Repurposing Phytochemicals as Anti-HIV Agents

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Abstract

Phytochemicals play crucial role in inhibiting key enzymes involved in HIV-1 replication. Repurposing of phytochemical based anti-HIV drug discovery through cross screening approaches and modern techniques is essential to provide better leads. Anti-HIV leads translated through phytochemicals could overcome current challenges of HIV therapy. Considering the immense potential of phytochemicals, this article summarizes the present status of the research carried out on their anti-HIV activities, with its limitations and future directions to foster drug discovery.

Keywords: HIV; Phytochemical; Anti-HIV; Drug discovery; Screening; Alkaloids; Flavonoids; Terpenoids

Opinion

The HIV epidemic is receding globally with a 38% drop in new infections (UNAIDS, 2014); however, it continues to pose as a major global public health challenge. The goal of an effective vaccine still remains elusive. Anti-retroviral treatment (ART) has increased the life span of people living with HIV (PLHIV) and 14.9 million people globally are receiving ART (WHO, 2015). Even though the mainstream highly active anti-retroviral therapy (HAART) potently suppresses the plasma HIV-1 viral load, it is unable to eradicate HIV completely. Therefore, there is a lifelong requirement for ART which will decrease the morbidity due to drug toxicity and acquisition of resistance [1,2]. Considering this, there is a continuous need to explore safe and efficacious anti-retroviral agents; which is a challenge that needs to be addressed through integrated approaches [3,4]. Azidothymidine (AZT) - a NRTI drug was the first accidental breakthrough in HIV therapy in 1980’s with its origin from cancer research on phytochemicals [5]. Acyclovir, Valacyclovir and various HIV protease inhibitors are subsequent statutory examples following this trend [6,7]. This can be attributed to the fact that the chemical novelty for chemical scaffolds in natural products is 40% higher than any other source [8]. Although natural products are extensively studied for anti-HIV activity, majority of these studies are restricted to preliminary screenings that aren't pursued to the molecular level with allied approaches for substantiated outcomes. Thus, we would like to give particular emphasis on a widened and upgraded exploratory approach for phytochemical research using modernized tools to catalyze drug discovery for HIV and HIV associated co-morbidities.

Phytochemicals and anti-HIV research

A significant number of literary reports suggest that various phytochemicals derived from numerous plant extracts possess anti-HIV activity [9]. Ethnopharmacological screening of medicinal plants has delivered various phytochemicals-biomolecules (alkaloids, flavonoids, polyphenols, triterpenoids, etc.) possessing varied biological properties. A significant number of literary reports suggest that various phytochemicals derived from numerous plant extracts possess anti-HIV activity.

These include the alkaloids (e.g. aromoline, FK-3000) [10], polyphenols (eg. Tanins-gallic acid, ellagic acid, gallotrycinic acids) [11] and triterpenoids (e.g. cucurbitacins, other derivatives) that flank most of the events involved in HIV replication cycle by impairing CD4 and gp-120 binding, synthesis of glycoproteins and inhibition of the enzyme-glycosidases. They act at both, the early stage of HIV life cycle by inhibiting reverse transcriptase and at a later stage by inhibiting cellular fusion and syncytia formation. Hydroxycinnamic acid derivatives (eg. coumarins and its derivatives) form another class of phytochemicals reporting potential inhibition of HIV replication, specifically targeting the HIV reverse transcriptase [12]. Flavonoids are well known for antioxidant properties [13] and these are also potent HIV reverse transcriptase inhibitors [14]. Other
phytochemicals like lectins debilitate virus-cell fusion; lignins interfere with host virus integration and target HIV protease, glycosides, saponins and xanthones act at reverse transcription and proteolytic post translational steps depicting anti-HIV activity [15]. A brief overview of the phytochemicals that possess anti-HIV activity, pinpointing the various stages of HIV life cycle has been given in graphical presentation (Figure 1).

Perusal of the literature reveals that some naturally derived phytochemical leads such as betulinic acid (PA-457) – also known as bevimat, calanolides, crotelmer (CAS 148465-45-6), DCX (PA-334B), 3,5-di-O-caffeoylquinic acid, MX-3253, 4-methylumbelliferone and setarud (IMOD™) have shown preclinical therapeutic efficacies [16,17] and have reached to different phases of clinical trials as promising anti-HIV agents.

Future direction for phytochemical research and perspectives

Phytochemicals have been a rich source of compounds for drug leads. Even though more than 4,000 phytochemicals have been cataloged and classified based on the protective function and physico-chemical characteristics, only few have been explored so far. However in part, the reasons behind their limited use are restricted to boundary barriers and lack of insistence. Indigenous efforts are needed to access the natural biodiversity beyond the geographical boundaries and thorough perseverance of the reported studies with innovative technical advances is essential. Consistent with the other researchers, we opine that drug discovery from new natural sources needs more attention and exploration with a different view point. Furthermore, for enhanced implications, researchers’ need to undertake evaluations and characterization of plants and plant constituents against disease based age old traditional claims arising from alternative medicine practitioners, with legitimate clinical findings. A systematic synchronization of the experience gathered in ethnopharmacology with authentic, high quality data existing in the natural product libraries may refine natural product screening approaches.

Nevertheless, appropriate biological target selection plays a crucial role in drug discovery. Screening physiological processes like macro and micro virus interactions that include glycosylation sites; antisense oligonucleotides or ribozymes targeting viral mRNAs; gene therapy approaches; immunotherapy; and so on needs to be counter fretted. Research on poorly understood antiviral potencies and modes-of-actions of various phytochemicals needs to be exploited for newer molecules. Cross screening approaches harnessing both ‘serendipitous’ screening strategies and rational drug design, as exemplified in the case of Zidovudine; Acyclovir, Valacyclovir and the HIV protease inhibitors needs to be strengthened with the medicinal chemists and biomedical researchers for new drugs from the phytochemical category [6,7,18].

With the emerging novel technologies, the existing natural products drug discovery platforms for phytochemical screenings warrant up gradations with the biology-oriented synthesis, activity profiling of extracts–structure activity relationship and integration of in silico approaches. Additional reformations about incorporating pharmaceutical properties–pharmacodynamics, pharmacokinetics studies, screening against additional viruses, which are less preferred over HIV-1 primary/lab adapted strains (eg. HIV-1 drug-resistant, HIV-2); use of new in silico approaches such as SELEX (US FDA guidelines) [19,20], receptor dependent QSAR (RD-QSAR) too needs attention. Up gradations of the in vitro assay platforms with additional holistic assays that tap the accessory genes of HIV (rev, protease and tat), is the current necessity [21]. Refurbishing the existing bioassays with in vivo system, the use of humanized mice and bio imaging need to be strengthened and applied to preclinical HIV drug research along with ADME (absorption, distribution, metabolism, and elimination) profiles [22]. Phytochemicals offer an exciting potential for anti-HIV drug discovery, provided the technical mechanistic hindrances are overcome with improvements. Phytochemicals that have served as an important source of drugs in the past should not be overlooked in the 21st century. We conclude the article with the sense of optimism that with the tools available with the advent of technology when explored could lead to path-breaking drug discovery from phytochemicals in the field of HIV research.

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Competing Interests

The author(s) declare that they have no competing interests.

References