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Phytochemicals May Arrest HIV-1 Progression

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The application of current antiretroviral chemotherapeutics such as antiHIV-1 RT drugs (nucleoside, nucleotide and non-nucleotide reverse transcriptase inhibitors) as well as antiproteases including those used in combinatorial therapy such as highly active antiretroviral; (HAART) has caused significant reduction in the rate of mortality of HIV-1 infected individuals. It has allowed sufficient rise in CD4+ve lymphocyte counts into the HIV-1 infected individuals and imparted relatively longer and healthier lives. Recent reports, however, have indicated that application of plant based principles may prove to be highly useful, affordable and efficient in order to arrest the HIV-1 progression. It may be accelerative in transition from development to usage. Also, the toxicity issues may be easily managed while treating AIDS patients with herbal preparations as these plant-ingredients are suitably metabolized and excreted out of body without much accumulation in human organs. Certain plant extracts such as green tea containing ((-)-Epigallocatechin-3-gallate (EGCG)), Brazil nut and Caocao containing immunopotentiators, grapes and red wine containing plenty of antioxidants which mimic oxidative stress induced by intake of antiHIV-1 regimen, Punica granatum (pomegranate) and several others have been recently shown to possess properties of intervention in HIV-1 proliferation [1].

The aqueous and ethanolic extracts of Phyllanthus amarus exhibits potential to inhibit the replication of even antiHIV-1 drug resistant variants in different ways viz., by blocking the interaction of gp120 with its primary cellular receptor CD4 as well as inhibition of activities of HIV-1 integrase, reverse transcriptase and protease enzymes (Frank et al., 2004). The ethanol extract of Nelumbo nucifera Gaertn. (Kamal) [2] as well as Pine Cone extract from Pinus yunnanensis [3] have been shown to contain some molecules which in isolation or in combination display strong antiHIV-1 activity. There are also sporadic reports that medicinal herbs can act as phytochemical therapy in the control of AIDS [4, 5]. It has been suggested by some workers that the bioactive compounds in the medicinal herbs work in coordination rather than in tandem in the restoration of the health of AIDS patients. Their mechanism of action, however, may vary to certain degrees [4,5]. This article presents a current account of reports available on phytochemicals isolated from various parts of different plant species which exhibit strong capability to block HIV-1 activity. These molecules possess immense possibility to be developed as potential antiHIV-1 chemotherapeutics in future.

Human immunodeficiency virus (HIV) is a lentivirus (a member of the retrovirus family) that causes Acquired Immunodeficiency Syndrome (AIDS), a condition in humans in which the immune system begins to fail, inviting various life-threatening opportunistic infections [6,7]. When HIV enters the human body, its target is a subset of T-lymphocyte immune cells that contain CD4 receptors [5].

All the antiHIV-1 drugs available to date to treat AIDS patients target HIV-1 reverse transcriptase (RT) and protease (PR). HIV-1 RT is responsible to catalyse the synthesis of complementary double stranded DNA (cDNA) which is later integrated into the human genome. HIV-1 protease (HIV-1 PR), on the other hand, catalyses the cleavage of the polyprotein chain synthesized on the viral transcript into specific viral components leading to maturation of the virus. HIV remains uninfectious because its work [8]. HIV-1 PR thus acts a promising target for therapy of the HIV infection. Unless the HIV life cycle is interrupted by specific treatment, the virus infection spreads rapidly throughout the body, which results in the weakness and destruction of the body's immune system [9].

Treatment of HIV/AIDS is limited due to unavailability and high costs of antiretroviral drugs (ARVs) together with limited infrastructure for monitoring of HIV/AIDS patients. Other factors adversely affecting the

treatment include rapidly emerging drug resistance and toxicity [10], which has always been a challenge to physicians for chemotherapy. The involvement of host cellular factors in viral progression makes the situation more complex [11]. To overcome these issues to the greater extent, the quest for new, effective and safe as well as affordable anti-HIV agents is a necessity [12]. Some alternative and complimentary medicines are being explored worldwide. Phytomedicines have shown great promise in the treatment of infectious diseases including AIDS-related opportunistic infections [13]. The pool of existing information indicate that the majority of traditional healers in Eastern, Southern and Western Africa use Combretaceae species for treatment of several medical conditions include respiratory diseases, sex-linked diseases, cancer, gastrointestinal and stress related disorders, parasitic, zoonotic and viral diseases including HIV-1 infections etc. [14-17].

Plants of the Combretum and Terminalia genera constitute majority of the Combretaceae family that are widely represented in Tanzania. At least 55 and 17 species of Combretum and Terminalia, respectively, are reported to be growing in Tanzania ranging from climbers, shrubs and big trees [18]. Most of these species are also found in other parts of tropical and warm temperate regions of the world [16,18]. Combretum adenogonium Steud. Ex A. Rich (Combretaceae) (syn: Combretum fragrans F. Hoffm or Combretum ghasalense Engl. & Diels) is a shrub or a small tree which grows up to 10-12 m high [18,19]. In various parts of Africa, the plant is used for treatment of several clinical conditions such as leprosy, cough and syphilis, snakebite, aphrodisiac, diarrhea, new and chronic wounds, malaria and even septic wounds and fungal infection of the scalp [20, 21]. Root, leaf and stem bark extracts of this plant have been investigated and established as having antifungal [22-24], antibacterial [25] and antiproliferative (Fyhrquist et al., 2006) [20] properties. Stem bark of C. adenogonium have shown to exhibit significant Clostridium chauvoei neuraminidase enzyme inhibitory activity [26]. Previous phytochemical analyses have shown that, extracts of stem barks, root and leaves of C. adenogonium contain flavonoids, tannins and few saponins [22, 27]. Furthermore, chemical analyses have shown that two phytosterols (β-sitosterol and stigmasterol) were isolated from the stem bark of C. adenogonium [28]. The extracts of C. adenogonium were found to contain antibacterial and anti HIV-1 protease activities but these extracts also exhibit some cytotoxic properties. After removing the cytotoxic constituents, these preparations may be used in managing HIV and AIDS-related opportunistic infections [29,30].

Aqueous ethanolic extracts of root and stem bark of C. adenogonium have exhibited moderate anti-HIV-1 protease inhibitory activity with IC50 value in higher µg range as compared to that of the acetyl pepstatin, a positive control, with an IC50 value of 2.2 µg/ml [24]. The anti-HIV-1 activity of C. adenogonium and its use in managing HIV/AIDS diseases is well supported by other species of Combretaceae [20, 24, 29, 30, 31].

It is important to note that a number of promising anti-HIV natural products have made it to the clinical level and are anticipated to be available to patients very soon [12]. The following natural products can be cited as promising anti-HIV agents of plant origin: baicalin (a flavonoid) [32] , calanolides (coumarins) [32], betulinic acid (a triterpene) [33,34], polycitone A (an alkaloid) [35], lithospermic acid, sulphated polysaccharides, cyanovirin-N [36], pokeweed antiviral protein [37] and alpha-trichobitacin (proteins). Phytochemical screening of the extracts indicated presence of flavonoids, terpenoids, alkaloids, tannins, glycosides and saponins [38].

Punica granatum (pomegranate) juice can act as an HIV -1 entry inhibitor. Neurath and coworkers (2005) [39] screened the fruit juices for their inhibitory activity against HIV-1 IIIB using CD4 as cell-receptor and CXCR4/CCR5 as cell co-receptors and reported that the juice of pomegranates contain the constituents with potential to inhibit HIV-1 progression by blocking its entry into the CD4+ve lymphocytes. The inhibitory property of this preparation was also found for infection by primary virus clades A to G and group O. This fruit juice also exhibits significant microbicidal properties; which is expected to block the cell to cell transmission of viruses. Their results indicated the possibility of producing a safe and cost effective anti-HIV-1 microbicide from pomegranate in future. They have proposed the mechanism of inhibition via arresting the docking process between the primary virus clades and the corresponding lymphocytes [39].

The green tea constituents have potential to block HIV-1 progression. Zhang et al (2012) [40] have investigated the effects of ((-)-Epigallocatechin-3-gallate (EGCG)), a chemical component isolated from green tea on Tat-induced HIV-1 transactivation and reported that EGCG inhibited activation of NF-κB pathway. EGCG inhibited Tat-induced long terminal repeat (LTR) transactivation process in a dose-dependent manner. Nrf2 signaling pathway may be the primary target for prevention of Tat-induced HIV-1 transactivation by EGCG [40]. Similarly, the potent anti-HIV activities and mechanisms of action of a pine cone extract from Pinus yunnanensis has also been proposed by other workers [41].

The Anti-HIV and immunomodulation activities of cacao mass lignin-carbohydrate complex have been displayed. Cacao mass LCC and LPS may synergistically stimulate iNOS protein expression, suggesting a different point of action. Cacao mass LCC induces tumour necrosis factor-

α production markedly less than LPS, and does not induce interleukin-1β, interferon-α or interferon-γ. ESR spectroscopy showed that cacao mass LCC, but not LPS, scavenged NO produced from NOC-7 [42]. Further, the skin and seed of grapes, berries, peanuts and red wine containing resveratrol, a polyphenolic plant-derived antioxidant, indicated that this molecule protected the AZT induced concentration-dependent cell death [43]. The AZT-induced cell death has been reported to involve both caspase-3 and -7 and poly(ADP-ribose) polymerase activation, coupled with increased mitochondrial ROS generation in human cardiomyocytes [44, 45].

The limited information available as mentioned above indicates that there is lot of potential in the natural products isolated from certain medicinal plants to use against HIV-1 infected individuals, which could be cost effective, safe and easily accessible to the AIDS patients. However, still more efforts are required to be made by researchers in this direction to find out a reliable natural product for AIDS treatment, though it can not be presumed anything now on the issue that the application of natural products would be able to block the progression of wild type and drug resistance virions without inducing another drug-resistance variants by way of generating new mutations.

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