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Toxicological Profiles of African Medicinal Plants Used in Trypanosomiasis Therapy: Mechanisms, Safety, and Knowledge Gaps

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Abstract

African medicinal plants have long played a central role in the management of trypanosomiasis, a neglected tropical disease that continues to impose severe health and socioeconomic burdens across sub-Saharan Africa. Traditional therapies derived from roots, barks, leaves, and seeds are widely used due to their accessibility, affordability, and ethnopharmacological relevance, particularly in regions with limited access to conventional chemotherapeutics. While numerous plant species have demonstrated antitrypanosomal activity through mechanisms such as parasite membrane disruption, oxidative stress induction, and inhibition of key metabolic enzymes, far less attention has been devoted to their toxicological profiles and safety margins. Understanding toxicity is critical, as bioactive phytochemicals including alkaloids, flavonoids, terpenoids, and phenolic compounds can exert off-target effects on host tissues. Acute, subacute, and chronic toxicity studies have revealed variable effects ranging from hepatotoxicity, nephrotoxicity, and hematological alterations to neurobehavioral changes, depending on plant species, extraction methods, dosage, and duration of exposure. Additionally, mechanisms of toxicity often overlap with therapeutic pathways, complicating the risk–benefit balance of plant-based interventions. Interactions with conventional antitrypanosomal drugs further raise concerns regarding synergistic toxicity or metabolic interference. This article critically reviews the toxicological profiles of African medicinal plants used in trypanosomiasis therapy, emphasizing molecular and cellular mechanisms of toxicity, safety evaluation methodologies, and existing experimental evidence. It also identifies major knowledge gaps, including limited standardized toxicity assessments, insufficient long-term and reproductive toxicity data, and the lack of translational studies linking preclinical findings to human safety. Addressing these gaps is essential for integrating traditional remedies into evidence-based treatment frameworks and for guiding the development of safer, plant-derived antitrypanosomal agents that align with global health and regulatory standards.

Keywords: African medicinal plants; Trypanosomiasis; Toxicological profile; Antitrypanosomal activity; Phytochemical toxicity; Safety assessment

1. Introduction

1.1. Trypanosomiasis as a Persistent Public Health Challenge in Africa

Trypanosomiasis remains a significant public health challenge across sub-Saharan Africa, affecting both human populations and livestock systems with far-reaching socio-economic consequences [1]. Human African trypanosomiasis and animal trypanosomiasis reduce workforce productivity, exacerbate poverty, and undermine agricultural sustainability in endemic regions [2]. The disease burden is disproportionately borne by rural communities where access to healthcare infrastructure is limited and vector control remains inconsistent [3].

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Existing chemotherapeutic options for trypanosomiasis are few, costly, and often associated with severe side effects, including neurotoxicity and organ damage [4]. In addition, the emergence of drug-resistant Trypanosoma strains has further reduced the effectiveness of standard treatments, complicating disease management strategies [5]. Treatment regimens frequently require prolonged hospitalization and skilled administration, creating barriers for affected populations.

As a result of these limitations, many communities continue to rely on traditional medicine as a primary or complementary approach to disease management [2]. This reliance reflects both cultural continuity and practical necessity, positioning indigenous therapeutic systems as central to ongoing trypanosomiasis control efforts [7].

1.2. Role of African Medicinal Plants in Trypanosomiasis Therapy

African medicinal plants play a prominent role in the traditional management of trypanosomiasis, drawing on extensive ethnomedicinal knowledge passed down through generations [5]. Healers across diverse ecological zones utilize locally available plant species to prepare remedies aimed at alleviating symptoms, reducing parasitaemia, or restoring general vitality [1]. These practices are deeply embedded in community health systems and often represent the most accessible form of care for affected individuals [6].

Commonly used plant parts include leaves, roots, bark, and seeds, prepared through decoctions, infusions, macerations, or topical applications depending on the plant species and cultural context [3]. Oral administration is most prevalent, though dosage regimens are rarely standardized. The perceived efficacy of these remedies is supported by long-standing empirical observation, reinforcing their continued use [7].

However, scientific validation of antitrypanosomal activity remains uneven. While some plant extracts have demonstrated in vitro or in vivo efficacy, many remedies lack rigorous pharmacological and toxicological evaluation [8]. This gap creates uncertainty regarding their safety, potency, and reproducibility despite widespread traditional endorsement [2].

1.3. Rationale for Toxicological Profiling and Safety Assessment

The growing interest in African medicinal plants as sources of novel antitrypanosomal agents underscores the need for comprehensive toxicological profiling [4]. Therapeutic efficacy alone is insufficient if accompanied by acute or chronic toxicity that compromises patient safety [6]. Many bioactive phytochemicals exert potent biological effects that may also disrupt normal physiological processes at higher doses or with prolonged exposure [1].

Systematic safety assessment is therefore essential to distinguish beneficial compounds from harmful ones and to establish safe dosage ranges [7]. Evidence-based toxicological evaluation supports the responsible integration of traditional remedies into modern healthcare frameworks, ensuring that plant-based therapies contribute meaningfully to sustainable trypanosomiasis control [3].

2. Phytochemical foundations of antitrypanosomal activity

2.1. Major Phytochemical Classes Implicated in Antitrypanosomal Effects

The antitrypanosomal activity of African medicinal plants is largely attributed to diverse classes of secondary metabolites with potent biological activity [11]. Alkaloids represent one of the most extensively studied groups, exhibiting strong trypanocidal effects through interactions with nucleic acids, enzymes, and membrane components [7]. Their heterocyclic structures enable intercalation into DNA and interference with parasite replication, although these same properties can also affect host cells [14].

Flavonoids constitute another prominent class, valued for their redox-modulating capacity and ability to disrupt parasite signaling pathways [9]. Structural features such as hydroxylation patterns, conjugated ring systems, and glycosylation influence their bioavailability and biological potency. Certain flavonoids demonstrate enhanced antitrypanosomal activity when planar structures facilitate enzyme binding or membrane association [12].

Terpenoids, including mono-, sesqui-, and diterpenes, contribute to antitrypanosomal effects through lipophilic interactions that compromise parasite membrane integrity [15]. Their structural diversity allows insertion into lipid bilayers, altering permeability and ion balance. Phenolic compounds, while often studied for antioxidant properties, can also exert pro-oxidant effects under specific conditions, contributing to parasite toxicity [8].

Structure–activity relationship studies highlight that increased lipophilicity, reactive functional groups, and molecular rigidity often correlate with stronger antitrypanosomal potency [10]. However, these same features may reduce selectivity, increasing the likelihood of host toxicity. Understanding how chemical structure governs both efficacy and safety is therefore essential for evaluating medicinal plant-derived compounds [13].

2.2. Mechanisms of Antitrypanosomal Action at Cellular and Molecular Levels

Phytochemicals exert antitrypanosomal effects through multiple cellular and molecular mechanisms that disrupt parasite survival and replication [15]. One common mode of action involves membrane disruption, where lipophilic compounds integrate into parasite plasma membranes, altering fluidity and permeability [9]. This destabilization leads to leakage of essential metabolites and ions, ultimately causing cell lysis.

Enzyme inhibition represents another critical mechanism. Many antitrypanosomal phytochemicals target parasite-specific enzymes involved in glycolysis, redox metabolism, or nucleic acid synthesis [11]. Inhibition of trypanosomal glycolytic enzymes is particularly effective, as the parasite relies heavily on glycolysis for ATP production. Compounds that interfere with trypanothione reductase disrupt redox homeostasis, weakening parasite defenses against oxidative stress [7].

Redox imbalance and mitochondrial dysfunction further contribute to parasite death. Certain flavonoids and phenolics induce excessive reactive oxygen species within Trypanosoma cells, overwhelming antioxidant systems and damaging proteins, lipids, and DNA [13]. Although African trypanosomes possess a single mitochondrion, its disruption has catastrophic consequences for energy metabolism and viability [10].

These mechanisms often operate synergistically, with phytochemicals affecting multiple targets simultaneously. While this multi-target activity reduces the likelihood of resistance development, it also complicates efforts to distinguish parasite-specific effects from generalized cytotoxicity [14].

2.3. Overlap Between Therapeutic and Toxic Mechanisms

A central challenge in plant-based antitrypanosomal therapy is the significant overlap between mechanisms responsible for therapeutic efficacy and those that produce toxicity in host systems [8]. Many phytochemicals act on fundamental cellular processes such as membrane integrity, redox balance, and enzyme function that are conserved between parasites and host cells [12]. As a result, compounds with strong trypanocidal activity often exhibit narrow therapeutic windows, where effective doses approach toxic thresholds [15].

Host–parasite selectivity remains difficult to achieve, particularly for alkaloids and terpenoids with high lipophilicity and reactivity [7]. Prolonged exposure or cumulative dosing may amplify off-target effects, leading to organ toxicity or systemic stress responses [10]. These challenges underscore the importance of integrating toxicity evaluation into early-stage screening rather than treating safety assessment as a secondary consideration [13].

Recognizing the mechanistic convergence of efficacy and toxicity is essential for advancing medicinal plants from traditional use toward evidence-based antitrypanosomal therapies [9].

3. Acute and subacute toxicological profiles of african medicinal plants

3.1. Acute Toxicity: LD_{50}, Target Organs, and Clinical Signs

Acute toxicity studies provide essential initial insight into the safety margins of African medicinal plants used in trypanosomiasis therapy by determining lethal dose thresholds and identifying early signs of systemic damage [18]. Most evaluations employ rodent models, particularly mice and rats, using oral or intraperitoneal administration to approximate traditional or experimental exposure routes [14]. LD_{50} values reported for antitrypanosomal plant extracts vary widely, reflecting differences in species, plant part used, and extraction method [21]. While some aqueous extracts demonstrate relatively high LD_{50} values suggestive of low acute toxicity, others particularly organic solvent extracts exhibit moderate to severe toxicity at comparatively low doses [16].

Target organ susceptibility during acute exposure frequently involves the central nervous system, liver, and gastrointestinal tract [19]. Behavioural endpoints commonly reported include reduced locomotor activity, tremors, piloerection, and altered feeding behaviour, indicating neurophysiological stress [22]. Physiological signs such as diarrhea, respiratory distress, and lethargy further signal systemic toxicity at higher doses [15].

Dose–response patterns often reveal steep toxicity curves, where small increases in dose result in disproportionately severe outcomes [17]. This narrow margin between therapeutic and toxic doses is particularly concerning for traditionally administered remedies lacking standardized dosing protocols. Acute toxicity findings therefore serve as critical early indicators of safety risk, guiding dose selection for subsequent subacute and efficacy studies [20].

3.2. Subacute Toxicity and Organ-Specific Effects

Subacute toxicity studies, typically spanning 14–28 days of repeated exposure, offer deeper insight into cumulative and organ-specific toxic effects that may not manifest during acute testing [14]. These investigations are especially relevant for medicinal plants used repeatedly in traditional settings or during prolonged experimental treatment regimens [21].

Hepatic toxicity is among the most frequently reported adverse effects. Elevated serum transaminases, altered bilirubin levels, and histopathological changes such as hepatocellular degeneration, fatty infiltration, and sinusoidal congestion have been documented following repeated administration of certain antitrypanosomal plant extracts [18]. These findings suggest impaired detoxification capacity and oxidative stress within hepatic tissues, likely linked to bioactive phytochemicals metabolized by the liver [16].

Renal toxicity is also commonly observed, reflecting the kidney's role in excreting plant-derived metabolites [22]. Subacute exposure has been associated with increased serum creatinine and urea levels, tubular necrosis, and glomerular damage in animal models [15]. Such alterations compromise renal filtration and fluid–electrolyte balance, raising concerns about cumulative dosing in vulnerable populations.

Hematological alterations provide additional evidence of systemic toxicity. Changes in red blood cell counts, hemoglobin concentration, and white blood cell profiles have been reported, indicating possible bone marrow suppression, hemolysis, or immune modulation [19]. In some cases, these effects may confound interpretation of antitrypanosomal efficacy, as anemia and immunosuppression also occur during infection itself [17].

Together, subacute toxicity data highlight that repeated exposure even at doses below acute toxicity thresholds can produce clinically relevant organ damage. These findings emphasize the need for cautious interpretation of traditional safety assumptions and underscore the importance of controlled dosing strategies [20].

3.3. Influence of Extraction Methods and Dosage Regimens

Extraction method significantly influences both the toxicity profile and apparent safety of medicinal plant preparations [21]. Aqueous extracts, which most closely resemble traditional decoctions and infusions, generally exhibit lower acute and subacute toxicity compared to organic solvent extracts [14]. This reduced toxicity is often attributed to lower concentrations of lipophilic and highly reactive compounds that are more efficiently extracted using ethanol, methanol, or chloroform [18].

Organic extracts, while frequently demonstrating enhanced antitrypanosomal potency, are also associated with increased systemic toxicity, particularly affecting hepatic and renal tissues [16]. These findings suggest that extraction efficiency amplifies both therapeutic and toxic constituents, narrowing safety margins [20].

Dosage regimen further modulates toxicity outcomes. Traditional dosing practices typically involve lower concentrations administered intermittently, relying on empirical observation to avoid overt harm [15]. In contrast, experimental studies often employ higher or more frequent dosing to demonstrate efficacy within short timeframes, potentially exaggerating toxicity risks [22]. Repeated high-dose exposure may overwhelm detoxification pathways, leading to cumulative organ damage not representative of traditional use [17].

These discrepancies highlight the importance of contextualizing toxicological data within realistic exposure scenarios. Bridging traditional knowledge with experimental rigor requires harmonizing extraction techniques and dosing regimens to ensure that safety assessments accurately reflect real-world use while maintaining scientific validity [19].

4. Chronic, reproductive, and developmental toxicity concerns

4.1. Chronic Toxicity and Cumulative Exposure Effects

Chronic toxicity represents a critical yet underexplored dimension of safety assessment for African medicinal plants used in trypanosomiasis management [24]. Unlike acute exposure, chronic toxicity arises from repeated or prolonged

use, reflecting realistic therapeutic scenarios in endemic regions where remedies may be consumed over weeks or months [20]. Repeated-use patterns increase the likelihood of cumulative physiological stress, particularly when dosing is unstandardized and guided by symptomatic persistence rather than defined treatment endpoints [27].

Bioaccumulation of phytochemicals or their metabolites is a major contributor to chronic toxicity risk. Lipophilic compounds, especially certain alkaloids and terpenoids, may accumulate in adipose tissue, liver, or neural compartments, exerting delayed toxic effects [22]. Over time, sustained metabolic processing of these compounds places a significant burden on detoxification systems, particularly hepatic cytochrome enzymes and renal excretory pathways [29]. Enzyme saturation or induction may alter normal metabolic balance, increasing susceptibility to oxidative stress and tissue injury [21].

Histopathological evidence from long-term animal studies indicates progressive liver fibrosis, renal interstitial damage, and gastrointestinal mucosal erosion following extended exposure to some antitrypanosomal plant extracts [25]. These effects may remain subclinical during early stages, complicating detection and risk communication. Importantly, chronic toxicity may not correlate directly with acute toxicity thresholds, meaning extracts deemed “safe” in short-term studies can still pose long-term health risks [23].

Understanding cumulative exposure effects is essential for evaluating real-world safety, particularly in populations with limited access to clinical monitoring. Chronic toxicity assessment therefore represents a foundational requirement for transitioning medicinal plants from traditional use to evidence-based therapeutic integration [26].

4.2. Reproductive and Developmental Toxicity Evidence

Reproductive and developmental toxicity poses serious concerns due to the potential for long-lasting and intergenerational consequences [28]. Although data remain limited, emerging evidence suggests that some medicinal plant extracts used for trypanosomiasis may interfere with reproductive physiology and fetal development when exposure occurs during sensitive life stages [21].

Studies in animal models have reported reduced fertility indices, including decreased sperm count, altered sperm morphology, and disrupted oestrous cycles following prolonged administration of certain phytochemical-rich extracts [24]. These effects are often linked to endocrine disruption or oxidative damage to gonadal tissues, mechanisms that may not produce immediate clinical symptoms but impair reproductive capacity over time [29].

Developmental toxicity is of particular concern during pregnancy. Exposure to bioactive plant compounds during gestation has been associated with embryotoxic effects, such as increased resorption rates, reduced fetal weight, and delayed skeletal ossification [26]. Teratogenic outcomes including limb malformations and neural tube defects have been observed in high-dose experimental settings, raising questions about safety margins during traditional use [22].

Placental transfer of small, lipophilic phytochemicals facilitates fetal exposure, while immature detoxification systems in embryos amplify vulnerability [25]. In communities where medicinal plants are consumed without restriction during pregnancy, these risks carry significant public health implications. The absence of systematic reproductive toxicity screening for most antitrypanosomal plants underscores a major knowledge gap [27].

Given the potential for heritable effects and developmental impairment, reproductive safety evaluation must be prioritized alongside efficacy studies to ensure that plant-based therapies do not inadvertently compromise future generations [20].

4.3. Neurotoxicity and Behavioural Alterations

Neurotoxicity represents another critical dimension of long-term safety, particularly for phytochemicals capable of crossing the blood–brain barrier [23]. Chronic exposure to certain alkaloids and phenolic compounds has been linked to structural and functional alterations in both central and peripheral nervous systems [28]. These effects may manifest as subtle behavioral changes rather than overt neurological pathology, complicating diagnosis and attribution [21].

Animal studies report impaired motor coordination, altered exploratory behavior, memory deficits, and anxiety-like responses following extended administration of some medicinal plant extracts [25]. Such findings suggest disruption of neurotransmitter systems, synaptic plasticity, or mitochondrial function within neural tissues [29]. Peripheral neurotoxicity, including sensory impairment and neuromuscular weakness, has also been documented, potentially affecting daily functioning [22].

For patients already burdened by trypanosomiasis-related neurological symptoms, additional neurotoxic effects may exacerbate disease impact and reduce quality of life [26]. Cognitive impairment, mood disturbances, and reduced functional independence represent significant but often overlooked outcomes of long-term exposure. These risks highlight the importance of incorporating behavioral and neurophysiological endpoints into safety assessment frameworks [24].

Addressing neurotoxicity is therefore essential not only for evaluating therapeutic safety but also for safeguarding patient well-being and functional recovery during and after treatment [27].

5. Herb–drug interactions and safety in combination therapies

5.1. Co-administration with Conventional Antitrypanosomal Drugs

In real-world settings, African medicinal plants are frequently co-administered with conventional antitrypanosomal drugs, either sequentially or concurrently, creating complex interaction scenarios that can alter therapeutic outcomes and toxicity risk [31]. This practice is common in endemic regions where patients combine hospital-prescribed treatments with traditional remedies to enhance perceived efficacy or mitigate side effects [27].

Pharmacokinetic interactions represent a primary concern. Many plant-derived phytochemicals influence drug absorption, distribution, metabolism, and excretion by modulating intestinal transporters or hepatic enzymes [34]. Enzyme induction or inhibition particularly involving cytochrome P450 isoforms can significantly alter plasma concentrations of antitrypanosomal drugs, leading to subtherapeutic exposure or drug accumulation [29]. For example, induction of metabolic enzymes may accelerate drug clearance, reducing efficacy, while enzyme inhibition can increase systemic toxicity by prolonging drug half-life [36].

These interactions are especially concerning given the narrow therapeutic windows of several antitrypanosomal agents. Altered pharmacokinetics may exacerbate known adverse effects, including neurotoxicity or organ damage, without clear clinical warning signs [32]. Compounding the issue, traditional remedies are rarely standardized, making interaction outcomes unpredictable. The lack of patient disclosure regarding herbal use further complicates clinical management, increasing the risk of unrecognized adverse interactions [28].

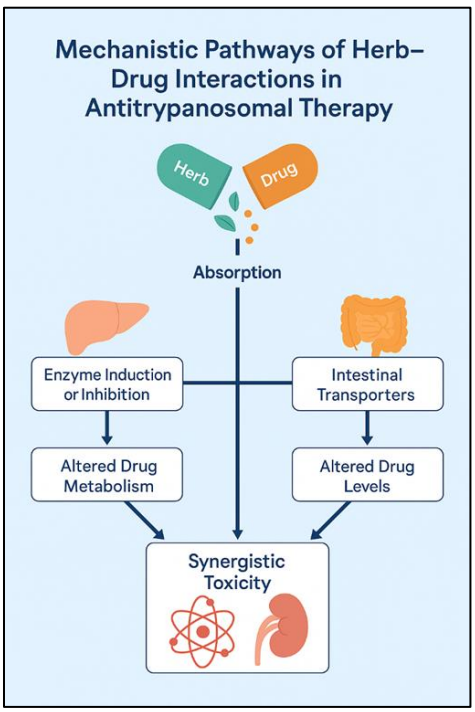

Figure 1 Mechanistic pathways of herb–drug interactions in antitrypanosomal therapy

5.2. Synergistic Toxicity and Metabolic Interference

Beyond pharmacokinetic effects, synergistic toxicity represents a significant hazard when medicinal plants and conventional drugs are used together [35]. Additive or synergistic organ toxicity may occur when both agents target the same physiological systems, particularly the liver and kidneys [27]. For instance, phytochemicals that induce oxidative stress may amplify drug-induced hepatotoxicity, overwhelming antioxidant defenses and accelerating tissue damage [33].

Metabolic interference further complicates safety profiles. Competition for detoxification pathways can lead to accumulation of reactive metabolites, increasing cellular stress and inflammatory responses [30]. In some cases, plant constituents may impair mitochondrial function or disrupt redox balance, intensifying drug-associated toxicity through convergent mechanisms [36].

These effects are rarely anticipated in traditional use contexts, where remedies are perceived as inherently protective. However, experimental evidence suggests that combined exposure can produce toxicity exceeding that of either agent alone, even at individually "safe" doses [29]. The absence of systematic interaction studies means that synergistic toxicity often remains undetected until severe adverse outcomes occur [34]. Understanding these risks is essential for developing safer integrative treatment strategies that acknowledge real-world usage patterns [31].

5.3. Implications for Clinical Practice and Traditional Medicine Use

The prevalence of herb–drug co-administration has important implications for both clinical practice and traditional medicine systems [28]. Clinicians operating in endemic regions must recognize medicinal plant use as a routine component of patient behaviour rather than an exception. Failure to account for herbal intake can lead to misattribution of adverse effects or ineffective dose adjustments [32].

From a public health perspective, improved communication between healthcare providers and traditional practitioners is essential to reduce unintended harm [27]. Educational initiatives that promote awareness of interaction risks without undermining cultural practices can support safer use [35].

Integrating toxicological evidence into treatment guidelines may help balance therapeutic benefit with safety, ensuring that plant-based remedies complement rather than compromise conventional antitrypanosomal therapy [30].

6. Toxicological assessment methodologies and limitations

6.1. Experimental Models Used in Toxicity Studies

Toxicological evaluation of African medicinal plants relies primarily on experimental models designed to detect adverse effects under controlled conditions [34]. In vivo animal models most commonly rodents remain the cornerstone of toxicity assessment, enabling evaluation of systemic effects, organ pathology, and dose–response relationships [27]. These models provide valuable insight into acute, subacute, and chronic toxicity but are limited by interspecies differences in metabolism, physiology, and exposure patterns [36].

In vitro approaches, including cell culture assays and organotypic models, offer complementary advantages by enabling mechanistic investigation and high-throughput screening [31]. Such models are particularly useful for identifying cytotoxicity, oxidative stress responses, and enzyme inhibition at the cellular level. However, they lack the complexity required to capture whole-organism interactions, bioaccumulation, and long-term systemic effects [29].

Both approaches face challenges in replicating traditional use scenarios. Experimental dosing often exceeds realistic exposure levels or employs purified extracts rather than crude preparations, potentially exaggerating toxicity [33]. Additionally, administration routes used in laboratories may not reflect oral or topical use patterns common in traditional medicine [28]. These limitations necessitate cautious interpretation of toxicity data and highlight the need for improved model selection aligned with real-world practices [35].

6.2. Biomarkers, Endpoints, and Histopathological Analyses

Toxicity studies commonly employ a range of biochemical, hematological, and histopathological endpoints to assess organ function and systemic health [30]. Serum biomarkers such as transaminases, creatinine, urea, and electrolyte levels provide early indicators of hepatic and renal impairment [36]. Hematological parameters including red and white blood cell counts offer insight into bone marrow function, immune modulation, and anemia risk [27].

Histopathological analysis remains a gold standard for confirming tissue damage, revealing structural alterations such as necrosis, inflammation, fibrosis, or cellular degeneration [34]. These observations provide critical context for interpreting biochemical changes and identifying target organs.

Despite their utility, biomarkers are not always specific to phytochemical-induced toxicity and may be influenced by infection status, nutritional deficiencies, or environmental stressors [29]. Behavioural and functional endpoints particularly for neurotoxicity are also inconsistently applied, limiting comprehensive risk assessment [31]. Standardizing endpoint selection and incorporating functional outcomes would improve comparability and relevance of toxicity findings [33].

6.3. Methodological Gaps and Lack of Standardization

A major limitation in the toxicological evaluation of antitrypanosomal medicinal plants is the lack of methodological standardization across studies [35]. Variability in plant identification, extraction methods, dosing regimens, exposure duration, and outcome measures undermines comparability and reproducibility [28]. In some cases, insufficient reporting of experimental details limits interpretation and replication [34].

The absence of harmonized guidelines for evaluating traditional medicines further exacerbates regulatory uncertainty [30]. Many studies focus on isolated endpoints without integrating multi-organ or long-term outcomes, creating fragmented safety profiles [36]. Additionally, negative or null toxicity findings are underreported, contributing to publication bias and skewed risk perception [27].

Addressing these gaps requires adoption of standardized protocols, transparent reporting, and interdisciplinary collaboration between toxicologists, ethnopharmacologists, and clinicians [31]. Improved methodological rigor will strengthen the evidence base needed to inform policy, guide clinical decision-making, and ensure that medicinal plants are evaluated with the same scientific scrutiny applied to conventional drugs [33].

7. Knowledge gaps, regulatory challenges, and ethical considerations

7.1. Insufficient Long-Term and Human Toxicity Data

One of the most significant barriers to translating African medicinal plants into safe antitrypanosomal therapies is the lack of robust long-term and human toxicity data [38]. While numerous studies document in vitro efficacy and short-term safety in animal models, far fewer investigate chronic exposure, cumulative toxicity, or interindividual variability relevant to human populations [33]. This imbalance creates a false sense of safety, as adverse effects associated with prolonged or repeated use may remain undetected until widespread application occurs.

Human toxicity data are particularly scarce. Ethical, logistical, and funding constraints limit controlled clinical evaluation of traditional remedies, resulting in reliance on anecdotal evidence or observational reports [40]. Such data lack standardized exposure metrics and are confounded by co-morbidities, nutritional status, and co-administration with conventional drugs [35]. Additionally, genetic diversity among human populations may influence susceptibility to toxicity, further complicating extrapolation from animal models [37].

The absence of long-term safety data undermines risk–benefit assessment and contributes to regulatory hesitation. Without evidence addressing chronic use, vulnerable populations—such as children, pregnant women, and individuals with compromised organ function—remain at heightened risk [34]. Addressing this gap is essential for responsible translation of plant-based therapies into evidence-based disease control strategies [39].

7.2. Regulatory Barriers to Plant-Based Antitrypanosomal Therapies

Regulatory frameworks present additional systemic barriers to the development of plant-derived antitrypanosomal agents [36]. Most regulatory agencies are structured to evaluate single-molecule pharmaceuticals, not complex botanical mixtures with variable composition [33]. As a result, traditional remedies often fail to fit existing approval pathways, even when preliminary efficacy data are promising.

In many African countries, medicinal plants are regulated as dietary supplements or traditional products rather than therapeutic agents, limiting incentives for rigorous safety evaluation [38]. Conversely, attempts to pursue formal drug approval require extensive toxicological, pharmacokinetic, and manufacturing data that are often beyond the capacity of academic or community-based researchers [40]. This regulatory mismatch discourages investment and slows translation.

International harmonization is also lacking. Differences in regulatory expectations across regions complicate multicenter studies and cross-border collaboration [35]. The absence of clear guidance on how traditional knowledge can be incorporated into regulatory dossiers further marginalizes indigenous medical systems. Consequently, potentially valuable therapies remain trapped between informal use and formal approval, exposing patients to unregulated risk while limiting scientific advancement [37].

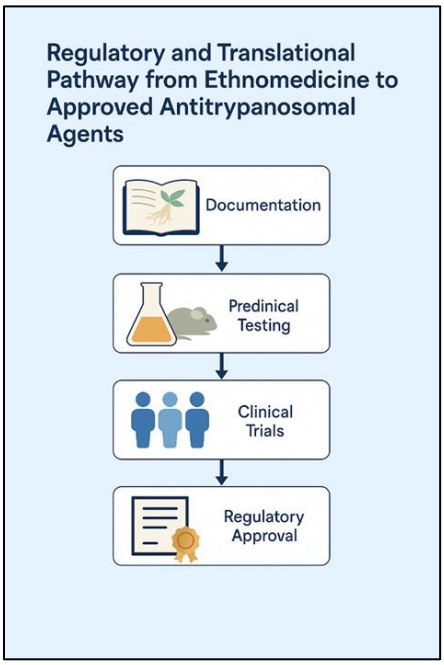

Figure 2 Regulatory and translational pathway from ethnomedicine to approved antitrypanosomal agents

7.3. Ethical Considerations in Traditional Medicine Research

Ethical challenges further complicate translation of plant-based antitrypanosomal therapies [39]. Traditional knowledge is often community-owned, raising concerns about informed consent, benefit sharing, and intellectual property rights when remedies are subjected to scientific investigation [34]. Exploitative research practices risk eroding trust and undermining collaboration between scientists and indigenous practitioners.

Safety research itself carries ethical responsibilities. Conducting toxicity studies without clear pathways for benefit realization may expose communities to harm without reciprocal advantage [36]. Conversely, failing to evaluate toxicity perpetuates unsafe use. Balancing cultural respect with scientific rigor requires transparent engagement, community participation, and equitable sharing of outcomes [33].

Ethical frameworks that integrate local values with international research standards are essential for ensuring that toxicological evaluation strengthens, rather than diminishes, the legitimacy and sustainability of traditional medicine systems [40].

8. Toward safer plant-derived antitrypanosomal therapies

8.1. Integrating Ethnopharmacology with Toxicological Science

A critical step toward safer plant-based antitrypanosomal therapies is the integration of ethnopharmacological knowledge with contemporary toxicological science [35]. Ethnomedicinal practices provide valuable insights into plant selection, preparation methods, dosing patterns, and contextual use that can inform realistic safety assessment [38]. Rather than treating traditional use as anecdotal, researchers can leverage this knowledge to design toxicity studies that reflect actual exposure scenarios [33].

Collaborative research models involving traditional healers, toxicologists, and clinicians enable bidirectional knowledge exchange [40]. Such partnerships improve plant authentication, reduce misidentification, and clarify cultural dosing

norms that influence toxicity risk. Integrating ethnopharmacology also facilitates prioritization, focusing resources on plants with sustained historical use and perceived efficacy rather than indiscriminate screening [36].

Importantly, this integration reframes toxicological evaluation as a supportive process aimed at optimizing safety rather than discrediting traditional practices. When communities are engaged as stakeholders, safety findings are more likely to be accepted and translated into improved usage guidelines [34].

8.2. Advanced Approaches: Omics, In Silico Toxicology, and Systems Biology

Emerging technologies offer powerful tools for addressing toxicological knowledge gaps [39]. Omics approaches including transcriptomics, proteomics, and metabolomics enable comprehensive profiling of biological responses to plant extracts, revealing early toxicity signatures before overt pathology occurs [33]. These methods support identification of molecular pathways affected by phytochemicals and help distinguish adaptive from harmful responses.

In silico toxicology further enhances efficiency by predicting toxicity based on chemical structure, target interaction, and metabolic fate [37]. Computational models can screen large numbers of compounds, prioritize candidates for in vivo testing, and anticipate herb–drug interactions [40]. Systems biology integrates these data streams, modeling complex interactions between phytochemicals, host metabolism, and parasite biology [35].

Together, these approaches reduce reliance on high-dose animal testing, accelerate risk identification, and support mechanism-based safety evaluation. Their application to antitrypanosomal medicinal plants represents a critical evolution from descriptive toxicity toward predictive and preventive toxicology [38].

8.3. Risk–Benefit Optimization and Rational Drug Development

Ultimately, the goal of toxicological evaluation is not to eliminate risk entirely but to optimize the balance between therapeutic benefit and safety [36]. Rational drug development approaches apply toxicity data to refine extraction methods, isolate safer bioactive fractions, and define dosing regimens that maximize parasite selectivity [34].

Risk–benefit optimization also supports decision-making about when plant extracts are appropriate as standalone therapies, adjunct treatments, or sources of lead compounds for semi-synthetic drug development [39]. Transparent communication of known risks empowers clinicians, traditional practitioners, and patients to make informed choices [33].

By embedding safety considerations at every stage from ethnobotanical selection to preclinical modelling plant-derived antitrypanosomal therapies can transition from empiricism to evidence-based application, fulfilling their therapeutic promise responsibly [40].

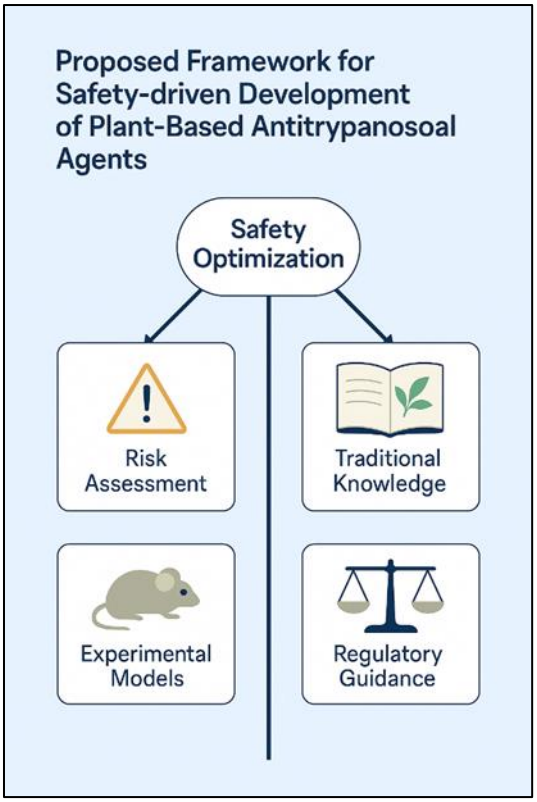

Figure 3 Proposed framework for safety-driven development of plant-based antitrypanosomal agents

9. Conclusions and future directions

African medicinal plants continue to hold substantial therapeutic relevance in the management of trypanosomiasis, particularly in regions where disease burden remains high and access to conventional treatments is constrained. Ethnomedicinal practices have preserved a diverse pharmacopeia of plant-based remedies with demonstrated antitrypanosomal potential, underscoring their value as sources of bioactive compounds and culturally embedded healthcare solutions. However, therapeutic promise alone is insufficient to justify widespread or prolonged use without a rigorous understanding of safety implications.

This review highlights that toxicity is not a peripheral concern but a central determinant of translational viability. Evidence from acute, subacute, chronic, reproductive, and neurotoxicity studies reveals that many antitrypanosomal plants exhibit narrow safety margins, cumulative risks, or context-dependent adverse effects. The frequent overlap between mechanisms of efficacy and toxicity reinforces the need for safety-first integration, where toxicological evaluation is embedded alongside bioactivity assessment from the earliest stages of research. Such an approach protects patients, strengthens clinical credibility, and prevents unintended harm, particularly among vulnerable populations.

Moving forward, a clear research trajectory must prioritize interdisciplinary collaboration. Integrating ethnopharmacology, toxicology, pharmacology, systems biology, and regulatory science is essential for generating evidence that is both scientifically robust and socially legitimate. Policy-aligned research frameworks are equally critical, enabling harmonized standards, ethical governance, and pathways for responsible translation. By aligning traditional knowledge with modern safety science and regulatory expectations, plant-derived antitrypanosomal therapies can progress from empirical use toward validated, sustainable, and equitable contributions to global health.

Compliance with ethical standards

Disclosure of conflict of interest

There are no conflict of interest

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