

Acetylcholinesterase inhibitory potential of five ivorian medicinal plants: A phytochemical and enzyme-kinetic investigation with relevance to Alzheimer's disease

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Abstract

Introduction: Alzheimer's disease (AD) is a chronic, progressive and irreversible neurodegenerative disorder and the leading cause of dementia worldwide. Among the mechanisms underlying its cognitive symptoms, the cholinergic hypothesis remains central: reduced synaptic acetylcholine, driven largely by heightened acetylcholinesterase (AChE) activity, is closely linked to memory and learning deficits. Current AChE inhibitors (donepezil, rivastigmine, galantamine) act only symptomatically and carry frequent gastrointestinal side effects, motivating the search for new, better-tolerated inhibitors from natural sources. **Objective:** This study evaluated, *in vitro*, the AChE-inhibitory potential of aqueous and hydroethanolic extracts from five Ivorian medicinal plants — *Garcinia kola* (seeds), *Griffonia simplicifolia* (seeds), *Voacanga africana* (root bark), *Hibiscus sabdariffa* (calyces) and *Zingiber officinale* (rhizomes) — using Ellman's colorimetric method. **Material and Methods:** Extraction yields were higher with the hydroethanolic solvent for all species (16.00–44.11%) than with water (5.77–17.90%). All ten extracts inhibited AChE in a dose-dependent manner. **Result and Discussions:** The hydroethanolic extract of *Garcinia kola* was the most potent (IC₅₀ = 3.01 µg/mL), followed by the aqueous extract of *Griffonia simplicifolia* (IC₅₀ = 11.71 µg/mL). Enzyme-kinetic analysis of these two most active extracts revealed a mixed-type inhibition pattern, with a decrease in V_{max} accompanied by an increase in K_m relative to the control. Preliminary phytochemical screening of the two extracts identified polyphenols, tannins, alkaloids, flavonoids and saponins as the most likely chemical classes responsible for the observed activity. **Conclusion:** These findings support *Garcinia kola* and *Griffonia simplicifolia* as promising, locally available sources of natural AChE inhibitors and provide an eventual pharmacological development as complementary or alternative agents against Alzheimer's disease.

Keywords: Alzheimer's disease; Acetylcholinesterase; Medicinal plants; *Garcinia kola*; *Griffonia simplicifolia*; Enzyme inhibition

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Introduction

Alzheimer's disease (AD) is a chronic, progressive and irreversible neurodegenerative disorder marked by a gradual deterioration of cognitive functions, in particular memory, reasoning, language and spatiotemporal orientation.^[1] It is the most common form of dementia worldwide, and its prevalence continues to rise as populations age.^[2] This trend is not confined to industrialised countries: Côte d'Ivoire has itself reported a growing number of clinical cases in recent years.^[3] Given its expanding burden and the heavy socio-economic consequences it imposes on patients, families and health systems, AD is today a major public-health priority.

Pathologically, AD is characterized by progressive synaptic dysfunction and loss, accompanied by neuronal degeneration in vulnerable brain regions, particularly

the hippocampus and cerebral cortex, which are critically involved in learning and memory.^[4] Among the mechanisms implicated in this decline, the cholinergic hypothesis occupies a central place. Acetylcholine, the principal neurotransmitter of the cholinergic system, plays a fundamental role in memory formation, learning and nerve-impulse transmission. In AD patients, a marked reduction in synaptic acetylcholine concentration disrupts neuronal communication and drives the characteristic cognitive deficits of the disease. This cholinergic deficit is associated with impaired cholinergic neurotransmission and altered cholinesterase activity. Acetylcholinesterase (AChE), the principal enzyme responsible for the rapid hydrolysis of acetylcholine at cholinergic synapses, therefore represents an important pharmacological target in AD.^[5]

Faced with this cholinergic deficit, current therapeutic strategies rely essentially on AChE inhibitors — donepezil, rivastigmine and galantamine — which increase synaptic acetylcholine availability and produce a temporary improvement in cognitive function. Despite their clinical value, these synthetic molecules present several limitations, including modest efficacy on disease progression and sometimes significant adverse effects, notably gastrointestinal disturbances.^[6] These shortcomings justify the search for new bioactive substances that are more effective, better tolerated, and potentially able to act on several mechanisms involved in neurodegeneration.

In this context, Medicinal plants appear as an important source of bioactive secondary metabolites, including polyphenols, flavonoids, alkaloids and terpenoids, many of which have demonstrated antioxidant, anti-inflammatory and neuroprotective activities relevant to neurodegenerative diseases.^[7] Côte d'Ivoire, owing to its rich plant biodiversity and its ethnopharmacological heritage, constitutes a potential reservoir of phytotherapeutic resources that could contribute to the discovery of new pharmacologically active molecules.

The five species selected for the present study were chosen for their local availability, their traditional uses, and certain biological properties of interest to the nervous system. The seeds of *Griffonia simplicifolia* are rich in 5-hydroxytryptophan (5-HTP), a direct precursor of serotonin, and are traditionally used for their effects on mood and mental well-being.^[8] The root bark of *Voacanga africana* is traditionally used to treat various conditions, including certain nervous disorders.^[9] The seeds of *Garcinia kola* are used in traditional medicine as a stimulant and aphrodisiac^[10]. The rhizomes of *Zingiber officinale* possess antioxidant, anti-inflammatory and neuroprotective properties, together with beneficial effects on cognitive function.^[11] Finally, the calyces of *Hibiscus sabdariffa* display antioxidant and neuroprotective properties as well as effects on cognitive function.^[12]

It is within this perspective that the present study is framed: an evaluation of the ability of five Ivorian medicinal plants, traditionally used against cognitive disorders, to inhibit acetylcholinesterase. The general objective was to assess, *in vitro*, the AChE-inhibitory potential of these five species in order to identify extracts that could serve as leads for future alternative treatments of Alzheimer's disease. The specific objectives were to: (i) evaluate *in vitro* the AChE-inhibitory activity of extracts from the selected plants; (ii) determine the kinetics of action of the most active extracts; and (iii) carry out a phytochemical screening of the most active extracts.

Materials and Methods

Plant material

The plant material consisted of root bark of *Voacanga africana*, seeds of *Griffonia simplicifolia*, rhizomes of *Zingiber officinale*, calyces of *Hibiscus sabdariffa*, and seeds of *Garcinia*

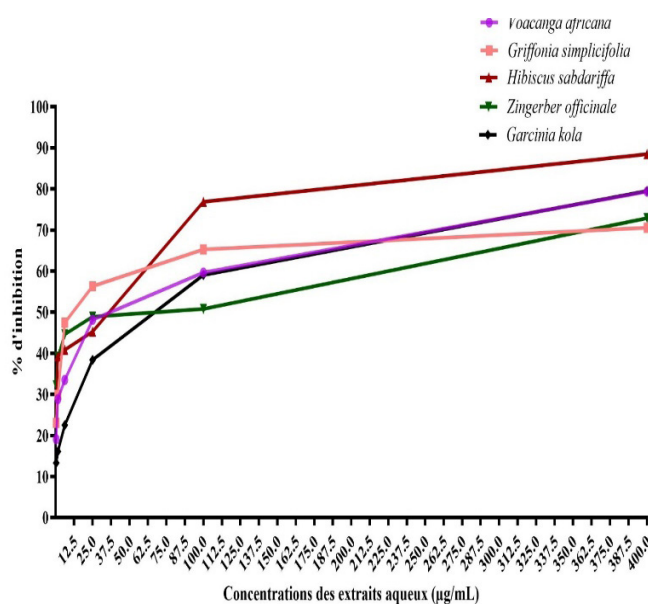


Figure 1a: Dose-response curves of AChE inhibition for the aqueous extracts

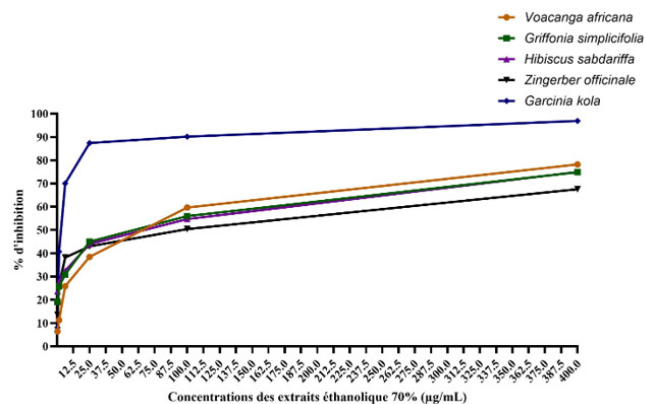


Figure 1b: Dose-response curves of AChE inhibition for the hydroethanolic extracts

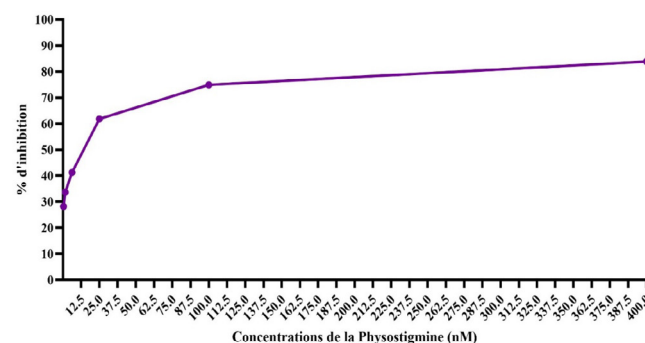


Figure 1c: Dose-response curve of AChE inhibition by the reference inhibitor physostigmine (concentration in nM).

kola. Plant organs were harvested in the village of Zanzansou, in the Iffou region of Côte d'Ivoire, in January 2026.

Reagents and equipment

Chemicals used included acetic acid, chloroform, 2% ferric chloride, concentrated hydrochloric acid, sodium acetate, ammonium hydroxide, a pure ethanol/HCl mixture (3/1, v/v), diluted ammonia, diluted hydrochloric acid, Dragendorff and Wagner reagents, 5,5'-dithiobis-(2-nitrobenzoic acid) (DTNB), acetylthiocholine iodide, hexane, physostigmine, commercial acetylcholinesterase, concentrated sulfuric acid, 10% lead acetate, 60° ethanol and methanol. Equipment included a laminar-flow hood, an oven, a CO₂ incubator set at 37°C, a centrifuge, a water bath, a spectrophotometer/microplate reader, and a precision electronic balance.

Preparation of plant powders and extraction

Plant organs were sorted, cut, washed and shade-dried at room temperature for two weeks, then ground into a fine powder. Aqueous and hydroethanolic extraction of the five organs was carried out following the method of Zirihi *et al.*^[13]: 100 g of powder from each organ was macerated in one litre of solvent (distilled water for the aqueous extraction, 70° ethanol for the hydroethanolic extraction). Mixtures were homogenised for five minutes, filtered successively through cloth, hydrophilic cotton and Whatman filter paper (3 mm), and the filtrates were dried in an oven at 50°C to obtain the crude extracts. Extraction yield was calculated as: Yield (%) = (mass of dry extract obtained / mass of plant material used) × 100.

Ellman's *in vitro* AChE inhibition assay

AChE-inhibitory activity was assessed using Ellman's colorimetric method,^[14] based on the hydrolysis of acetylthiocholine iodide by AChE, releasing thiocholine, which reacts with DTNB to form the yellow 5-thio-2-nitrobenzoate anion (TNB), measurable at 412 nm. Assays were performed in 96-well microplates with a total reaction volume of 200 µL per well, comprising 90 µL phosphate buffer (pH 8.0), 20 µL of extract at various concentrations, 20 µL of AChE and 20 µL of DTNB. Plates were incubated at 37°C for 15 minutes before the addition of 50 µL of acetylthiocholine

iodide substrate. Absorbance was read immediately (t = 0) and again after 5 minutes (t = 5) at 412 nm. Stock extract solutions were prepared at 10 mg/mL and serially diluted to yield the test range 1000, 250, 62.5, 15.625 and 3.9 µg/mL; physostigmine was used as the reference inhibitor over an analogous nanomolar concentration range (1000–3.9 nM).

Enzymatic velocity was calculated as $V = [\text{Abs}(t = 5 \text{ min}) - \text{Abs}(t = 0 \text{ min})] / \Delta t$, and the percentage inhibition as % inhibition = $[(V \text{ control} - V \text{ sample}) / V \text{ control}] \times 100$. Dose-response curves were plotted in GraphPad Prism (version 11), and IC₅₀ values (the concentration inhibiting 50% of AChE activity) were obtained by non-linear regression.

Enzyme kinetics (V_{max} and K_m)

For the two most active extracts, the extract concentration was fixed at 400 µg/mL (400 nM for physostigmine), while the substrate (acetylthiocholine iodide) concentration was varied across six levels: 0.0625, 0.125, 0.25, 0.50, 1 and 2 mM. The reaction was otherwise conducted as above, with absorbance read at t = 0 and t = 5 min. V_{max} and K_m were determined using GraphPad Prism (version 11), with Lineweaver-Burk double-reciprocal plots used to characterise the type of inhibition relative to the uninhibited control.

Phytochemical screening

Standard qualitative colorimetric and precipitation reactions were used to screen the two most active extracts (aqueous *Griffonia simplicifolia* and hydroethanolic *Garcinia kola*) for the main classes of secondary metabolites: sterols and polyterpenes (Liebermann-Burchard-type reaction with concentrated sulfuric acid), polyphenols (2% ferric chloride), flavonoids (2% lead acetate), catechic tannins (Stiasny reagent), gallic tannins (ferric chloride after sodium acetate saturation), anthocyanins and leucoanthocyanins (acidified/alcoholic colour reactions), coumarins (alkaline hydrolysis/acidification), quinones,^[15] alkaloids (Dragendorff and Wagner reagents), and saponins (persistent foam test). Colour changes or precipitate formation, scored qualitatively (present, abundant, or absent), indicated the presence of each chemical class.

Table II: IC₅₀ values (µg/mL) of the anti-AChE activity of the aqueous and hydroethanolic extracts, compared with physostigmine.

Plant species	Aqueous extract IC ₅₀ (µg/mL)	Hydroethanolic (70%) extract IC ₅₀ (µg/mL)
<i>Griffonia simplicifolia</i>	11.71	58.92
<i>Voacanga africana</i>	38.26	65.63
<i>Garcinia kola</i>	68.59	3.01
<i>Hibiscus sabdariffa</i>	36.69	66.03
<i>Zingiber officinale</i>	74.30	95.19
Physostigmine (reference)	13.81 nM (0.0038 µg/mL)	

Table 1: Extraction yield (%) of the five plant species with water and 70% ethanol.

Plant species	Aqueous extract yield (%)	Hydroethanolic extract yield (%)
<i>Griffonia simplicifolia</i>	8.47	16.00
<i>Voacanga africana</i>	10.38	44.11
<i>Garcinia kola</i>	5.77	28.43
<i>Hibiscus sabdariffa</i>	17.90	25.33
<i>Zingiber officinale</i>	12.45	32.77

Table 3: Phytochemical composition of the aqueous extract of *Griffonia simplicifolia* seeds and the hydroethanolic extract of *Garcinia kola* seeds. (++) abundant; + present; – absent)

Chemical group	<i>G. simplicifolia</i> (aqueous, seeds)	<i>G. kola</i> (hydro- ethanolic, seeds)
Total polyphenols	+	++
Flavonoids	–	+
Quinones	–	–
Catechic tannins	++	++
Gallic tannins	++	++
Anthocyanins	–	–
Leucoanthocyanins	–	–
Coumarins	–	–
Alkaloids (Dragendorff)	++	+
Alkaloids (Wagner)	–	–
Saponins	+	–
Sterols and polyterpenes	–	–

Results

Extraction yields

Extraction yields for the five species, obtained with distilled water and 70% ethanol, are summarised in Table I. For every species, hydroethanolic yields exceeded aqueous yields. Aqueous extraction yields ranged from 5.77% (*Garcinia kola*) to 17.90% (*Hibiscus sabdariffa*), while hydroethanolic yields ranged from 16.00% (*Griffonia simplicifolia*) to 44.11% (*Voacanga africana*). The gap between the two extraction modes was most pronounced for *Garcinia kola*, *Voacanga africana* and *Zingiber officinale*, and more moderate for *Griffonia simplicifolia* and *Hibiscus sabdariffa*.

AChE-inhibitory activity and IC₅₀ values

Both aqueous and hydroethanolic extracts of all five species inhibited AChE in a dose-dependent manner. Dose-response curves (Figures 1a, 1b, 1c) were used to derive IC₅₀ values by non-linear regression; the resulting values are given in Table II.

Among the aqueous extracts, *Griffonia simplicifolia* showed the strongest inhibitory activity (IC₅₀ = 11.71 µg/mL), followed by *Hibiscus sabdariffa* and *Voacanga africana*, which displayed moderate activity (IC₅₀ = 36.69 and 38.26 µg/mL, respectively). *Garcinia kola* and *Zingiber officinale* showed the weakest aqueous activity (IC₅₀ = 68.59 and 74.30 µg/mL, respectively). Among the hydroethanolic extracts, in contrast, *Garcinia kola* stood out with an exceptional IC₅₀ of 3.01 µg/mL, followed by *Griffonia simplicifolia* (IC₅₀ = 58.92 µg/mL); *Voacanga africana*, *Hibiscus sabdariffa* and *Zingiber officinale* showed the weakest hydroethanolic activity (IC₅₀ = 65.63, 66.03 and 95.19 µg/mL, respectively). All plant extracts remained less potent than the reference inhibitor physostigmine (IC₅₀ = 13.81 nM, equivalent to 0.0038 µg/mL).

Enzyme kinetics of the most active extracts

Kinetic analysis was carried out on the two most active extracts — the aqueous extract of *Griffonia simplicifolia* and the hydroethanolic extract of *Garcinia kola* — and on physostigmine as reference. For the uninhibited control, V_{max} was 0.1053 U/mg and K_m was 0.0923 mM.

In the presence of the hydroethanolic extract of *Garcinia kola*, V_{max} fell to 0.0088 U/mg while K_m rose to 0.21 mM; the corresponding Lineweaver-Burk plot showed a higher y-intercept and an x-intercept shifted to the right relative to the control. The aqueous extract of *Griffonia simplicifolia* produced an analogous kinetic profile, with V_{max} reduced to 0.0094 U/mg and K_m increased to 0.23 mM, again with a higher y-intercept and a right-shifted x-intercept on the double-reciprocal plot. Physostigmine, used as reference, showed a distinct profile: V_{max} fell sharply to 0.00014 U/mg while K_m increased more moderately, to 0.14 mM, with a markedly steeper Lineweaver-Burk slope than the control. In all three cases, the simultaneous decrease in V_{max} and increase in K_m is characteristic of a mixed-type inhibition mechanism.

Phytochemical screening of the most active extracts

Preliminary phytochemical screening of the aqueous extract of *Griffonia simplicifolia* seeds and the hydroethanolic extract of *Garcinia kola* seeds is summarised in Table III. Total polyphenols were detected in both extracts, more abundantly in the hydroethanolic extract of *G. kola*. Catechic and gallic tannins were detected in both samples. Alkaloids were abundant in the aqueous extract of *G. simplicifolia* and moderately present in the hydroethanolic extract of *G. kola*. Saponins were detected exclusively in the *G. simplicifolia* extract, while flavonoids were detected exclusively in the *G. kola* extract. Quinones, anthocyanins, leucoanthocyanins, coumarins, sterols and polyterpenes were not detected in either extract.

Discussion

This study set out to explore the AChE-inhibitory potential of Ivorian medicinal plants, in a context where the available synthetic AChE inhibitors — donepezil, rivastigmine and galantamine — remain purely symptomatic, offer modest efficacy, and are often poorly tolerated, notably because of gastrointestinal side effects^[16]. Such limitations justify the search for new natural molecules capable of modulating cholinesterase activity while offering better tolerability; medicinal plants constitute an important source of bioactive compounds with demonstrated neuroprotective, antioxidant, anti-inflammatory and anticholinesterase properties^[17,18,19].

Extraction yields varied according to both solvent and plant material, and were consistently higher with the hydroethanolic solvent. This is likely explained by the ability of a water-ethanol mixture to extract compounds of differing polarity — both polar and semi-polar constituents — thereby broadening the range of secondary metabolites recovered^[20].

The particularly high yields observed for *Voacanga africana* (44.11%) and *Zingiber officinale* (32.77%) suggest a high content of ethanol-extractable metabolites in these species, consistent with observations reported by Bekoe et al. (2024)^[9] for *Voacanga africana* and by Ali et al.^[21] for *Zingiber officinale*.

A high extraction yield, however, does not necessarily translate into greater biological activity. Several studies have shown a weak correlation between extraction yield and pharmacological activity, the latter depending more on the nature of the extracted molecules than on their total quantity^[22]. The present results illustrate this point clearly: *Voacanga africana* had the highest hydroethanolic yield but did not show the highest anticholinesterase activity.

The dose-dependent inhibition observed for all ten extracts confirms the presence of compounds able to interact, directly or indirectly, with AChE. The hydroethanolic extract of *Garcinia kola* stood out with a particularly remarkable IC₅₀ of 3.01 µg/mL, markedly lower than that of the other species tested, reflecting a strong affinity of its constituents for the enzyme. This finding is consistent with earlier work describing the neuroprotective properties of *Garcinia kola*: Farombi et al.^[23] and Akinmoladun et al.^[24] showed that the biflavonoids of this species have important antioxidant and neuroprotective properties, while Ijomone and Obi^[25] showed that kolaviron, a biflavonoid isolated from *G. kola* seeds, inhibits AChE in the hippocampus and striatum of rats — the first experimental evidence of this molecule's potential as a natural AChE inhibitor. The strong activity of the hydroethanolic extract observed here may be related to a greater extraction of phenolic compounds, consistent with the abundant polyphenol content revealed by phytochemical screening; molecular modelling studies have shown that polyphenols can interact with the catalytic site of AChE via hydrogen bonds and hydrophobic interactions with aromatic residues lining the enzyme's catalytic gorge^[26].

The aqueous extract of *Griffonia simplicifolia* showed the second-best activity (IC₅₀ = 11.71 µg/mL). Although this species is best known for the high 5-HTP content of its seeds^[27], few data are available on its anticholinesterase activity. Phytochemical screening revealed a strong presence of alkaloids and tannins in this extract. Alkaloids constitute one of the most important chemical families among natural AChE inhibitors — galantamine itself, currently used in the symptomatic treatment of AD, is an alkaloid extracted from plants of the genus *Galanthus*^[28] — so the alkaloid content of the *G. simplicifolia* aqueous extract may well contribute to the observed activity; tannins may also contribute.

Voacanga africana, *Hibiscus sabdariffa* and *Zingiber officinale* showed more moderate activity. For *Voacanga africana*, the moderate inhibition observed could be related to its monoterpene indole alkaloids: Zhao et al. showed that several such alkaloids isolated from *V. africana* seeds inhibit AChE, and these compounds could plausibly contribute to the activity observed here^[29]. For *Hibiscus sabdariffa*, the moderate activity could be linked to phenolic compounds known for their antioxidant and neuroprotective properties;

according to Da-Costa-Rocha et al. (2014)^[30], the species is particularly rich in anthocyanins, flavonoids and phenolic acids, molecules capable of reducing oxidative stress and inflammation, two mechanisms strongly implicated in AD pathophysiology — so even though its anticholinesterase activity was modest in this study, *H. sabdariffa* could still contribute to neuroprotection through complementary mechanisms. The results obtained with *Zingiber officinale* were comparable to those reported by Oboh et al., who showed that gingerols and shogaols display moderate AChE-inhibitory activity while also exerting anti-inflammatory and antioxidant effects that could slow neurodegenerative processes^[31].

Phytochemical screening highlighted polyphenols, tannins, flavonoids, alkaloids and saponins in the two most active extracts, consistent with the literature identifying these chemical families as the principal classes of metabolites involved in AChE inhibition^[32]. Polyphenols, and flavonoids in particular, constitute an important class of natural compounds associated with AChE inhibition^[32], an activity that may relate to their capacity to interact directly with the enzyme. Alkaloids likewise represent a major family of natural cholinesterase inhibitors, several members of which have shown AChE-inhibitory activity^[29]. Tannins, for their part, can influence enzymatic activity through interactions with proteins^[33]. The combined presence of these secondary metabolites in the crude extracts studied here could therefore contribute jointly to the inhibitory activity observed — a hypothesis reinforced by the work of Wagner and Ulrich-Merzenich, who showed that the biological activity of complex plant extracts can be influenced by interactions among their different chemical constituents^[29], and by Rasoanaivo et al., who similarly emphasised that plant extracts may owe their biological effects to the joint contribution of several co-occurring compounds.^[34]

The kinetic study deepened this mechanistic picture. In the presence of either *Garcinia kola* or *Griffonia simplicifolia* extract, V_{max} decreased sharply while K_m increased — a combination that characterises mixed-type inhibition, in which the active molecules can bind both free enzyme and the enzyme-substrate complex. Similar observations were reported by Ahmed et al., who showed that *Calligonum polygonoides* exerted a mixed-type inhibition of AChE, characterised by an increase in K_m and a decrease in V_{max}.^[35] This mode of inhibition may be of particular pharmacological interest, since it allows inhibition of AChE to be maintained even as substrate concentration rises, unlike strictly competitive inhibitors.

Despite the interest of these findings, several limitations must be acknowledged. First, the study relies exclusively on *in vitro* assays; biological activity observed in a simplified enzymatic system does not necessarily reflect real therapeutic efficacy. Factors such as intestinal absorption, hepatic metabolism, bioavailability, potential toxicity, and the ability

of active molecules to cross the blood-brain barrier can considerably influence *in vivo* activity.^[36]

Conclusion

This study aimed to evaluate the AChE-inhibitory potential of five Ivorian medicinal plants — *Garcinia kola*, *Griffonia simplicifolia*, *Voacanga africana*, *Hibiscus sabdariffa* and *Zingiber officinale* — against acetylcholinesterase, a key enzyme implicated in the cognitive deficits of Alzheimer's disease.

Extraction yields varied by species and solvent, with hydroethanolic extracts generally outperforming aqueous extracts — underlining the importance of solvent choice in the extraction of potentially bioactive secondary metabolites. Anticholinesterase evaluation showed that all extracts tested exerted dose-dependent AChE inhibition. Among the species studied, the hydroethanolic extract of *Garcinia kola* displayed the highest activity (IC₅₀ = 3.01 µg/mL), while the aqueous extract of *Griffonia simplicifolia* also showed remarkable activity (IC₅₀ = 11.71 µg/mL), highlighting the particularly interesting potential of these two species as natural sources of AChE inhibitors.

Phytochemical screening of the most active extracts revealed the presence of polyphenols, tannins, alkaloids and saponins, chemical groups recognised in the literature for their neuroprotective properties and their capacity to inhibit AChE; the observed activity therefore appears to result from a synergistic action among several secondary metabolites rather than the effect of a single compound. Kinetic analysis showed that the active extracts exerted a mixed-type inhibition of AChE, characterised by a decrease in V_{max} together with an increase in K_m, indicating simultaneous interaction with the free enzyme and the enzyme-substrate complex — a mode of action of pharmacological interest, since it allows inhibition to be maintained even as substrate concentration rises.

Overall, this study contributes to the scientific valorisation of Ivorian medicinal plants and highlights, in particular, *Garcinia kola* and *Griffonia simplicifolia* as promising sources of natural molecules that could contribute to the development of new therapeutic approaches for Alzheimer's disease. These results nonetheless remain preliminary and require confirmation through further investigation.

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