basilicum Origanum onites, O. vulgare, O. munitiflorum, O. majorana, Rosmarinus officinalis, Salvia officinalis, Satureja cuneifolia*	γ-terpinene, 4-allylanisole, (-)-carvone, dihydrocarvone, D-limonene, (-)-phencone, cuminyl alcohol, cuminylaldehyde, cuminol, trans-anethole, camphene, soborneol, (-)-borneol, L-bornyl acetate, 2-decanol, 2-heptanol, methylheptane, farnesol, nerol, isopulegol, citral, citronellal, citronellol, geraniol, geranyl ester, linalool, linalyl oxide, linalyl ester, α-pinene, β-pinene, piperitone, (-)-menthol, isomenthone, carvacrol, thymol, vanillin, and eugenol	MDBK cells: Oils: 0.8-1.6 Components: 0.8-3.2	A. *graveolens*: 0.025 *F. vulgaris*, mentha and Origanum (0.2) Citronellal, linalyl oxide, 2-heptanol, 2-decanol, eugenol & nerol: 0.025
[8]	*Lepechinia salvifolia* *Lepechinia vulcanoica* *Mintostachys mollis* *Ocimum campechianum*	*Lepechinia spp*: limonene (18.9%), germacrene (10.4%), 1 octen 3 ol (8.8%) *O. c:* methyl eugenol (53.9%), caryophylllene (13%), bulnesene (5.4%), germacrene (3.4%)	Vero cells: *L.s*: 231.7 *L.v*: 188.5 *M.c*:267.4 *O.c*: 811.1	*L.s:* 68.8 (HSV-1) *L.v*: 112 (HSV-1) *M.c*: 70.7 (HSV-1) *O.c*: (HSV-1) *L.s*: 81.9 (HSV-2) *L.v*: 68.9 (HSV-2) *M.c*: 68 (HSV-2) *O.c*: 74.3 (HSV-2)
[13]	*Sinapis arvensis, Lallemantia royleana,* *Pulicaria vulgaris*	*S.a*: 1-butenyl isothiocyanate (18.4%), benzyl isothiocyanate (15.1%), Cubenol (15.1%), dimethyl trisulfide (6.1%), octadecane (4.1%) *L.r*: trans-pinocarvyl acetate (26.0%), pinocarvone (20.0%), verbenone (7.1%), (E)-β-ocimene (4.1%), trans-carveol (5.3%), 3-thujen-2-one (5.1%), pulegone (4.4%) *P.l*: isobutyrate (16.9%), menthan-2-one (4.3%), 1-methyl-1,2 propanedione (4.13%), 2,5-dimethoxy-p-cymene (4.01%)	Thymol: 140 Carvacrol: 510 Sinapis arvensis *S.a*: 540 *Lallemantia royleana*: 710 *Pulicaria vulgaris*: 10	Thymol: 20 Carvacrol: 370 Sinapis arvensis *S.a* *S.a*: 350 *Lallemantia royleana*: 110 *Pulicaria vulgaris*: 10
[9]	*Zataria multiflora* *Eucaliptus caesia* *Rosemary* *Artemisia kermanensis* *Satureja hotensis*	*Z. m:* [thymol (33.1%), carvacrol (25.9%), p-Cymene (11.3%) and a-Pinene (3.9%)]. Rosemary [a-Pinene (23.9%), camphene (8.7%), camphor (10.97%), verbenon (15.4%), p-Cymene (7.5%), and 3-octanone (5.6%)]. *A.k*: [p-Menth-1, 5-dien-8-ol (4.4%), camphor (14.4%), and b-thujone (6.2%)] *S. h:* [carvacrol (32.4%), g-terpinene (32.0%), thymol (10%), p-Cymene (6.6%), and a-terpinene (4.3%)] *E. caesia:* [1,8-Cineol, p-Cymene (14.1%), g-Terpinene (12.4%), a-Pinene (7.7%), terpinene-4-ol (5.6%)]	Vero cells: *Z.m*: 1660 *E.a*: 2870 *A.k*: 2540 *S.h*: 2450 *R.o*: 2580	*Z.m*: 30 *E.a*: 70 *A.k*: 40 *S.h*: 80 *R.o*: 60

Influenza virus

It is a seasonal and highly transmissible virus which mainly attacks the respiratory way. It is formed by the subtypes A and B. It is highly mutable leading to the constant emergence of world influenza pandemics. For instance, the avian influenza virus has spread all over the world, especially the H5N1 and H9N2 viruses. The latter subtype is able to infect not only chick population but also manifest a high mortality rate in people [29]. The viral elements have two key proteic antigens, haemagglutinin (HA) and sialidase (neuraminidase, NA) on the surface, which play a major role on the attachment, fusion, and virus progeny release. The receptor for HA is the terminal sialic acid residue of the host cell surface sialyl-oligosaccharides, whereas sialidase catalyses the hydrolysis of terminal sialic acid residues from sialyl-oligosaccharides. Particularly, HA is responsible for virus entry into the cells, whereas NA is in charge of virus progeny exit from cells by removing sialic acid from the cell and virus surface preventing viral self-aggregation. Further, NA allows for viral penetration on the mucosa of the respiratory tract. There are two families of synthetic drugs used for the treatment and prevention of influenza. The first one is comprised by the inhibitors of the M2 ion channel (rimantadine and amantadine), whereas the second one is formed by neuraminidase (NA) inhibitors (oseltamivir and zanamivir). However, treatment with these drugs leads to a rapid development of resistant variants. Moreover, entry of the virus into the cells is mediated by trypsin-like proteases which activate the fusion of the glycoprotein precursors of Influenza virus. Therefore, protease inhibitors could halt viral entry and their multiplication. The viral infection starts with binding viral HA to sialic acid on the cell surface follow by virus endocytosis internalization. Meanwhile, the virus fuses with endosomal membranes and inactivate host cell protein synthesis and cell replication, resulting in cells cytolysis or apoptosis.

Table 2 lists the main studies of anti-influenza virus activity conducted on several EOs. This antiviral activity could happen in one or several steps of the viral reproductive cycle. For instance, the EO of *Melissa officinalis* is effective in the pre-infection, post-infection and adsorption stage, but the latter is the prevalent antiviral mechanism. Further, HA assays on red blood cells showed that the EO had no effect on the HA. Therefore, inhibition of viral propagation was not performed by HA inhibition suggesting another antiviral mechanism such as virion structural damage. Other phenolic compounds such as hydroxytyrosol obtained from olive fruits has shown antiviral activity against the H9N2 subtype without affecting the HA independent of the infection stage. Likewise, Lemon balm EO suppressed H9N2 viral replication, especially before cell infection but not through the HA blockage [30].

Compounds such as polyphenols from *Geranium sanguineum* have showen a direct anti-influenza activity, whereas bioflavonoids such as ginkgetin obtained from *Ginkgo biloba* and *Cephalotaxus harringtonia* showed inhibitory activity due to sialidase inhibition. Likewise, an alkaloid from *Uncaria rhynchophyl*la and the alkaloid thalimonie from *Thalictrum simplex* also exhibit inhibitory effects against the virus [31]. Likewise, red ginger oil reduced the HA titer incubated in chicken embryonated egg via allantoic sac [32]. Further, terpinen-4-ol, terpinolene, and terpineol from tea tree EO interfere with the early stage of the viral replicative cycle. Particularly, the EO and terpinen-4-ol exhibited an inhibitory effect on the acidification of endosomes and lysosomes impeding the influenza virus growth in MDCK cells preventing uncoating and hence envelope fusion [33]. Further, MDCK cells infected by oil-treated virus express viral mRNA, but minimal amounts of protein. Virus inhibition was attributed to deterrence of viral protein synthesis. Thus, activity of tea tree EO was mainly attributed to terpinen-4-ol it has the ability to bind to the virus surface, thereby inhibiting HA binding to the cellular receptors. The same mechanism has been detected in *Echinacea purpurea* and *Agrimonia pilosa* extracts. The antiviral effect of cathechins from green tea is also mediated by binding to HA receptors and physical alteration of the viral membrane [34].

Another study showed that exposure of the cells to the EO from *Cinnamomum zeylanicum* for 10 minutes exerted anti-HA and NA activity on human erythrocytes (O Rh+) [35]. Possibly, the trans-cinnamaldehyde, which was the major compound of Cinnamomum inhibited viral protein, but not mRNA synthesis at the post-infection phase [36]. On the other hand, the antiviral activity of certain citrus species such as *C. reshni* could be attributed to its high content of limonene, whereas the anti-H5N1 activity of *Fortunella margarita* oil is ascribed to their high content of α-terpineol. These two compounds have a common cyclohexenyl moiety which have been confirmed to have anti-influenza activity and led to the synthesis of anti-influenza drugs such as oseltamivir [37].

A study conducted on several *Eucalyptus* spp determined *E. globulus* with the highest anti-influenza activity, mainly attributed to α-pinene and limonene. Conversely, *E. odorata* oil contained mainly the ketone cryptone and hence the largest cytoxicity, whereas species rich in 1,8-cineole and α-pinene, were less cytotoxic [38], [39].

Coronavirus (SARS-CoV virus)

It is an encapsulated RNA virus belonging to the *Coronaviridae* family. It causes a severe acute respiratory syndrome (SARS) in humans by transmission of tiny droplets or personal contact. Particularly, the SARS-CoV-2 exhibits a large infectivity and resistance even under harsh environmental conditions. This virus has three known proteins such as the spike protein (S) that binds to the host receptor, a membrane protein (M) and envelope protein (E). Currently, there are no vaccines widely available to the public and the commercial synthetic antivirals are not effective for its treatment. *In silico* molecular docking techniques have been useful to predict the inhibitory effect on SARS-CoV-2 proteins. The EOs from *L. nobilis*, *T. orientalis*, and *J. oxycedrus* have exhibited anti-SARS-CoV, but their mechanism is still unknown [40]. Likewise, *Moringa spp* containing gallic acid, flavonoids and anthraquinones were found to have promising anti-SARS-CoV-2 activity [41], [42]. Artemisia *annua*, *Lindera aggregata* and *Pyrrosia lingua* have been reported to possess antiviral effect against SARS-CoV. Emodin from *Polygonum multiflonum* also inhibits the interaction between S-protein of SARS-CoV and ACE2 receptor (angiotensin-converting enzyme 2 used to infect host cells). Phenolic compounds from black tea such as isotheaflavin-3-gallate, tannic acid, 3- and aflavin-3,31-digallate also inhibit the chymotrypsin-like protease of SARS-CoV2 [43]. A study conducted on EO compounds from garlic demonstrated that allyl disulfide and allyl trisulfide inhibited ACE2 and PDB6LU7 (protease) preventing the invasion to the host cells [44]. Another computational study conducted on several SARS-CoV-2 proteins such as Mpro, endoribonucleoase ADP-ribose-1″-phosphatase, RNA-dependent RNA polymerase, spike protein, and ACE2 found (E)-β-farnesene and (E,E)−farnesol as potential inhibitors of such proteins [45]. Terpenoid phenols and phenyl propanoids such as anethole, cinnamaldehyde, carvacrol, geraniol, cinnamyl acetate, L-4-terpineol, thymol and pulegone demonstrated potential to inhibit the viral spike glycoprotein [46]. Likewise compounds of *Ashwagandha spp* such as withaferin-A, withanone, and caffeic acid phenethyl ester obtained from propolis inhibited the Mpro protein and other proteases [47]. Furthermore, EOs from geranium and lemon have shown significant ACE2 inhibitory effects, which are mainly attributed to the content of citronellol and limonene, respectively [48]. The EO of *Melaleuca cajuputi* also inhibited ACE2 and PDB6LU7 protease. The most potent inhibiting activity of the compounds studied in the decreasing order was: terpineol, guaiol, linalool, cineol, β-Selinenol, α-Eudesmol, and γ-Eudesmol [49].

Table 2: Antiviral activity of EOs against influenza virus

Reference	EO source	Main components	Citotoxic dose CC50 µg/mL	Effective dose ED50 (µg/mL)
[35]	*Cinnamomum zeylanicum* *Citrus bergamia*, *Thymus vulgaris*	*Cinnamomum zeylanicum*: eugenol, *Citrus bergamia*: linalyl acetate, linalool, limonene, terpinene, pinene *Thymus vulgaris*: 1,8 cineole, terpenyl acetate, borneol	MDCK & Human lung epithelial cells (A549): *Citrus bergamia*: 16 *Cinnamomum zeylanicum*: 12.3 *Thymus vulgaris*: 14.3	H1N1: *C.z*: 1.5 *C.b*: 3.12 *T.v*: 3.12
[37]	*Citrus reshni* (Cleopatra mandarin)	Limonene (40.5 %), β- linalool (23.2 %), terpinen-4-ol (8.3 %), monoterpene hydrocarbons (63.5 %), oxygenated monoterpenes (33.7 %)	MDCK: 4.9	H5N1: 2.5
[36]	*Eucalyptus spp*	α-Terpineol, 1,8-cineole (Eucalyptol), α-pinene, β-pinene, Sabinene, Camphene, Limonene, etc	Vero: 0.25	*H. Influenza*: 1.25
[29]	*Fortunella margarita*	α -terpineol (55.5%), t-carveol (5.5%), limonene (1.7%), murolene (5.5%) and cadinene (2%)	MDCK: 239.5	H5N1: 6.8
[50]	*Heracleum spp*	octyl acetate (5-5%) and octyl isobutirate (1.4 - 63%) in seeds	Albino mice: 0.25-0.4 mL	Additional length incubation (days) 0.8-3.7 (type A) 0.4-2.2 (type B)
[33]	*Melaleuca alternifolia*	terpinen-4-ol, terpinolene, and terpineol	MDCK: 250	H1N1: M.a:6 terpinen-4-ol: 20 terpineol: 250 terpinolene: 12.5
[40]	Laurus nobilis, Juniperus oxycedrus, *Thuja orientalis*, *Cupressus sempervirens*, *Pistacia palaestina*, *Salvia officinalis*, *Satureja thymbra*	*L. nobilis:* b-ocimene (21.8%), 1,8-cineole (9.4%), a-pinene (3.7%), eremanthin (3.7%), dehydrocostus lactone (7.6%). *T. orientalis:* a-pinene (35.7%), d-3-carene (9.5%), a-cedrol (9.6%). *J. oxycedrus:* a-Pinene (27.4%), b-myrcene (18.9%), a-phellandrene (7.1%), limonene (6.7%), d-cadinene (2.2%). *S. thymbra:* p-cymene (10.8%), a-pinene (10.2%), thymol (9.9%), sabinene (8.6%), g-terpinene (7.6%), trans-caryophyllene (3.7%) *C. sempervirens:* a-pinene (53.6%), a-terpinene (18.9%), thymol (3.8%), terpinolene (3.2%). *S. officinalis* (94.3%), 1,8-cineole (43.6%), a-thujone (13%), sabinene (7%), camphor (5.7%), a-pinene (4.72%)	Vero cells: *L. n:* 500 *T. o*: 1000 *J. o:* 1000 C. s: 1000 BHK-21: 100	SARS-CoV: *L. n:* 120 *T. o*: 130 *J. o*: 270 *C. sempervirens*: 700 Poliovirus (Sb-1): *J. o*: 20
[31]	*Melaleuca alternifolia*	1,8-cineole, terpinen-4-ol, α-terpineol, γ-terpinene	MDCK: Tea trea: 250 Terpinen 4 ol: 500 Terpinolene: 120 a-terpinene: 120 r-terpinene: 120 P-cymene: 500 a-terpineol: 500	H1N1 Tea trea: 6 Terpinen 4 ol: 25 Terpinolene: 12 a-terpinene: 12 r-terpinene: 120 P-cymene: 500 a-terpineol: 250
[30]	*Melissa officinalis*	Geranial (citral A, 26 %), Neral (citral B, 19 %), Caryophyllene-E (11.3 %) and Caryophyllene oxide (11.8 %)	MDCK: Pre-infection: 500	Avian influenza virus (H9N2): 5
[39]	Tea tree *Eucalyptus spp*	NR	M13 phage	Exposure for 15 min Tea tree: no count (Influenza A) E spp: 10 PFU/mL (Influenza A) Tea tree: 1000 PFU/mL (M13 phage) E spp: 500 PFU/mL (M13 phage)

Human immunodeficiency virus (HIV)

This virus is part of the *retroviridae* family and causes the acquired immunodeficiency syndrome (AIDS). This virus uses RNA as a genetic material and hence the synthetic antiretroviral therapy is based on a combination of reverse transcriptase and protease inhibitors. Particularly, the reverse transcriptase turns viral RNA into DNA, which in turn is compatible with the cell DNA. HIV is transmitted by sexual contact and through contaminated needles with blood products. Some natural compounds such as flavonoids are antagonist of reverse transcriptase, integrase and protease proteins. Likewise, coumarins such as calanolide A obtained from *Calophyllum lanigerum* have exhibited good reverse transcriptase inhibition.

Further, the extracts of *Baccharis trinervis inhibited* HIV replication when added simultaneously to the virus, preventing virus attachment (adhesion), virus-cell fusion and cell-to-cell fusion and inactivation of reverse transcriptase. Likewise, *Thuja orientalis* and *glycyrrhiza glabra* have anti HIV activity, but the real mechanism is still unknown. The DNA Bombyx mori nuclear polyhedrosis virus (BmNPV) has been taken as a surrogate for HIV and Ebola virus studies. BmNPV attacks silk worms causing their death within 96 h. However, larvae treated with ε-cinnamaldehyde had an 11% survival rate, whereas the administration of a nanosilica-(ε)-cinnamaldehyde complex improved the survival rate to 25%. Other compounds such as agastanol (*Agastache rugosa*), uvaol (*Crataegus pinnatifida*), garciosaterpene A (*Garcinia speciosa*), vaticinone (*Vatica cinerea*), glycyrrhizin (*Glycyeehiza spp*), baicalin (*Scutellaria baicalensis*), taxifolin (*dihydroquercetin*), flavonoid glucuronide (*Charysanthemum morifolium*) and calanolide A (*Calophyllum lanigerum*) have shown a promising HIV inhibition [51], [2].

Hepatitis A, B and C viruses

Hepatitis A (HAV) is a member of the *Picornaviridae* family and has six genotypes (I to VI), but only genotypes I to III infect humans. Infection occurs through the fecal-oral route by ingestion of contaminated food or water. Washing of berries, blueberries and raspberries with chlorinated water (200 ppm) reduced virus titer to 1.8, 2.4 and 0.6 $\log_{10}$. The latter is explained by the rough surface topography which protects the virus against chorine treatment. Usually, the HAV concentration in these fruits ranges from 2.8×10^2 to 2.4×10^3 genomic copies per gram. On the other hand, the hepatitis B virus (HBV) causes a serious infection leading to cirrhosis or liver cancer and possibly death. Similarly, hepatitis C virus (HCV) causes acute and chronic liver disease, including cirrhosis and liver cancer. HCV spreads mainly by direct contact with blood. Few synthetic drugs such as ribaviridin, lamivudine and interferon are used for their treatment. However, the therapeutic effectiveness of interferon for these viruses is ~30%. Alkaloid compounds such as oxymatrine and matrine obtained from *Sophora spp* inhibit viral replication reducing destruction of liver cells and improving bile flow. Interestingly, the HCV genome encodes for a single protein which is processed by cellular and virus-encoded proteases. Thereby, *Acacia nilotica, Boswellia carterii, Embelia schimperi, Piper cubeba, Quercus infectoria, Trachyspermum ammi* and *Syzygium aromaticum* extracts have shown promising HCV protease inhibition [52].

Norovirus

Noroviruses belong to the *Caliciviridae* family and are characterized by having a single-stranded RNA having no envelope. They cause acute gastroenteritis leading to a high morbidity. Like hepatitis A, it is transferred through the person-to-person contact or the fecal-oral path. It is resistant to harsh conditions and has a high infectivity. Murine norovirus-1 (MNV-1) and feline calicivirus-F9 (FCV-F9) are employed as substitutes for studying norovirus biology. Oregano EO and its major compound carvacrol inhibit mainly MNV by interfering with the virion capsid, whereas α-thujone mainly inhibited FCV-F9 rather than MNV-1 [53]. Likewise, mint, oregano and clove EOs interfere directly with the virus reducing the MNV-1 virus titre from 0.7 to 1.6 $\log_{10}$ [54], [55].

Coxsackie (enterovirus) virus

It is a non-enveloped virus belonging to the *Picornaviridae* family and has a linear single-stranded RNA. It causes type 1 diabetes, myocarditis and neurological pathologies among infants [56]. The oil from *Desmanthus virgatus* and *Eucalyptus camaldulensis* have been proved to be effective against Coxsackievirus B4 and have schistosomicidal activity [57]. Similarly, *E. globulus* oil showed good antiviral activity against coxsakievirus B3 either in the pre-adsorption of infective stage, whereas *Eucalyptus astringens* was only effective in the adsorption step [38], [58].

Poliovirus (PV)

It is a non-enveloped, single-stranded RNA virus belonging to the *Picornaviridae* family. It causes poliomyelitis reaching the central nervous system resulting in flaccid paralysis. *B. dracunculifolia* and propolis inactivate PV possibly by blockage of cell receptors, affection of the viral replication cycle and RNA degradation before virus entry into the cells. Clove and oregano EOs also showed antiviral activity against PV [59]. Likewise, *Achillea fragrantissima, Jasonia montana* and *Globularia Arabica* presented a high antiviral activity against PV. This activity was ascribed to monoterpene ketones and sesquiterpene lactones. Particularly, the anti-PV of *Jasonia Montana* was due to its content of methoxyflavones including 3-methoxyflavones [23].

Newcastle disease virus (NDV)

It is a viral disease caused by a virus from the *Paramyxoviridae* family and attacks birds including chicken causing respiratory and nervous symptoms. The *Zataria multiflora* EO once incubated with the cells before viral infection showed no activity indicating that the oil compounds cannot bind to the cell receptors involved on the attachment step. However, when the oil was concomitantly added with the virus a high inhibitory effect was produced indicating a direct virucidal effect [60].

Dengue (DENV) virus

Dengue is an enveloped RNA virus and belongs to the *Flaviviridae* family. It exists as four serotypes (DENV-1, DENV-2, DENV-3 and DENV-4). Several compounds found in EOs have shown anti DENV activity. For instance, β-Caryophyllene and citral have shown DENV inhibition at different stages of the virus infectivity, especially at early steps of the virus cycle by interfering with the virion envelope structures which are required for virus adsorption and penetration. Some compounds inhibit specific steps of intracellular replication of the virus and others are inhibitors of viral proteins [61]. It is known that the envelope possesses the E and M proteins which mediate the penetration and fusion within the host cells. If

the oil compound interacts with sites of the E protein the adsorption and fusion processes will be affected. The EO of *Lippia citriodora* contains geranial and neral which halt the virus adsorption and penetration, but have no effect on the post-adsorption steps. This could be attributed to blockage of the E and M viral proteins. Other species such as *Uncaria tomentosa* (alkaloids), *Zostera marina* (zosteric acid), *Lippia origanoides* and *Hyptis spp* have also decreased the virus infectivity [62].

Yellow fever (YF) and Japanese Encephalitis (JE) viruses

YF is an enveloped RNA virus belonging to the *Flaviviridae* family and causes hemorrhagic fever. Compounds of EOs such as carvone, citral, carvacrol, limonene and thymol explain the virucidal effect on YFV. Some of these compounds are found in *A. Arborecens, L. Origanoides* and *O. Vulgare* [63]. On the other hand, JE is an enveloped RNA virus belonging to the *Flaviviridae* family. It is also transmitted by mosquitoes and ticks [64].

Junin virus (JUNV)

This is a RNA virus belonging to the *Arenaviridae* family that causes the Argentine haemorrhagic fever. The virus compromises the neurological, vascular and immune systems leading to a large mortality rate. The EOs from *Heterotheca latifolia* and *Tessaria absinthioides* have also shown antiviral activity against JUNV [65].

Table 3: Antiviral activity of EOs against miscellaneous viruses.

Reference	EO source	Main components	Citotoxic dose CC50 µg/mL	Efective dose ED50 (µg/mL)
[53]	*Artemisia princeps*	Thujone (67%), Camphor, borneol	CRFK and RAW 264.7: a-thujone (25 mM), borneol (5 mM), camphor (25 mM)	murine norovirus-1 (MNV-1) and feline calicivirus-F9 (FCV-F9): 100 (by thujone)
[54]	*Thymus capitatus* *Origanum elongatum* *Mentha suaveolens*	*Thymus c:* carvacrol (59-69%), p-cymene (4.8-5.6%), γ-terpinene (2.8-3.8%) and β-caryophyllene (2.6-2.9%). *Origanum e*: carvacrol (19.2-40.1%), thymol (3.6-14.2%). *M. s:* piperitenone oxide (41.8%), (-)-isopulegol (12%) and limonene (7.4%)	RAW 264.7 cells	murine norovirus (MNV-1) log reduction: *M.s*: -0.87 *O.e*: -0.75 *T. c*: -0.5
[66]	*D. virgatus*	*D. virgatus:* phenylpropanoids (31.5%, methyleugenol 33%), sesquiterpene hydrocarbons (25.0%, β-bisabolene 13.2%) and oxygenated sesquiterpenes (20.1%)	HEp-2 cell: 543.4 (ethyl acetate) & 372.7 (methanol)	Coxsackievirus B (CV-B): 98.2 (ethyl acetate) 60.1 (methanol)
[38]	*Eucalyptus spp.*	1,8-cineole (35.4%), cryptone (10.9 %), α-pinene (8.6%), p-cymene (8.7 %), α-terpineol (5.3%), trans-pinaocarveol (3.5 %), phellandral (3.3 %), cuminal (3.3%), globulol (3.1 %), limonene (2.2 %), aromadendrene (1.8 %), sapthulenol (1.8 %) terpinene-4-ol (1.0 %).	Vero cells: *E. maidenii* (253.5), *E. sideroxylon* (247.3), *E. cinerea* 204.5, *E. odorata*, *E. leucoxylon*, E. *lehmannii*, *E. astringens and E. bicostata* (6.2 - 16 mg/mL)	Coxsakievirus B3 *E. bicostata*: 4.8 mg/mL *E. astringens*: 8.4 mg/mL *E. cinerea*: 131 mg/mL *E. maidennii*: 150 mg/mL
[67]	*Houttuynia cordata*	β-pinene (2.6), campene (2.2), Bornyl acetate (1.4), 2-undecanone (1.7), Caryophyllene (1.7), Houttuynin (81%)	Vero cells: 181.8	Coxsackie virus: CVB3: 22.2 CVB6: 15
[57]	*Eucalyptus camaldulensis*	α-phellandrene (24.8%), 1,8-cineole (19–3%), α-pinene (12.8%) and γ-terpinene (11.8%)	HEp-2, MA104, BGM, and Vero cells: 100	Coxsackievirus B4: 10 Rotavirus Wa strain: 10
[59]	*Baccharis dracunculifolia*, propolis	a-pinene, b-pinene, limonene, trans-caryophyllene, aromadendrene, a-humulene, germacrene D, bicyclogermacrene, d-cadinene, nerolidol, spathulenol, viridiflorol, guaiol and a-murolol.	HEp-2 cells: 250	Poliovirus: Oil: 250 g/mL Propolis: 100 *B. dracunculifolia* (31%), *B. dracunculifolia* (29%), propolis (10%), cinnamic acid (10%) and caffeic acid (8%) reduction
[60]	*Zataria multiflora*	Thymol, carvacrol	Vero cells: 670	Newcastle virus Log10 reduction: 0.35
[65]	*Aloysia gratissima* *Artemisia douglasiana* *Eupatorium patens* *Heterotheca latifolia* *Hyptis mutabilis* *Lippia junelliana* *Lippia turbinata* *Tessaria absinthioides*	*A.g*: Caryophellene oxide (15.8%), cadinol (17.4%), chrysanthenyl acetate (5.6%), limonene oxide (5.3%), b-caryophellene (4.8%) *H.l:* borneol (940%), camphor (24.3%), limonenene (5.1%) *L.j:* piperitenone oxide (36.5%), limonene (23.1%), camphor (7.9%), spathulenol (6.5%) *L.t:* limonene (60.6%), piperitone oxide (17.4%), b-caryophellene (6.4%) *T.a:* caryophellene (12.2%), b-damacenone (8.6%), eudesmole (8.5%), gurjunene (5.8%)	Vero cells: *A. g*: 150 *H.l:* 500 *L.J*: 500 *L.t:* 313 *T.a*: 263	*A.g:* 65 (HSV-1) *H.l:* 90 (JUNV) *L.J:* 20 (JUNV) *L.t:* 14 (JUNV) *T.a:* 63 (JUNV)

Reference	EO source	Main components	Citotoxic dose CC50 µg/mL	Efective dose ED50 (µg/mL)
[64]	*Trachyspermum Ammi*	α-pinene (35-60%), p-cymene, limonene	Vero cells: 1mg/mL	Japanese encephalitis virus (JEV) 0.5mg/mL
[61]	NA	β-caryophyllene, citral, (R)- (-)-carvone, (S)-(+)-carvone, (R)-(+)-limonene, ρ-cymene, geranyl acetate, nerol, and α-phellandrene	β-caryophellene: Vero cells: 120 mM HepG2: 170 mM	β-caryophellene: DENV (HepG2): 22 mM DENV (Vero cells): 8-15 mM
[62]	*Lippia alba*, *Lippia citriodora*,	*L.a:* Carvone: 39.7, Limonene: 30.6, Bicyclosesquiphellandrene: 8.9, Piperitenone: 4.5 Piperitone: 2.8 *L. C:* Geranial: 18.9, Neral: 15.6, Limonene: 10.7 1,8-Cineole: 5.0, Spathulenol: 4.7, Geraniol: 2.7 trans-β-cariofilene: 2.3, Nerol: 2.0	Vero cells: *L. alba*: 139.5 *L. citriodora*: 57.6	DENV-1,2,3,4 & YFV-17 DD *L. alba*: 0.4-32.6 *L. citriodora:* 1.9-33.7
[63]	*Lippia alba*, *Lippia origanoides*, *Oreganum vulgare*, *Artemisia vulgaris*	L.a: Carvone (51), Limonene (33), bicyclosesquiphellandrene (7) L.o: Carvacrol (44), Thymol (15), γ-terpinene (10) O.v: trans-Sabinene hydrate (21), Thymol (11) Carvacryl methyl ether (11), γ-Terpineno (5.2) p-Cimene (4.5) *a.v:* α-Thujone (38.1), β-Thujone (10.6), 1,8-Cineole (8.8), trans-Carveol (3.1), Sabineno (2.8)	Vero cells: *L. alba* 90, *L. origanoides* 98, *O. vulgare* 98, *A. vulgaris* 98	DENV-1,2,3,4 : *L. alba, L origanoides and O. vulgare*: 3.7 *A. vulgaris:* 11.1 YFV: 3.7-11
[52]	*Citrus limon*, *Citrus sinensis*, *Citrus paradisi*, *Rosmarinus officinalis*	*Citrus spp:* limonene, sesquiterpenes, and hydrocarbons; oxygenated products (citral), ketones, acids, alcohols (linalool), and esters	Frp3 cells : Orange: 1000 Grapefruit: 1000 Lemon: 5000 Rosemary: 500	Log_{10}Hepatitis A (HAV) reduction: Orange: 2.14 Grapefruit: 2.89 Lemon: 2.84 Rosemary: 2.94

Miscellaneous viruses

Another study compared the effect of EOs on human respiratory syncytial virus (HRSV), human rotavirus (HR) and bovine viral diarrhea virus (BVDV). HSRV is an enveloped RNA virus belonging to the *Paramyxoviridae* family. It is responsible for bronchiolitis and pneumonia in children and elderly people. A rhinovirus (RV) is a non-enveloped virus with a double strand RNA. It causes gastroenteritis leading to morbidity and mortality, whereas the BVDV is an enveloped RNA virus. The EO of Mexican oregano inhibited these viruses in different stages of virus infection and replication, whereas carvacrol was effective only when at the adsorption stage. In fact, carvacrol has been effective in this phase independent of the viral genome type. Further, carvacrol inactivated RV after virus inoculation indicating a mechanism independent of virus membrane fusion since this virus does not contain a capsid [68].

Zoonotic viruses

Several types of viruses are confined to animals and causes deaths and economic loses. For instance, the bovine herpes virus type 5 (BHV-5) causes necrotizing meningo-encephalitis and neurotropism in cattle. Further, avian metapneumovirus (aMPV) is responsible for turkey rhinotracheitis causing the swollen head syndrome. The murine hepatitis virus type 3 (MHV-3), is a coronavirus which causes diarrhea, hepatitis, splenolysis, immune deficiency and chronic nerurological disorders. The porcine parvovirus (PPV) causes sterility in swine, leading to mummification and embryonic death. The bovine respiratory syncytial virus (BRSV) causes upper and lower respiratory symptoms and plenty of nasal secretions. The EO from *Aniba rosaeodora* is particularly effective during the viral replication phase due to the presence of linalool. In fact, it acts on enzymes responsible for transcription of viral proteins. Conversely, *Maytenus* spp was only effective at the adsorption phase by inhibiting the cellular receptor for BHV-5 adhesion [69]. ORF is another viral endemic disease in sheep, goats and other ruminants which is also transmitted to humans. It causes infectious labial dermatitis and sores. The EO of *Achillea fragrantissima* is able to block the ORF cell membrane receptor and induces the production of cytokines reducing viral infectivity [70].

Phytoviruses

There are several types of viruses which attack plants including Tobacco mosaic virus (TMV, *Virgoviridae* family), cucumber mosaic virus (CMV, *Bromoviridae* family) and potato leaf roll virus (PLRV, *Luteoviridae* family). Particularly, these three types of viruses possess a capsid and a RNA genome [71]. There are some EOs with outstanding antiphytoviral activity. For instance, The EOs from *Teucrium spp* decreases the CMV infectivity due to the high content of sesquiterpenes. Further, **the** *T. guyonii* EO contains carvacrol, thymol, and o-cymene which are responsible for their antiphytoviral activity [72], [73]. The *Satureja Montana* EO contains thymol and carvacrol, which are differentiated by the position of the hydroxyl group resulting in a distinguished antiviral activity. Thereby, carvacol was more potent against TMV, whereas thymol was more effective against CMV. Other compounds such as sequiterpenes, β-pinene and limonene have also shown antiphytoviral activity [74]. Likewise, the

Piper betel oil has shown efficacy against PLRV- infected *Chenopodium amaranticolor* [75]. Further, the EO of *Melaleuca alternifolia* and *Plectranthus tenuiflorus* inhibit the TMV. Likewise, *Satureja Montana* and *Micromeria graeca* decreased the viral load of CMV in infected plants (*Nicotiana glutinosa*). Sesquiterpenes such as b-caryophyllene, caryophyllene oxide, germacrene, and a-bisabolol were responsible for this antiviral activity. Likewise, compounds such as eugenol improved plant resistance by stimulating the endogenous production of nitric oxide and salicylic acid in tomato plants [64]. On the other hand, the EO of *Thuja orientalis* and *Artimisia campestris* inhibited more than 65% PLRV replication by forming conjugates with the protein virus resulting in the capsid disintegration. Similarly, the *Aloe vera* and *Fargesia nitida* latexes and clove EO have been able to inhibit mRNA expression [76].

Table 4: Antiviral activity of EOs against zoonotic and plant viruses

Reference	EO source	Main components	Citotoxic dose CC50 µg/mL	Efective dose ED50 (µg/mL)
[58]	*Osmunda regalis*	Hexahydrofarnesyl acetone (11.8%), 2,4-di-t-butylphenol (6.8%), phytol (6.5%), neophytadiene (4.6%), 1-octadecene (4.4%), 1-eicosene (4.4%), and 1-hexadecene (4.1%).	Hep-2 cells: 1772	2.24
[56]	*Teucrium pseudochamaepitys*	Palmitic acid, (26.1%), apiole, caryophyllene oxide, myristicin, E-β-damascenone, α-cubebene, β-caryophyllene and elemicin (7.1%, 6.3%, 4.9%, 4.6%, 3.9%, 3.5% and 3.3%, respectively).	Hep-2 cells : 653.6	589.6 µg/mL No effective
[71]	*Eryngium alpinum and E. amethystinum*	*E. spp:* Caryophyllene oxide (21.6%), bicyclogermacrene (11.8%), and germacrene D (10.3%), pinene (12%), camphor (4.8%)	Host plant	CMV~80% reduction
[73]	Satureja montana	Carvacrol (19.4%) and thymol (16.6%), linalool (5.9%) γ-terpinene (6.9%) and α-terpinene (4.9%)	*Chenopodium amaranticolor*	Tobacco Mosaic Virus (TMV): 29.2% reduction Cucumber Mosaic Virus (CMV): 24.1% reduction
[73]	*T. polium, T. flavum, T. montanum and T. chamaedrys*	β-caryophyllene (7.1-52.0%) and germacrene D (8.7-17.0%), pinene (8-12%), limonene (4-7%), linalool (3%), thujone (5%)	*Chenopodium quinoa*	CMV: 25-40% reduction
[75]	*Cuminum cyminum* *Curcuma longa* *Nigella sativa* *Carum copticum* *Anethum graveolens Piper nigrum Foeniculum vulgare*	NR	NA	Papaya ring spot virus (PRSV) *Nigella s. & Carum c*. >75% *Anethum g, Piper n.* & *Foeniculum v.* >50% Cuminum and Curcuma 80%
[76]	*Eucalyptus citriodora, Clove buds, Fennel seeds. Latex of Aloe vera, Calotropis procera* and *Ficus*	*Eucalyptus citriodora*: pinene (6.9%), limonene (6.9%), eucalyptol (83.9%), terpineol (1.6%). Clove: eugenol (69%), caryophyllene (3.4%), acetyl eugenol (28%) Fennel: p-anisole (62%), anisole (22%), fenchone (6.6%), eucalyptol (5%) *Calotropis gigantea* (leaf and latex): aminoacids, anthraquinones, flavonoids. Ficus: flavonoids, alkaloids, organic acids and triterpenes.	NA	Potato leaf roll virus (PLRV) *Thuja orientalis*:81.7 *Artimisia campestris:* 63.6%
[70]	*Achillea fragrantissima*	*Santolina*: triene (2%), 2,5,5-trimethyl-3,6-heptadien-2-ol (8.23%), eucalyptol (8.2%), trans-2,7-Dimethyl-4,6-octadien-2-ol (24.4%), 1,5-Heptadien-4-one-3,6-trimethyl (7.7%) *Artemisia:* alcohol (3.5%), à Thujone (34%), Cissabinol (1.9%), Lavandulol (0.71%), 2-Octen-4-ol, 2-methyl (2 %)	rats	ORF virus (small pox) 40% reduction
[69]	*Maytenus ilicifolia Aniba rosaeodora* *Bursera aloexylon*	NR	MDBK (VHB-5, BRSV): 187.8 CER (aMPV): 104.8 L929 (MHV-3) CRFK (PPV)	*Aniba r* (aMPV): 20.9 *Maytenus* I (VHB-5): 389 PPV, MHV-3 & BRSV: inactive
[68]	*Lippia graveolens*	Carvacrol (56.8%), O-cymene (32.2%), and thymol (2.7%)	Cells and MDBK, MA104 cells, HEp-2: HHV-1: 735 ACVR-HHV-1: 735 BoHV-2: 568 HRSV : 735 BVDV: 568	HHV-1: 99.6 ACVR-HHV-1: 55.9 BoHV-2: 64 HRSV: 68 BVDV: 123

CONCLUSIONS AND PROSPECTS

Based on the different assays and the screening approach with the different viruses, a great amount of antiviral molecules have been identified from several essential oils extracted from plants. These natural compounds exhibit fewer side effects in comparison to the synthetic counterparts. The mixture of compounds in essential oils creates a synergistic antiviral effect and prevents the emergence of resistance mechanisms since they attack the virus at different infective stages. Nevertheless, the promising antiviral effect of these compounds needs to be proved in clinical trials. The great challenge for humanity is to discover and develop new standardized preparations based on natural medicines, having a variety of molecules which selectively inactivate the viral replication in a particular viral cycle step. These formulations must also be safe for the host and protect the damaged immune system from future infections.

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