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Natural Antivirals against Human Viruses

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Editorial

Over the past two decades there has been intense study of antivirals from plants that have antiviral activity against viruses affecting plant and animal kingdoms. This volume of Virology and Mycology has a report by Awasthi et al. [1] on the antiviral activity against plant mosaic viruses affecting commercial important bean plants. A number of viruses that can cause diseases in humans can be either neutralized or its replication can be inhibited. There has been an explosion of research in the antiviral activity in recent years against human diseases caused by pathogenic viruses, which are known to affect millions of people across the globe and cause significant morbidity and mortality. As a champion of evidence based natural products of preventive and therapeutic agents, I would like to dedicate this editorial to those who have labored on researching natural products against all odds, often experiencing a hostile and elitist opposition to the discovery of natural products. The challenges to translating the findings of natural products are many and this editorial will conclude with steps one needs to take in order to obtain regulatory approval from agencies like the FDA and the EU regulatory group. Very few of the newly found compounds are anywhere close to finding human use. The one Secomet V (the active agent of which is Fulvic acid) that has reached human observational trial stage in HIV patients reported by Van Rensburg et al. in 2010 is a precursor to more proper trials, which have been presumably underway [2]. But the promise of Secomet V, a broad spectrum natural product, first reported by Kotwal et al., [3] takes exceedingly long periods to go from bench (discovery and laboratory testing) to bedside (administered in patients). This passage of over a decade is due to the underfunding of natural products evidence based research in the western world and the low impact they make in the publication arena in top medical journals like Nature Medicine, who look down upon the struggling researchers from the natural products field. Then there are those like pomegranate, found and consumed universally and known to have health benefit and documented to have broad spectrum activity (Table 1) against enveloped viruses like HIV, Influenza, Herpes and non-enveloped food borne viruses Noroviruses, have yet to establish therapeutic levels for human use, making them less practical for realization of their valuable potential. There are a number of naturally found compounds that have been identified against medically important viruses, which together contribute to annual infections of over billion people around the globe, and have been grouped here and summarized in tables. They include the antivirals to human hepatitis viruses (Table 2), viruses causing respiratory infections (Table 3), picornaviruses which cause a number of diseases (Table 4), human herpes viruses (Table 5) and Human Immunodeficiency virus (Table 5). In addition to the medically important viruses included in the tables there are other viruses of pediatric importance viz the Rota virus which causes diarrhea leading to severe dehydration and significant infant deaths also has a natural antiviral that has been identified [4]. With such a wide range of a repertoire of identified antivirals from natural sources like plants, what are the possibilities of how they could find human use? As in the case of Fulvic acid and pomegranate juice, they could be therapeutically used to neutralize pathogenic viruses like HIV, Influenza in human tissues and thus described as the enveloped virus neutralizing compounds (EVNCs). The advantage of such compounds is that they are not susceptible to the vagaries of mutations and drug resistance due to their mode of action, which is not dependent on the changes in amino acid sequence due to mutations [5]. EVNCs could be used in prophylaxis, as vaccine generating agents and maybe even as microbicides. Although microbicides have yet to realize their promise in providing women control over their sexual activity while ensuring that transmission is blocked. Finally, what steps will have to be taken following identification of antiviral activity? Guidelines are summarized in Table 7. The science preceding the translation has to be robust, if not the long path to human use can be costly waste of time and resources. It will be evident from the work in the field of natural antivirals that scientists from China are the leaders in the field and hopefully will continue to receive support to take on the long journey to finding their way into human use. A decade ago, in an editorial, I had envisioned that HIV could be eradicated by 2050 [49]. But amongst the medicines that could achieve that goal, I had an expectation that natural medicine would play a significant role. After reviewing the

Antiviral/Active Ingredient	Source	Antiviral Activity	Reference
Fulvic Acid	Sucrose, Carbohydrate	Enveloped viruses	[2,3,5,6]
Pomegranate Polyphenols, juice	*Punicagranatum* (Pomegranate)	Enveloped viruses, Food borne surrogate viruses	[5,7-10]
Resveratrol+	Red vine leaves, Japanese knotweed	HIV (in comb. With nucleoside analogues) EBV	[11,12]
Ethanol extract	*Warscewicziacoccines* (Vahl) Kl. (Rubiaceae)	HIV and HBV	[13]

Table 1: Broad Spectrum Natural Antivirals against human viruses.

Antiviral/Active Ingredient	Source	Anitiviral Activity	Reference
Sesquiterpenoids and alkaloids	Roots of *Alangiumchinense*	HCV	[14]
Oleanolic acid and ursilic acid	*Fructus LigustriLucidi*	HCV	[15]
Longumosides and amide alkaloids	*Piper Longum*	HBV	[16]
epigallocatechin Lucidone	Green Tea	HBV	[17]
Lectins	*Linderaerythrocarpa*	HCV	[18]
3-hydroxy caruilignan	Red&Blue green algae *Swieteniamacrophylla* stems	HCV HCV	[19,20]
Ladanein (BJ486K), a flavonoid	*Marrubiumperegrinum*	All HCV genotypes	[21]
Hypercin	John's Wort	HCV	[22]

Table 2: Natural Antivirals against human hepatitis viruses.

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Antiviral/Active Ingredient	Source	Antiviral Activity	Reference
Cimifugin Carnosic acid	*Cimicifugafoetida, Rosmarinusofficinalis*	RSV RSV	[23,24]
Polybromocatechol	Rhidophyta, *Neorhodomelaaculeata*	Rhinovirus	[25]
Sesquiterpenecoumarins	*Ferula assafoetida*	Influenza	[26]
Herbal marine compound (HESA-A)	Herbal marine	Influenza	[27]
Chalcones	Glycyrrhiza leaflets	Influenza	[28]
Liquid extract	Elderberry	Influenza	[29]
diarylheptanoids	*Alpiniakatsumadai*	Influenza	[30]

Table 3: Natural Antivirals against human respiratory viruses

Antiviral/Active Ingredient	Source	Antiviral Activity	Reference
Diterpenoids, sesquiterpenoids	Roots of *Illicimmajus*	Coxsackie B3	[31]
Sesquiterpenoids and alkaloids	Roots of *Alangiumchinense*	Coxsackie B3	[14]
Polysaccharides	*Azadirachtaindica*	Poliovirus	[32]
Gallic acid	*Woodfordiafruticosa* flowers	Enterovirus 71	[33]
Raoulic acid	*Raouliaaustralia*	Picronaviruses	[34]
Punicagalin		Enterovirus 71	[35]

Table 4: Natural Antivirals against Picornaviruses.

Antiviral/Active Ingredient	Source	Antiviral Activity	Reference
Sulfated galactans	*Cryptopleuraramosa* (red sea weed)	HSV-1 and HSV-2 replication in Vero	[36]
Rhamnogalacturonan	Cell wall Pectin polysaccharides	HCMV cytotoxicity	[37]
Chebulagic acid and punicalagin (Hydrolyzable Tannins)	*Terminaliacebula* Retz (dried fruits)	HSV-1 and HSV-2 entry and spread	[38]
Verbascoside	Lepechinia species	HSV-1 and HSV-2	[39]
Bark extract	*Azardirachtaindica* (Neem)	HSV-1	[39]
Extract	Blackberry	HSV-1	[40]

Table 5: Natural Antivirals against human Herpes viruses.

Antiviral/Active Ingredient	Source	Antiviral Activity	Reference
Griffithsin	*Griffithsia* (Red algae)	HIV clade C in comb. With Tenofovir, maraviroc and enfuviridae)	[41]
Quinoline alkaloids, Theaflavins	*Euodiaroxburghiana*	HIV entry	[42]
Diterpenes, Extract	*Coleus Forskohlii,* Dandelion, *Coleuparvifolius*	HIV replication, RT, HIV integrase	[43,44]
Niruriside	Phyllanthum	HIV REV/RRE inhib.	[45]
Coumarin & xanthone	Calophyllum	HIV RT	[46]
Recombinant MAP 30	Bitter melon	HIV	[47,48]

Table 6: Natural Antivirals against HIV.

progress in just the past 3 year, I am optimistic but the determination to take on the challenges may have to be very strong and the support from their respective countries to the scientists on this frontier has to be absolute and unconditional.

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1.	Test for antiviral activity in a large number of natural sources/extracts in an appropriate cell culture assay.
2.	Determine the highest concentration at which there is no cell toxicity.
3.	Test for reduction of infectious virus counts
4.	Identify the mechanism of action.
5.	Identify the compound/s that has the activity and determine the structure.
6.	Chemically synthesize the compound, determine the structure and test for activity.
7.	Perform safety, efficacy and toxicity assays on the active compound in an experimental animal model
8.	Go through the national regulatory bodies to perform observational and phase 1-4 human trials

Table 7: Steps in potential therapeutic use of natural antivirals against disease causing human viruses.

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