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Medical Plants and Natural Compounds as Anti-Viral Agents: Present and Future Trends

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Abstract

Medicinal plants and natural compounds were used to treat a variety of infectious diseases. Many of the plants and natural compounds is a good source for drug discovery of infectious diseases. Among several other diseases are viral infections, as Human immunodeficiency virus type 1 (HIV-1) and (HIV-2), herpes simplex virus type 1 (HSV-1) and type 2 (HSV-2), hepatitis and newly emerging infectious viruses as COVID-19. A great number of medicinal plants and natural compounds have a significant effect for viral infections, and some compounds showed broad-spectrum antiviral effect. This review article showed potential antiviral effects of medicinal plants and natural compounds against several groups of viruses.

Keywords: Medicinal Plants, Natural Compounds, Antiviral Agents, Drug Discovery

1. Introduction

Viruses are intracellular parasites consisted of strands of genetic information either in the form of DNA or RNA and are enclosed via lipid core or envelope [1]. The main feature is the use of the host cell to replicate new viruses through the process of acquiring the reproductive tools of the host cell. Hence, this leds to cell invasion which causes diseases as bloody African fever [2]. Each virus strain is confined to a unique shape in respect to molecules of the surface that work through the same way, i.e., "key-in-alock", which causes entrance of viruses inside host cells [1]. The main characteristics of viruses are their genetic variation, mode of transmission, replication into host cells and their ability to persist into the host body. The therapeutic indices can be used in order to regulate the level of infections caused by viruses. Viruses are not autonomous in the nature, and so they necessitate a host body or living cell for the replication process [1,3]. Many studies have reported the inhibitory effects of medicinal plants extracts on the replication of several viruses [4]. Identification of the antiviral mechanisms from these natural agents leds to the detection of the viral life cycle, such as viral entry, replication, assembly, and release. Hence, there is too urgent need to discover new antiviral agents that are very effective for the management and control of viral infections when vaccines and standard therapies are lacking.

1.1 Medicinal plants with Antiviral Potential

Carica papaya leaf extract showed a potent SARS-Coronavirus-2. This observed effect was due to the presence of 40 compounds as (isorhamnetin, kaempferol, myricetin, naringenin) as in the leaves, where the flavonoids and its analogs represent (27%) of the total content and these compound were very active against SARS-Coronavirus-2 [5].

Terminalia arjuna Wight & Arn Bark was tested for antiviral effect. The ethanolic bark extract proved antiviral effect and this observed effect is due to the presence of a bioactive compound Arjunetin which showed a promising effect against SARS-CoV-2 (Gandarvakottai et al., 2021).

Bauhinia variegate leaves were tested for antiviral effect. Different extracts of the plant leaf were tested for its effect for against rotavirus in vitro. The all extracts proved antiviral effect against rotavirus at the different doses 7.8, 15.6, 31.25, 62.5, 125, 250, 500, and 1000 μ g/mL), and the most effective was methanol extract and this is due to the presence of high content of polyphenol in the extract [6].

Justicia adhatoda L. is from Acanthaceae family. Methanolic extract of leaves has antiviral effect for influenza and herpes

simplex virus. The alkaloidal compound anisotine was identified of the plant leaves. Anisotine proved a good inhibition of the main protease (Mpro) of SARS-CoV-2. The assay proved that inhibitory potential of this alkaloid is higher compared that of lopinavir [7].

Achyranthes aspera L. is from Amaranthaceae family. It has a potent antiviral agent named oleanolic acid which proved antiviral effect against (herpes simplex virus type-I, and type II [8]. Allium sativum L. is from Amaryllidaceae family. The different extracts of A. sativum proved effect against SARS-CoV-2 [9]. Mangifera indica L. is from Anacardiaceae family. It proved antiviral effect against influenza virus. It has bioactive compound named, mangiferin. This compound has a good antiviral effect against HSV-I and HIV [10]. Alstonia scholaris (L.) is from Apocynaceae family. The plant has high content of total alkaloids that proved anti-inflammatory and antiviral effects. The total alkaloids showed antiviral effect against IAV [11].

Aloe vera (L.) is a plant from Asphodelaceae family? A. vera gel has antiviral effect for HSV-I. This research work proved that the gel is very good for oral HSV-I infection [12]. Eclipta prostrata L. is from Asteraceae family which proved strong antiviral effect. This plant was used in folklore medicine to treat blood borne hepatitis and snake bite The active compound of this plant is phytosterol, Coumestan which has a good antiviral effect against HCV [13].

Diospyros lotus fruits methanol (70%) extract showed a potent anti-HIV. Several compounds were isolated and identified of the extract and the most bioactive compound as anti-HIV agent was gallic aicd [14]. Ailanthus excelsa bark chloroform extract was tested for antiviral effect. The extract showed a potent anti-viral effect against herpes Simplex virus type 1 in-vitro by 82.6% at dose of 50 µg. The bioactive major component that chloroform extract has is the alkaloidal compound, canthin-6-one [15].

Citrus sinensis peel methanol extract was tested for antiviral effect. The extract was very effective as antiviral agent against HSV-1. Some Polyphenols isolated and identified of the plant proved antiviral effect among these, galangin and pelargonidin (Hamed et al., 2014). Bombax ceiba L., is from Bombacaceae family. The Flowers have kaempferol-3-O-6"--O-E-p-coumaroyl)- β -D-glucopyranoside. This compound has a good antiviral effect on respiratory syncytial virus (RSV) (Zhang et al., 2015), and also it proved anti- SARS-CoV-2 effect [16].

Anogeissus acuminata (Roxb.) is from Combretaceae family. The plant has bioactive compounds as anolignan A and anolignan B which proved antiviral effect against HIV-I [17]. Cyperus rotundus L. is from Cyperaceae family. The essential oil of the rhizomes proved inhibitory effect against HAV, HSV-I, and CVB. The major constituent was, Caryophyllene oxide showed a significant inhibitory effect against HSV-I [18].

Albizia procera (Roxb.) is from Fabaceae family. The plant

showed a significant antiviral effect against IAV. Different extracts of the bark extracts proved antiviral for IVA. The major constituents were (+)-catechin and protocatechuic acid. Catechin proved antiviral effect against IAV intergase, but protocatechuic acid effect was moderate [19]. Swertia angustifolia var. pulchella (D. Don) Burkill is from Gentianaceae family. The herb extract showed a good effect against HSV-I [20].

Ocimum tenuiflorum L. is from Lamiaceae family. It has bioactive compounds as antiviral agents, as ursolic acid, eugenol, 1,8-cineole, and rosmarinic acid which showed the inhibition of HSV-I and II [21]. Ocimum americanum is from Lamiaceae family which is named American basil. Rosmarinic and oleanolic acids are the major essential oils identifed from the herb. Oleanolic acid proved the inhibition of HIV-I protease whereas rosmarinic acid showed the inhibition of internal ribosome entry site of EV-71 (Chung et al., 2017).

Azadirachta indica A. Juss., is from Meliaceae family. The plant has several medicinal effects. At the concentration of $50-100 \mu g/$ ml, the bark aqueous extract showed antiviral effect for HSV-I. Gedunin and pongamol are the antiviral bioconstituents identified from A. Indica [22-24].

Phyllanthus niruri L. is from Phyllanthaceae family. The plant showed antiviral effect. Aqueous extract of total plant proved antiviral against hepatitis virus [25]. Piper longum L. and Piper nigrum L. are from Piperaceae family. P. longum has piperine is a significant anti-HBV compound [26]. P. nigrum has guaiol which proved antiviral effect of 6LU7 and 7JTL (crucial targets of coronavirus (Pandey et al., 2021).

Rosa centifolia L., is a flowering plant from Rosaceae family. The plant leaves proved antiviral effect. Methanolic extract from the leaves has anti-HIV activity [27]. Aegle marmelos (L.) is from Rutaceae family. The plant has a bioactive compound seselin that has effect against multiple targets of SARS-CoV-2. The study of in silico molecular docking proved that compound has a good inhibition to the receptors SARS-CoV-2S, and free enzyme of the SARS-CoV-2 [28].

A number of some citrus fruits as Citrus limon (L.) Osbeck, and Citrus sinensis (L.) Osbeck, are from Rutaceae family. All of the plants have vitamin C in high content and this vitamin fastens healing from COVID-19 [29]. Essential oils extracted from the fruits proved anti- HAV [30]. Camellia sinensis (L.) (green tea) is from Theaceae family. Some bioactive constituents as antiviral agents as epigallocatechin-3-gallate (EGCG), epicatechin gallate and epicatechin (EC) were identified. EGCG proved a significant antiviral effect. It causes the inhibition of RNA and DNA synthesis and antigen expression in HBV. It has a potent antiviral effect on HCV, and IAV [31].

Boehmeria nivea L. is plant from Urticaceae family. A study

proved that root ethanolic extract showed anti-HBV effect. The possible mechanism involved potential inhibition of DNA of HBV [32]. Zingiber officinale is a plant from Zingiberaceae family. Aqueous extract from the rhizome proved anti- HCV and anti-CHIKV effects. The bioactive compounds were gingeronone A and 6-gingerol, and these compounds have potent anti-SARS-CoV-2 effect in molecular docking studies. 6-gingerol compound has the ability to inhibit SARS CoV-2 [33].

Curcuma longa L. is a plant from Zingiberaceae family. This

plant rhizome showed anti-HBV activity, and also a randomized

controlled trial showed the potent effect of curcumin for preexposure prophylaxis of COVID-19 [34,35].

2. Natural Compounds as Antiviral Agents

Phytochemicals, as alkaloids, coumarins, flavonoids, terpenoids, saponins, and peptides have antiviral efficacy.

2.1. Alkaloids

Many of the alkaloids present in the plants proved antiviral effect and these compounds from different plants from various plant families.



2.2. Camptothecin

Camptothecin compound was identified from Ophiorrhiza mungos leaves and this compound was very effective against herpes virus [36].



2.3 Atropine

Atropine compound was identified from Atropa belladona L. This bioactive compound has the ability to inhibit the multiplication of enveloped viruses [37].

Canavanine compound which is identified from Carnavalia ensiformis L. has the ability to inhibit influenza virus and Semliki Forest virus [38].



2.4. Canavanine

Caffeine compound which was identified from Theobroma cacao L. and Coffea species have the ability to suppress the grown of influenza virus [37].



2.5. Caffeine

Chelidonine compound was isolated from Chelidonium majus L. and this bioactive compound proved antiviral effect on Herpes virus and influenza virus [39].



2.6. Chelidonine

Emetine compound which was isolated from Cephaelis ipecacuanha A. Rich. is very effective against Herpes virus [40].



2.7. Emetine

Cordycepin compound which is identified from Aspergillus nidulans plant. It is active against Herpes simplex and influenza viruses [41].



2.8. Cordycepin

Lycorine is a bioactive compound which is identified from Clivia miniata and it is the most important alkaloid of the Amaryllidacea family, it proved antiviral effect on several RNA and DNA viruses [42].



2.9. Lycorine

Papaverine compound was identified from the opium of Papaver somniferum It proved antiviral effect against HIV [43].



2.10. Papaverine

Odorinol compound which is identified of Aglaia roxburghiana. It was effective against Ranikhet disease virus [44].



2.11. Odorinol

Schumannificine was identified of Schu-manniophyton magnificum root bark. It showed a good effect against HIV and anti-Herpes simplex [45].



2.12. Schumannificine

Solasonine compound is a steroidal glucoalkaloid which was identified of Solanum nigrum and S. khasianum fruits. It can inhibit tobacco mosaic virus. [46].



2.13. Solasonine

Leurocristine compound was isolated and identified of Catharanthus roseus L. G. Don. It is very effective against influenza viruses [47].



2.14. Leurocristine

Some Sesquiterpene alkaloids which were identified of Tripterygium hypoglaucum and Tripterygium wilfordii proved antiviral effect. Triptonines B proved a significant anti-HIV [48].



2.15. Triptonine B, Coumarins

Coriandrin compound was identified from Coriandrum sativus. It is very effective against HIV (Towers, 1989).



2.16. Coriandrin

Novobiocin compound is identified from Streptomyces spheroids and it showed a potent antiviral activity [49].



2.17. Novobiocin

Soulatrolide compound was isolated and identified from Calophyllum teysmanii latex. It was very effective against HIV [49].



2.18. Soulatrolide

Calanolide A was identified of Calophyllum lanigerum. It is a significant inhibitor to the non-nucleoside reverse transcriptase of the HIV virus. This compound prevents the entry of HIV into healthy T-cells nucleus [50].



2.19. Calanolide A

Glycycoumarin and Licopyranocoumarin were identified from Glycyrrhiza glabra. These bioactive compounds have antiviral effect for HIV [45].



2.20. Glycycoumarin



2.21. Licopyranocoumarin, Flavonoids

Fisetin compound which was identified of some Rhus species (proved antiviral effect against pseudorabies virus [51].



2.22. Fisetin

Apigenin compound is identified from different plants in the plant kingdom. It is very effective against Herpes virus [51].



2.23. Apigenin

luteolin 7-O- β -D-glucoside is an antiviral compound that is very effective against herpes and poliomelytis viruses and this compound was identified of Matricaria inodora L [52].



2.24. luteolin 7-O-β-D-Glucoside

Isoquercitrin is a potent antiviral compound which was identified of Wald- steinia fragarioides Michx. It was very active against Herpes simplex type 1 virus [53].



2.25. Isoquercitrin

Morin compound was identified of Chlorophora tinctoria L. It showed antiviral effect on activity against pseudorabies virus [51].



2.26. Morin

Naringin compound was identified of Citrus paradisi Macfad. It showed antiviral effect on vesicular stomatitis virus [54].



2.27. Naringin

Quercetagetin compound was identified of the flowers of many species of Compositae. It proved anti-HIV effect [55].



2.28. Quercetagetin

Rutin compound was identified in several plants. It has antiviral effect against vesicular stomatitis virus [51].



2. 29. Rutin

Quercetin 3-methyl ether compound proved antiviral effect [55].



2.30. Quercetin 3-Methyl Ether

Taxifolin compound is found in Acacia catechu. It has antiviral effect (Harborne, 1988).



2.31. Taxifolin

Some isoflavonoids, afromosin and formononetin were identified of Wisteria brachybotrys Sieb. These compounds have a potent antiviral activity on the Epstein-Barr virus early antigen (EBV-EA) activation[56].



2.32. Afromosin Formononetin

Volkensiflavone compound was identified in Rhus succedania L. This compound antiviral effect for influenza B virus [57].



2.33. Volkensiflavone

Pachypodol compound was identified from Begonia glabra plant. It proved antiviral activity [55].



2.34. Pachypodol

The Biflavonoids, robustaflavone and hinokiflavone were identified from Rhus succedanea L. and Garcinia multiflora Champ. These compounds showed a potent effect against HIV-1 reverse transcriptase (RT), with IC50 values of 65mM.and proved a moderate activity against HIV-1 (Lin et al., 1997).



2.36. Hinokiflavone

Wogonin compound was identified from Scutellaria baicalensis. This bioactive compound has the ability to suppress HBV surface antigen production without cause cytotoxicity. Wogonin has a significant effect on HBV DNA [58].



2.37. Wogonin, Lignans

Dihydroanhydropodorhizol compound was identified of Bursera schletchtendalii. It showed anti-HSV-1[59].



2.38. Dihydroanhydropodorhizol

The lignin compound, diphyllin, which was identified of Justicia aerial parts proved a potent antiviral effect against vesicular stomatitis virus [60].



2.39. Diphyllin

The antiviral effect of Podophyllum peltatum aqueous extract of was investigated. The most active compound that has a potent antiviral effect was podophyllotoxin which has antiviral effect for Herpes simplex type 1 virus [61].



2. 40. Podophyllotoxin

Kadsulignan N was identified of Kadsura coccinea seeds. It showed a potent anti-HIV effect in vitro [62].



2.41. Kadsulignan N

Trachelogenin compound was identified of Forsythia intermedia and Ipomoea cairica. It has antiviral effect for HIV-1 [63].



Trachelogenin , R1=OMe, R2= OH

► Other natural compounds

Castelanone is compound from a quassinoids type. It was identified in Castela tweediei root bark. It showed antiviral effect against the oncogenic Rous sarcoma



2.42. Castelanone

Chaparrinone compound was identified in Quassia undulata seeds. It proved antiviral effect against the oncogenic Rous sarcoma virus [64].



2.43. Chaparrinone

Cochinolide was identified in Homalium cochinchinesis root bark. It showed antiviral effect against HSV-1 and -2 [65].



2.44. Cochinolide

Pentagalloylglucose compound was identified of Paeonia albiflora Pallas. It was very effective against against Herpes virus [41].



2. 45. Pentagalloylglucose

Aphidicolin compound is an diterpene which identified of Cephalosporium aphidicola fungus. It can inhibit Herpes simplex strains 1 and 2 [66]



2.46. Aphidicolin

Nyctanhes arbor-tristis seeds was investigated for its bioactive compounds. The three iridoid glucosides, arbotristoside A, arbotristoside B and arbotristoside C were identified. These compounds were very effective against encephalomyocarditis virus and Semliki Forest virus [67].



2.47. Arbotristoside C

Dolabellane compound was identified from Dolabella californica. It was very effective against influenza and adenovirus viruses [68].



2.48. Dolabellane

Gentisic acid compound was identified of Citrus cultivars leaves and roots. This compound proved antiviral potential [69].



2.49. Gentisic Acid

Some compounds as guttiferones A, B, C, D and E. which were identified of Garcinia livinstonei have antiviral effect for HIV infection [70].



2.50. Guttiferone D

Woodorien compound was identified of Woodwardia orientalis rhizomes. It has antiviral for Herpes simplex virus type 1 (HSV-1) [71].



2.51. Woodorien

Coriariin A compound was found in Coriaria japonica leaves. It was very effective for HIV [72].



2.52. Coriariin A

Salicin and salireposide were identified of Populus trichocarp. These compounds were very active at 25 mg/ml against Semliki forest virus [73].



2.53. Salicin

Galloylquinic and caffeoylquinic acids, were identified of Guiera senegalensis. These compounds were very active against HIV [69].



3,4,5-tri-O-Caffeoylquinic acid Some bioactive anthraquinones as emodin, and rhein, and the flavonoid compound, chrysin, were identified of Rheum genus were tested for SARS-CoV activity. It was that emodin proved the strongest effect and also significantly blocked the S protein and ACE2 interaction with IC50 value of the dose of 200 μ M [74].



2.54. Emodin

Glycyrrhizin, a saponin which identified of Liquorice roots, has antiviral effect for SARS-associated coronavirus with EC50 value ranging from 300 to 600 mg [75].



2.55. Glycyrrhizin

Some oligostilbenes as dibalanocarpol and balanocarpol were identified of Hopea malibato Foxw. These compounds showed HIV-inhibitory effect [76].



2.56. Balanocarpol

Caffeic acid was identified of Coffea Arabica. It has a moderate effect against influenza virus, and it is very effective against Herpes simplex, vaccinia and polio viruses [77].



2.57. Caffeic Acid

The plant Conospermun incurvum has a bioactive compound named, Conocurvone and this compound is a potent an anti-HIV agent [78].



2.58. Conocurvone

Hypericin and pseudohypericin are condensed anthraquinones of Hypericum perforatum. Hypericin was Effect against human immunodeficiency virus (HIV) [79].



2.59. Hypericin

Agrimoniin compound was identified from Rubus idaeus leaves. This compound was very effective against HIV [72].



2.60. Agrimoniin

Chebulagic acid compound was identified of Terminalia chebula, While gemin D was identified from Geum japonicum. Both of these tannins can inhibit HIV binding [63].



Gemin D Chebulagic Acid Garlic is very important therapeutic name for the treatment of various diseases that can cause by bacteria, fungi, viruses and protozoa. Allicin, the bioactive compound that was identified of Allium sativa L. It was very effect against some viruses as Herpes simplex virus, and human rhinovirus type 2 [80].



2.61. Allicin

Thiarubine-A, was identified of Chaenactis douglasii. Cytomegalovirus and Sindbis virus, these viruses membranes, were very highly sensitive to Thiarubine-A [81].



2.62. Thiarubine-A

β-Aescin was identified of Aesculus hippocastranum. It was very effective on influenza viruses [82].



2.63. β-Aescin

Arjunolic acid was identified of Cochlospermun tinctorium A. Rich rhizome. It proved a potent antiviral effect on EBV-EA activation in Raji [83].



2.64. Arjunolic Acid

Chikusetsusaponin was identified of Panax japonicus rhizomes. It proved anti-HIV effect [84].



2.65. Chikusetsusaponin

Digitoxin, was identified of Digitalis purpurea L. It can inhibit poliovirus replication [85].



2.66. Digitoxin

Gleditsia saponin C was identified of Gleditsia japonica fruits. It antiviral effect for HIV [86].



2.67.n Gleditsia Saponin C

Gymnemic and Glycyrrhizic acids were identified of Gymnema sylvestre leaves. It proved anti-influenzal effect [87].



2.68. Gymnemic Acid



2.69. Glycyrrhizic Acid

1-Beta-Hydroxyaleuritolic acid 3-p-hydroxy-benzoate was identified of Maprounnea africana. It caused a significant inhibitory effect of DNA polymerase of human im-munodeficiency virus-1 reverse transcriptase [88]. Lancilactone C was identified of Kadsura lancilimba roots. It can inhibit HIV replication with an EC50 value of 1.4mg/ml [89].



2.70. Lancilactone C

Lanatoside D was identified of Digitalis lanata Ehrh. It was very effective against influenza, Herpes and vaccinia viruses [85].



2.71. Lanatoside D

Nigranoic acid compound was identified of Schisandra sphaerandra Stapf. It proved a good effect in many anti-HIV reverse transcriptase and polymerase assays [90].



2.72. Nigranoic Acid

Salaspermic acid was identified of Triterygium wilfordii Hook root. It showed good inhibitory effect of HIV reverse transcriptase and HIV replication in H9 lymphocyte cells (Hiller, 1987).



2.73. Salaspermic Acid

Strophanthin G was identified of Strophanthus kombe Oliv. It was very effective on influenza, Herpes and vaccinia viruses [41].



2.74. Strophanthin G

Proscillaridin A and scillarenin compounds were identified of Urginea scilla Steinh (Liliaceae). Proscillaridin A was very effective on influenza, Herpes and vaccinia virus (Koch & Sandor [85].



2.75. Proscillaridin A

Betulinic and platanic acids were identified of Syzigium claviflorum (Roxb.) leaves. Betulinic acid showed a good Inhibitory effect on HIV replication in H9 lymphocyte cells [91].



2.76. Betulinic Acid

Oleanolic acid which was identified from Prosopis glan-dulosa, showed a good inhibitory activity of HIV. Pomolic, alphitolic arjunolic acid, betulinic acids which were identified of Rosa woodsii Lindl. and Syzygium claviflorum Wall, have the antiviral effect for HIV [92].





2.78. Pomolic Acid Phitolic Acid

Some triterpenes as Ursonic acid, Hydroxyhopanone were identified of Balanocarpus heimii King. These compounds showed antiviral effect against Herpes virus [93].



2.79. Acid Ursonic Hydroxyhopanone

Escin was identified of Aesculus chinensis Bge. seeds. It showed a moderate anti-HIV protease effect [94-105].



3. Conclusion

Viral infections are considered the most fatal forms of diseases (e.g., hepatitis, HIV, Corona virus). Vaccination policies are the most important weapons for the management of viral attacks, but some specific vaccines are not available and these days, many viral infections are an endemic nature that are existing in the world. In the light of this, it is of great importance to open the horizons of new medicine to novel therapeutic potentials as the use of plant principles. The viral infections can be treated by many of antiviral agents from traditional sources of medicinal plants. Herbal extracts that have bioactive constituents can inhibit the replication process of at any stage in the viral replication cycle. By reviewing the most sources of phytochemicals, the different compounds with antiviral potential, their mechanisms of action did a fundamental starting point for the development of future research and the development of novel therapeutic aids. Natural compounds are used as novel sources for pharmaceuticals by combining newer methods/aspects of drug discovery. In view of the signification number of plant extracts that have yielded positive results it seems reasonable to conclude that there are probably numerous kinds of antiviral agents in these materials. Further characterization of the active ingredients will reveal useful compounds. Some of these compounds belong to a wide range of different structural classes, e.g. coumarins, flavonoids, tannins, alkaloids, lignans, terpenes, and anthraquinones, polysaccharides, proteins and peptides. There may also be novel phytochemicals. Although large numbers of new compounds have been isolated from medicinal plants only some have been marketed as pharmaceutical products. Some compounds have been or are undergoing various phases of clinical trials.

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