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Antiviral Effects of Anthocyanins and Phytochemicalsas Natural Dietary Compounds on Different Virus Sources

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Abstract

Virus, an infectious agent is the main reason causing the deaths by life-threatening diseases, including HIV, cancer, influenza, herpes, dengue, hepatitis, chikungunya all around the world. Virus infections are a global health concern, due to worldwide travel and gradual modernization, the viral eruption is an epidemic menace and can be avoided by minimizing publicity to infectious viruses. Even with so many precautions, viral diseases can still spreadand cause great risk to human health and requires proper sanitation by disinfectants or anti-viral agents.Very few vaccines are available that can effectively treat viral infections. As there are many advances progressing in the health care sector, there are some efficient anti-viral treatments and therapies, still some virus does not have effective vaccinations and therapies yet.Forthe past few years, there has been an intensive effort to study the defense mechanism of natural products such as foods and drinks we normally consume in our day-to-day life that may inhibit some anti-viral activitiesand some advantages over synthetic vaccines.The development of natural vaccines, that work against the virus is still a major goal. As it has been identified that the natural dietary compounds such as phytochemicals, anthocyanins, flavonoids, curcumins, polyphenols, and many more have some health benefit properties which may include anti-inflammation, anti-oxidant, anti-bacterial, anti-cancer, anti-viral, anti-fungal activities. This mini-review generally summarizes the antiviral activities of anthocyanins and phytochemicals from various natural plant sources on different virus origins.

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Introduction

For over 100 years, traditional medicines from natural compounds have been used and have many health beneficial properties such as anti-bacterial, anti-carcinogenic, anti-viral, anti-fungal, anti-oxidant, and many more. The viral diseases caused in humans can be inactivated and safely treated by these sources.[1] Natural antivirals act against the common viral diseases including influenza virus, viruses responsible for respiratory infections, hepatitis, dengue virus, herpes virus in humans, causing no side effects due to their mode of action and are also cost-efficient. However, there have been many discoveries and identification of vaccines that work against the viral disease but still, there are some deadly virus family or genre around in nature that are unidentified and have no effective vaccine yet.[2] Due to these reasons, there is a critically important urge to spot novel natural effective alternatives. Identification of compounds that could attack the specific single viral targets leading to a vaccine (direct-acting anti-viral), that is only effective to that particular host and has no or little effect on other viral sources is the target.[3]

Discussion

Challenges In The Anti-Viral Treatment

The virus life cycle for every different type of virus depends mainly on its cellular factors and pathways.[4] Still, for many viral infections, there is not effective vaccines, drugs or therapies.There are many records for the ineffectiveness and viral resistance of anti-viral vaccines towards the viral diseases and is causing a major problem in anti-viral treatment.[5] Considering the unexpected spread of old or new strains of viral pathogens, it is critically important to prepare for the anti-dote and preventive measures to control the outspread.[6]

However, the main concern lies within the aspects to control the existing viral diseases, to regulate the studies for controlling continual viral spread for which there is no developed vaccine.More usage of natural anti-viral dietary supplements or compoundsis necessary so that the use of synthetic vaccines that have elevated costs, poor treatment responses, inadequate response, side effects, efficacy limitations, drug interaction toxicity can be.[7,8] suggested,another challenge is to create a vaccine with broad-spectrum anti-viral activities for viruses that are highly diverse. The main advantage of these vaccines is that they can target a number of viruses of different families or genres at the same time.Also, more research work is required to know about the adverse effects of anti-viral vaccines, to understand unknown pathways and mechanisms of anti-viral treatments to establish new plant-derived natural compounds anti-viral agents, and drugs.[7]

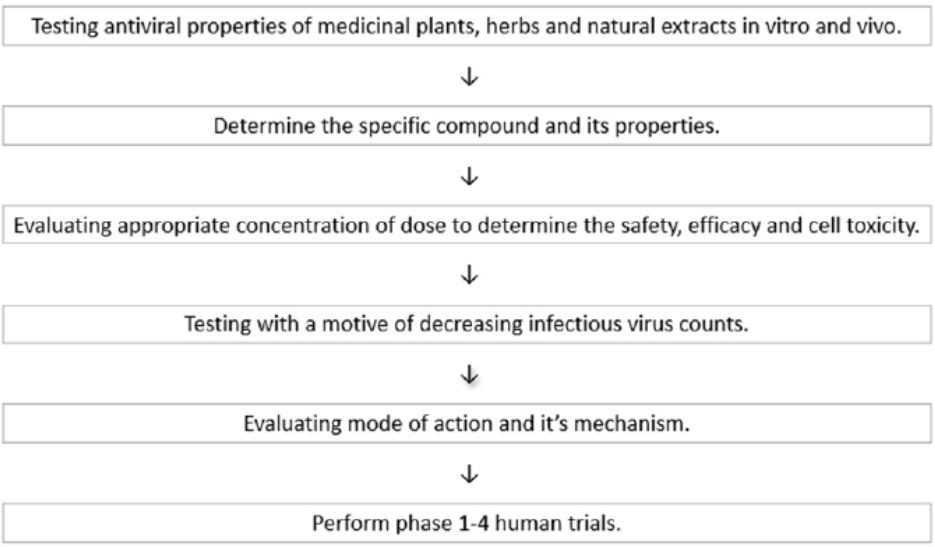

Fig. 1: Flow chart of a possible procedure for evaluating properties of natural compounds against viral diseases

Natural Compounds as Anti-Viral Agents

Over the years, the natural compounds have shown their significant role in providing availability for numerous anti-fungal and anti-bacterial infections. Because of their medicinal properties, plants have been used as traditional remedies. According to the World Health Organization, 80% of the total population is dependent on medicines and vaccines from plant sources.9Various natural compounds have mild or no side-effects, high biological specificity, high chemical diversity, and targets multiple host sites by different pathways with minimal cost.[7] The involvement of natural compounds for vaccines has many advantages due to their distinct conglomerate network that is unique when compared to another form of vaccine sources. Thus, these compounds come with a complex structure and can be a hurdle when synthesizing from plants, but this disadvantage can be overcome by genetic engineering or by organic bio-synthesization.[8]

Plant sources have many beneficial natural compounds that help in inhibiting viral replication, viral penetration in the host cell.[10] Previously it has been proved, that coumarins, flavonoids, and terpenoids possess anti-viral activities for the treatment of HIV (Human Immunodeficiency Virus) infection by protease inhibition, replication, integration and, reverse transcription.[11] Anti-viral activities against HSV (Herpes Simplex Virus) were identified by naturally occurring compounds that comprise of pro-anthocyanidins, geraniin, flavonoids, terpenoids, and excoecarianin. HSV-1 was inhibited by chebulagic acid and punicalagin by resisting the viral entry phase and showing anti-RSV effects. The replication phase of the virus cycle was inhibited by flavonoids including apigenin, ladenein, luteolin, and quercetin.Nuclear factor kappa-B (NF-κB) can be supressed by tricyclic coumarin.[12] Recently, some compounds like, anthocyanins, alkaloids, chalcones, flavonoids, polyphenols, and xanthones were identified as anti-influenza agents.[8]

Anthocyanins

Anthocyanins get easilydegraded by the intestinal microflora and are proven to showcase their anti-viral healing properties towards the prevention and depletion of viral diseases.[13] The bioavailability and adsorption of anthocyanins after oral administration is critical and maximum concentration is achieved after one to two hours and can be increased by the dosage of phytic acid, by using nano-formulations like nano-emulsions, nano-complexes, nano-particles, and nano-liposomes.[14,15]

Chemical Structure

Anthocyanins are usually the water-soluble pigments found naturally in various foods showing multiple functions within the plant (related to the different parts of the plant), and belongs to the structural class of glycosylated polyphenols. The general anthocyanin structure (Figure 2.) comprises a benzyl ring (A) attached to a heterocyclic ring with oxygen (C) with is attached to a third benzyl ring (B).[16] This type of structure is the reason for structural diversity offering varying stability and colors to the compound.

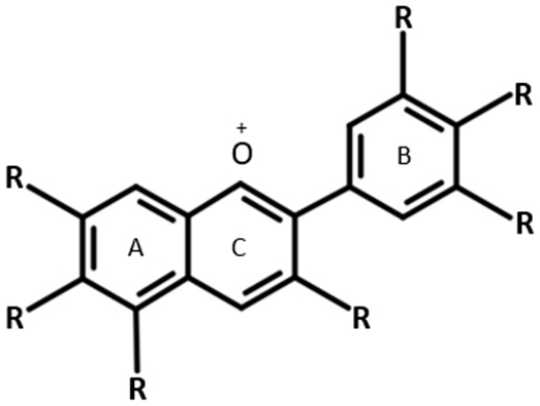

Fig. 2: The general structure of anthocyanin

Properties of Anthocyanins

Anthocyanins are one of the most dominant compounds that play a key role in human health. Anthocyanins present in vegetables and fruits include cardio-protection, decreasing lipid pre-oxidation, anti-aging, neuroprotective, anti-inflammatory,anti-obesity, anti-diabetic, anti-allergy, anti-microbial effects, and free radical scavenging.[17] These compounds from natural sources acts as an anti-influenza agent.[18, 19] They have also been identified for improving visual function by improving the blood flow of retin and decreasing eye fatigue in.[20] Some of the anthocyanins showed significant hepatoprotective and immunomodulatory effects.

Antiviral Activity of Anthocyanins Against Influenza

Some anthocyanins including cyanidin, cyanidin 3-O-arabinoside, delphinidin, malvidin, pelargonidin, peonidin and petunidin derived from natural source blackcurrant berries *ribes nigrum L.* showed strong antiviral activity against Influenza A and B.[21] As reported by,[22] anthocyanins from red potatoes *Solanum stenotomum* and *S. tuberosum* including p-coumaric, pelaergonidin-3-rutinoside-5-glucoside acylated, were identified tohave antiviral activities. However, [23] investigated the antiviral activity against influenza A and B and according to the results, the purified anthocyanin from Solanum sp.were effective against Influenza A and B. In another study on black raspberry seed (RCS) *Rubus corneanus*, it was found that RCS exhibits activities against both Influenza A and B by binding to hemagglutinin protein and disrupts viral particles.[24] Mulberry extracts (*Morus alba L.* (MA)) from mulberry juice (MAJ) and seeds (MAS) included xyanidin-3-rutinoside and showed a weak inhibition against Influenza B in the pre-treatment stage. Whereas, in cocoa seeds (CS, *Theobroma cacao L.*), cyanidin-3-arabinoside and cyanidin-3-galactoside are the two main anthocyanins found and affect Influenza A and B in a dose-dependent manner by inhibition of adsorption phase of the virus.[25] Purified antiviral anthocyanin, cyanidin-3-sambubioside from black elderberry (Sambucus nigra) extract had an anti-viral effect against the influenza virus.[26]

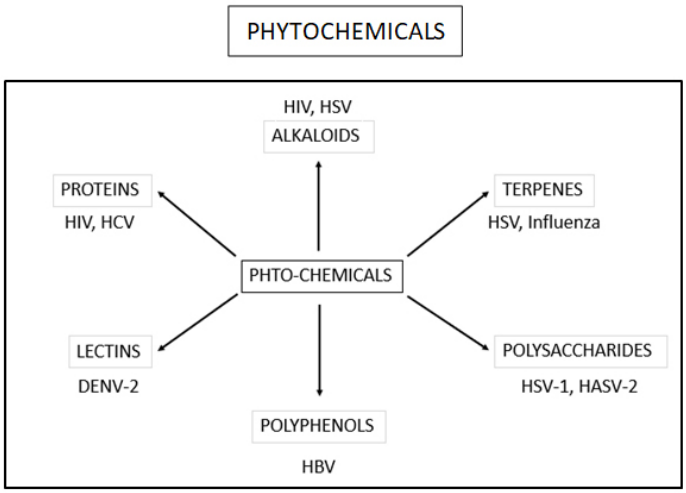

Fig. 3: Different types of phytochemicals (alkaloids, terpenes, polysaccharides, polyphenols, polyphenols, lectins, proteins) that shows anti-viral properties against various viruses

Antiviral Activity of Anthocyanin Against Hepatitis Virus

The expression of HCV NS3 protease was reduced in a dose-dependent manner by an *S. nigrum* seeds (SNS) extract, showing anti HCV activity.[27] Delphinidin has been proved as one of the most promising anthocyanin anti-viral agents. It disrupts the HCV adsorption and attachment in the inoculation phase. The anthocyanins from grapes (*vitis vinifera L.*) include delphindin, cyanidin, malvidin petunidin,and peonidin. According to the antiviral activity against Hepatitis A of anthocyanins from grape seed extract was dose-dependent and increased with time.[28]

Antiviral Activity of Anthocyanin Against Herpes Virus

Ina study by,[29] about total anthocyanins content (TA) of strawberries from five different cultivators for in vitro anti-HSV activity and showed that aromas and camarosa had the highest TA whereas, camino has the lowest and studied the relationship between the amount of anthocyanin present and the detected anti-HSV. However, as reported by,[30] the antiviral activity of anthocyanins from strawberries (*Fragaria x ananassa*) revealed that for the complete inhibition of HSV-1 (Herpes Single Virus), a concentration equal or higher than 20µg/ml is needed. The *S. paniculatum* extract suppressed the replication of HHV-1

(Human Herpes Virus).[31] The Lamiaceae family which has excellent anti-viral activity includes plants like basil, sage, thyme but still, there is not a lot of information for the remaining plants of the family.[32,33,34] This family consists of many anthocyanins including cyanidin and peonidin based pigments. In a study conducted by[35] the extracts indicated anti-viral effect in a time-dependent manner and had efficacy in anti-HSV before adsorption stage but no efficacy in the replication stage.

Phytochemicals

Phytochemicals are the primary and/or secondary metabolites originating from the plant source(Kamboj *et al.,* 2012)[57] There are various types of phytochemicals that have anti-viral properties. Different classes of phytochemicals are shown in Figure 3. The development of anti-viral vaccines from phytopharmaceuticals is a new hope. Currently, only a few of the phytochemicals have been extracted, purified, and researched for the medicinal properties.[38] These phytochemicals including alkaloids, carotenoids, terpenes, polyphenols have been reported to poses anti-viral activities against influenza virus, dengue, hepatitis, herpes, HIV. Inhibition of virus can be achieved at different levels of infection.The virus generally attacks the cell wall of the host cell and adsorbs the receptors.39 Thus,these phytochemicals need to be focused on animal and human studies to check their efficiency for anti-viral therapies.

Antiviral Activity of Phytochemicals Against Influenza

Potential phytochemicals against the influenza virus (H1N1, H5N1, H5N2, H3N2) include flavonoid, alkaloid, lignan, coumarin, terpenes, and terpenoids.[40] *Radix isatidis* plant is a Chinese herb that has antiviral properties against the influenza virus.[41] Alkaloids show inhibition of the influenza virus at various stages of the infection. Alkaloid homonojirimycin (HNJ) from *Commelina communis*, had a great influence on the influenza.[42] Whereas, another compound dendrobine from *Dendrobium nobile* was analysed and results showed that it inhibited influenza A virus replication.[43] Betulin showed antiviral properties against influenza A.[44] Flavonoids from aerial parts of S. plebeia inhibited the replication of influenza A in a dose-dependent manner.[45] Kumar *et al*., (2010)[58] reported that quinazoline alkaloid shows antiviral properties against Influenza virus A.

Antiviral activity of Phytochemicals Against Hepatitis Virus

The quercetagetin and stilbenes have proved to inhibit the activity of the hepatitis C virus.[46,47] Saikoponins from *Buleurum kaio* root showed a strong response at the early virus cycle towards the hepatitis C virus.[48, 49] studied the inhibition of HCV by *Phyllanthus urinaria*.[49] A low-level inhibitory effect was observed from a flavonoid compound from *F. cunninghamii* against hepatitis A virus.[50] In another study by,[51] *Enantia chlorantha* from Nigeria showed antiviral properties against hepatitis A, B, C, and D.3-hydroxy caruilignan C extract from *Swietenia macrophylla* and 3-HCL-C showed antiviral activity against hepatitis B and C virus respectively as observed by.[52]

Antiviral Activity of Phytochemicals Against Herpes

Phytochemicals from *Phaleria macrocarpa* inhibited major antiviral activity against HSV.[53, 54] However, a potential flavonoid genistein present in soy-based products was identified that inhibits the herpes B virus after the replication stage.[55] Recently in a study by[56] *Rhinacanthus nasutus* plant showed antiviral properties against herpes infection. According to Kapoor *et al.,* (2017)[59] phytochemicals such as oxyresveratrol from *heartwood*, CDM (11-dihydroxymeliacarpin) from the leaves of *melia azedarach* L., and lignin-carbohydrate complex from *prunella vulgaris* targets HSV-1 and HSV-2 by inhibiting the early and late phase of the replication and inhibiting late protein synthesis.

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D.C. wrote the manuscript.and M.H.P. conceived the idea and approved the final manuscript.

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Conflict Of Interest

The author(s) have no financial and conflict of interest to declare.

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