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Potentials of nutritional therapy, phytopharmaceuticals and phytomedicine in the prevention and control of Ebola virus in Africa

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Abstract: With more than 15000 people infected with Ebola Virus Disease (EVD) leading to more than 7000 deaths in Liberia, Serra Leone, Guinea, Nigeria and Senegal, Ebola Virus Disease remains one of the most dreaded scourges and concerns in contemporary international health (CIH). We note in this essay, that current intervention strategies for the containment of emerging infectious diseases such as Ebola may remain inadequate unless an integrated health intervention (IHI) strategy is adopted. Focus on vaccine development is, undoubtedly, critical but unlikely soon. Synthetic antiviral therapy (AVT) or antifiloviral therapy (AFT) such as using Zmapp, Favipiravir and Brincindofovir amongst others may remain therapeutically inadequate to contain not only Ebola but future scourges. For one fact, as already observed, Zmapp, TKM-Ebola and Favipiravir are hopeful but clouded with toxicity concerns and like any antibiotic of single molecular base likely to be resisted by the bug over time. In this article, our position is that, the medical approach to confront Ebola should be a multidisciplinary approach with equality. This will mean providing a medical care that protects health care workers, searching for an effective vaccine and antiviral therapy that is cost effective, weaving cultural, environmental and community based approaches to preventing the spread as well as fostering and incorporating nutritional therapy, traditional medicine as an integrative package for infectious diseases control. We attempted to highlight that african nutriceticals and phytomedicine could be useful in the control of infectious diseases such as Ebola through the use of medicinal plants such as Garcinia kola extracts and the exploitation of mushroom extracts such as *Ganoderma lucidum* containing selenium, Iron, zinc, 7-8% crude protein, 26-28% carbohydrates and a range of bioactive protein that can boost the immune system of patients with Ebola virus hemorrhagic fevers. Evidence in grey literature demonstrates profound antiviral activities from extracts of Garcinia kola on a range viruses including Ebola virus. Kolaviron, a class of flavonoids from garcinia kola, have been found with profound antiviral activity while compounds from cordycep mycelium such as beta glucans also reported in Ganoderma lucidum and some mushroom species have profound immune boosting potentials against many viral infections. A computerized data base for these compounds for drug development could be generated for use by pharmaceutical companies. It is concluded that, nutritional therapy, phytopharmaceuticals from medicinal plants, could be used not only as drug leads but could clinically complement current management of Ebola virus diseases in African hospitals.

Keywords: Phytopharmaceuticals, Nutrition, Traditional Medicine, Ebola, Bitter Kola, EVD, Phytoimmunotherapy

1. Introduction

Ebola virus disease (EVD) currently has neither treatment nor a vaccine. Attempts to come up with a treatment using Zmapp and favovir are being used experimentally but with seemly fears of toxicity and response are still slow. An attempt to exploit monoclonal antibodies to for vaccine is

still underway. We hypothesize that plant based immune boosters from tropical medicinal plants could potentially stimulate the immune system and treat Ebola virus disease (Yongabi,2014) Ebola infectious is one of the most devastating and debilitating tropical viral diseases. Although these diseases cause significant morbidity and mortality in humans, no specific vaccine is presently available and socio-economic situations in most EVD endemic areas do not readily permit the use of non WHO recommended therapeutic strategies. Novel therapeutic approaches that could complement or replace the current treatment options are therefore now being sought.

One of the potentially valuable therapeutic strategies currently under consideration in this article is the enhancement of the host immune response through the use of naturally derived compounds from medicinal mushrooms and plants. *Ganoderma lucidum* from Cameroon as well *Cordyceps sinensis*, a highly prized entomopathogenic fungus, is known to non-specifically enhance immunity and resistance against a number of infectious diseases ranging from bacterial, fungal, viral to protozoa and is therefore has been used for treatment of a number of infectious diseases. Similarly, Epigallocatechin gallate, the main active components of *Camella sinensis* (Green Tea), has also been reported to have beneficial effects in a variety of diseases due to its anti-inflammatory, anti-oxidative, anti-proliferative, anti-bacterial, immune modulating and anti-viral effects.

Significant information have been lost already because of the transfer of ancient wisdom by oral tradition and most young people despise this knowledge as western education has not favored it all along. In this article, an understanding of the role traditional medicine and African cultures could play in the treatment and control of Ebola is presented. Attempts will be made to show the validity of existing traditional medicines/recipes using research models and how the need to refine some of the crude medicines into semi or acceptable forms such as capsules or tablets after establishing suitable dosages for the semi crude medicines and having an understanding on their toxicity. These will create a new line of safe and affordable health care products for the treatment, management and prevention of Ebola from ancient knowledge.The need for protective and immune-restorative therapies in the treatment of Ebola and the remarkable biological and pharmacological actions of *Cordyceps sinensis* and Epigallocatechin gallate from these mushrooms and green tea as reported in literature suggest the need to evaluate the protective and therapeutic efficacies. The therapeutic efficacy of Ganoderma sporophore, Garcinia kola, occimum gratissimum from Africa as well as Termitomyces spp, CordySupa, Cordyceps sinensis and Epigallocatechin in the treatment, prevention and co support therapy for the Ebola hemorrhagic fevers.

2. Background Information

Ebola virus Disease (EVD) disease is an emerging human disease caused by infection with *Ebola virus* leads to the development of high fevers and pyrexia with 90% mortality. EVD is devastating and has killed more than 7000 people mostly from Liberia, Serria Leaone, Guinea and Nigeria. The virulence of EVD is so devastating but the need to study in detail the mechanism of pathogenicity is imperative and ongoing at the moment.EVD may also be producing a diffusible cytotoxin and or a neurotoxin with immunomodulatory properties, which may be leading potentially impaired capacity to produce Th1, Th2, and Th17 cytokines in the early stage of the disease. Interestingly, these immunological defects are resolved after antiviral therapy (Phillips et al., 2009), indicating clearly that the virulent factor in EVD infection may be persistence in human hosts by limiting the generation of adaptive cellular immune response. Thus, the ultimate goal of our research paper is not just to provide an apt and concise review of the protective and therapeutic efficacy of Tropical dietary administration of Ganoderma, Termitomyces CordySupa mushroom extracts that may be used to manage Ebola virus disease / infection but an advocacy for its clinical use. This study may help to provide some useful information for administration of these dietary nutriceuticals which can offer protection if administered to Ebola infected patients.

Ganoderma lucidum and Cordyceps sinensis, a macrofungi, has been known to have numerous pharmacological and therapeutic potentials. The main constituent of the extract derived from this fungus comprises of novel polysaccharides, consisting of both 5 and 6 carbon sugars joined together in branching chains by both α- and β-glycosidic bonds (Holliday and Cleaver, 2008). These special polysaccharides are known to exert their biological and pharmacological actions through binding to special receptors on dendritic cells, macrophages, natural killer cells, neutrophils, and lymphocytes; initiating a cascade of events that lead to the expression of heightened cellular immune response and killing of infectious microbial agents (Chen et al, 2005). Recently the effects of *C. sinensis* against Group A streptococcal infection, a lethal skin infection, were studied in mice and the results showed that mycelium extract protected experimental mice by decreasing bacterial growth and dissemination, thereby increasing mouse survival rate. IL-12 and IFN-γ expression and macrophage phagocytic activity also increased after *C. sinensis* treatment (Kuo et al, 2005). In a related study, *C. sinensis* mycelium extract was reported to increase phagocytosis in human monocytic cells and abrogate inhibition of phagocytosis caused by streptococcal pyrogenic serotoxin B by causing cytokine production (Kuo et al 2006, Kuo et al 2007). None of these studies has been conducted on Ebola virus disease. The potential immune enhancement of these extracts could play a critical role in the treatment of Ebola virus infection. Intriguingly, the novel polysaccharides in Cordyceps and Ganoderma known to be potent stimulators of macrophages (Chen et al, 2007), therefore dietary administration of CordySupa, *Cordyceps sinensis* and Epigallocatechin gallate-based supplement as an immunopotentiating agent may result in enhanced cellular

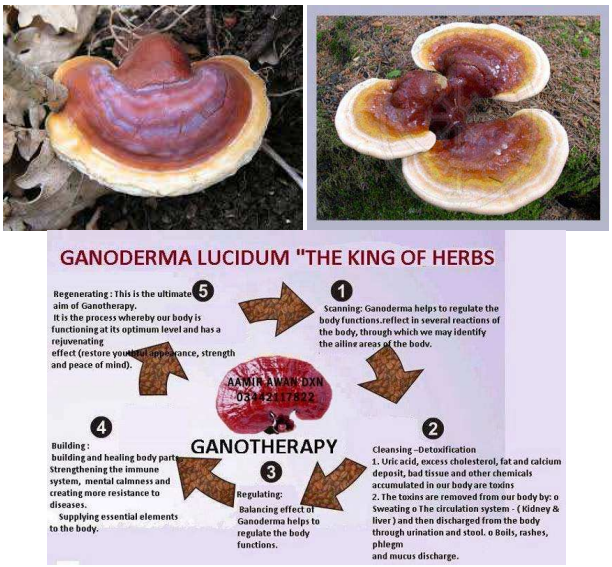
immune response and rapid microbial killing of *Ebola* virus. Besides the above novel polysaccharides, *Cordyceps sinensis and ganoderma lucidum* has been known to contain another novel biologically active compound known as Cordycepin (3′-deoxyadenosine), a nucleoside differing from adenosine by lack of oxygen in the 3′ position of its ribose sugar and Beta glucans from ganoderma. Chen et al (2008) and Holbein et al. (2009) recently reported that during the process of transcription (RNA synthesis), some enzymes (polymerases) are not able to distinguish between adenosine and Cordycepin. This leads to incorporation of 3-deoxyadenosine or Cordycepin, in place of normal nucleoside preventing further incorporation of in-coming nucleosides, leading to premature termination of transcription. Cordycepin therefore is extremely toxic to not just bacteria but virus, and cancerous cells but completely non toxic to normal human cells (Holliday and Cleaver, 2008).

The normal mammalian cells have an inherent repair mechanism that allows for the removal of the wrongly inserted nucleoside from the inserted portion of the RNA/DNA so that a right-full non-modified new nucleoside could be inserted (Holliday and Cleaver, 2008). This special mechanism of action is what has made Cordycepin very effective against a wide range of pathogenic organisms. Cordycepin as naturally occurring compound therefore may play a useful role treating and preventing Ebola hemorrhagic fevers. *Cordyceps sinensis* has also been shown to contain other pharmacologically active compounds such as peptides, steroids, vitamins, essential minerals, amino and fatty acids (Holliday, 2008), which play vital physiological roles in the body. Epigallocatechin gallate (EGCG), the main bioactive compound in C*amellia sinensis* plant just like the above pharmacologically active compounds in Cordyceps sinensis, has been shown to have remarkable antibacterial, antiviral , anti-oxidant, anti-inflammatory and anti-cancer effects (Jeon *et al*., 2014).

Considering the multiple mechanism of actions of the bioactive compounds in Cordyceps sinensis and in addition to the remarkable biological and pharmacological EGCG, it is very likely that active ingredients in Cordyceps sinensis may act synergistically with epigallocatechin-3-gallate from *Camellia sinensis* (Green Tea) to limit the *growth* of Ebola virus if administered perhaps before the viral infection and may therefore serve prophylactic agent in the treatment of and contraction of Ebola infection through enhancement of IL-12 and IFN-γ expression and macrophage phagocytic activity. The administration of CordySupa^{TM} may also abrogate inhibition of phagocytosis caused by mycolactone, enhance the production of nitric oxide (NO) and suppressed the apoptosis of $CD4^+$ T-cells. It will therefore be interesting to monitor serum levels of IFNγ, IL-12, NO and $CD4^+$ T-cells as well as IL-10 in Ebola infected patients undergoing this therapy.

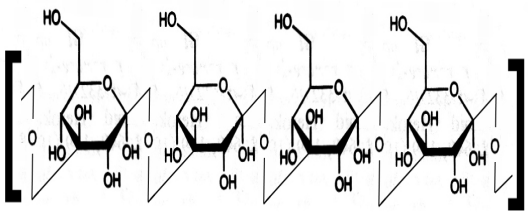
Immune boosting using nutriceuticals are very critical in the management of viral infections. In a study in Cameroon, Yongabi (2010) demonstrated the beneficial effects of using tropical nutriceuticals in boosting the immune system of patients with HIV/AIDS taking highly active antiretroviral drugs. These immuno- stimulatory phytonutrients could play a supportive therapeutic role in the management, treatment and prevention of Ebola hemorrhagic fevers.

Picture 1. *Phytomune, an organic cocktail of extracts from tropical macrofungi and plant seeds containing beta glucans for immune boosting therapy for viral infections. Produced by the Phytobiotechnology Research Foundation labs, Cameroon*

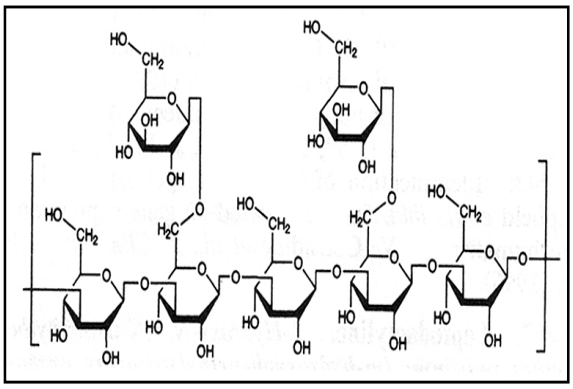


Picture 2. *Ganoderma lucidum extracts contain B glucans that are immune stimulants for the treatment of many viral infections*

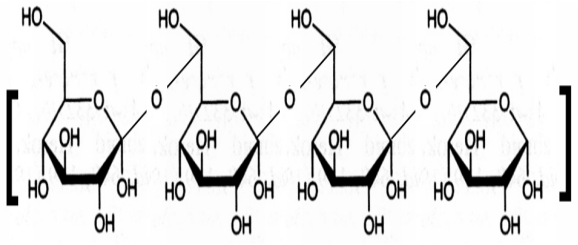
Picture 3. *Cordycep sinensis, another mushroom containing amongst others, Beta glucans*



Beta Glucans are glucose biopolymers (complex polysaccharides) each type of Beta Glucan has a unique structure in which glucose is linked together in different ways, giving them physical characteristics and bioactivities



Basic 2nd Structural Beta Glucans



1-6 Beta Glucan (Agaricus blazei)

Several lines of evidence show that Beta Glucans have the ability to enhance the non-specific immunity and resistance against viral infections. Boosting the host immune defense mechanism remains the most proven method to treat viral infections.

Apart from immune boosting activities, many tropical plants have been identified with broad spectrum antiviral activities but would need to be demonstrated through in vivo studies as well as appropriate clinical trials (Yongabi et al, 2009; Yongabi, 2014). However, these studies would have to be carried out to demonstrate their efficacies on emerging viral infections such as Ebola and other hemorrhagic fevers.

One of such plants that have shown antiviral activities against a number of viruses including Ebola virus is *Garcinia kola,* commonly called bitter kola. Although controversies in African communities exist as to whether bitter kola is effective and if it can be used potentially as a phytomedicine or phytodisinfectant to manage, treat and prevent Ebola. In this article, attempts to review, vividly, the antiviral evidence of *Garcinia kola* especially are captured. Madubunyi in 1995 in Pharmaceutical Biology, vol.33.No.3, pp232-237 isolated antiviral compounds called Kolanone- polyisoprenyl benzophonone.This study as well as well as earlier studies identified hydroxybiflavanonol with both Bacteriostatic, fungistatic against *Staph aureus, Aspergillus flavus, Candida albicans, Ecoli* respectively.

The antiviral activity of Bitter Kola is not a thesis but no longer a hypothesis. Olatunde Farombi (2011), Drug Metabolism and Toxicology Research Laboratories, Department of Biochemistry, College of Medicine, University of Ibadan, published in "Nuts and Seeds in Health and Disease" reported the antiviral activity of Garcinia kola. The study uphold that bitter kola contains active ingredients for the cure of viral infections. Nigeria based Drug Research and Development firm listed in the National Agency for Food and Drug Administration (NAFDAC), long before EVD became a reality in Nigeria produced a drug made from Bitter Kola – "Garcinia-IHP" from Intercedd Health Products. Analyses of bitter Kola (Garcinia kola) seeds show hepatoprotection. Farombi opined in his article that *Garcinia kola* seed extracts have beneficial effect to life threatening diseases such as anti diabetic, immunodulatory, antiviral, anti-inflammatory and antioxidant.Kolaviron has been identified as the specific antiviral bioflavonoid in bitter kola as suggested by both in vitro and invivo model systems.

Farombi's work (2011) corroboroted Professor Iwu, who's work " Garcinia kola: A new look at an old adaptogenic agent,antiviral efficacy of bitter kola" (16th International Botanical Conference at St Louis, USA also demonstrated antiviral activities of bitter kola. Another Nigerian scientist, Maurice Iwu a senior research associate at the therapeutics dep't of Walter Reed Army Institute of Research Washington DC, stated that Garcinia kola edible seed show remarkable antiviral activity against Punta Toro, Pichinde,Sandfly fever, Influenza, Venezuelan Equine Encephalomyelitis , Ebola and common cold

The Botanical Society of Nigeria in Abuja maintains that kolaviron from Biter Kola remains the only known fruit to contain active chemical compounds that could tackle Ebola virus Disease (EVD) and also noted that bioflavonoids are unique to Garcinia genus. What lends Garcinia kola to closer study for its potential value against Ebola, however, not only antiviral but remarkable immune boosting and antioxidant property, ability to inhibit kinases and several signaling pathways

Picture 4. *Garcinia kola Garcinia kola fruit and leaves*

In the light of the current EVD outbreak, sourcing for

traditional medicine could be a useful guide toward potential drug leads for developing potent pharmaceutical for the treatment of Ebola disease. Plants are already playing a role in the current drug development as seen with Zmapp. For instance, expression of an immunogenic Ebola immune complex is being done in *Nicotiana benthamiana,* the tobacco plant. A geminiviral replicon system was used to produce an Ebola immune complex (EIC) in *Nicotiana benthamiana*. Ebola glycoprotein (GP1) was fused at the C-terminus of the heavy chain of humanized 6D8 IgG monoclonal antibody, which specifically binds to a linear epitope on GP1. Co-expression of the GP1-heavy chain fusion and the 6D8 light chain using a geminiviral vector in leaves of *Nicotiana benthamiana* produced assembled immunoglobulin, which was purified by ammonium sulfate precipitation and protein G affinity chromatography. Immune complex formation was confirmed by assays to show that the recombinant protein bound the complement factor C1q (Plant Biotechnol J. Sep 2011; 9(7): 807–816, Feb 1, 2011. doi: 10.1111/j.1467-7652.2011.00593.x

There is no doubt that plants may provide useful insights in to drug development for Ebola, but may also be useful in the development of phytovaccines for EVD. The World Health Organization has actually acknowledge plants as a Source for synthetic drug with Aspirin,opiates,emetic Digitalis to stimulate heart muscle, Quinine for malaria, as well as more than 119 distinctive chemical substances which are as good as orthodox drugs. Some phytochemicals for treatment of a number of ailments already exist on the market as per the table below.

In conclusion, the need to explore phytomedicine and nutritional therapy for potential drug development as well as potential use as immune boosting nutriceuticals for the treatment, management and prevention of Ebola virus disease should be exploited.

Table 1. *Some phytochemicals for treatment of a number of ailments already exist on the market as per.*

Plant spp	Action	Constituents	Countries
Ancistrocladus korupensis	AntiHIV	Michellamine B	Cameroon, Ghana
Cinchorria succirubra	Antimalarial	Quinine -1st antimalarial	West African Countries
Artemisia annua		Artemisin	
Zinger officinale	Antimalarial		China, Africa
		Gingerol quingerone	
	Spice carminative		Nigeria
Ancistrocladus abbreviates	-	-	-
Rosea Vica Caranthus rosea (Roseperiwinkle)			
	Antileukaemia and Hodgkin	Vincristine, Vinblastine,Triterpenes,	
	Disease	Tannins,Alkaloids	Worldwide
Chrysanthemum cinerarisfolium			Madagascar
		Pyrethrins	
	Insecticides		Ghana, Rwanda,Tanzania,South Africa
Corynanther	Male stimulant	Corynanthidine	Ghana
Pachyceras			
Syringium aromaticum			
	Dental caries	Eugenol terpenoids	East Africa, Madagascar
Pachyceras	Aphrodisiac	Yohimbine	Cameroon
Agavastsalan	Corticosteriods aoral contraceptives	Hecoqenin	Tanzania
Prunus africanus	Aphrodisiac	Steriod-triterpenes n docos anol	Cameroon
Physostigma venenosum	Ophalmia		Calabar (Nigeria) Ivory Coast
		Physostiggimine (esterine)	
Tamarindus	Insecticides	Pectins	Egypt
Rauvolfia vomitoria	Tranquilizer,Antihypertensive	Reserpine, yohimbine	Nigeria,Zaire, Rwanda, Mozambique

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