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# Natural products and medicinal plants role as an antiviral agent- Review Article

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**ABSTRACT:** Viral infections are vital issue in pathology. Recent growing pandemics due to globalization and the easiness of travel confirmed the necessity of preventing these infections as a major public health risk. In spite of significant progress in drug development and disease immunization, there is a lack in preventive vaccines and effective antivirus, because of viruses tendency to genetic mutations in when they intrude on the living cell, and generating new virual patterns differ from the original. The research into the molecular virology has opened up new approaches to understand the properties of viruses and their mandatory intrusione nature, in addition to their pathogenesis. Unfortunately, the required antiviral drugs must possess selective antiviral efficacy without interfering with the biological pathways of the host cells.

As Viruses are the main cause of death worldwide, in addition to the side effects of their chemical inhibitors, Natural products representing in medicinal plants emerge as a new alternative source of antiviral agents which can fulfill the renew need to such safe effective antiviral medications.

**Search goal:** This review aims to study and analyze puplished data about plants containing antiviral chemical compounds with antiviral efficacy from 1995 to 2021, It discusses their role in curbing the spread of viruses and treating their infections.

**Inclusion and exclusion criteria:** Clinical trials, *in vitro* and *in vivo* trials are included. In addition, reference articles, only English articles were accepted, during the period (1995-2021). Articles that need further analysis were excluded.

**Quality assessment:** to assess the quality of each article, different parts such as title, abstract, introduction, methods, results, and conclusion were examined.

## I. INTRODUCTION

**Current therapeutic routs for viral disease and its limitation:** The antiviral medication could be classified into viral adsorption and entry inhibitors, uncoating inhibitors, viral nucleic acid synthesis inhibitors, integration inhibitors, protease inhibitors, release inhibitors[5,147]. The interaction between the virus and the host cell membrane (receptors) is the first stage of the viral life circle, which is called entry and infusion, the integration inhibitors which prevent the virus in this stage can be used successfully, and that is where the anti-acquired immune deficiency virus[161,178,43] and respiratory syncytial virus prevention[61,192] were used. Chemokine receptors targeting [84,99] and the glycoprotein receptors interactions supposed to have a crucial role in the entry stage. A new fatty peptide was discovered, it was named Myrcludex B, it blocks $Na^+$ taurocholate co-transporting (NTCP) which is the main receptor for entering hepatic B virus, and hepatic disease virus into hepatic cells[132,7]. Moreover, the low acidity (PH) for the endosome activated the proton channels after the virus entry to increase the internal viral acidity and weaken the electrostatic interaction; helping to detach the viral coat with the host cell.[145] More of coating inhibitors were used against

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Vol. 9, Issue 2 , February 2022

influenza virus by inhibiting proton channels function, but drug resistance emerged and raised concerns about using these drugs in wide range.[49]

After uncoating, the nucleic acid synthesis is the third step of viral life cycle, which is mediated with viral enzymes such as RNA polymerase, DNA polymerase, transcriptase, these enzymes became a target for many viral diseases like hepatic virus B [33]and herpes simplex virus 1\2, and HIV 1\2. There are more targets and more antiviral drugs for AIDS virus compared to other viruses. These drugs are classified into nucleoside reverse transcriptase inhibitors (NRTIs), nucleotide reserve transcriptase inhibitors (NtRTIs), non-nucleoside reserve transcriptase inhibitors (NNRTIs) [34]. The existence of repeated viral drug resistance, which is a serious problem, that emerged with the nucleic acid synthesis inhibitors. In addition, the occurrence of the rapid u1575 mutation limited the efficacy of the first generation drugs (delavirdine, efavirenz) [32]. On the other hand, the second-generation drugs of NNRTIs (etravirine, rilpivirine) which possess flexible structure enables them to beat the common mutations related to the first generation drug resistance [2,162]. Most of the antiretroviral therapies cannot stop the viral infection, instead of that they reduce the restore of immune system performance. Besides, the results of long-term use of these drugs caused toxicity and resistance [136, 138,143,176], so there is a vital need to new antiviral generations with new targets.

In fact, the traditional chemical antiviral drugs are limited due to the increasing resistance, the deficient biological response and the undesirable side effects. Commonly, the same standard doses of the antiviral drugs lead to different bioavailability and clinical results. Many agents contribute to this contrast in individuals such as, the accompanied medicines, and the current other diseases, the genetic factors, the sexual related metabolism, and the commitment during treatment, all the previous factors remarkably affected the antiviral activity. Further then, the hypersensitivity interactions, the toxicity cases and the variability due to the resistance, are deeply influence the repeat, the intensity and the appearance of the bad side effects of the clinical aspects of some antiviral medication [181, 19]. To conclude, the masterpiece antivirus agent should have the maximum efficacy with the least toxicity and trivial levels of developed drug resistance. Then, innovation of distinct treatment strategies becomes a persistent need, and more research should be conducted to provide sufficient knowledge about new antiviral mechanism and developing special effective innovative treatment such as plants.

In the past few years, the effectiveness of some natural products and synthetic antiviral compounds has assessed in vitro and in vivo. Only a few of them have approved for clinical use by Western health authorities [185]. However, some treatments have evaluated by preclinical and clinical studies, which have led to more possibilities for the discovery of new antiviral agents with a promising future. Among these antiviral substances, there are some natural compounds that have isolated from medicinal plants used in complementary and traditional medicine ( such as polysaccharides[149], polyphenols [172], flavonoids, anthocyanins [170], phenyl carboxylic organic acids [89], and terpenes[196] , Alkaloids and phenolic compounds [136], organic acids isolated from algae [52], amino acids [50]). Many other secondary metabolites have shown a unique antiviral mechanism of action and have a promising future for clinical antiviral research [185]. There are some approaches for selecting plants to assess their antiviral efficacy, including comprehensive screening of randomly selected plants, medicinal use of some plants in the medical heritage and available literature, and by studying the [185] chemo-taxonomical plant families. Over all, the plant kingdom is one of the best sources of new antiviral agents.

## II. The role of Natural products in viral disease prevention and treatment

For many years, natural medicines have been used for the treatment and prevention of viruses [131, 187, and 86] where many natural compounds especially small bioactive molecules act as multi-target agents with high biochemical specificity and chemical diversity at lower cost and more diverse mechanisms. These compounds considered as new leader compounds and formulas for the synthesis of antiviral compounds, so medicinal plants provide conventional and alternative antiviral promising activities. Significant progress has made in by using many natural products plant-derived in the treatment of HIV infection. The promising effects of terpenes and coumarins have previously demonstrated, especially in preventing and mitigating HIV infection. Studies found that flavonoids inhibit fusion[98], some of them inhibit integration[95], reverse transcription[85], protease[121], replication[214] and maturation[207]. All of these mechanisms that mentioned are possible mechanisms of action for some terpenes in the fighting against HIV, coumarins also inhibit reverse transcriptase, which explains their anti-HIV effect, and it has recently shown that tricyclic coumarins inhibit the activation of nuclear factor kappa - (NF-kB) and thus, prevents HIV replication *in vitro*[90]. So far, several active ingredients from medicinal plants have tested for their anti-influenza agents, including flavonoids [123], polyphenols [170], alkaloids [166], and anthocyanins [89], chalcones [31], xanthines [30] and homoisoflavonoids [67]. These compounds are considered to be anti-influenza viruses by inhibiting the enzyme neuronidase [188] NA. Many research have shown the

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Vol. 9, Issue 2 , February 2022

effectiveness of some natural products against the hepatitis virus HBV These compounds include polyphenols, isochlorogenic acid [51], dehydrocheilanthifoline, and some other amide alkaloids that have shown anti-HCV effects [68,211]. Curcumin also downregulates the HBV transcription, as well as the excretion of peroxisome proliferator-activated receptor-gamma coactivator 1-α (PGC-1α), thereby preventing HBV gene replication and expression [153]. Medicinal herbs also showed inhibitory activity in *in vitro* tests by inhibiting the protease to combat HCV [63], and many flavonoids showed anti-hepatitis C activity at different stages of the virus life cycle. Ladanein compounds, a flavonoid compound that blocks the entry stage of the virus, while quercetin compounds Luteolin and apigenin are active in the stage of viral replication. Honokiol is a derivative of lignan inhibits the entry or transcription stages of HCV [16], and silymarin inhibits HCV at various stages, including fusion, assembly, and transmission, naringenin inhibits the assembly phase of HCV [16] Silymarin has also shown immunomodulatory, anti-inflammatory, and hepatoprotective effects [123]. The alkaloids of *Sophora Styphnolobium japonicum* have antiviral ability, it prevent cirrhosis of the liver. It reduces liver cell destruction, inhibits viral replication, and enhances bile flow [105]. It is also important to identify new major anti-HSV compounds with novel mechanisms of action, belonging to the following potent natural compounds: essential oils[35], terpenoids, polyphenols, phenolics, flavonoids (such as Houttuynoids[21], proanthocyanidins[29] proanthocyanidins, and tannins, geranipoin[200] and hippomanin[200] Excoecarianin[24]) these compounds have also shown promising effects against the herpes simplex virus (HSV)[80], and some tannins such as chebulagic acid and punicalagin have an entry-inhibitor effect on HSV-1. These water-soluble tannins inhibit the entry phase of the virus. The viral entry phase, including attachment and penetration, thus yields antiviral effects against RSV[103]. New natural antiviral compounds include chromone glycosides such as Uncinoside A [104], biflavonoids such as genkwanol [62], flavones [189], which protect against RSV by an unclear mechanism, and resveratrol, which reduces the RSV virus inflammation by reducing the production of interferon IFNγ levels[212] in addition to the role of many plants essential oil in inhibiting viruses *in vitro*[100].

## III. Practical section

The current survey of the published research was conducted according to the previously mentioned data. This review included many viruses, and it was arranged according to the target viruses in tables containing information from these researches.

## IV. Results

Studies showed the effectiveness of some natural products and herbal antiviral medicines against a specific type of virus, as summarized in Tables 1 to 17.

Table (1) Medicinal plants and natural anti-coronavirus compounds

This table contains information published during the study period about twenty-five natural anti-coronavirus plants and compounds:

| Mechanism of action | Virus name | Latin name | Research type | Extract type | Compounds name | No. |
|---|---|---|---|---|---|---|
| Inhibits both target cell adhesion and penetration stages | HCov-22E9 | *Buplerum spp*[100] *Heteromorpha spp. Scrophularia scorodonia* | In *vivo* | Aqueous | Saikosaponin (A,B2,C,D) | 1 |
| Several mechanisms, including induction of immune cytokines, induction of phagocytosis, and reduction of HMGBI concentration in endotoxin-stimulated macrophages | Cov-19 SARS Cov-2 | *Camilla sinensis* | In both in *vitro* and in *vivo* | Aqueous extract | EGCG Epigallocatchin gallate[186] | 2 |
| Protease inhibitor | SARS-CoV | *Lycoris radiate*[100] | In *vivo* | Various extracts | Lycorine | 3 |
| Inhibits both target cell adhesion and penetration stages | | *Artemisia annua*[100] | In *vitro* | ethanol extract | Unknown | 4 |
| Inhibiting RNA polymerase | SARS CoV-19 | Many plants with essential oil | In *vitro* | Essential oil | E,E-alpha farnesene, e-beta-farnesene, EE farnesol[169] | 5 |
| Inhibits both target cell adhesion and penetration stages | | *Lindera aggregate*[100] | In *vivo* | Aqueous | Saikosaponin (A,B2,C,D) | 6 |
| Inhibition of an enzymeSARS-Cov 3 | SARS | *Isatis indigotica*[100] | In *vivo* | Roots ethanolic | Phenol compounds | 7 |

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Vol. 9, Issue 2 , February 2022

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| CL protease | | | | extract | | |
| Interfering with spike proteins and membrane glycoprotein | SARS Cov2 Cov19 | *Zingiber officinale roscoe*[163] | In *vivo* | Dried rhizomes | betasesquipheland rene | 8 |
| Helicase inhibitor | SARS- Cov | *Myristica fragrance*[100] | In *vivo* | Seed extract | Myristicine Seco-tillarine | 9 |
| Inhibition of viral polymerase and enzyme SARS-CoV 3CL protease | SARS - Cov | *Houttuynia cordata*[100] | In *vivo* | Aqueous extract | unknown | 10 |
| The spike glycoprotein is the therapeutic target | SARS-Cov SARS-cov2 Cov-19 | *Rheum officinalis*[59] | *In vitro* | | Emodin extract | 11 |
| The spike glycoprotein is the therapeutic target | SARS-Cov SARS-cov2 Cov-19 | *Panax ginseng* [197] | *In vitro* | Roots extract | Gensoside Rb2 | 12 |
| The spike glycoprotein is the therapeutic target | SARS-Cov SARS-cov2 Cov-19 | *African trifolium*[88] | *In vitro* | | secomet-V | 13 |
| The spike glycoprotein is the therapeutic target | SARS-Cov | *Galla chinensis*[203] | *In vitro* | | tetra-O-galloyl-β-D-glucose | 14 |
| inhibit viral S and N protein expression of the HCoV-OC43 | HCoV-229E HCo-OC43 | *Stephaniae tetrandraeradix*[82] | *In vitro* | | bisbenzylisoquinoline alkaloids-tetrandrin | 15 |
| Affects the 3CLprostability, interacts with and binds to 3CLpro active site | SARS-Cov 2 Cov-19 | *Gingko biloba and other* | *In vitro* | | Quercetin[1] hesperidin, catechins [17] | 16 |
| inhibitory effect on SARS-CoV-2 3CLpro, competitive with protease active side | SARS- Cov 2 | *Triterygium regelii* [160] | *In vitro* | | celastrol, pristimerin, tingenone, iguesterin | 17 |
| Closly binding to the 3CLpro | SARS-cov | *Many plants* | *In vitro* | | betulinic acid[193] | 18 |
| anti-SARS-CoV 3CLpro, inhibited the cleavage activities of the 3CLpro | | *Isatis indigota*[102] | *In vitro* | Roots extract | sinigrin, indigo, aloemodin hesperetin | 19 |
| Inhibitory effects on the expression of various pro-inflammatory cytokines responsible for the "cytokine storm" | Cov-19 SARS-Cov2 | *Cutcuma longa* | *In vitro, In vivo* | Roots | Curcumine[208] | 20 |
| eukaryotic initiation factor-4A(eIF4A), an RNA helicase, inhibited cap-dependent viral mRNA translation of MERS-CoV and HCoV-229E in human embryonic lung fibroblast (MRC-5) cells with EC50value of 1.3 nM and 3 nM, respectively | | *Aglaia spp.*[57-20] | *In vitro* | | Silvestrol[124] | 21 |
| eIF4A inhibitors that prevent its binding to RNA and reduce HCoV-229E replication | H Cov-299 | *Isis hippuris*[18] | *In vitro* | | Hippuristanol(poly hydroxysteroid) | 22 |
| Targeting the eukaryotic translation elongation factor 1A (eEF1A) a cellular factor required for the enzymatic delivery of aminoacyl tRNAs to the ribosome[216] | Gastrointistis corona virus[216] SARS Cov2[194] SARS-CoV-2 B.1.1.7[154] Cov 19 [144] | *Aplidium albicans*[48] | In vitro and in vivo, clinical phase 1,2 | | Plitidepsin (cyclic depsipeptide) | 23 |
| inhibit viral entry irrespective of the entry pathway | SARS Cov2 Cov-19 | *Mallotus oppositifolius*[177] | *In vitro* | | pheophorbide a (Pba) | 24 |
| strong anti-3CLpro activity | Corona virus SARS Cov2 Cov-19 | *Isatis indigoticaFort, Torreya nucifera L. Psoralea corylifolia L. Rheum palmatum L*[110] | *In vitro* | | bavachinin, psoralidin, betulinic acid, curcumin hinokinin | 25 |

ISSN: 2350-0328
International Journal of Advanced Research in Science, Engineering and Technology
Vol. 9, Issue 2 , February 2022

Table (2) Medicinal plants and natural anti-entero viruses compounds:

This table contains information published during the study period on seven natural anti-enterovirus plants and compounds

| Mechanism Of action | virus name | Plant Latin name | study style | Extract type | Compound name | No. |
|---|---|---|---|---|---|---|
| Inhibition of virus multiplication and inhibition of viral transcription | Entero Virus | *Ocimum basilicum*[100] | *In vivo* | Water and alcohol extracts | Ursolic acid, apigenin, linalool | 1 |
| Attachment inhibition, hemagglutinin | Entero virus | Vaccinium[100] macrocarpum Aiton | *In vitro* | Organic extract | anthocyanidine | 2 |
| Attachment inhibition, hemagglutinin | Rota virus | Vaccinium macrocarpon Aiton[39] | *In vitro* | Organic extract | anthocyanidine | 3 |
| unclear | Entero virus 71 | *Raoulia*[100] *australis* | *In vitro* | Not mentioned | Raoulic acid | 4 |
| unclear | Entero virus 71 | *Woodfordia fruticose*[100] | *In vitro* | Aqueous and ethanol flower extract | Gallic acid | 5 |
| Interference with viral transcript | EV71 | *Camellia sinensis* | *In vitro* | Aqueous extracts | Epigallocatechine gallate[58] | 6 |
| OSW-1 binds to one of the two established OSBP ligand binding sites and induces prophy-lactic antiviral activity | EV2 | *Ornithogalum saundersiae*[155] | *In vitro* | Bulbs extract | Orsaponin OSW-1 | 7 |

Table (3) Medicinal plants and natural anti-dengue virus compounds:

This table contains information published during the study period on seven natural anti-dengue virus plants and compounds:

| Mechanism of action | virus name | Plant Latin name | study style | Extract type | Compound name | No. |
|---|---|---|---|---|---|---|
| Inhibit dengue adsorption to the host and post-entry viral replication | Dengue Virus-2 | Several plants *Scutellaria baicalensis*[100] | In *vitro* | | Baicalein flavon[100] | 1 |
| Inhibits viral replication but not the viral attachment and entry processes | Den V2 | Many plants | In *vitro* | | Quercitin[100] | 2 |
| Disrupts viral protein synthesis without affecting viral RNA replication | DenV 2 | Several plants | In *vitro* | | Narasin[100] | 3 |
| Act at the early stage of viral infection | Serotypes of the virus Denv 1-4 | Sea algae[100] Canistrocarpus cervicornis, Padina gymnospora, Palisada perforate, and Caulerpa racemose | | Alcoholic extracts | Un known | 4 |
| Inactivate free virus particles and inhibit early viral entry including attachment and penetration phases; do not affect viral cell-to-cell transmission | Den v -2 | *Terminalia chebula Retz*[100] | In *vitro* | Isolated constituents | Chebulagic acid, punicalagin | 5 |

ISSN: 2350-0328
International Journal of Advanced Research in Science, Engineering and Technology
Vol. 9, Issue 2 , February 2022

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| Serin protease inhibitor | | *Azadirachta indica*[40] | In *vitro* and | aqueous extract | Bi flavon | 6 |
| Inhibition of reverse transcription | | *Daucus maritimus*[120] | *In vitro* | Seeds ethyl acetate extract | Not identified | 7 |

Table (4) Medicinal plants and natural anti-coxakie virus compounds:

This table contains information published during the study period about twelve natural anti coxakie- virus plants and compounds:

| Mechanism of action | virus name | Plant Latin name | Study type | Extract type | Compound name | No. |
|---|---|---|---|---|---|---|
| inhibits viral infection and replication | Coxsachi virus B2 | *Ocimum basilicum*[100] | *In vivo* | Water and alcohol extracts | Urosolic acid, Linalool, epigenin | 1 |
| unclear | C | *Raoulia australis*[100] | *In vitro* | | Raoulic acid | 2 |
| Inciting interfron type 1 | | *Bulperum Kaoi*[90,23] | *In vitro* | Aqueous and alcoholic extracts | Saiko saponins | 3 |
| Inhibition of the multiplication of the virus in the stage of the blood and the entry of the cell | | *Aegle marmelos*[11] | *In vitro* | Leaf and root extracts | Marmelide | 4 |
| Not clear | Coxsackie B, type3 | *Conyza Canadensis*[92] | *In vitro* | Different store feeds for air parts | Not identified | 5 |
| Not clear | B, type 3 | *Helichrysum aureonitens*[79] | In vitro | Bud Extract | Galangin | 6 |
| Not clear | | ***Eugenia caryophyllata*[173]** | In vitro | Flowering heads | Essential oil | 7 |
| Not clear | | *Organum vulgare*[173] | *In vitro* | leaves | Essential oil | 8 |
| Not clear | | *Wild berry*[133] | *In vitro* | Methanolic extract | Anthocyanine& polyphenols | 9 |
| Anti replication | Cox B3 | *D.viscosa*[77] | *In vitro* | Different extrracts | Unidentified | 10 |
| Not clear | Cox B1 | *Melaleuca alternifolia*[46] | *In vitro* | Essential oil | Terpinen-4-ol | 11 |
| OSW-1 binds to one of the two established OSBP ligand binding sites and induces prophy-lactic antiviral activity | Cox A21 | *Ornithogalum saundersiae*[159] | *In vitro* | Bulbs extract | Orsaponin OSW-1 | 12 |

ISSN: 2350-0328
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Vol. 9, Issue 2 , February 2022

Table (5) Medicinal plants and natural anti-hepaptitis virus compounds:

This table contains information published during the study period about twenty-eight natural anti-hepatitis virus plants and compounds:

| Mechanism of action | Study style | Plant Latin name | virus name | Extract type | Compound name | No. |
|---|---|---|---|---|---|---|
| Unclear | In vitro | *Laggera alata*[100] | B | Isolated substance | Isochlorogenic acid | 1 |
| Unclear | In vitro | *Piper longum*[100] | B | Isolated substance | Amid alkaloids | 2 |
| Radical scavenging, glutathione standarization | In vitro | Morus alba L.[129] | B | Seeds extract | Anthocyanidine, polyphenols | 3 |
| HBs Ag binding inhibitor | | *Hybanthus enneaspermus* | B | Methanolic extract[6] | | 4 |
| block the HBV DNA polymerase | | *Terminalia bellerica*<br><br>*Enicostemma axillare* | B | Methanolic extract[6] | | 5 |
| Downregulate virus mRNA transcription suppress virus polymerase activity and the release of the virus into Hep-G/2.2.15 cells | | *Phyllanthus amarus* | B | Different extracts[93] | | 6 |
| Inhibited HBV particles maturation | | *Bombyx mori L.* | B | Warm extract[65] | | 7 |
| inhibited HBeAg and HBsAg secretion into themedium and inhibited HBV DNA replication in Hep-G/2.2.15 cells | | *Boehmeria nivea* | B | Ethyl acetate extracts[190] | | 8 |
| unclear | In vitro | *Saxicola corydalis*[100] | B | Isolated substance | Dehydrocheilanthifolin | 9 |
| Prevent HBe Ag expression and the virus nuclear acid multyplication | In vitro | *Bulperum*[100] | B | Isolated substance | Saikosaponin C | 10 |
| Unclear | In vitro | *Polygonum cuspidatum*[100] | B | Alcoholic extracts | Not identified | 11 |
| Unclear | *In vitro* | *Phyllanthus urinaria*[200] | B | Isolated substances | Methyl ester dehydrochebulic acid, methyl brevifolincarboxylate | 12 |
| Host cellular factor targeting | | *Pulsatilla chinensis*[201] | B | | Betulinic acid | 13 |
| Host cellular factor targeting | | *Liriope platyphylla L*[61] | B | | PRP-Et | 14 |
| Unclear | In vitro | *Spirulina platensis*[106] | A | aqueousextract | unidentified | 15 |
| Adsorption or in virus replication | In vitro | *Dianthus caryophyllus*[13] | A | Seed Extract | unidentified | 16 |
| Attachment, adsorption stage | In vitro | Vitis vinifera L[173] | A | Seeds extract | Anthocyanidine glycoside | 17 |
| promotes the JAKATSTAT | In vitro | *Silybum marianum*[123] | C | Standard extracts | Silymarin compounds | 18 |

ISSN: 2350-0328
International Journal of Advanced Research in Science, Engineering and Technology
Vol. 9, Issue 2 , February 2022

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| pathway associated with IFN | | | | | | |
| Anti oxidant | In vitro | *Silybum marianum*[100] | C | | Flavo lignans | 19 |
| Inhibitor of virus replication by suppressing the pathway AKT-SREBP-1 | In vitro | *Curcuma Longa*[100] | C | Isolated substance | Curcumin | 20 |
| Block the entry to the target cell | *In vitro* | *Green tea*[100] | C | | Epigallocathine3-gallate | 21 |
| Preventing the transmission of the virus from one cell to another | *In vitro* | *Green tea* | C | Isolated substance | Griffithisin[72] | 22 |
| Prevents access to the target | *In vitro* | *Marrubium peregrinum* | C | Isolated substance | Ladanein[16] | 23 |
| Inhibiting virus invasion | *In vitro* | *Rosa rugosae flos*[100] | C | Isolated substance | Tellimagrandin | 24 |
| Disable free viruses ,interfere with infusion and linkage, inhibiting cell to cell transmission | *In vitro* | *Terminalia chebula Retz*[100] | | Isolated substances | Chebulagic acid ,punicalagnin | 25 |
| Inhibition of viral protease | *In vitro* | *Trachyspermum ammi*[9] | C | Metanol fruit extract | un identified | 19 |
| Protease inhibition | *In vitro* | *Embelia schimperi*[9] | C | Metanol fruit extract | Benzoquinon | 20 |
| Protease inhibition | *In vitro* | *Solanum nigrum*[9] | C | Metanol and chloroform seed extract | unidentified | 21 |
| Unclear | *In vitro* | *Daucus maritmus*[120] | C | Seeds | unidentified | 22 |
| Replication inhibition protease expression reduction RNA. | *In vitro* | *Solanum genus*[55] | | | anthocyanidine | 23 |
| Interfering with Entry steps | | *Trichilia dracaena, Detarium microcarpum, Phragmanthera capitate*[45] | c | Roots<br>Stems<br>Leaves | | 24 |
| Anti replication inhibitory effect of NS3 helicase activity | *Isolated cells* | *Alloeocomatella polycladia*[199] | C | Ethyl acetate extract | | 25 |
| Inhibiting HCV NS3/4A protease | *In vitro* | *Fusarium equiseti*<br>*Padina pavonica*<br>*(brown alge)*[53] | C | Organic extracts | | 26 |
| inhibit HCV replicase (HCV NS5B) activity | *In vitro* | *Eclipta alba*[169] | C | Aqueous extract | | 27 |
| Inhibiting HCV replication | *In vitro* | *Entada Africana*[176] | C | Many Fractions | | 28 |

Table (6) Medicinal plants and natural anti-measles virus compounds:

This table contains information published during the study period about nine natural anti-measles virus plants and compounds:

| Mechanism of action | Study style | Plant Latin name | Extract type | Compound name | No. |
|---|---|---|---|---|---|
| unclear | *In vitro* | Spicebush[115] | | Cherokee remedy | 1 |
| unclear | *In vitro* | *Rhus succedanea*[100]<br>*Garcinia multiflora* | Ethyl acetate | Biflavons | 2 |

ISSN: 2350-0328
International Journal of Advanced Research in Science, Engineering and Technology
Vol. 9, Issue 2 , February 2022

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|---|---|---|---|---|---|
| unclear | *In vitro* | *Spirulina platensis*[100] | | Calcium spirolan | 3 |
| Inhibit virus entry to the target | *In vitro* | *Crotolus durissus terrificus*[100] | Snake toxin | unidentified | 4 |
| unclear | *In vitro* | *Zanthoxylum chalybeum*[100] *Warburgia ugandensis* | Plant extract | Unidentified | 5 |
| Stops viral infection | *In vitro* | *Olinia rochetiana*[100] | | unidentified | 6 |
| unclear | *In vitro* | *Cajanus cajan*[100] | Stem, root extract | unidentified | 7 |
| Interfere with infusion and virus transmission | *In vitro* | *Terminalia chebula Retz*[100] | Isolated substances | Chebulagic acid , punicalagin | 8 |
| Unclear | *In vitro* | *Podophyllum peltateum*[100] | aqueousextract | Podophyllotoxin | 9 |

Table (7) Medicinal plants and natural anti-Herpes simplix virus compounds:

This table contains information published during the study period about twenty-nine natural anti-herpes simplex virus plants and compounds:

| Mechanism of action | Study style | Plant Latin name | virus name | Extract type | Compound name | No. |
|---|---|---|---|---|---|---|
| unclear | *In* | *Thymus vulgaris* *Rosemarinus officinale* *Salvia officinale* *Mellisa officinale* *Mentha piperita* | HSV1,2 | Aqueous and methanol extract | Anthocyanidin polyphenol[66] | 1 |
| unclear | *In vivo vitro* | Aronia melanocarpa Michx[183]. | HSV1 | Fruit juice | Anthocyanidin | 2 |
| inhibit HSV-1 replication decreasing the immediate-early (IE) gene expression and infectivity | *In vivo* | *Cuncumma longa*[211] | HSV 1 | | Curcumine | |
| interfere with the expression of HSV-1 viral proteins by preventing their transcription or translation, with viral DNA synthesis | *In vitro* | *Pistacia vera. L*[126] | HSV 1 | | | 3 |
| Inhibiting transcription | *In vitro* | *Cassia javanica*[100] | HSV2 | Isolated substance | Epiafzelechin | 4 |
| unclear | *In vitro* | *Rosa damascene* *Citrus aurantium* | | Essential oil | Farnesol[175] | 5 |
| unclear | *In virro* | *Salvia officinale* *Populus spp.* *Teucrium polium* | | Essential oil | Caryophyllene[175] | 6 |
| Unclear | *In vitro* | *Pinus spp.* *Abies alba* *Juniperus comminis* | | Essential oil | Alpha- pinene[175] | 7 |
| Unclear | *In vitro* | *Melalerca alternifolia* | HSV1 | Essential oil | [175] Gamma- trepinene Alph -pinene | 8 |
| unclear | *In vitro* | *Melaleuca alternifolia* *Lavendula angustifolia* | | Essential oil | Trepinen-4-ol[175] | 9 |

ISSN: 2350-0328

International Journal of Advanced Research in Science, Engineering and Technology

Vol. 9, Issue 2 , February 2022

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|---|---|---|---|---|---|---|
| | | *Juniperus comminis* | | | | |
| unclear | *In vitro* | *Thymus vulgaris*[175] | HSV1 | Essential oil | Thymol | 10 |
| unclear | *In vitro* | *Eucalyptus globulus*[175] | HSV 1 | Essential oil | | 11 |
| unclear | *In vitro* | *Eugenia caryophyllata*[175] | HSV1 | Essential oil | eugenol | 12 |
| unclear | *In vitro* | *Melissa officinale*[175] | HSV1, 2 | Essential oil | Citral , citronellal | 13 |
| unclear | *In vitro* | *Citrus spp*[175] | HSV1 HSV2 | Essential oil | citral | 14 |
| unclear | *In vitro* | *Anisum vulgare*[175] *Foeniculum vulgare* | HSV1 | Essential oil | Trans anitol | 15 |
| unclear | *In vitro* | *Phyllanthus uninaria*[100] | HSV2 | Isolated substances | Hippomanin A, Geranin, 1,3,4,6-tetra-0-galloyl-beta-D-glucose, Excoecarianin | 16 |
| Stimulating productionα-TNF γ-TNF | Rats | *Melia azedarach*[3] | HSV2 | Isolated substance | Meliacine | 17 |
| viral entry including attachment and penetration phases; do not affect viral cell-to-cell transmission | *In vitro* | *Terminalia chebula Retz*[100] | HSV1 | Isolated substance | Chebulagic acid , puniclagin | 18 |
| suppresses NF-kB activation, which is essential for HSV gene expression | *In vitro* | *Houttuyania cordata*[60] | HSV1 | Isolated substances | Hottuynoids A-E, Quercitine | 19 |
| anti-binding effects | *Vero cells* | *Prunus dulcis*[125] | HSV | | Poly phenol | 20 |
| inhibiting adsorption and infusion | *In vitro* | *Rhododendron ferrugineum*[60] | HSV1 | | Various flavonoid | 21 |
| Viral killing activity | *In vitro* | *Black berry*[183] | HSV1 | | anthociannidin | 22 |
| Inhibits stages of absorption and viral penetration | *In vitro* | *Myrothamnus flabellifolia*[100] | HSV1 | | proanthocyanidin | 23 |
| Inhibition of viral protein synthesis | *In vitro* | *Digitalis lanata*[100] | HSV1 | Isolated substance | Glucoevatromonoside | 24 |
| unclear | *In vitro* | *N.nepetella* *N.coerulea* *N.latifolia*[31] | HSv1,2 | Water extracts | unspesified | 25 |
| Inhibition replication | *In vitro* | *S.minor magnolia*[106] | HSV1 | Water extracts | unidentefied | 26 |
| Antiviral inhibitor in the adsorption phase | *In vitro* | *Vigna angularis*[(77)] | HSV 1,2 | | Anthocyanine | 27 |
| Targets the cellular factor eIF4E | *In vitro* | *Cephalotaxaceae family* | HSV1 | Isolated substance | Homoharringtonin[38] | 28 |
| Viral glutatin inhibitorGST | *In vitro* | *Santalum album L*[14] | HSV1,2 | Essential oil | santalol | 29 |

ISSN: 2350-0328
International Journal of Advanced Research in Science, Engineering and Technology
Vol. 9, Issue 2 , February 2022

Table (8) Medicinal plants and natural anti-HIV virus compounds:

This table contains information published during the study period about twenty-seven natural anti- HIV plants and compounds:

| Mechanism of action | Study type | Plant Latin name | Extract type | virus name | Compound name | No |
|---|---|---|---|---|---|---|
| unknown | *In vitro* | *Artemisia annua*[100] *Artemisia afra* | aqueous | HIV | artemisin | 1 |
| Anti virus entry | *in vitro* | *Punica granatum L*[130] | juice | HIV1 | anthocyanidin | 2 |
| Prevents reproduction by inhibiting activation Nf –KB | *In vitro* | *Calophyllum brasiliense*[100] | Hexan leaf extract | | Tricyclic coumarins, calanolides B, C, Apetalic acid | 3 |
| Down regulated expression | *In vitro* | Vitis vinifera L[127] | Seeds extract | HIV 1 | Anthocyanidine glycosides | 4 |
| Inhibition of an enzyme integrase | *In vitro* | *Agastache rugose*[121] | Methanol extract roots | HIV 1 | Rosmarinic acid | 5 |
| Unknown | *In vitro* | *Chrysanthemum morifolium*[94] | Flower extract | | Flavonoid glucorinic epigenin | 6 |
| unknown | *in vitro* | *Vatica cinerea*[214] | Isolated substances | | Tri terpenes | 7 |
| Activating MAKP and $NF_KB$ pathway | *In vitro* | *Scutellaria baicalensis Oroxylum indicum* | Isolated substances | | Flavonoid Baicalin[85] | 8 |
| Non-nucleoside RT inhibitor | *In vitro* | *Calophyllum lanigerum*[76] *Calophyllum gunus* | Latex | | Coumarin, calanolide A-C | 9 |
| Inhibition of reverse transcription | *In vitro* | *Daucus maritimus*[124] | seeds | | unknown | 10 |
| Inhibiting viral DNA integration with host | *In vitro* | *Pelargonium sidoides*[128] | Roots | | Phenolic compounds Essential oil | 11 |
| Inhibition of reverse transcription | *mice* | *Geum japonicum*[198] | aqueous extract | | unknown | 12 |
| unknown | *In vitro* | *Kadsura heteroclite*[150] | stems | | Tri terpenes, lignan | 13 |
| Inhibiting virus entry | *In vitro* | *Monotes africanus*[117] | Organic leaves extract | | Flavonoids Laroadendrin Diprenyl caempferol Bonanniol A Nacarangin | 14 |
| Inhibition of reverse transcription | *In vitro* | *Panax gensing*[206] | Roots | | Panaxagin | 15 |
| Prevent infection of host cells | *In vitro* | *Quillaia saponaria*[156] | Aqueous extract | | Tri terpen saponin | 16 |
| Unknown | *In vitro* | *Rhizophora apiculate*[142] | leaves | | Poly saccharides | 17 |
| Inhibition of reverse transcription | *In vitro* | *Rhus succedanea*[101] | Isolated substances | | biflavonoids | 18 |
| Inhibition of reverse transcription | *In vitro* | *Shepherdia argentea*[205] | Leaves extract | HIV1 | Tannins, shephagenin | 19 |
| viral entry including attachment and penetration phases; do not affect viral cell-to-cell transmission | *In vitro* | *Terminalia chebula*[8] | Metanolytic summary | | Chebulinic acid, chebulin | 20 |
| | *In vitro* | *Garcinia speciose*[159] | Bark and stem extract | HIV1 | Protosane triterpene | 21 |
| Inhibiting HIV protease | *In vitro* | *Crataegus pinatifida*[122] | | | Tri terpenes | 22 |
| Inhibition of reverse transcription | *In vitro* | *Vigna unguiculata*[202] | Seed proteins | | ungullin | 23 |

ISSN: 2350-0328
International Journal of Advanced Research in Science, Engineering and Technology
Vol. 9, Issue 2 , February 2022

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| nhibits cellular entry of HIV by binding to high-mannose glycans present on the surface of the HIV envelope protein gp120 | *In vitro* | *Griffithsia sp.* | | | Griffithsin(amino acid lectin)[107] | 24 |
| inhibit HIV fusion with host cell membranes during entry | *In vitro* | *Siliquariaspongiamira bilis*<br>*Stelletta clavosa* | Sponge extract | | mirabamide-A, a cyclic depsipeptide [146] | 25 |
| RT-inhibitor activity against drug-resistant HIV-1 isolates of both the nucleotide analogue (AZT) and nevaripine | *In vitro* | *Justica gendarussa*[215] | | | Patentiflorin A | 26 |
| inhibiting late-stage processing the gag protein and resulted in the release of non-infectious viral particles | *In vitro* | *Syzigium claviflorum*[75] | | | Betulinic acid, dehydro butilinic acid | 27 |

Table (9) Medicinal plants and natural anti-inluenza virus compounds:

This table contains information published during the study period about thirty-two natural anti- influenza virus plants and compounds:

| mechanism of action | Study style | Plant Latin name | virus name | Extract type | Compound name | No. |
|---|---|---|---|---|---|---|
| Adsorption phase | *In vitro* | *Teobroma cacao*[73] | Avian influenza, influenza B | Aqueous extracts | anthocyanidin | 1 |
| Reducing hemaggultinin | *In vivo*<br>*In vitro* | Aronia melanocarpa Michx.[140] | 1,2 | | anthocyanidin | 2 |
| Anti TNF alpha stimulating lymphocyte T | *In vitro* | *Lycium barbarum L*[148] | Inf V | | anthocyanidin | 3 |
| unclear | *In vivo*<br>*In vitro* | *Sambucus nigra*[100] | IFA, IFB | Aqueous extract | | 4 |
| Attachment inhibition | *In vitro* | *Morus alba L*[83] | b | Seeds extract | Anthocyanidin polyphenol | 5 |
| inhibition, hemagglutinin, and inhibiting viral particles | *In vivo* | , *Rubus coreanus Miq*[96] | A,b | | Anthocyanidin, polyphenols | 6 |
| Inhibition of replication Immune stimulation | *In vitro* | [133] wild berry plants | A | Methanolic extract | Anthocyanidin polyphenols | 7 |
| Attachment inhibition, hemagglutinin | *In vitro* | Vaccinium macrocarpon Aiton[191] | B | | Anthocyanidine polyphenols | 8 |
| Preventing virus entry and inhibiting hemagglutinin and NA activity | *In vitro* | *Pelargonium sidoides*[100] | IFA | | unidentified | 9 |
| Curb RNA levels and polymerase activity | *In vitro* | *Taraxacum officinale*[100] | IFA | | unidentified | 10 |
| unclear | *In vitro* | *Illicium oligandrum*[100] | IFA | | Apirooliganone B | 11 |
| InhibitorNA | *In vitro* | *Glycyrrhiza inflate*[100] | iFA | | Chalcones | 12 |
| Anti NA | *In vitro* | *Polygala karensium*[100] | IFA | | Xanthones | 13 |
| Anti NA | *In vitro* | *Caesalpinia sappan*[100] | IFA | | Homo iso flavonoids | 14 |
| inhibitor RNAinterfering with<br>Viral coating | *In vitro* | *Agrimonia pilosa*[168] | | Various polarity extract | Inidentified | 15 |

ISSN: 2350-0328

International Journal of Advanced Research in Science, Engineering and Technology

Vol. 9, Issue 2 , February 2022

| | | | | | | |
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| Destroying the viral coat and inhibiting its function | *In vitro* | *Aloe barbadensis*[54] | | Heating leaves with glycerin | polysaccharides | 16 |
| unclear | *In vitro* | *Bergenia ciliate*[151] | | methanol extract roots | inidentified | 17 |
| Inhibition of viral multiplication and hemagglutenation | *In vitro* | *Camilla sinensis*[17] | | Aqueous extract | catechine | 18 |
| Modification theviral membrane of to prevent the Viral entry | *In vitro* | *Citrus incanus*[41] | | Various extracts | Polyphenol | 19 |
| Producing antibodies virus | *In vitro-in vivo* | *Clinacanthus siaminsis*[195] | | Ethanol leaves extract | unidentified | 20 |
| Inhibiting viral growth and reduce its spread in the lungs | *In vitro-in vivo* | *Commelina communis*[43] | | Ethanol extract | alkaloids | 21 |
| Inhibition of the expression of virus proteins on the surface of the cell | *In vitro* | *Geranium sanguineum*[69] | | Methanol extract | Poly phenols | 22 |
| unclear | *In vitro* | *Narcissus tazetta*[134] | Inf A, H1N1, H3N2, H5N1, B | bulbs | Lectin | 23 |
| Hemagglutinating activity | *In vitro In vivo* | *Pandanus amaryllifolius*[135] | Inf A, H1N1 | leaves | pandanin | 24 |
| | *In vitro* | *Rhinacanthus nasutus*[137] | INF Type 1 | Aero organs | lignan | 25 |
| AMPK pathway modulating | *In vitro* | *Scutellaria baicalensis*[167] | INF A,B | Roots | Flavonoids Wogonin | 26 |
| Unclear | *In vitro* | *Melaleuca alternifolia*[46] | H1N1 | Essential oil | Alpha- terpineol | 27 |
| Un clear | *In vitro* | Solanum stenotomum S. tuberosum[217] | A,b influenza | | Anthocyanidin pelargonidin-3-rutinoside-5-glucoside | 28 |
| unclear | *In vitro* | S. paniculatum[182] | (HHV-1) 1‘ (VACV-WR) | Ethanol extract | Neotigogenin, | 29 |
| Prevention viral attachment and entry and spreading viruses from the injured cells | *In vitro In vivo* | *Ribes nigrum*[64] | Influenza a, b | fruit | Anthocyanidin malvidin ‘ pelargonidin ‘ peonidin | 30 |
| unclear | *In vitro* | *Cicer arietinum*[10] | parainfluenza | Fruit peels, aerial, seeds extrac | Phenolic compounds | 31 |
| Interfering with viral adsorption | *In vitro , hella cells* | *Allium sativum*[116] | parainfluenza | | Allicin, methyl allyl thio sulfinate | 32 |

ISSN: 2350-0328
International Journal of Advanced Research in Science, Engineering and Technology
Vol. 9, Issue 2 , February 2022

Table (10) Medicinal plants and natural anti-syncytical virus compounds:

This table contains information published during the study period about eleven natural anti- syncytial virus plants and compounds:

| Mechanism of action | study style | Plant Latin name | Extract type | Compounds name | No. |
|---|---|---|---|---|---|
| Entry and penetrationphases | *In vitro* | *Terminalia chebula*[100] | Aqueous , alcoholic extract | Chebulagenic acid, punicalagin | 1 |
| Un clear | *In vitro* | *Selaginella uncinata*[100] | | Uncinoside A, B | 2 |
| Un clear | *In vitro* | *Radix wikstroemiae*[100] | Isolated substances | Genkwanol B, C, Stelleranol | 3 |
| unclear | *In vitro* | *Lophatherum gracile*[100] | | flavones | 4 |
| Immune stimulation Replication inhibiting | *In vitro* | Wild berry plants[133] | Methanol extract | Anthocyanidine , polyphenols | 5 |
| RegulatesIFN-γduring Infection | *In vitro* | *Vitis venifera*[127] | Seed extracts | Resveratrol | 6 |
| Attachment and stimulates secretionINF-β | *In vitro* | *Cimicifuga foetida*[100] | | Cimicifugin | 7 |
| unclear | *In vitro* | *Narcissus tazetta*[135] | bulbs | Proteins, tazetta, lectin | 8 |
| Inhibiting virus entry | *In vitro* | *Schefflera heptaphylla*[97] | | 3,4,di-0-caffeoylquinic acid | 9 |
| unclear | *In vitro* | *Barleria prionitis*[20] | | 6-0-trans-p-coumaroyl-8-0acetylshanzhiside methylester, irdiod | 10 |
| unclear | *In vitro* | *Markhamia lutea*[63] | | Luteoside,verbascoside,isoverbascoside | 11 |

Table (11) Medicinal plants and natural anti-rubella virus compounds:

This table contains information published during the study period about natural anti- rubella virus plants and compounds:

| Mechanism of action | Study type | Plant Latin name | Extract type | Compound name | No. |
|---|---|---|---|---|---|
| Inhibiting virus entry | *In vitro* | *Canavalia ensiformis*[63] | Isolated substance | Lectins | 1 |

Table (12) Medicinal plants and natural anti-vesicular stomatitis virus compounds:

This table contains information published during the study period about seven natural anti- vesicular stomatitis virus plants and compounds:

| Mechanism of action | Study style | Plant Latin name | Extract type | Compounds name | No. |
|---|---|---|---|---|---|
| Interfere with virus entry | | *Allium sativum*[159] | Bulbs , essential oil | Ajoene, allicicn,methyl allyl thiosulfunate, | 1 |
| Inhibition of virus multiplication | *In vitro* | *Cedrela tubiflora*[27] | Leaves extract | Acidic polysaccharides | 2 |
| unclear | *In vitro* | *Justicia procumbens*[71] | Methanol extract ,aerial parts | justisidinA,B, diphyllin derivatives | 3 |
| Inhibition of virus multiplication | *In vitro* | *Melia azedarach*[13] | Leaves extract ethyl acetate | Miliacarpin, tetranotriterpiooids, 1-cinnamoyl-3-11-digydroxymeliacarpin | 4 |
| unclear | *In vitro* | *Nepta nepetella L*[112] *N.coerulea* | Aqueous extracts | unidentified | 5 |

ISSN: 2350-0328
International Journal of Advanced Research in Science, Engineering and Technology
Vol. 9, Issue 2 , February 2022

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| | | *N.tuberosa* | | | |
| unclear | *In vitro* | *Dittrichia viscosa*[112] | Aqueous extracts | unidentified | 6 |
| Inhibit the entry of virus | *In vitro* | *Sanguisorba officinalis*[69] | Aqueous extracts | unidentified | 7 |

Table (13) Medicinal plants and natural anti-rhino virus compounds:

This table contains information published during the study period about five natural anti- rhinovirus plants and compounds:

| mechanism of action | Study style | Plant Latin name | Virus type | Extract type | Compounds name | No. |
|---|---|---|---|---|---|---|
| Interfering with viral entry and adsorption | *In vitro, Hella cells* | *Allium sativum*[157] | Human rhino virus | Bulbs , essential oil | Ajoene, allicicn,methyl allyl thiosulfunate | 1 |
| unclear | *In vitro* | *Prunus genus*[209] | | Fruit extract | Flavonoids | 2 |
| Interfering with spike proteins and membrane glycoprotein | *In vitro* | *Zingiber officinale roscoe*[70] | | Dried rhizomes | Beta-sesquiphelandrene | 3 |
| inhibited RNA replication of rhinoviruses | *In vitro* | *Lagerstroemia speciosa L*[139] | Rhino virus 4 | Leaves extract | Ellagic acid | 4 |
| OSW-1 binds to one of the two established OSBP ligand binding sites and induces prophy-lactic antiviral activity | *In vitro* | *Ornithogalum saundersiae*[155] | Rhino virus2 | Bulbs extract | Orsaponin OSW-1 | 5 |

Table (14) Medicinal plants and natural anti-polio virus compounds:

This table contains information published during the study period about seven natural anti- poliovirus plants and compounds

| Mechanism of action | Study style | Plant Latin name | Extract type | Compounds name | No. |
|---|---|---|---|---|---|
| unclear | *In vitro* | *Eugenia caryophyllata*[175] | Essential oil | eugenol | 1 |
| Immune stimulation, replication inhibition | *In vitro* | Wild berry[133] | Methanol extracts | Anthocyanidne, pholyphenol | 2 |
| Unclear | *In vitro* | *Origanum aromaticum*[175] | Essential oil | unidentified | 3 |
| unclear | *In vitro* | *Melaleeuca alternifolia*[46] | Essential oil | unidentified | 4 |
| Inhibition of multiplication | In vitro | *Anagallis arvensis*[141] | | Tri terpen saponin | 5 |
| unclear | In vitro | *Pterocaulon sphacelatu*[163] | Alcoholic extract | unidentified | 6 |
| unclear | In vitro | *Sanguisorba minor*[112] | Various extracts | unidentified | 7 |

Table (15) Medicinal plants and natural anti-adeno virus compounds:

This table contains information published during the study period about six natural anti- adeno virus plants and compounds

| Mechanism of action | Study type | Plant Latin name | Extract type | Compounds name | No. |
|---|---|---|---|---|---|
| unclear | *In vitro* | *Eugenia caryophyllata*[175] | Essential oil | unidentified | 1 |
| Un clear | *In vitro* | *Origanum vulgare*[175] | Essential oil | unidentified | 2 |

ISSN: 2350-0328
International Journal of Advanced Research in Science, Engineering and Technology
Vol. 9, Issue 2 , February 2022

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| Inhibiting MCP-1 | *In vivo* | mulberry Morus alba L.[95] | Seeds extract | Polyphenols ,anthocyanidin | 3 |
| unclear | *In vitro* | *Melalerca alternifolia*[46] | | Essential oil | 4 |
| Inhibition of multiplication in the early phases of cellular circuit | *In vitro* | *Caesalpinia pulcherrima*[25] | Aqueous leaves, stems, seeds, fruit, extract | Quersetin | 5 |
| unclear | Both *In vitro* *In vivo* | *Punica granatum L*[99] | Peel extract | anthocyanididn | 6 |

Table (16) Medicinal plants and natural compounds anti-west Nile virus and Japanese encephalitis:
This table contains information published during the study period about two natural anti- west Nile virus and Japanese plants and compounds

| Mechanizm of action | Study style | Plant Latin name | Virus name | Extract type | Compounds name | No. |
|---|---|---|---|---|---|---|
| Inhibition of reverse transcription | *In vitro* | *Daucus maritimus*[120] | West Nile virus | Seeds extract | unidentified | 1 |
| unclear | *In vitro* | *Glycyrrhiza glabra*[12] | Japanese encephalitis virus | Root extracts | Glycyrrhizin | 2 |

## V. DISCUSSION

Antiviral results indicate that pure anthocyanins isolated from plants may have an effective role against viral infection[66], as research demonstrated the antiviral effects of cyanidin-3-sambubioside (C3S) from (*Sambucus nigra*) extract. From a pharmacological and mechanistic point of view, and according to the molecular steric positioning of this compound, it binds to the lumen 430 adjacent to the InfV neuraminidase components, since this antiviral compound is distantly bound to Asp 151 and Glu 119, which are involved in the synthesis of neuraminidase and play an important role in enzyme resistance, it could be a promising treatment strategy and constitutes a new class of antiviral drug effective against InfV virus[174]. Subsequent studies also demonstrated the inhibitory activity of C3S for mutants of H274Y, and the inhibitory activity of C3S virus. Oseltamivir antivirus and the anti-mutant-type (MT) and wild-type (WT) mechanisms were elucidated by various quantitative chemical techniques and dynamics. Molecular and docking methods, through which it is possible to predict the causes leading to the phenomenon of drug resistance[74] , In another study, some scientists tried to discover new and innovative natural compounds that are highly effective against HCV and determine their mode of action. Among the eight selected compounds, delphinidin was found to be an anthocyanate and considered a suitable choice as a new class of inhibitors of flaviviridae, as this compound works to disrupt the adhesion and adsorption of HCV using E1E2 gp from the envelope of different HCV genotypes, where its activity occurred in the stage of vaccination only [16]. In another study, the effect of anthocyanins, delphinidin and cyanidin was tested on viral infections of the flaviviruses family, including west Nile virus (WNV), dengue virus (DENV) and zika virus (ZIKV). Delphinidin reduced WNV, and another research showed that delphinidin interferes with the stages of adhesion, adsorption and entry stages in the viral cycle and has a direct veridical effect, which shows that the antiviral activity against West Nile virus is due to the inhibitory activity of viral fusion [74].
Finally, in accordance with the importance of selective natural antiviral compounds in the fight against viral diseases, elucidating the exact pharmacological mechanisms of their effect could pave the way for the treatment of viral infections.

## VI. The therapeutic and clinical application of natural products antivirals

Several plants such as elderberry (*Sambucus nigra* L.) have used in traditional medicine in the treatment of viral diseases such as cold and cold symptoms many years ago until now [184]. Some independent clinical trials have proven the effectiveness of elderberry extract against InfV A and B infections[87], and in a randomized, double-blind, placebo-controlled study in which the effectiveness of elderberry extract was evaluated in the treatment of influenza virus infections InfV A and B, the results showed its therapeutic efficacy and safety [210]. In another randomized, double-blind, placebo-controlled clinical study, elderberry extract significantly reduced symptoms of cold seizure and its duration and also reduced the severity of cold attacks among air travelers [180]. It has also proven that the fruits of sea

ISSN: 2350-0328
International Journal of Advanced Research in Science, Engineering and Technology
Vol. 9, Issue 2 , February 2022

buckthorn, *Hippophaë rhamnoides* L. has an immune-stimulating activity and [47], and the daily dose of the anthocyanins is 200 mg / day [187].

As for the bioavailability and pharmacokinetics of these isolated compounds, it has studied on some isolated anthocyanins. It was found that the concentrations of anthocyanins in the plasma are very low, and recent studies have revealed rapid absorption followed by rapid metabolism and excretion of anthocyanins via the kidneys and bile as methyl derivatives or in the form of glucuronidated or in the form of its glycoside derivatives. Some clinical studies have shown that anthocyanins are poorly absorbed [109]; generally, it was found that the bioavailability of anthocyanins in vivo is about 0.26-1.8% [15]. The maximum concentration of anthocyanins in plasma is after 1.5 hours and in urine after 2.5 hours [109]. The metabolites are present in the urine up to 24 hours and the basic anthocyanin may appear [15]. Studies also have shown that anthocyanins are rapidly absorbed from the stomach [78], and anthocyanins have shown to be rapidly degraded by the gut microflora present in the gastrointestinal tract, although metabolized compounds are notably unstable under all conditions. In addition, in Neutral pH they converts naturally into aldehydes and phenolic acids [78]. There are also various ways to enhance the stability and then bioavailability of anthocyanins. As some studies have shown that the consumption of anthocyanins with foods affects the phase of absorption and excretion for example, in humans or in rats [36]. Nuts, grains and seeds that are rich in phytic acid enhance the bioavailability of the anthocyanins present in blackcurrant [114]. Another way to enhance the bioavailability of anthocyanins is by using Nano formulations such as nanoparticles, Nano complexes, Nano liposomes, and emulsions Nano emulsions [56], and pharmaceutical Nano particles use biodegradable and biocompatible Nano particles to target infection sites [113]. Polymer-based Nano particles are a novel approach to enhance the bioavailability of unstable hydrophilic drugs such as anthocyanins. This approach helps in improving bioavailability and increasing stability. It was proven that encapsulation of anthocyanates by polylactic glycolic acid (PLGA) and polyethylene glycol (PEG) did not affect its properties, in addition it enhance it nerves protective properties. The use of anthocyanins in the form of controlled release Nano particles enhances their bio distribution, protects them from cellular metabolism degradation within the digestive system, and allows them to target specific sites affected by viruses [4].

## VII. CONCLUSION

In this review, we conclude that there are a plenty of natural compounds and herbal extracts with high potential anti-virus activities especially against corona viruses and other viruses such as retro viruses. In addition, we highlighted the available antiviral chemotherapies and proposed alternative plant-derived antiviral compounds with mechanisms of action. Our particular highlighted compounds were anthocyanin derivatives.

## VIII. SUGGESTIONS

Additional studies should include the search for basic plant antiviral compounds whose chemical structure can be relied on to synthesize effective derivatives by structure-effect relationship to find drugs more effective against many viral infections, and the study of the synergistic effects of more appropriate treatment results capable to enhance the immunity and to reduce the cost of the treatment. Drug delivery must be also improved using new technologies and new nanotechnology which vacillate the uses and enhance the potentially effect against the targeting receptors in the viruses. However, it is crucial to confirm the effects of key plant-derived compounds in clinical studies.

As many viruses still without preventive vaccines and effective antiviral treatments; eliminating these viral diseases appears to be difficult. Nevertheless, natural products serve as an excellent source of biodiversity for discovering new antivirals, uncovering new structure–activity relationships, and developing effective preventive/curative strategies against viral infections. It has observed that many natural products and herbal ingredients possess potent antiviral activity and their discoveries may support the development of derivatives and therapeutic evidence. For example, glycerol derivatives in the form of novel anti-hepatitis B virus agents, acetoxime derivatives from the Mediterranean mollusk *Hexaplex trunculus* as an inhibitor against HSV-1, and caffeic acid derivatives as a new type of NA antagonist for influenza. Likewise, studies that chebulagic acid and punicalagin are able to prevent infection with many viruses due to their GAG-competitive properties could help in the development of broad-spectrum antivirals for the prevention and control of these viral pathogens. Many studies in this area are only preliminary, and we believe that natural products will continue to play an important role in the development of antiviral drugs.

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International Journal of Advanced Research in Science, Engineering and Technology

Vol. 9, Issue 2 , February 2022

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