African potato (*Hypoxis hemerocallidea*): a systematic review of its chemistry, pharmacology and ethno medicinal properties

Celia M. J. Matyanga 1,2*, Gene D. Morse 3, Mazuru Gundidza 4 and Charles F. B. Nhachi 1

**Abstract**

**Background:** African Potato (*hypoxis hemerocallidea*), is used for enhancing immune system in Southern Africa. It is among the plants of intense commercial and scientific interest; hence, the aim of this study was to describe its chemistry and pharmacology.

**Methods:** PubMed, Cochrane Controlled Trials Register (CENTRAL) and Google Scholar were searched independently for relevant literature. The last search occurred in October 2018. Other research material was obtained from Google. The following search terms were used, but not limited to: "African Potato" "hypoxis" "hemerocallidea" "rooperol." Articles that were explaining the chemistry and pharmacology of *hypoxis hemerocallidea* were included.

**Results:** Thirty articles from PubMed, Cochrane and Google Scholar were eligible. Three webpages were included from Google. Results showed that the tuberous rootstock (corm) of African Potato is used traditionally to treat wasting diseases, testicular tumours, insanity, barrenness, impotency, bad dreams, intestinal parasites, urinary infection, cardiac disease and enhancing immunity. The plant contains hypoxoside, which is converted rapidly to a potent antioxidant, rooperol in the gut. The corm contains sterols, sterol glycosides, stanols, terpenoids, saponins, cardiac glycosides, tannins and reducing sugars. A dose of 15 mg/kg/day of hypoxoside is reportedly therapeutic. Preclinical studies of African Potato have shown immunomodulation, antioxidant, antinociceptive, hypoglycaemic, anti-inflammatory, anticonvulsant, antibacterial, uterolytic, antimotility, spasmolytic and anticholinergic effects. The common side effects of African Potato are nausea and vomiting, which subside over time. In vitro, African Potato demonstrated inhibitory effects on CYP1A2, 2C9, 2D6, 3A4, 3A5, CYP19-metabolism and induction of P-glycoprotein. In vivo, it did not alter the pharmacokinetics of efavirenz or lopinavir/ritonavir.

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Background
Medicines from natural sources have increased in popularity over orthodox medicines. Natural plants offer vast chemical diversity, which produce physiological changes in the human body [1]. In 2016, the worldwide annual market for herbal medicines was valued just above US$ 71 billion, and global health debates are focusing on traditional medicines [2]. Traditional medicines were used in historical eras and in populations in Africa, Asia, and Latin America and continue to be used due to cultural beliefs [3]. In the year 2002, severe acute respiratory syndrome (SARS) became a global disease outbreak, first appearing in China [4]. Many emergency measures were taken but there was no effective treatment [5]. The World Health Organization (WHO) reported that traditional medicine played a prominent role in the strategy to eradicate SARS in China. By late July 2003, no new cases were being reported [4].

Eighty percent of Africans use some form of traditional medicine [3] and the highest prevalence is among people living with HIV/AIDS (PLWHA) [6, 7]. African Potato is one of the medicinal plants used for the management of human immunodeficiency virus (HIV) symptoms in Southern Africa. Its use in Africa is widespread and it is among the medicinal plants of intense commercial and scientific interest [8, 9].

African Potato, scientifically known as hypoxis hemerocallidea syn. Hypoxis rooperi belongs to the Hypoxidaceae family. Other common names include star lily, magic muthi or yellow stars [9]. The plant grows in the wild and is most prevalent in Southern Africa (mainly South Africa, Lesotho, Mozambique, and Zimbabwe). It is also found further into East Africa. The African Potato plant is easily identified by its star-shaped bright yellow flowers and green strap-like leaves. The tuberous rootstock (corm) is traditionally used to treat a wide variety of ailments. Extracts of the corm are used to make decoctions, which are taken as tonics against wasting diseases, tuberculosis, testicular tumors, other cancers, and HIV/acquired immunodeficiency syndrome (AIDS) [10]. Traditionally, African Potato was used for insanity, barrenness, bad dreams, intestinal parasites, urinary infection and cardiac diseases among other diseases [11]. Nowadays it is used to increase immune function, for headache, dizziness, prostate hypertrophy, burns, and ulcers [10].

Albrecht, who thoroughly researched on African Potato, administered a methanolic extract of H. hemerocallidea to patients with HIV over 2 years in the mid-1990s. He reported that the CD4+ lymphocyte counts in these patients remained stable, while the serum p24 HIV antigen decreased and there was a decrease in expression of the HLA-DR CD8+ lymphocyte activation marker [12]. The HLA-DR CD8+ is used for identification of T lymphocytes and elevated levels are observed in HIV infection [13]. Albrecht concluded: “these studies have demonstrated that rooperol has potent, diverse and important pharmacological properties relevant to cancer, inflammation and HIV” [12].

The aim of this paper is to describe the chemistry, pharmacology and clinical properties of African Potato. Other objectives include identifying research areas for further study of the plant due to its widespread scientific interest. Reviewing the studies conducted on African Potato will reveal areas of further research.

Methods
This systematic review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14]. A detailed literature review was conducted to describe the chemistry, pharmacology, clinical properties and pharmacologic claims made against African Potato.

Identification of articles
The literature search was done using PubMed, Cochrane Controlled Trials Register (CENTRAL) and Google Scholar. These databases were searched independently for relevant literature through October 2018. The search was re-run on 16 May 2019 and no new studies were found. Other research material was obtained from open searches using Google. The following MeSH (Medical Subject Headings) terms and keywords were used, but not limited to: “African Potato” OR “hypoxis” OR “hemerocallidea” OR “rooperol”. An example of the search details in PubMed is given below: “African Potato”[All Fields] OR
“hypoxis”[MeSH Terms] OR “hemerocallidea”[All Fields] OR “rooperol” (Supplementary Concept).

Eligibility criteria
The material that described the chemistry, uses and pharmacology of hypoxis hemerocallidea were included. Other plant species were not included. The “sort by relevance” feature in Google Scholar was used; and where applicable, current articles and websites were selected for discussion. We did not restrict publication date. Clinical trials were included in the search. Table 1 shows the inclusion/exclusion criteria.

Results and discussion
Thirty-three articles were used for data collection. Figure 1 shows the flow diagram for the data collection. The general characteristics of the articles and the data extracted are shown in Table 2.

Pharmacology and chemistry
Hypoxis species have been reported to produce a variety of phytoglycosides; extensive research has been focused on the norglucosidase hypoxoside and its aglycone rooperol. The main glycoside that is isolated from the Hypoxis spp. is hypoxoside [21]. Following oral administration, hypoxoside is metabolized in the gut to rooperol by β-glucosidase. There are two glucose units at the ends of two benzene rings on hypoxoside [10]. These units are oxidized by β-glucosidase to form the aglycone, rooperol. The enzyme β-glucosidase is found mostly in the gastrointestinal tract (GIT) and is released by rapidly dividing cancer cells. Rooperol is the biologically active compound that is associated with claims of medicinal properties [11].

Other constituents in hypoxis include various sterols and their glycosides, and these may have biological importance. H. hemerocallidea contains β-sitosterol (BSS), β-sitosterol glucoside (BSSG), campesterol and stigmasterol [39]. These plant sterols (phytosterols) have biologic roles in animal and human health. Phytosterols are incorporated into functional foods and inhibit the absorption of cholesterol from the diet. They also have prophylactic and therapeutic uses in hypercholesterolemia, cardiovascular disease and atherosclerosis [40].

Among the phytosterols, β-sitosterol and its glycoside have been studied most for their pharmacological effects [41]. In vitro, the combination of BSS and BSSG indicated anti-inflammatory effects mediated by the inhibition of interleukin 6 and tumor necrosis factor secretion. The anti-inflammatory effects of the mixture relieved rheumatoid arthritis in humans. Another small pilot study reported that the BSS/ BSSG mixture resulted in significant improvement in allergic rhinitis/sinusitis after 12 weeks and this was attributed to immunological changes in the cytokine profiles produced by lymphocytes [40]. In vitro, phytosterols can affect different levels of tumor development and they have immune-modulating properties [41]. Phytosterols initiated programmed cell death (apoptosis) in human colon cancer, breast cancer, and prostate cancer. The probable mechanism was the activation of the protein phosphatase A2 pathway and the sphingomyelin cycle [22].

Rat models suggest that phytosterols may offer protection against breast, colon and prostate cancer [39]. In Phase I clinical trials, BSS has proven to be safe [15]. Si-
tosterols are poorly absorbed from the gastrointestinal tract. In humans, oral bioavailability is no more than 5% and it is 9% in dogs [23]. However, with advanced formulation technology many targeted drug delivery systems may provide alternative approaches for compounds with low bioavailability [45]. If successful, targeted delivery systems could aid in the delivery of phytosterols to facilitate clinical trials. An important knowledge gap is the drug interactions that may occur in immunocompromised patients who require many other medications (polypharmacy).

In another study, domestic cats were infected with a model of HIV. Cats treated with phytosterols maintained

Table 1 Inclusion/exclusion criteria

| Criteria                  | Inclusion                                                                                                                                                                                                 | Exclusion                                                                                      |
|---------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------|
| Study design              | Clinical trial, quantitative, qualitative and mixed methods study, systematic/ narrative reviews                                                                                                           | None                                                                                           |
| Population                | All ages, all species                                                                                                                                                                                    | None                                                                                           |
| Location                  | Any country                                                                                                                                                                                              | None                                                                                           |
| Date                      | Studies available up to October 2018.                                                                                                                                                                     | Studies published after October 2018                                                           |
| Language                  | English or translated to English                                                                                                                                                                         | Not translated to English                                                                       |
| Research focus            | Describing the chemistry, uses and pharmacology of African potato (hypoxis genus)                                                                                                                       | Describing other plant species or genus                                                         |
| Document type             | Full text article of research articles, clinical trials, systematic reviews, scientific reports, ethnopharmacological studies, ethnobotanical surveys, commentaries, case reports, conference proceedings. | Full text of document not available                                                              |
stable CD4 cell counts compared to placebo; the mortality between the two groups was significantly different [24]. In humans, an open-label study compared the efficacy of BSS/BSSG with placebo in HIV-infected treatment-naive patients. During the time of the study, antiretroviral treatment (ART) was not affordable to most patients. Within 12 months, patients with > 500 CD4 cells/μl at baseline maintained their CD4 cell count and plasma viral loads were significantly decreased. Those with advanced HIV at baseline (< 200 CD4 cells/μl) still had disease progression. Patients in the BSS/BSSG arm maintained a favorable TH1 response and their cell-mediated immunity was likely to be responsible for their response [20]. These findings concur with clinical trials that were conducted later that early initiation of ART delays the time to AIDS events [46]. In addition, there should be more research on herbs that enhance immune function in immunocompromised individuals to slow the progression of the disease. Again, due to polypharmacy, possible drug-herb interactions should be considered. Phytosterols are associated with faster clinical recovery in pulmonary tuberculosis [16] and possess anti-inflammatory, wound healing, analgesic, anti-helminthic, anti-mutagenic, anti-oxidant, neuroprotective and anti-diabetic properties [41].

There is limited knowledge on other secondary metabolites of hypoxis. As of 17 October 2018, a literature search found one study in Zimbabwe that compared the phytochemical profiles and cytotoxicity of four species of hypoxis. These were *H. hemerocallidea*, *H. rigidula*, *H. galpinii* and *H. obtuse*. Although this study did not quantify the phytochemicals, corm extracts of all four species indicated the presence of terpenoids, saponins, cardiac glycosides, tannins and reducing sugars. All species screened negative for alkaloids, flavonoids, and anthraquinones [1]. In other plant species, these phytochemicals are claimed to have curative activity against several pathogens [47]. The phytochemicals identified in this study can be attributed to the biologic activities of *hypoxis*. Terpenoids have antimicrobial and antioxidant properties and they are explored as cytotoxic and antineoplastic agents [48]. Saponins from plant sources have various pharmacologic effects like antimicrobial, anticancer, anthelmintic, antioxidant, antidiabetic, anticonvulsant, analgesic, antispasmodic, hypocholesterolemic, antitussive and cytotoxic activities.
Cardiac glycosides inhibit the Na⁺/K⁺ pump thus slow the heart rate and increase the contractility of the heart muscle. Although they improve the cardiac output and heart function, their use is associated with toxicity because of a narrow therapeutic index. Tannins have anti-oxidative activities; due to these properties, they are anti-carcinogenic and anti-mutagenic. In addition, tannins have antimicrobial properties, accelerate blood clotting, reduce blood pressure, decrease serum lipid levels and modulate immune responses. Reducing sugars have a regulatory role in plants, controlling their growth and development to provide resistance against diseases.

It is well known that combining several bioactive compounds result in a greater pharmacological response than using the single components. With traditional medicines, isolating the desired phytochemicals and combining them can result in achieving the desired pharmacological response. More laboratory and clinical studies with hypoxis are required in this area of research.

**Table 2: General characteristics of included studies**

| Study number | Study design | Author, year [reference] | Data extracted |
|--------------|--------------|--------------------------|----------------|
| 1. | Clinical trial | Albrecht et al., 1995 [15] | Safety of β-sitosterol; dose and metabolic pathway of hypoxoside |
| 2. | Donald et al., 1997 [16] | Pharmacological effects of phytosterols |
| 3. | Mogatle et al., 2008 [17] | African potato drug interactions |
| 4. | Gwaza et al., 2013 [18] | African potato drug interactions |
| 5. | Berges et al., 1995 [19] | Clinical properties, the dosage of β-sitosterol |
| 6. | Pilot study, open-label intervention | Bouic et al., 2001 [20] | Pharmacological effects of β-sitosterol |
| 7. | Quantitative, experimental | Boukes GJ et al., 2010 [21] | Pharmacology |
| 8. | Awad et al., 2000 [22] | Mechanism of action |
| 9. | Bouic et al., 1996 [23] | Pharmacology and bioavailability of β-sitosterol |
| 10. | Lamprecht et al., 2000 [24] | β-sitosterol and the glucoside mixture improving CD4 count |
| 11. | Albrecht et al., 1995 [25] | Mechanism of action, metabolism and pharmacokinetics of hypoxoside |
| 12. | Kruger et al., 1994 [26] | Metabolism of hypoxoside |
| 13. | Nair et al., 2007, [27] | Metabolism of African potato |
| 14. | Gwaza et al., 2009 [28] | Drug interactions of hypoxis extracts |
| 15–22. | Experimental preclinical (in vivo) | As shown in Table 3 | Pharmacologic activities of Africa Potato in different species |
| 23. | Qualitative screening | Zimudzi C, 2014 [1] | Chemistry |
| 24. | Nair et al., 2006 [37] | Dosage of African potato |
| 25. | Systematic review | Ncube et al, 2013 [38] | Uses of African potato and dosage forms (and strengths) available |
| 26. | Narrative review | Drewes SE et al, 2008 [10] | Chemistry, ethnopharmacological properties |
| 27. | Mills E et al., 2005 [11] | Pharmacology, chemistry, ethnopharmacological properties |
| 28. | Bouic, 2001, [39] | Chemistry and pharmacological uses |
| 29. | Ling et al, 1995 [40] | Pharmacological uses, mechanism of action of phytosterols |
| 30. | Saeidnia et al, 2014 [41] | Pharmacological effects |
| 31. | Not applicable - Website | Natures Health website, [42] | Dosage of African potato capsules |
| 32. | Green Herbs & Nutrition’s Stores website, [43] | Dosage of African potato capsules |
| 33. | Puer Orijins catalogue, [44] | Other dosage forms available |

Cardiac glycosides inhibit the Na⁺/K⁺ pump thus slow the heart rate and increase the contractility of the heart muscle. Although they improve the cardiac output and heart function, their use is associated with toxicity because of a narrow therapeutic index. Tannins have anti-oxidative activities; due to these properties, they are anti-carcinogenic and anti-mutagenic. In addition, tannins have antimicrobial properties, accelerate blood clotting, reduce blood pressure, decrease serum lipid levels and modulate immune responses. Reducing sugars have a regulatory role in plants, controlling their growth and development to provide resistance against diseases.

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**Preclinical pharmacologic activities (Table 3)**

**Absorption and metabolism**

After oral administration, hypoxoside is not absorbed and undergoes enzymatic hydrolysis. In the circulatory system, hypoxoside is converted to rooperol (Fig. 2) by β-glucosidase. Intragastric administration of hypoxoside in mice resulted in deconjugation by bacterial β-glucosidase to form rooperol in the colon. In mice, neither hypoxoside nor rooperol metabolites were detectable in the blood.
Table 3  Preclinical (in vivo) Pharmacologic Activities of Africa Potato in different formulations

| Species                  | Dose and administration                        | Parameters assessed                                                                 | Conclusions                                                                                                                                   | Reference |
|--------------------------|------------------------------------------------|--------------------------------------------------------------------------------------|-----------------------------------------------------------------------------------------------------------------------------------------------|-----------|
| Male rats                | Acute testing: 0.45; 0.90 and 1.8 mg/ kg infusion | Urine volume and total urinary outputs of creatinine, sodium, and potassium.          | Increased plasma creatinine concentration, renal fluid, and electrolyte retention and reduced GFR compared with controls, APE may impair renal function. | [29]      |
|                          | Chronic: APE 30 mg/ kg infusion                   |                                                       |                                                                                                                                             |           |
| Healthy mice             | Corm aqueous extract (100–800 mg/kg i.p.)        | Effect against pentylenetetrazole-, picrotoxin- and bicuculline-induced seizures.    | APE has anticonvulsant activity possibly by enhancing GABAergic neurotransmission and/or action in the brain.                                | [30]      |
|                          | Phenobarbitone and diazepam used as the reference |                                                       |                                                                                                                                             |           |
| Rats and guinea-pigs     | Corm aqueous extract 25–400 mg/ml orally         | Uterine horns isolated from rats and guinea-pigs.                                     | Extract showed uterolytic activity                                                                                                           | [31]      |
|                          |                                                       |                                                       | Inhibited the amplitude and sometimes, the frequency of the spontaneous, rhythmic contractions.                                                |           |
|                          |                                                       |                                                       | Relaxed pregnant uterine muscles.                                                                                                           |           |
|                          |                                                       |                                                       | Mechanism is unknown, probably mediated through a non-specific spasmodytic mechanism.                                                        |           |
|                          |                                                       |                                                       | Extracts to 2.5 g/kg did not produce any toxic manifestations or mortalities.                                                              |           |
| Newborn suckling rats    | African Potato ethanol or aqueous extract (50 mg/kg and a high dose of 200 mg/kg) via a stomach tube | Viscera removed for gross and microscopic morphometric measurements.                 | At a low dose, the mean weight gain was significantly increased.                                                                             | [32]      |
|                          |                                                       |                                                       | The high dose of aqueous extract increased the weight of the caeca.                                                                           |           |
|                          |                                                       |                                                       | The low dose of alcohol extract reduced the pancreas weight.                                                                               |           |
|                          |                                                       |                                                       | No adverse effects, no signs of pathology.                                                                                                   |           |
| Healthy rats and mice    | Corm aqueous extract (APE, 50–400 mg/kg, orally)  | Effect against castor oil-induced diarrhea, entero-pooling, intestinal transit, and intestinal fluid. | APE delayed the onset of copious diarrhea, reduced number, and weight of wet stools, inhibited the severity of diarrhea, inhibited intestinal transit and delayed gastric emptying. | [33]      |
|                          | Atropine and loperamide used as positive controls |                                                       | Speculated mechanism that the sterols, stanols and sterolins, especially rooperol and β-sitosterol are responsible for anti-motility, spasmodytic and anticholinergic effects. |           |
| Healthy mice             | AP methanolic extract (15 mg of extract orally)   | After Brachyspira hyodysenteriae –induced typhlocolitis; weight loss, gross and histological lesions, MPO activity, and intestinal epithelial proliferation were evaluated. | AP extract reduced weight loss, the severity of typhlocolitis, inflammation and intestinal epithelial proliferation.               | [34]      |
| Albino rats              | Aqueous corm decoction (10 ml/kg) and 20 ml/kg orally | Parameters assayed were TBARS, SGOT, SGPT, GSH, ascorbic acid, tocopherol, superoxide dismutase and glutathione peroxidase in RBC and in the liver. | Protection from oxidative stress generated by chloroquine, strengthen the antioxidant system under normal conditions. | [35]      |
| STZ – Induced diabetic male Wistar rats | Aqueous solution (200 mg/kg or 800 mg/kg) administered orally | Oxidative stress biomarkers, hepatic injury, and selected biomarkers in the liver and kidney. | Both dosages showed significant antihyperglycemic effects, both showed antioxidant effects in the liver tissue. | [36]      |

AP African Potato, APE African Potato aqueous extract, i.p. Intraperitoneal, GFR glomerular filtration rate, GSH reduced glutathione, MPO myeloperoxidase, RBC red blood cells, SGOT serum glutamate oxaloacetate transaminase, SGPT serum glutamate pyruvate transaminase, STZ streptozotocin, TBARS thiobarbituric acid reactive substance.
There were only Phase II metabolites of sulphates and glucuronides present in the bile of mice, rats, and dogs [25]. However, in humans and baboons, these metabolites appear in the plasma at relatively high concentrations [26]. The end products of the hydrolysis were rooperol, dehydroxyrooperol and bis-dehydroxyrooperol [15]. The metabolic pathway of African Potato is illustrated in Fig. 3.

The presence of rooperol was analyzed in faeces and urine in humans. After administration of 1 g of hypoxoside, rooperol was present in faeces at 6-h post-dosing. No rooperol was detected in urine after 24 h. Some of the rooperol was absorbed from the colon and some were eliminated in the faeces. The formation and absorption of rooperol was a zero-order saturable process [15].

Drug interaction studies
The effects on cytochrome P450 (CYP) - mediated metabolism of African Potato were studied in vitro using cell lines. The African Potato extracts demonstrated inhibitory effects on CYP3A4-, 3A5- and CYP19-mediated metabolism and high induction of P-glycoprotein (P-gp) as compared to ritonavir, the positive control [27]. Another study evaluated the effect of hypoxis on drug interactions in vitro using human liver microsomes. In methanol extracts, at least 95% inhibitory effects were observed for CYP1A2, 2C9, 3A4 and 2D6 compared to positive controls. Aqueous hypoxis extracts led to moderate CYP inhibition. The extracts of hypoxis indicated no significant inhibition of P-gp although the authors suggested some effect on P-gp was possible at higher concentrations than those used in the assays [28].

These in vitro results served as the foundation for in vivo interaction studies for African Potato. A study conducted in South Africa determined the effect of African Potato on efavirenz pharmacokinetics. Ten healthy volunteers participated in this single-dose, two-phase sequential study over 31 days [17]. Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) effective against HIV-1. It is the backbone of combination antiretroviral therapy (cART) in Africa and is mainly metabolized by CYP2B6 and to a lesser extent CYP3A4 [54]. For the South African study, the following parameters were used to determine interactions: AUC{sub}0–48, C{sub}max, T{sub}max, T{sub}1/2, and K{sub}el. The results indicated that the 90% confidence intervals (CI) for C{sub}max and AUC{sub}0–48 were within the limits of 80–125% interval. Thus, the investigators concluded that the African Potato did not alter efavirenz pharmacokinetics. The investigators recommended that further research is needed to investigate African Potato and other antiretrovirals especially those that are P-gp substrates or CYP3A4 metabolites [17]. Although this study had a clear and concise methodology, the sample size calculations were not well explained, especially considering the intra-individual variability of the AUC and C{sub}max for efavirenz. In addition, single-dose studies do not
consider induction that occurs during chronic dosing.

Another study investigated the effect of African Potato on the steady-state pharmacokinetics of ritonavir-boosted lopinavir (LPV/r). Lopinavir/ritonavir is a potent HIV protease inhibitor combination that is used with other antiretrovirals for the treatment of HIV infection. Lopinavir (LPV) increases ritonavir (RTV) concentrations through inhibition of CYP3A4. LPV is metabolized primarily by hepatic and gastrointestinal CYP3A4. They hypothesized that since in vitro studies indicate that extracts of African Potato have a significant inhibitory effect on CYP3A4 this could lead to an increase in exposure, associated with an increased cholesterol/diabetes risk. This study was an open-label, two-period; fixed sequence, crossover pharmacokinetic drug interaction study. Sixteen healthy, HIV-seronegative adult volunteers between 18 to 60 years were enrolled. The following parameters were used to determine interactions: AUC$_{0-18}$, $C_{\text{max}}$, $C_{\text{trough}}$, $T_{\text{max}}$, $T_{1/2}$, CL$_{F}$ and $K_{el}$. Results indicated that steady-state plasma concentration-time profiles of LPV with and without African Potato were similar as reflected by the 90% confidence intervals that were within the 80–125% limit. The effect on ritonavir was not analyzed in this study. Total cholesterol and triglycerides were elevated but within limits during LPV/r treatment [18]. The investigators concluded that African Potato had no significant effect on the steady-state pharmacokinetics of LPV. This study was well designed although the results cannot be generalized to other populations. It would have been ideal to use participants from Africa, where African Potato use is prevalent. Clinical studies involving African Potato or its constituents are summarized in Table 4.

Both the South African and USA studies were testing African Potato in healthy individuals. Literature reveals that African Potato is widely used for its immune-enhancing properties in HIV infected individuals [11]. Since African Potato has shown to be safe and well tolerated in healthy individuals, further research should focus on people living with HIV/AIDS. It would also be necessary to study the interactions of African Potato in HIV infected individuals taking other antiretroviral drugs.

**Dosage recommendations**

Traditionally, African Potato is cut into cubes or shredded and boiled in water for 20 min before the decoction

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**Fig. 3 Metabolic Pathway of African Potato in Humans [11, 23]**

Hypoxis spp  
main glycoside isolated  

hypoxoside  

β-glucosidase  

rooperol  
Metabolized in liver  
Eliminated in faeces  

Phase II biotransformation  

rooperol  

digluconoride (minor)  

half-life 20 hrs  

rooperol monoglucuronide - monosulphate (major)  

half-life 50 hrs  

First order kinetics  
Eliminated in urine  

mixed rooperol disulphate (minor)  

half-life 20 hrs
is consumed orally. A survey conducted among traditional healers in South Africa was used to calculate the dose of African Potato. An average of about 20 g of freshly shredded African potato boiled in 250 mL of water was prescribed for daily consumption. African potato was mainly prescribed to boost immunity [37].

For the treatment of benign prostatic hyperplasia, African Potato dosed at 20 mg of β-sitosterol three times a
day was found to be therapeutic [19]. According to literature, an oral dose of 15 mg/ kg/ day is reportedly therapeutic [18]; however, it is unknown whether this dose is effective for all the claims against African Potato. Other sources state that 2400 mg taken daily is therapeutic [15]. Standardized capsules are available online which contain from 300 to 350 mg hypoxis hemanroididea. The doses for these formulations vary; some stating one capsule twice daily and some stating two tablets 3 times a day for the first 5 days, then one tablet 3 times a day [42, 43]. In South Africa, herbal formulations of African Potato are mainly used to enhance the immune system. The herbal formulations are available as capsules, tonics, creams and tinctures containing 300–500 mg hypoxis hemanroididea or sterols/ sterolins [38]. With the many claims against the plant, it is unknown if this dose is a standard dose. Besides capsules, other formulations available include powders, face creams, night cream, nasal spray, soap, tissue oil, toner and exfoliator [44]. There is a knowledge gap in the therapeutic dosage for herbal medicines since most of the recommended doses are based on anecdotal information [11]. Furthermore, there is limited research in clinical trials using herbal medicines [55]. This is an area of research that could be explored further, even with African Potato.

Conclusion
African Potato rootstock (corm) is used to treat a wide variety of ailments. It is mainly used as an immunostimulant in people living with HIV/ AIDS. The active components include rooperol, which is an antioxidant and several phytosterols. The mechanisms of action for all the pharmacological actions are unknown. Some of the pharmacological actions were reported in older studies and there is a need for studies to substantiate the claims using current technology and with the application of systems pharmacology. African Potato is of intense commercial and scientific interest and more clinical trials should be performed to evaluate dosage regimens. The plant shows a good safety profile although there are no studies that have demonstrated safety in children, pregnant and lactating women. More research is required to substantiate the many claims that recommend the use of African Potato. There are important research gaps on the possible interactions with conventional drugs, especially those used in HIV/AIDS.

Supplementary information
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Abbreviations
AIDS: Acquired immunodeficiency syndrome; AP: African Potato; APE: African Potato aqueous extract; ART: Antiretroviral treatment; AUC: Area under the concentration-time curve within a dosing interval; BSS: β-sitosterol; BSSG: β-sitosterol glucoside; cART: Combination antiretroviral therapy; Cl\text{\textsubscript{\textit{r}}}: Apparent clearance; C\text{\textsubscript{\text{max}}}: Maximum concentration following dose administration; C\text{\textsubscript{\text{max}}}: Plasma concentration at the end of the dosing interval; CYP: Cytochrome P450; GFR: Glomerular filtration rate; GIT: Gastrointestinal tract; GSH: Reduced glutathione; K\text{\textsubscript{\text{el}}}: Elimination rate constant; HIV: Human immunodeficiency virus; i.p: Intraperitoneal; LPV/r: Ritonavir-boosted lopinavir; LPV: Lopinavir; MFO: Myeloperoxidase; NNRTI: Non-nucleoside reverse transcriptase inhibitor; P-gp: P-glycoprotein; PLWHA: People living with HIV/ AIDS; PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RBC: Red blood cells; RTV: Ritonavir; SARS: Severe acute respiratory syndrome; SGOT: Serum glutamate oxaloacetate transaminase; SGPT: Serum glutamate pyruvate transaminase; ST2: Streptozotocin; TBARS: Thiobarbituric acid reactive substance; T\text{\textsubscript{max}}: Time to reach C\text{\textsubscript{max}}; T1/2: Half-life; WHO: World Health Organization

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Authors’ contributions
CM conceptualized the research and GM, MG and CN approved the topic. CM conducted the literature review and all authors analysed the results of the review. All authors participated in giving feedback on the manuscript. All authors have read and approved the final manuscript.

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Availability of data and materials
All data generated and reviewed during this study was included in this manuscript and in the tables and figures.

Ethics approval and consent to participate
The data used in this review article was obtained from articles and web pages that were already published in scientific journals. The data was cited, therefore, no ethical approval or consent to participate are applicable.

Consent for publication
Not applicable.

Competing interests
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Author details
1Department of Clinical Pharmacology, College of Health Sciences, University of Zimbabwe, Harare, Zimbabwe. 2School of Pharmacy, College of Health Sciences, University of Zimbabwe, Harare, Zimbabwe. 3Center for Integrated Global Biomedical Sciences, School of Pharmacy and Pharmaceutical Sciences, University at Buffalo, Buffalo, NY, USA. 4Department of Pharmaceutical Technology, School of Industrial Sciences and Technology, Harare Institute of Technology, Belvedere, Harare, Zimbabwe.

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