

Alkaloids from *Strychnos usambarensis*: chemical diversity and biological potential

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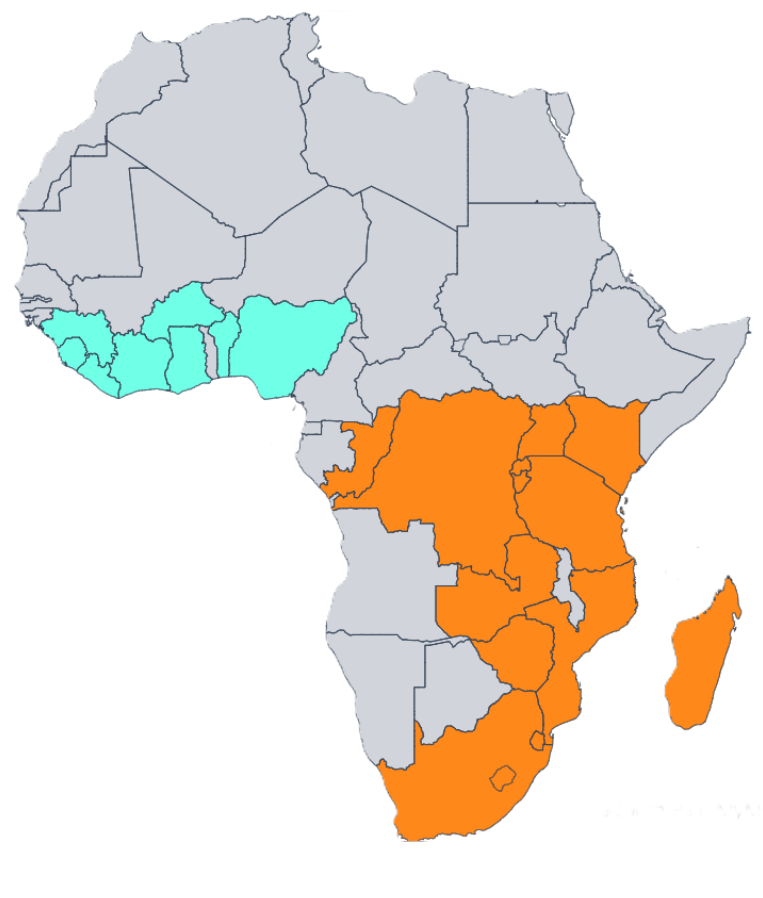
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Introduction

Natural products remain a valuable source of bioactive molecules, with their chemical diversity providing a major foundation for drug discovery. Within the Loganiaceae family, the genus *Strychnos* is particularly noteworthy for its remarkable diversity of indole alkaloids. *Strychnos usambarensis*, an African species historically recognized as a source of curare-like compounds, represents a particularly rich and complex source of indole alkaloids and comprises two distinct morphotypes, each displaying a distinct alkaloid profile [1]. This exceptional chemical diversity is characterized by a wide range of molecular architectures, whose structural features strongly influence their biological properties. A broad spectrum of activities has been reported for these alkaloids, including antiplasmodial, antiamoebic, cytotoxic and antiviral activities [2-4] . This work explores the diversity of *S. usambarensis* alkaloids and the biological potentialities associated with their distinct structural features.

Ethnobotanical Context

Native to Africa



■ Liana form

■ Tree form

Used traditionally as arrow poison



Banyambo hunters in the Akagera Park, Rwanda

Preparation consists of an aqueous decoction of the plant material, followed by prolonged boiling to concentrate the extract into a viscous paste suitable for application to arrow tips [5] .



Two morphotypes

Strychnos usambarensis Gilg ex Engl.



Tree form



Liana form

In West and Central Africa, the species generally grows as a liana. By contrast, in East and Southern Africa it takes on a small tree form. The morphological difference between these forms is the presence of tendrils in the climbing form. Liana and tree forms exhibit partially distinct alkaloid compositions [6].

Phytochemical Diversity

Organ-specific distribution



Root bark : the curarizing chemical core



Leaves : diverse and dynamic alkaloid network

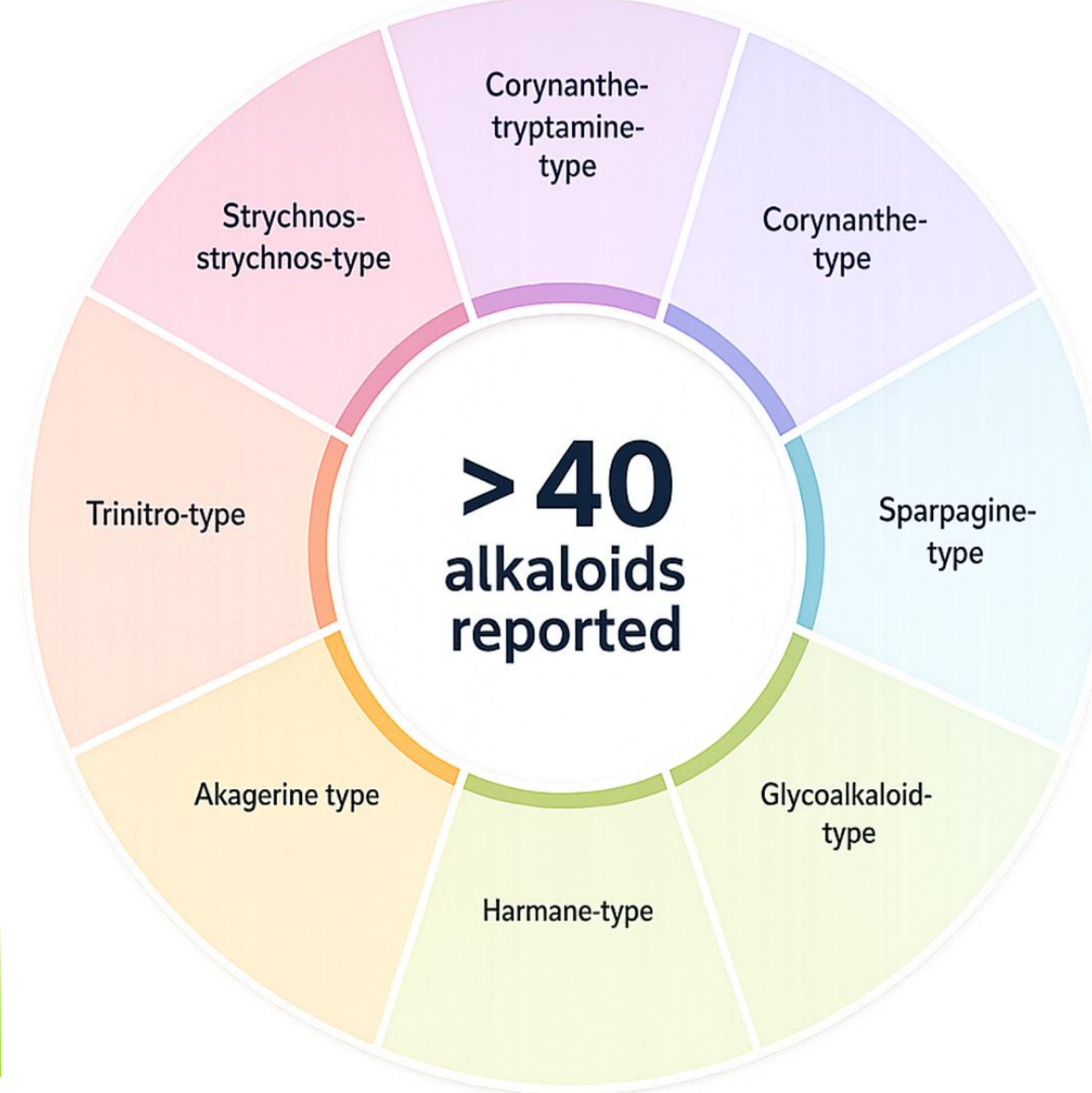


Stem bark : an intermediate chemical interface and morphotype signal



Fruits : minor reservoir and developmental signatures

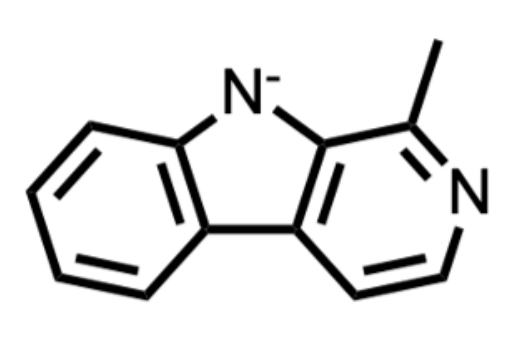
A wide range of structural families



>40 alkaloids reported

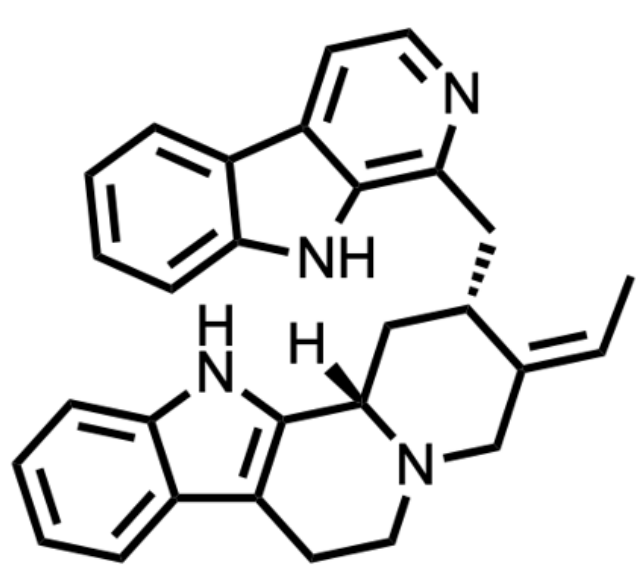
Chemical alkaloid diversity

MONOINDOLIC
Simple scaffold



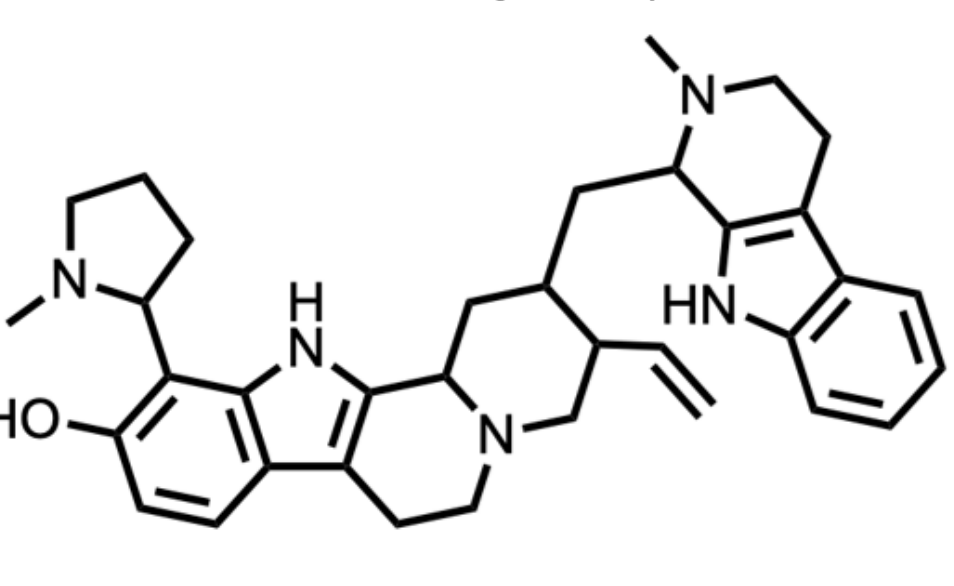
e.g. Harman

BISINDOLIC
Diverse oxidation and substitution



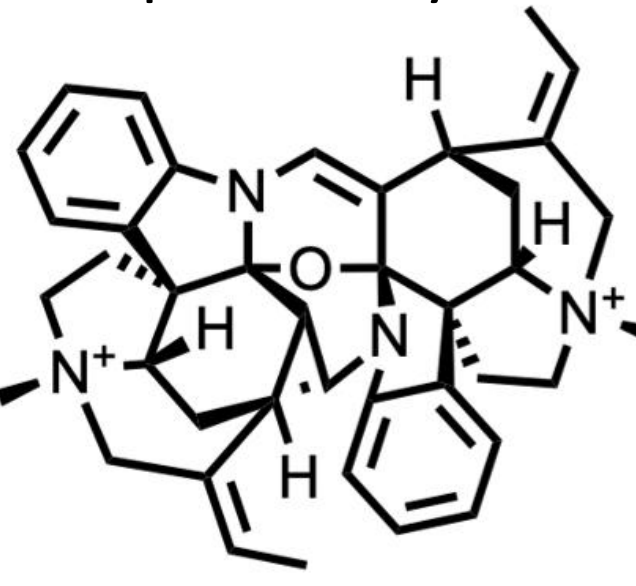
e.g. Usambarensine

HETEROTRIMERIC
Five nitrogen system



e.g. Strychnopentamine

DIQUATERNARY
Dual quaternary centers



e.g. C-curarine

Biological Activities

The remarkable structural diversity of *Strychnos usambarensis* alkaloids is reflected in a broad spectrum of biological activities [2-4]. Distinct alkaloid families display different pharmacological profiles. Monomeric alkaloids generally show moderate activities, except for potent cholinesterase inhibition associated with neuroprotective potential. Bisindolic alkaloids display broad bioactivities, including antiplasmodial, antiamoebic, antiviral, and cytotoxic effects. Heterotrimeric alkaloids are among the most potent, particularly against *Plasmodium falciparum* and cancer cells, whereas diquaternary bisindolic alkaloids are exclusively associated with curare-like neuromuscular blockade. This scaffold-dependent activity highlights the functional diversification of the *S. usambarensis* alkaloid network.

Comparative bioactivity profiles of alkaloid classes from *S. usambarensis*

Biological activity	Neuromuscular blockade	Antiplasmodial	Antiamoebic	Antiviral	Antifungal	Cytotoxicity	Neuroprotective
Alkaloids class							
Monoindolic alkaloids	○	●	○	●	●	●	●●●
Bisindolic alkaloids	(non curarizing) ●	●●	●●●	●●●	○	●●●	n.r.
Heterotrimerics alkaloids	○	●●●	●	●	n.r.	●●●	n.r.
Diquaternary alkaloids	●●●	○	○	n.r.	n.r.	○	n.r.

○ : no significant activity

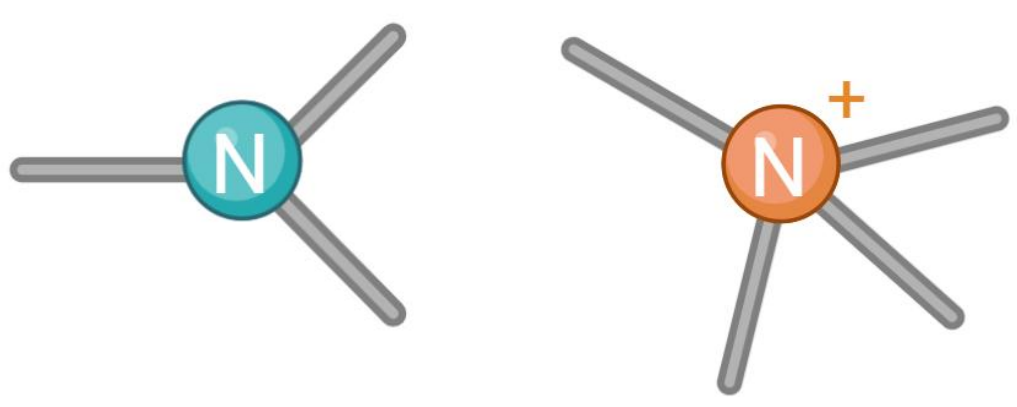
● : moderate activity

●● : high activity

●●● : very high activity

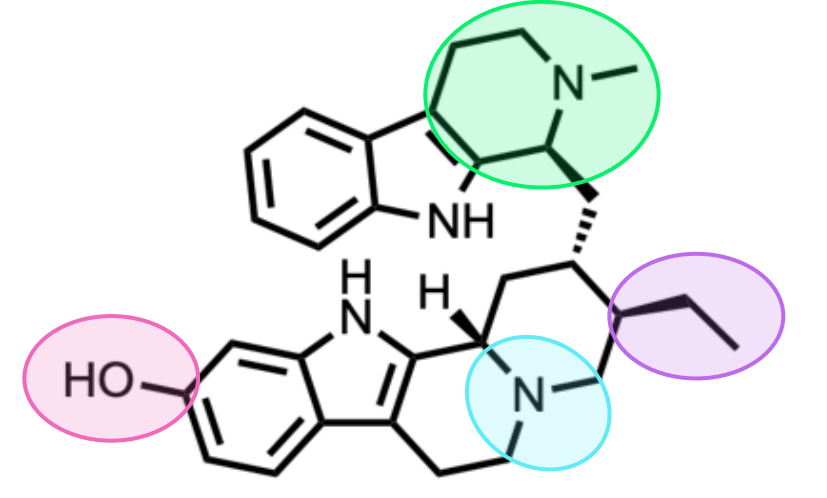
n.r. : non reported

IONIZATION STATE
Controls biological compartmentalization



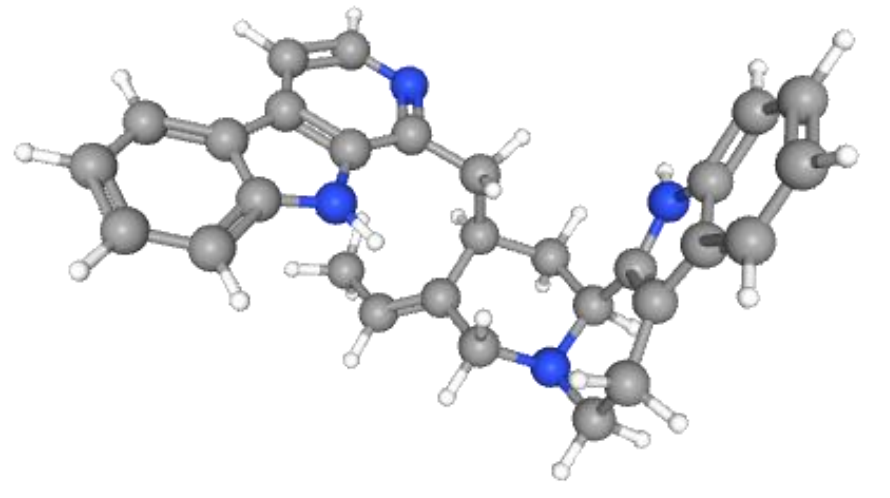
Quaternary compounds lack membrane permeability and act extracellularly, tertiary analogues access intracellular targets.

OXIDATION AND SUBSTITUTION
Drive target specificity



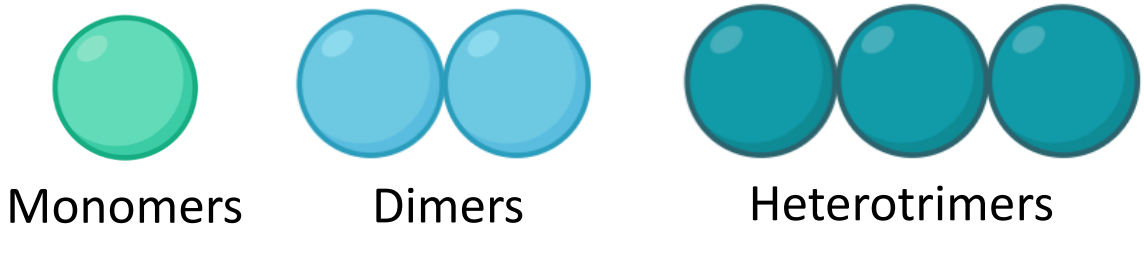
The usambarane scaffold acts as a modular platform in which subtle oxidation and substitution changes redirect biological activity and selectivity.

TRIDIMENSIONAL TYPOLOGY
Determinant of Biological Activity



Molecular topology shapes biological activity, as non-planar conformations can retain target interactions.

MOLECULAR ASSEMBLY
And structural diversity



Molecular size defines a balance between enhanced target interactions and reduced physicochemical accessibility.

Conclusion & Perspectives

Strychnos usambarensis emerges as a valuable source of pharmacologically relevant indole alkaloids, providing a hierarchical set of lead structures ranging from simple monomers to complex heterotrimeric architectures, offering complementary opportunities for drug discovery. Among these, strychnopentamine, isostrychnopentamine and usambarensine stand out as promising scaffolds, while oxidized and hydrogenated derivatives and monomeric alkaloids provide additional starting points for structural optimization. While highly assembled alkaloids offer enhanced potency and functional diversity, simpler frameworks provide greater accessibility for chemical modification. Together, these compounds offer versatile platforms for generating new analogues and modulating potency, selectivity and pharmacological properties. The exploration of the two morphotypes and their underexplored alkaloid profiles could further expand this promising chemical space.

Aknowledgements :

This work was supported by the University of Liège and FNRS (research credits). The authors wish to thank all the Pharmacognosy laboratory for their support.

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