

**Review Article**

Oxidative Role of HIV/AIDS: Antiretroviral Drugs and Medicinal Plants with Anti-HIV Activity

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Abstract: More than three decades after its outbreak, the Acquired Immune Deficiency Syndrome (AIDS) remains a great mystery because there is neither an existing vaccine against its causative agent (the human immune deficiency virus) nor a cure against it. Worst of all is the popular attention that is tuned to the AIDS virus, ignoring oxidative stress which is the major cause of mortality in HIV/AIDS as in many other chronic diseases. Antiretroviral drugs introduced in 1996 have been shown to increase oxidative stress among other drug-related complications. With these backdrops, an antioxidant therapy is necessary to accompany antiretroviral treatment without which its beneficial effects are null. The present review aims to discuss the Oxidative Role of HIV/AIDS and antiretroviral drugs as well as some plants that have recently been revealed to be rich sources of antioxidants.

Keywords: Oxidative Stress, HIV/AIDS, Antiretroviral Drugs, Anti-HIV Plant Products

1. Introduction

Acquired immunodeficiency syndrome (AIDS) is a disease of the human immune system caused by a pathogen, human immunodeficiency virus (HIV). This leads to the onset of a clinical condition which is characterized by progressive reduction of the efficacy of the immune system. Such individuals become susceptible to opportunistic infections by any pathogen. The transmission of HIV has been found through direct contact of a mucous membrane or the bloodstream of one person with a bodily fluid containing HIV from other person. The bodily fluids may include blood, semen, vaginal fluid, pre-seminal fluid, and breast milk. This mode of transmission of HIV-1 may involve sex (vaginal, anal, or oral) between a healthy and an HIV-1 infected partners, HIV-1 contaminated blood transfusion, contaminated hypodermic needles, exchange between HIV-1+ve mother and the child during pregnancy (mother to child transmission, MTCT), childbirth, breastfeeding or other exposure to one of the above bodily fluids [1]. The

acquisition of HIV infection and development of remedies against AIDS are some of the most daunting challenges of the 21st century. In its 2007 reports, the Joint United Nations Programme on HIV/AIDS estimated that over 6800 persons become infected with HIV and over 5700 persons die from AIDS every day [2]. According to World Health Organization (WHO) and UNAIDS, India harbors the world's third-largest population suffering from HIV/AIDS, the number being 5.5 million as estimated in 2005. Due to availability and application of antiretroviral (ARV) drugs, awareness about HIV/AIDS and systematic measures taken by the Government, it took 10 years to get this number reduced to half (less than 2.5 million) as per an estimate made by these agencies during 2007. Possibly, the major contributor to the significant reduction in the number of HIV-1 infected individuals in India could be the introduction of highly active antiretroviral therapy (HAART) regimens in 1996. HAART has been reported to cause a 50% decline in AIDS mortality by decreasing rates of MTCT, opportunistic infections and the incidences of HIV-associated dementia

[3-6]. The present review aims to discuss the Oxidative Role of HIV/AIDS and antiretroviral drugs as well as some plants that have recently been revealed to be rich sources of antioxidants.

2. Oxidative Stress

The human body is made up of various defense systems among which is the antioxidant defense system. This system is made of substances of both endogenous (enzymes and intracellular molecules like glutathione) and exogenous (vitamins, micronutrients and phytochemicals) origins. These substances are characterized by their ability to delay or inhibit the destruction of cellular components by free radicals, paramagnetic substances with which they are in equilibrium under healthy conditions. In pathological situations, the antioxidant capacity of cells to scavenge the excess production of reactive oxygen species falls short, leading to the overwhelming of the balance between reactive oxygen species (ROS) and the antioxidant system in favor of the reactive oxygen species in a condition known as oxidative stress [10, 11, 12]. This situation is the consequence of excessive metabolism occurring inside the host system [13, 14].

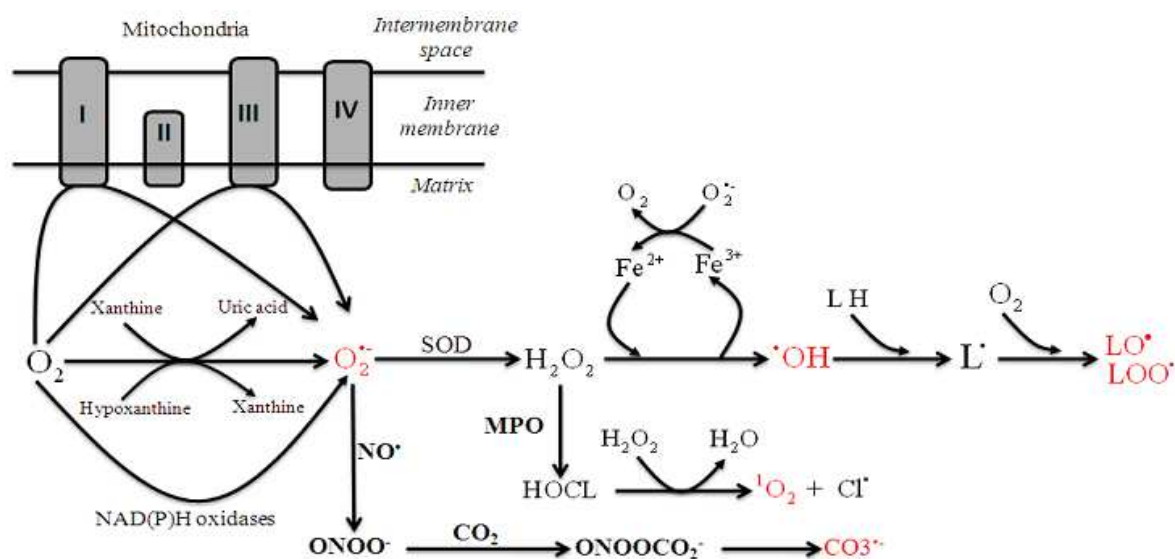


Figure 1. Different routes of production of free radicals [19, 20].

2.3. Free Radicals in Normal Physiology

In moderate concentration, free radicals are indispensable to a wide spectrum of biological processes [21]. In most enzymatic reactions, catalysis involves electron transfer and so, the catalytic cycle passes through free radical intermediates [15]. A remarkable area of free radical use is in the defense mechanism of monocytes (macrophages and neutrophils) during immune response to pathogens. Following infection, monocytes (macrophages and neutrophils) generate ROS [15, 19]. At rest, neutrophils for example consume very little oxygen during glycolysis; however, this oxygen

2.1. Free Radicals

Free radicals are paramagnetic molecular species with one or more unpaired electrons in their outermost shell [15, 16] and are important intermediates in natural processes involving cytotoxicity, control of vascular tone, and neurotransmission [17]. This electronic imbalance makes them highly unstable and as a result, they tend to abstract an electron from nearby molecules to attain some stability [15]. The three major reactive oxygen species that are of physiological significance are superoxide anion, hydroxyl radical, and hydrogen peroxide [10].

2.2. Origins of Free Radicals

Free radicals are usually from various sources, that may be endogenous (e.g. O_2^- , H_2O_2 , OH^\bullet , NO , $HOCl$ etc.), or present in the environment (e.g. RNOS in cigarette smoke) [14, 18]. Endogenous free radicals originate from metabolic processes, stressful events and ageing, while pollution, dietary factors (food additives, alcohols, grilled, fried, browned or burned foods, hydrogenated vegetable oils, etc.), toxins (e.g. carbon tetrachloride, paraquat) and drugs (e.g. Adriamycin, bleomycin, chlorpromazine) account for the exogenous sources of free radicals generation [17]. Also, vigorous physical exercise has been found to raise the free radical status of the body [17].

consumption increases too many folds (respiratory burst) during phagocytosis [15, 17, and 14]. With the glycolytic pathway highly provisioned, its terminal products already in excess retro inhibit its key enzymes such that excess of activated glucose is diverted to the hexose monophosphate shunt (HMS) that produces NADPH. NADPH oxidase in the leukocyte membrane reduces excesses of the molecular oxygen to superoxide, which, through the intermediary of hydrogen peroxide, is transformed into hypochlorous acid ($HOCl$), a potential toxin to microbes [15, 17]. Another free radical, nitric oxide (NO) formed from the action of NO synthase on arginine, is highly documented for playing in

signal transduction pathways. On the walls of vascular smooth muscles, covalent modification of adenylate cyclase by NO-binding triggers a series of redox reactions that lead to vasodilation [14, 17, and 22]. Besides, most non-adrenergic non-cholinergic (NANC) neurons are activated in the same way as vascular smooth muscles [22].

2.4. Oxidative Stress and Cellular Death

Several pathological conditions have been revealed to be the consequence of oxidative stress, which is secondary to infections and life styles of individuals. Cellular death or apoptosis is a normal phenomenon that enables the elimination of worn out cells and tissues. However, under conditions of oxidative stress, cellular death no longer follows the natural principles and so there results an imbalance between the rate of cells death and replacement. This results in wasting and a number of age-related diseases such as Alzheimer disease, Parkinson disease and AIDS. Much research work has documented the mechanism of this induced apoptosis on three major biological molecules: DNA, proteins and lipids. For the membrane lipids, the hydroxyl radical initiates chain reactions at the level of polyunsaturated fatty acids by first abstracting a hydrogen atom from the side chain of a polyunsaturated fatty acid [23]. The chain reactions lead to the formation of lipid free radicals and peroxides, which invariably damages the molecular structure of membrane lipids, including those of the defense cells [14]. The membrane thus loses its regulatory functions, leading to uncontrollable influx and efflux of various substances and consequently cell death. In proteins, hydroxyl radical attack on nucleophile centers on the side chains of such amino acids as proline, histidine, cysteine, etc. can be deleterious. The products of oxidative damage may fragment, increasing the susceptibility of the protein to digestion; they may cross-link with one another and produce aggregates that are resistant to digestion [14]. When this happens to membrane proteins for example, they lose their physiological functions in signal transduction with significant consequences to the cell. For the DNA molecule, free radical attacks have been shown to be at the origin of base alterations and strand breaks, leading to various cancers and mutations.

3. Human Immune Deficiency Virus/Acquired Immune Deficiency Syndrome (HIV/AIDS)

3.1. History of HIV/AIDS

The history of HIV/AIDS dates back to the late 70s when an unusual type of cancer (Kaposi sarcoma) was noticed on the skins of homosexual men and injection drug users (IDU). In 1981, this new syndrome was termed 'AIDS' with its etiologic agent (HIV) identified a couple of years later (1983) [1]. The infection rate increased by 14% between the years 1997 and 2001, with the number of new cases having decreased among

homosexual men and IDUs while increasing among heterosexuals [1].

3.2. Oxidative Role of the Human Immunodeficiency Virus (HIV): Role of Viral Tat Protein

There is enough evidence today in support of the claim that HIV-infected persons are exposed to serious threats of oxidative stress. Oxidative stress is enhanced by chronic inflammation (characteristic to chronic diseases) that is associated with activation of lymphocytes and phagocytes, and is accompanied by the direct or indirect effects of several opportunistic pathogens [24]. In HIV infection, the viral Trans activator (tat) proteins in association with the direct activities of viral particles contribute in increasing oxidative stress.

The Trans activator gene (Tat) is one of the 9 genes (gag, pol, env, tat, rev, vif, vpr, vif, and nef) contained in the viral genome which encodes for approximately 15 viral proteins, each with a particular target [24]. The tat protein, coded by the tat gene is known to be responsible increased viral transcription and this could be through the activation of immature T-lymphocytes into host cells suitable for viral infection [24, 25]. Among the host cells produced are macrophages and neutrophils. These cells use reactive oxygen species (ROS) which is a positive modulator of immune activation essential in eradication of viral infection, but also in immune-induced cellular injury [24]. Resting neutrophils use mostly glycolysis and little oxygen for their energy production, but this consumption increases several folds during phagocytosis, during which more glucose is metabolized via the hexose monophosphate shunt [15]. This situation is known as respiratory burst during which NADPH oxidase located in leukocyte cell membrane catalyzes reduction of molecular oxygen to the superoxide anion which, in the presence of superoxide dismutase (SOD) is reduced to hydrogen peroxide (H₂O₂) [15]. In the presence of myeloperoxidase, a lysosomal enzyme present within the phagolysosome, H₂O₂ reacts with chloride ions (Cl⁻) to produce hypochlorous acid (HOCl), a potential bactericidal substance [15]. Increased production of ROS like superoxide anion, hydroxyl radical and H₂O₂ may be in relation to an increased activation of polymorphonuclear leukocytes during viral infection or through the influence of the pro oxidant effects of pro inflammatory cytokines produced by activated macrophages during viral infection [24]. One study reveal that tat protein expression from HIV-1-infected HeLa cells amplified the activity of tumor necrosis factor alpha (TNF- α) responsible for the activation of necrotic factor κ B (NF- κ B) [25]. NF- κ B is found to be implicated in the formation of reactive oxygen intermediates, while suppressing the expression of Manganese-dependent SOD [25]. Also, NF- κ B is bound to kinase inhibitor nuclear factor- κ B (IKB) in the cytoplasm in its active form, but factors like ROS and TNF- α release it from IKB [25-27].

All the above findings reveal that tat in one way or the other disrupts the redox balance in favor of the pro oxidants that activate (NF- κ B), viral transcription and disease progression, thus the need for an antioxidant therapy

3.3. HIV-Induced Oxidative Stress Enhances AIDS

3.3.1. Role of CD4⁺ T-Cell Immunodeficiency

Cellular CD4⁺ T-cell immunodeficiency is the hallmark of HIV infection [24, 25]. This CD4⁺ T-cell depletion is the necessary condition for the development of AIDS. Various factors account for the apoptosis of CD4⁺ T-cells among which, viral proteins, inappropriate secretion of inflammatory cytokines by activated macrophages and toxins produced by opportunistic microorganisms [24].

Having seen the role STAT protein plays in the activation of NF- κ B which is in turn responsible for production of reactive oxygen intermediates as well as the suppression of Mn-dependent SOD, it is beyond reasonable doubt that oxidative imbalance sets in seen the role played by SOD as one of the antioxidant enzymes system.

The role of HIV-induced activated phagocytes in oxidative stress is not only related to reactive oxygen species production but also related to the release of pro oxidant cytokines such as TNF- α and IL-1, which promote iron (Fe) uptake by the monocyte-macrophage system [24]. Iron constitutes one of the microelements of our system, and cognizant of the roles these micronutrients play in our enzyme systems especially antioxidant enzymes, it is certain that their depletion as a consequence of inappropriate phagocytic activities affects the translation of these proteins, leading to oxidative imbalance. Micronutrient depletion is also attributed to viral activities as they fetch from the micronutrient pool of the host system to synthesize viral proteins [28]. The effects of free radicals on biological molecules seen earlier may also concern those of immunological cells. Oxidative stress-induced apoptosis seen earlier could also be responsible for the depletion of CD4 cell count, exposing the system to the opportunistic infections seen in AIDS [29]. In addition, microorganisms that result from these opportunistic infections like all other cells require micronutrients (which come from the host's antioxidant defense system) and the host's energetic reserves to carry out their metabolic processes. The metabolism taking place in the body becomes abnormally elevated as it is now comprised of that of the host cells and pathogens. The toxins produced by these pathogens exert their effects on host cells through free radical attacks. The depletion of the antioxidant defense system, liberation of toxins and increased metabolism enormously raises the free radical status, enhancing wasting and aging. Wasting syndrome experienced by AIDS patients implicates glycolysis, glycogenolysis, lipolysis, proteolysis and negative nitrogen balance. Wasting is seen in various cancers, including AIDS-related cancers and it is worth-mentioning the role of TNF- α in the propagation of these cancers and in the induction of oxidative stress.

3.3.2. Role of Nitric Oxide (NO)

Nitric oxide (NO) is a signal transducer synthesized in the endothelium, macrophages and the brain, by endothelial nitric oxide synthase (eNOS), inducible nitric oxide synthase (iNOS), and neuronal nitric oxide synthase (nNOS) respectively [24]. iNOS expression is induced by oxidative stress and pro inflammatory cytokines especially interferon gamma (IFN- γ), the

main stimulus released from cells infected and destroyed by viruses. IFN- γ is among the primary pro inflammatory mediators induced by NF- κ B. NO is a positive vasomodulator, but in excesses, it may contribute to tissue damage in several inflammatory and infectious diseases [24]. Part of the excess NO produced reacts with superoxide to form peroxynitrite (ONOO⁻), a potent oxidant capable of per oxidizing membrane lipids [24]. This accounts for the dementia, neurological and cardiovascular disorders experienced by HIV/AIDS patients. HIV-associated dementia for example, results from modification of the permeability of blood-brain barrier, argument based on the findings which reveal the deleterious effects of free radicals on biological membranes [30, 31].

3.4. Antiretroviral (ARV) Drugs: Antiretroviral Classes, Mechanisms of Action and Toxicity (Contribution to Oxidative Stress)

HIV/AIDS belongs to the class of chronic diseases. A chronic disease is one with no existing immunization and cure, only manageable with regular treatment and follow-up.

AIDS treatment has ever since shifted from mono therapy to bi-therapy and then to tri-therapy currently instituted in most countries. Early, following its discovery, AIDS treatment involved a single drug therapy based on zidovudine (AZT), the first antiretroviral drug introduced in 1987. The toxicity of this drug, coupled with the development of drug-resistant strains of the AIDS virus over the years encouraged much research which culminated in the current adoption of 'combination antiretroviral therapy' (cART), also known as 'highly active antiretroviral therapy' (HAART), introduced in 1996 [7]. The HAART (cART) is defined as treatment with two (2) or more nucleoside reverse transcriptase inhibitors in combination with at least one (1) non-nucleoside reverse transcriptase inhibitor [33, 34], and is often based on triple-drug regimens [35]. Prescription of antiretroviral drugs as combination regimens is based on tolerability, cost, compliance, and reduced viral resistance [36, 37]. Antiretroviral therapy had ever since been recommended when CD4 count is ≤ 200 cells/mm³ due to toxicity but since 2012, prescription is recommended when the CD4 count is ≤ 350 cells/mm³ probably due to the discovery of more less toxic therapeutic regimens. In Cameroon, a combination of nevirapine, stavudine, and lamivudine or lamivudine and zidovudine are usually prescribed, but there is no standard prescription [37]; it depends on the factors listed above and on the health institution concerned. There are currently six classes of compounds employed in the treatment of HIV/AIDS: (1) nucleoside reverse transcriptase inhibitors (NRTIs), (2) nucleotide reverse transcriptase inhibitors (NtRTIs), (3) non-nucleoside reverse transcriptase inhibitors (NNRTIs), (4) protease inhibitors (PIs), (5) fusion inhibitors (FIs), and (6) co-receptor inhibitors (CRIs) and integrase inhibitors (INIs) [36]. However, despite the beneficial effects derived from their combinations, scientific findings reveal that the various classes of antiretroviral show some deleterious effects in their mechanisms of action [36] as follows:

3.4.1. Nucleoside Reverse Transcriptase Inhibitors (NRTIs)

Drugs in this class include zidovudine, didanosine, lamivudine, zalcitabine, emtricitabine, stavudine. They are often associated with NNRTIs and PIs [36]. They inhibit reverse transcription of viral RNA to DNA within the host cell. The NRTIs have to be phosphorylated intracellularly, successively to the 5'-mono-, 5'-di-, and 5'-triphosphate, before they can interact with the HIV reverse transcriptase as an alternative substrate or competitive inhibitors [36]. They thus compete with any of the natural substrates dTTP, dCTP, dATP, dGTP for reverse transcriptase reaction.

Long-term use of these drugs gives rise to a broad spectrum of tissue toxicities (hematologic disorders, myopathy, cardiac toxicity, and hepatotoxicity) [36]. These toxicological effects are said to be related to defective mitochondrial DNA replication secondary to drug-induced inhibition of mitochondrial DNA polymerase gamma (DNA pol- γ) [36, 38].

3.4.2. Nucleotide Reverse Transcriptase Inhibitors (NtRTIs)

They belong to the acyclic nucleoside phosphonates. Important members of this class are tenofovir and adefovir. Members of this class act similarly to the NRTIs through chain termination in competition with dATP, but they need only two (2) phosphorylations to be converted to their active form, since they are already phosphorylated in their parental forms [36]. They are incorporated into DNA via the phosphonate group which makes their excision by exonucleases more difficult than if they were incorporated via the readily cleavable phosphate group [36].

3.4.3. Non-nucleoside Reverse Transcriptase Inhibitors (NNRTIs)

This class is made up of efavirenz, nevirapine, etravirine, and rilpivirine [36]. Unlike NRTIs, they neither require cellular activation nor incorporation into nascent viral DNA [36]. They are non-competitive inhibitors that bind into a hydrophobic 'pocket' in the P66 subunit of HIV-1 reverse transcriptase located close to the NRTI binding site. When NNRTI binds, reverse transcriptase active site is deformed, inhibiting the reaction from occurring. Nevirapine is particularly noted for its hepatotoxic effects through elevated aspartate amino transferase (ASAT), and alanine amino transferase (ALAT) [36].

3.4.4. Protease Inhibitors (PIs)

This group is comprised of a handful of drugs: saquinavir, ritonavir, indinavir, nelfinavir, amprenavir, fosamprenavir, atazanavir, darunavir, tipranavir [36]. These drugs bind viral protease enzyme and prevent cleavage of gag and gag/pol proteins into structural functional proteins and enzymes that are necessary for the formation of new viral particles [36]. One of the reported toxicological effects of PIs is the impairment of glucose metabolism, provoking hyperglycemia and diabetes mellitus [36].

3.4.5. Entry, Fusion and Integrase Inhibitors

Entry and fusion inhibitors prevent viral access to cells by blocking cellular receptors. Enfuvirtide is the currently

used fusion inhibitor. Being a painful sub cutaneous injection, it is rarely used [36]. It is thought of increasing risk of bacterial pneumonia through possible association with hematotoxicity [36].

Integrase strand transfer inhibitors prevent viral DNA from integrating into host DNA. Raltegravir is the first approved drug in this class without any remarkable side effect [36]. The major problem with this drug is the easy development of resistance by virus which may limit its long-term efficiency [36].

3.4.6. Antiretroviral-Induced Oxidative Stress: (Experimental Proof)

Most or all of the above-mentioned pathologies induced by antiretroviral drugs are mediated by free radical damage to cells. Elevated plasma levels of ASAT and ALAT in nevirapine-induced hepatotoxicity is a testimony of liver cells damage due to oxidative stress. Many research findings have shown the contribution of HAART in enhancing oxidative stress. Recent studies reveal that, not only do HAART enhance oxidative stress, but the magnitude of oxidative stress varies with composition of the therapeutic regimen [8, 9, 37], confirming the differential toxicity of the various classes of antiretroviral seen earlier. In one of such studies, plasma CD4 of patients on HAART-1 (zidovudine, lamivudine, nevirapine: 699.63 ± 539.85 lymph/mm³) was significantly ($P < 0.05$) higher than that of patients on HAART-2 (zidovudine, lamivudine, efavirenz: 471.37 ± 276.60 lymph/mm³), with CD4 of both HAART patients significantly different from that of pre-HAART patients (505.53 ± 389.73 lymph/mm³) [8]. The following trends were also observed in their serum malondialdehyde (MDA) and Selenium (Se), important markers of oxidative stress: $MDA (HAART-2) > MDA (HAART-1) > MDA (pre-HAART) > MDA (control)$; $Se (control) > Se (pre-HAART) > Se (HAART-1) > Se (HAART-2)$ [8]. The observed differences between HAART-1 and HAART-2 demonstrate the difference in the toxicity of the two combinations. The observed decrease in serum selenium is an indication of the deprivation of the patients' microelements pool by the HIV and other pathogens (which fetch from the pool to synthesize their proteins and enzymes) from opportunistic infections, and the condition that has been responsible for their proliferation should be oxidative imbalance of the host's system in favor of pro oxidants. Knowing the role selenium among other microelements (zinc, copper, iron, etc.) play in the synthesis of antioxidant enzymes, it is no doubt that their deficiency leads to overwhelming of the antioxidant defense system by pro oxidants, enhancing microbial activities. The higher serum MDA level observed in patients on HAART is an evidence of higher lipid peroxidation in these patients as compared to naïve (pre-HAART) patients and controls. But how this oxidative imbalance comes about can be easily explained. Since the antiretroviral drugs were not designed to discriminate nuclear (their target) from mitochondrial DNA, it is probable that mitochondrial DNA is attacked secondary to their actions. Mitochondrial DNA polymerase gamma (DNA pol- γ) is the enzyme that replicates

and maintains mitochondrial DNA [7]. The proteins encoded by mitochondrial DNA participate in electron transport complexes of oxidative phosphorylation and so, inhibition of γ -DNA results in mitochondrial DNA depletion and altered oxidative phosphorylation, energy deprivation, all of which contribute to accumulation of free radicals [7] due to blockage of key reactions of the electron transport chain [37] especially those of complexes I and III.

4. Medicinal Plants with Anti - HIV Activity

Plants and their products can be utilized as a source of new anti-HIV drugs. Many natural products have been shown to possess anti-HIV activity and some of these are in advanced stage of clinical testing [38].

Table 1. Plant posses anti-HIV activity.

| Plants | Active ingredient | Assay Model | Mechanism |
|-------------------------|--------------------------|--|--|
| Andrographis Paniculata | Leaf extract (Aq.) | MT-4 cell Assay | Inhibition of HIV protease & reverse transcriptase (RT) |
| Areca Catechu | Seed extract procyanidin | - | Inhibition of HIV protease |
| Curcuma Longa | Curcumin | E coli integrase assay, HeLA H ₁₂ | Inhibition of HIV integrase, Tat mediat. transactivation |
| Ceriops decandra | Aqueous Extract | MT-4 cell Assay | Inhibit Virus adsorption |
| Cinnamomun aromiticum | Bark Extract | MT-4 cell Assay | Inhibit virus induced cytopathogenicity |
| Eugenia jambolona | Bark Extract | - | Inhibition of HIV proteise |
| Gossypium herbaceum | Gossypol | In vitro | Inhibit viral replication |
| Glycyrrhiza glabra | Glycyrrhine | OKM-1, MT-4 cells | Inhibition of Giant cell formation, viral absorption |
| Helictus isora | Whole Plant | - | Inhibition of HIV Protease |

5. Conclusion

The pitfalls of antiretroviral drugs in the management of AIDS have stimulated much research in the domain of non-conventional medicine. This has been welcomed by the western biomedicine upon realization of certain advantages it offers especially in supplementing biomedicine in certain situations. Much of AIDS-related research is currently focused on seeking plant products that curb oxidative stress-related deaths, as oxidative stress has been revealed to be the principal cause of mortality in this pandemic as in many other chronic diseases. Many plants have recently been revealed to be rich sources of antioxidants

Authorship Contribution

All authors contributed to the designing, preparation, editing, and final review of the manuscript.

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