Advances in Bioresearch
Adv. Biores., Vol 16 (6) November 2025: 515-527

Print ISSN 0976-4585; Online ISSN 2277-1573
Journal's URL:http://www.soeagra.com/abr.html
CODEN: ABRDC3
DOI: 10.15515/abr.0976-4585.16.6.515527

Advances in Bioresearch

REVIEW ARTICLE

Therapeutic and pharmacological efficacy of *Cryptolepis sanguinolenta* (Lindl.) Schlechter and their active constituents: In-depth Review

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ABSTRACT
The present study aims to meticulously evaluate and analyse the extensive information about the botanical assessment, geographical distribution, ethno- medicinal attributes, and phytochemical components of cryptolepine derivatives that have been extracted from Cryptolepis sanguinolenta (Lindl.) Schltr. is an Apocynaceae plant famous for its traditional use in West African medicine it is a potent therapeutic for antimalarial, anticancer, and anti-inflammatory capabilities that have garnered attention, it's important to study alternate therapy strategies, especially by discovering innovative drugs with several modes the primary categories of alkaloid derivatives that exhibit biological activity include cryptolepine, isocryptolepine, neocryptolepine, quindoline, and cryptospirolepine. The present study focuses on the phytochemical analysis of Cryptolepis sanguinolenta to investigate its pharmacological characteristics and potential therapeutic application. It is imperative to conduct additional studies to fully understand its biological mechanism of action and explore its potential therapeutic applications. The complex principles governing these activities are a fundamental basis for future investigations and potential applications across various domains.
Keywords: *Cryptolepis sanguinolenta, Natural compounds, phytochemical constituents, Pharmacological aspects*

Received 24.08.2025 Revised 01.10.2025 Accepted 11.11.2025

How to cite this article:
Shourya Pratap, Abhilasha Mittal, Sambit Kumar Parida, and Vipin Kumar Pandey. Therapeutic and pharmacological efficacy of *Cryptolepis sanguinolenta* (Lindl.) Schlechter and their active constituents. Adv. Biores. Vol 16 [6] November 2025. 515-527

INTRODUCTION

The utilization of medicinal plants can be traced back to ancient civilizations, as exemplified by the Rigveda and Atharveda, and remains a prominent component of healthcare on a global scale(1-3), medicinal plants are being studied as a possible way to fight many diseases, including AIDS(4), malaria(5), tuberculosis (6), conditions causing inflammation(7), and cancer (8). The utilization of medicinal plants in the search for novel pharmaceutical agents is rooted in the presence of bioactive compounds within them, which can be harnessed for drug development, exploration, and therapeutic effects(9, 10). Traditional medical systems such as Unani and Ayurveda have significantly impacted the healthcare sector in India several studies have highlighted the significant contributions made by these systems (11-15). The genus sanguinolenta, despite its significance in West Africa as a subject of medicinal plant research, needs comprehensive reviews regarding its conventional applications, in phytochemistry, and pharmacological potential for therapeutic effects. This rigorous approach involves a comprehensive search and analysis of relevant scholarly articles, books, and other credible sources to gather a comprehensive understanding of the existing knowledge and research on *Cryptolepis sanguinolenta*. These reviews are critical for gaining a deeper understanding of this genus' therapeutic properties and guiding future research efforts, investigation will likely be an invaluable asset for professionals and researchers who are fascinated by alternative treatment and drug discovery.

MATERIAL AND METHODS

Plant profile:

The plant *Cryptolepis sanguinolenta* belongs to the family Apocynaceae subfamily Periplocoideae, genus *Cryptolepis,* species *sanguinolenta,* phylum Magnoliophyta, division Equisetopsida, subclass Magnoliidae, order Gentianales, and superorder Asteranae, is native to West Africa but commonly found in countries such as Ghana, Nigeria, and Ivory Coast has been authenticated with "World Flora Online" and MPNS for the manuscript(16) (Table I). It grows like a shrub, with a dense and bushy upright stem that reaches heights of 1.6 to 6.6 feet(17). The leaves have a smooth, glossy, dark green appearance they are shaped like a lance or ellipse, with sharp tips that grow in pairs, directly across from each other on the stem the size of the leaves can vary, typically measuring between 5-12 centimeters in length(18). The flowers are small have a tube-like shape usually greenish-yellow and are arranged in clusters at the ends of the branches have a pleasant fragrance (19). The people of Bantu, Ghana, Hausa, Ewe, Twi, and Yoruba have different tribal names associated with them these names include Kolimekari, Ghana Quinine, Gangnamau, Kadze, Nibima, and Paran Pupa, respectively various studies have been conducted on these groups, such as the ones by (20-24). The picture of *C. Sanguinolenta* is shown in Figure 1.

Search strategy and study selection:

The process of study selection in systematic reviews is a critical step that follows the PRISMA guidelines, which have been shown to uncover substantial variability in the literature(25, 26). The comprehensive analysis of existing literature about the ethno-medicinal applications, phytochemistry, biological properties, and toxicity profiles of diverse plant extracts elucidates a plethora of promising opportunities inherent in natural resources. Several studies have been conducted to investigate the utilization of scientific databases from different sources, including PubMed, ScienceDirect, Scopus, and Google Scholar numerous studies have been conducted to investigate the utilization of indigenous medicinal plants to gain a comprehensive understanding of the diverse flora. The aforementioned studies collectively emphasize the significance of native knowledge and highlight the ongoing necessity for further research in the field of ethnopharmacology. The manuscript selection process for publication is a crucial step that emphasizes the importance of empirical quality, conceptual transparency, and the pertinent nature of the study. The aforementioned studies collectively emphasize the significance of maintaining methodological rigor, clarity, and relevance when choosing manuscripts for publication.

Data extraction and processing:

Researchers have conducted extensive research on the ethnobotanical and phytochemical aspects of the traditional uses of *Cryptolepis sanguinolenta* (Lindl.) Schltr. Plants to combat various ailments additionally, to conduct a global analysis of the initial release output of plant-based medicines and aromatherapy. The researchers can acquire a thorough comprehension of the plants under investigation, encompassing their traditional applications, chemical components, and potential biological effects, all of which can serve as valuable insights for future research endeavors. The data collected for the pharmacology investigation encompassed various parameters these parameters include the experimental approach, whether in-vivo or in-vitro, the specific concentrate should be a fraction or a retrieved molecule under evaluation or dose of the substance, the type of parasite, microbe, or cell line used the method of administration, and the outcomes of the study, including key findings and the evaluated action mechanisms.

Indigenous uses:

Traditional medicine in West Africa and Ghana has primarily used this extract of roots from *Cryptolepis sanguinolenta* (Lindl.) Schltr., due to its potential to treat malaria is known to contain significant alkaloids like cryptolepine, which has been studied by various researchers(27-29). The root and bark contain significant bioactive alkaloids that have shown higher in-vitro antiplasmodial activity compared to chloroquine these compounds include cryptolepine, hydroxycryptolepine, and qunidoline(30). Pharmaceutical preparations use various alkaloids such as quinine, cinchonine, isocryptolepine, and vincristine(31) a team of researchers from the University of Ibadan in Nigeria, led by S.O. Duke, the first discovered isocryptolepine as a minor alkaloid in *Cryptolepis sanguinolenta* this discovery was documented in several studies conducted by (32-34) studies have shown its effectiveness against both strains of *Plasmodium falciparum*, including those that are resistant to chloroquine. Research has also discovered its potential antitumor, antiviral, and anti-inflammatory properties (35, 36). Isocryptolepine alkaloids have also demonstrated promising potential as therapeutic agents for a range of diseases, including cancer, viral infections, and inflammation they have demonstrated significant anti-tumor activity against various types of cancer cells, such as those found in the lungs, prostate, and breast(37, 38) (Table II).

PHYTOCHEMICAL CONSTITUENTS

The phytochemical analysis of different parts of the plant has shown that it contains a wide range of metabolites including alkaloids, glycosides, resins, carbohydrates, tannins, flavones, carnosic acids, ursolic acid, and cryptolepine. The tap roots of plants are the predominant part that is commonly employed for medicinal purposes, as documented by (39-41). Figure 2 visually depicts the derived primary alkaloid extracted from *Cryptolepis sanguinolenta* (Lindl.) Schltr.

PHARMACOLOGICAL ACTIVITY

Anti-plasmodial activity:

Malaria is a disease of significant mortality and highly lethal illness, is caused by Plasmodium parasites and transmitted to humans through the bites of infected female Anopheles mosquitoes, it is pervasive in torrid and sub-equatorial provinces, with a particular focus on Africa(42-46), and the current drugs are showing resistance, so there is need to discover new components(47-50). Unfortunately, the effectiveness of current drugs is being compromised due to the emergence of drug resistance, necessitating the urgent exploration of novel therapeutic components. The utilization of *Cryptolepis sanguinolenta* within the Ghanaian populace to manage uncomplicated malaria holds considerable importance, as evidenced by the studies conducted by(51, 52). The presence of indole alkaloids in *C. sanguinolenta* has a significant impact on the composition of numerous antimalarial herbal preparations notably; the antimalarial properties of these preparations are largely attributed to the substantial contribution of indole alkaloids(53, 54). We have subjected the aqueous root extracts of *c. sanguinolenta* to in-vitro and in-vivo inhibition experiments to evaluate their potential activity against different strains of Plasmodium falciparum to target enzyme P*f*DHFR-TS the results of these experiments have shown promising outcomes, indicating the extract's effectiveness against both chloroquine-sensitive and chloroquine-resistant parasite strains the potency of these compound inhibiting parasite growths is demonstrated by the IC_{50} values ranging from 1 to 2μg/ml(55, 56). The minor alkaloid isocryptolepine has demonstrated significant efficacy against both chloroquine-sensitive and chloroquine-resistant strains of Plasmodium falciparum to target the enzyme P*f*DHFR-TS it exhibited moderate antimalarial activity with an IC_{50} range of 1177nM against chloroquine-resistant parasites. Furthermore, a modified synthetic 8-bromo-2-chloroisocryptolepine displayed even greater activity in targeting the enzyme P*f*DHFR-TS, with an IC_{50} value of 85nM against the chloroquine-resistant strain W2mef. The measure of DNA damage in single-cell gel electrophoresis, Olive Tail Moments, went up about the same amount when exposed to 2-fluorocryptolepine and 8-chloro-7-nitrocryptolepine however, the study was found to be statistically significant at concentrations of 200μM for cryptolepine and 100μM for 8-chloro-7-nitrocryptolepine, as reported by (57-60). For the discrimination of alkaloids, we have to employ IC_{50} values that are chronic as the proportion of cytotoxicity over antimalarial activity, as proclaimed (54) (Table III). The modification of the Cryptolepine molecule at the carbon 11 position with different side chain compounds (3f, 3g, and 3i) has shown significant activity against chloroquine-resistant P. falciparum W2 strains IC_{50} values of 20, 32, and 22 were found for the compounds with propyl, butyl, and cycloalkyl-diamine side chains(61). The compound 7-isopropyl-isocryptolepine has demonstrated significant activity against strains of Plasmodium falciparum (3D7) the IC_{50} and IC_{90} values of ICL-M were measured at 148.31±22.87 and 243.39±17.99nM, respectively(35). The neocryptolepine exhibited antiplasmodial activity against the K1 and 3D7 strains interestingly; analogue 3o demonstrated good selectivity on K1, with values of 1041.7 and 1225.7. The ester-modified neocryptolepine shows great potential in combating malaria, particularly compound 8a, which contains a 3-aminopropyl amino group at the C11 position, this compound has demonstrated significant antimalarial activity with a low IC_{50} value of 24.8nM(62, 63). The addition of a methyl group to 3-aminopropyl amino at carbon 6 and a chlorine atom at the carbon 2 position result in a modified structure of isocryptolepine, this modification shows a significant decrease in cytotoxicity and a notable increase in antimalarial activity, with an IC_{50} of 11nM against the CQS strain (NF54) and approximately 17nM against the CQR strain (K1) the resistance indices (RI) of 1.6 shows that these changes in compounds can overcome resistance in the CQR strain (64) (Figure 3).

Anticancer activity:

Cancer is a complex, ensuing disease that can affect various regions of the body it arises when specific cells in the body undergo uncontrolled growth and division, resulting in the formation of an abnormal mass of tissue known as a tumour these exists a wide range of cancer types, each with its distinct characteristics, treatment options, and prognosis(65, 66). Complementary and alternative medicine (CAM) has seen an increase in popularity among cancer patients seeking supplementary assistance and relief from symptoms or adverse effects associated with conventional treatments the utilization of natural remedies, specifically herbal supplements, as a therapeutic approach for cancer, is currently being investigated(67, 68). Researchers have found that the compound known as isocryptolepine cognate exhibits strong anti-proliferative activity against A549 and HCT116 cancer cells, scientists have found that the methyl localization effect and the presence of substituent groups at the C2 position of the quinoline moiety are very important in determining how well cryptolepine derivatives can intercalate into DNA, the neocryptolepine analogues 7c exhibits the highest level of anti-proliferative activity against MV4-11 leukaemia cells, as evidenced by its IC_{50} value 0.012±0.002μM. Compounds 7f and 7i demonstrate comparable and significant anti-proliferative efficacy against A549 lung cancer cells, as evidenced by their IC_{50} values of 0.190±0.027μM and 0.194±0.063μM, and on HCT116 colon cancer cells, as evidenced by their IC_{50} values of 0.117±0.055μM and 0.116±0.078μM, respectively. The analogue 7b exhibits unfavorable properties, as it exhibits a twofold increase in cytotoxicity against normal BALB/3T3 cells, with an IC_{50} value of 0.401±0.015μM, in comparison to other neocryptolepine analogues. The antiproliferative activity of isocryptolepine analogues against cancer cell lines was investigated. The antiproliferative effects of compound 10e were strong against the cancer cell lines MV4-11, A549, and HCT116, with IC_{50} values of 0.05±0.01μM, 0.11±0.07μM, and 0.01±0.00μM, the compound also demonstrates significant cytotoxicity against normal BALB/3T3 cells, with an IC_{50} value of 0.08 ± 0.02μM(69)(Figure 4). The synthesis and evaluation of Neocryptolepine 5-methyl-5H-indolo[2,3-b]quinoline analogues were conducted to assess their potential efficacy against Ehrlich ascites carcinoma (EAC) both in-vitro and in-vivo, during the evaluation it was observed that the neocryptolepine analogues demonstrate a higher level of cytotoxic qualities against EAC cell line when compared to cisplatin, this suggests that the neocryptolepine analogues may have greater potential as cytotoxic agents in the treatment of EAC. The analogues 6b and 6d exhibited notable cytotoxicity, as evidenced by their IC_{50} values of 6.4×10−5 and 1.5× 10±4μM, respectively. The aforementioned values serve as indicators of the relative effectiveness of the substances in suppressing the proliferation of cancerous cells. Moreover, it is worth noting that both analogues exhibited significantly greater antiproliferative activities in comparison to the reference drug, thalidomide (IC_{50} = 2.6 × 10−4μM), as well as the natural compound I (IC_{50} = 5.4 × 10−4μM), this compelling evidence strongly indicates that these analogues possess a promising potential for enhanced efficacy in the treatment of cancer(70). The present study involved the synthesis and evaluation of a series of novel isoxazolo [50, 40:5, 6] pyrido[2,3-b] indoles derivatives to investigate their potential as anticancer agents the neocryptolepine derivative 7d has been found to exhibit significant anticancer activity against HeLa, MCF-7, and NCI-H460 cell lines, with IC_{50} values of 19.72±1.3μM, 18.82±1.5μM, and 16.68±1.1μM, similarly, compound 7g has demonstrated significantly greater potential anticancer activity against the same cell lines, with IC_{50} values of 23.62±2.5μM, 22.52±2.8μM, and 20.45±2.3μM, respectively(71). The indolo[3,2-c] quinoline derivative, which has been synthesized by amalgamation, was subjected to in vitro testing against a cancer cell line against HeLa cells, with an IC_{50} value of 0.52μM, furthermore, it has been observed that the compound exerts its anti-proliferative and pro-apoptotic effects by targeting DNA, topo I, and topo II(71).

Anti-inflammatory activity:

Inflammation is an essential and inherent immune system reaction in the human body, serving to protect and heal various bodily organs however; an excessive or prolonged state of inflammation can give rise to a range of autoimmune disorders, such as cancer(72, 73). It is observed that cryptolepine shows a significant role in anti-inflammatory effects through its ability to inhibit the production of nitric oxide (NO) and reduce the levels of nuclear factor kappa-light-chain enhancer of activated B cells (NF-kB) in research, in-vivo results demonstrate that cryptolepine effectively lowers the production of NF-kB and NO in RAW264.7 cells that have been activated by LPS. In the in-vivo study, the administration of cryptolepine at doses ranging from 10 to 40 mg/kg via intraperitoneal injection resulted in a significant decrease in rat paw oedema and pleurisy induced by carrageenan, within the context of IL-1b-induced SK-N-SH neuroblastoma cells, it was observed that the application of cryptolepine at concentrations ranging from 2.5 to 20nM result in a significant decrease in the synthesis of pro-inflammatory mediators, specifically TNFa, IL-6, and PGE2. The anti-neuroinflammatory effect of cryptolepine appears to be facilitated through the involvement of NF-kB and p38 signaling pathways(74).

Antifungal & Antibacterial activity:

From a global perspective, it is evidence that infectious diseases caused by bacteria and fungi present a substantial risk to the well-being of the human population, the emergence of drug resistance in certain bacteria and fungi has led to a decline in the efficacy of existing antibacterial and antifungal therapies, highlighting the urgent requirement for the development of new antibiotics(75-78). In 2019 a significant number of deaths, specifically 1.27 million out of 4.95 million, were attributed to diseases caused by antibiotic-resistant bacteria infections on global mortality rates, surpassing the number of deaths caused by HIV/AIDS 864,000 and malaria 643,000(79). Isocryptolepine derivatives are evaluated for the effectiveness against several fungal species, including *P. zeae, R. solani, B. cinerea, M. oryzae, S.*

sclerotiorum, and *F. oxysporum f. sp. Vasinfectum*, the EC_{50} values for B-3, A-1, A-0, A-2, B-1, and B-2 were determined to be 4.77μg/mL, 6.27μg/mL, 2.72μg/mL, 8.81μg/mL, 15.88μg/mL, and 8.96μg/mL(80). Neocryptolepine has been found to exhibit antibacterial activity specifically against gram-positive bacteria, with MIC value being observed to be less than 100μg/ml which is comparatively lowers(81). *Cryptolepis sanguinolenta* has shown that the extracts of *L. camara*, *C. sanguinolenta*, and *Z. leprieurii* were very effective at killing strains that are resistant to rifampicin, the minimum inhibitory concentrations for these extracts were measured at 176, 97, and 45μg/mL, M. smegmatis demonstrated the lowest level of activity among the tested strains, with MICs of 574, 325, and 520μg/mL for *L. camara, C. sanguinolenta*, and *Z. leprieurii* extract(82). The antibacterial efficacy of several instances exhibited a range of 2-4mg/mL against methicillin-resistant S. Aureus found that the values obtained for methicillin and berberine were significantly higher than those for the substance which were similar to those for vancomycin(83).

Antihyperlipidemic Activity:

The LDL cholesterol is harmful it can deposit cholesterol in the walls of arteries, over time this leads to the formation of plaques, which narrow the arteries and make them less flexible if a plaque ruptures, potentially leading to serious or fatal cardiovascular events(84). Statins and fibrate medications that act on fatty acids and triglycerides have emerged as the foremost pharmacological intervention for the management of hyperlipidemia, but they are generally considered a second-line treatment option(85). The extract of cryptolepine from the plant species *Cryptolepis sanguinolenta* was evaluated for its effect on the uptake of low-density lipoprotein (LDL) using HepG2 cells cryptolepine exhibited significant activity in stimulating the uptake of low-lipid lipoproteins (Table IV), this prosecution emphasizes the potential of isocryptolepine as a promising candidate for further investigation in the development of new antihyperlipidemic agents(86, 87).

Anti-diabetic Activity:

Diabetes mellitus (DM) is a condition characterized by disrupted energy metabolism, often resulting in elevated blood sugar levels due to inadequate insulin production there are two distinct kinds of diabetes type I and type II(88). An autoimmune attack on beta cells, which produce insulin, is the main contributory factor to type I (T1DM) diabetes this attack typically begins in individuals who have a genetic susceptibility(89). T2DM is a prevalent metabolic disease characterized by reduced insulin secretion from pancreatic β-cells and resistance to insulin in peripheral tissues such as muscle and fat, as a result of these two shortcomings, cells struggle to efficiently take in glucose from the bloodstream, leading to hyperglycemia(90). Proper treatment or management of diabetes can prevent serious medical complications such as cardiovascular disorders, strokes, nerve damage, kidney problems, foot ulcers, and vision impairment. Although there is no definitive solution for diabetes, adopting a healthy lifestyle that incorporates consistent physical activity, a well-rounded diet, and effective medication management can effectively manage the condition and minimize the likelihood of repercussions(91). The extract of *Cryptolepis sanguinolenta* plant has shown promising effects on glucose metabolism, cholesterol levels, and pancreatic β cells in research the Wistar albino rats weighing between 130 and 170gm were administered varying quantities of the extract (50mg/kg, 150 mg/kg, and 250mg/kg body weight) orally once a day for 21 days, the reduction in circulating glucose, total cholesterol, triglyceride, and LDL cholesterol levels enhances its potential as a therapeutic option for metabolic diseases. There were notable decreases ($P<0.05$) in abstinence blood glucose levels after the 21-day course of treatment compared to the initial measurements(92). The cryptolepine alkaloids have antihyperglycemic effects in reducing glucose levels in animal models of non-insulin-dependent diabetes mellitus due to their ability to enhance glucose uptake by 3T3-L1 cells, resulting in a reduction in blood glucose levels(93, 94). Hyperglycaemia was observed on day 3 after induction when the average fasting blood sugar level was 4.56±0.22 mmol/L, which increased to 20.34±1.29 mmol/L in rats with diabetes the levels of FBS dropped significantly ($P<0.001$) when CRP (10, 30, and 100 mg/kg) and glibenclamide (a hypoglycaemic control drug) were given they went from 3.0 - 4.2 mmol/L. The control group did not show any substantial fluctuations in blood glucose levels(95).

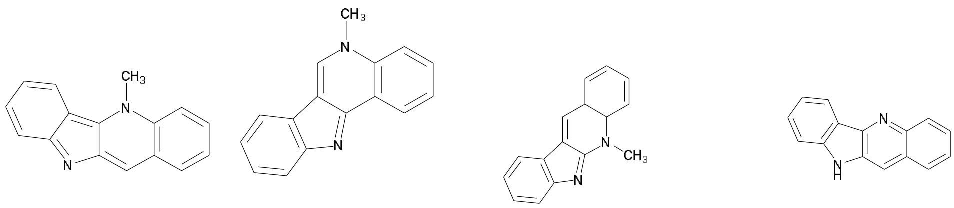
Antitumor Activity:

A tumor is an abnormal mass of tissue that forms when cells grow and divide more rapidly than normal tumors can be benign (non-cancerous) or malignant (cancerous) in the beginning tumors do not spread to other parts of the body, malignant tumors can invade nearby tissues and metastasize, spreading cancer cells to other regions. Tumor growth can cause a range of symptoms depending on its location and size, and treatment typically involves surgery, chemotherapy, radiation, or targeted therapies. Early detection often improves treatment outcomes. Gastric tumors can develop in different parts of the stomach, and the cancer often grows slowly over many years, symptoms may include indigestion, stomach pain, nausea, and weight loss, but they often appear in advanced stages, making early detection challenging.

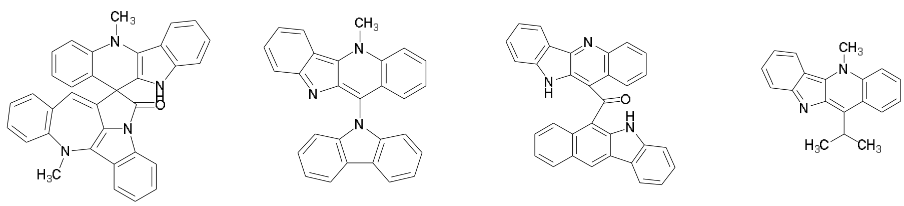
Neocryptolepine has a strong inhibitory effect on gastric cancer cells by affecting the PI3K/AKT/mTOR signaling pathway, it has significantly impeded both the growth and movement of AGS cells. In addition, the way it works seems to disrupt the function of mitochondria, which ultimately causes a decrease in membrane potential and initiates cell death in AGS cells, as indicated by the IC_{50} value 148nM(96). Neocryptolepine rhodamine compounds were synthesized and evaluated for their potential antiproliferative activity contrary to two types of cancer cells: MDA-MB-231 (breast cancer) as well as HepG-2 (Hepatoma cancer). A recent study suggests that two molecules, 9b and 11c, exhibited remarkable activity against the proliferation of hepatoma cancer as compared to standard drug 5-fluorouracil (97), as indicated in (Table V). The anticancer effects of a new neocryptolepine derivative called N1-(5-methyl-5H-indolo[2,3-b] quinoline-11-yl) benzene-1,4-diamine, N-(2-aminoethyl)-5-methyl-5H-indolo[2,3-b] quinoline-11-amine hydrochloride and Etoposide the research examined the effects of these compounds on Ehrlich solid tumor and hepatocellular (HepG2) as well as colon (HCT-116) carcinoma cell lines(98) shows comparable better result as shown in figure 5.

Fig.1: The leaves and flower of *Cryptolepis sanguinolenta*

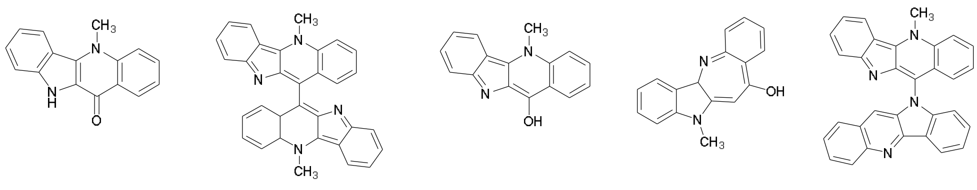
Fig.2: Structure of alkaloids isolated from the root of *Cryptolepis sanguinolenta*



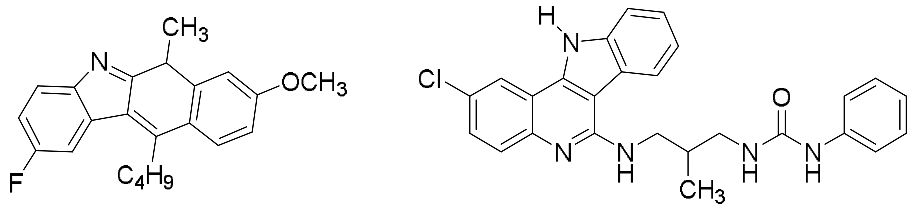
Cryptolepine (1) Isocryptolepine (2) Neocryptolepine (3) Quindoline (4)



Cryptospirolepine (5) Cryptolepicarboline (6) Cryptomisrine (7) 11-isopropylcryptolepine (8)



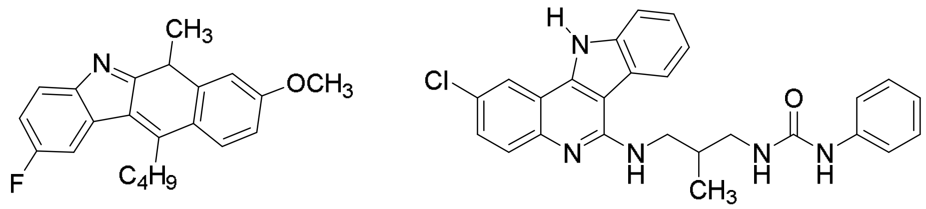
Cryptolepinone (9) Biscryptolepine (10) Hydroxycryptolepine (11) Cryptoheptine (12) Cryptoquindoline (13)



11-butyl-2-fluoro-8-methoxy-6-methyl-6H-benzo[b]carbazole

1-(3-(2-chloro-11H-indolo[3,2-c]quinolin-6-ylamino)-2-methylpropyl)-3-phenylurea

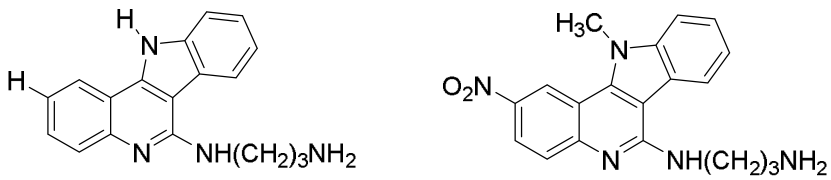
Fig.3: Modified Structure of Isocryptolepine



11-butyl-2-fluoro-8-methoxy-6-methyl-6H-benzo[b]carbazole

1-(3-(2-chloro-11H-indolo[3,2-c]quinolin-6-ylamino)-2-methylpropyl)-3-phenylurea

Fig.4: Structure of Isocryptolepine cognate



N-(3-aminopropyl)-11H-indolo[3,2-c]quinolin-6-amine

N-(3-aminopropyl)-11-methyl-2-nitro-11H-indolo[3,2-c]quinolin-6-amine

Fig.5: Structure of novel Neocryptolepine

Table No. 1: Taxonomical classification of *Cryptolepis sanguinolenta*

S.N.	Kingdom	Plantae
1.	Phylum	Magnoliophyta
2.	Class	Equisetopsida
3.	Subclass	Magnoliidae
4.	Order	Gentianales
5.	Superorder	Asteranae
6.	Family	Apocynaceae
7.	Subfamily	Periplocoideae
8.	Genus	*Cryptolepis*
9.	Species	*Sanguinolenta*

Table No. 2: Indigenous uses of *Cryptolepis sanguinolenta*

S. N.	Part of Plant	Indigenous uses	References
1.	Root	Fever, antimicrobial, &septicemia.	(99, 100)
2.	Root	Abdomen and bowel disturbances	(19)
3.	Root	Tuberculosis	(39, 94)
4.	Root	Hepatitis, wounds	(101)
5.	Roots & leaves	Hypertension, puffiness, pyrexia, malaria	(102)
6.	Fresh aerial parts	Diarrhea	(103)
7.	Not specified	Respiratory diseases, enteric diseases	(104)
8.	Not specified	Insomnia	(41)
9.	Not specified	Amoebiasis	(105)
10.	Not specified	Diabetes	(92)

Table No. 3: IC_{50} values of various antimalarial alkaloids and selectivity index (SI)

S. N.	Alkaloid	IC_{50}	SI	Strain	Resistance
1.	Quinine	0.413	ND	W2	CQR
2.	Isostrychnopentamine	0.152	49	W2	CQR
3.	Strychnogucine B	0.085	176	W2	CQR
4.	Tubulosine	0.024	0.9	INDO	CQR
5.	Cryptolepine	0.114	9	K1	CQR
6.	Neocryptolepine	2.610	1.2	K1	CQR
7.	Isoneocryptolepine	0.230	19	K1	CQR
8.	N-methyl-isocryptolepine	0.017	747	K1	CQR
9.	2-bromoneocryptolepine	4.0	>8	W2	CQR
10.	2,7-dibromocryptolepine	0.049	122	K1	CQR

Table No. 4: Dil.-LDL uptake results for indoloquinoline alkaloids from *Cryptolepis sanguinolenta* and berberine in HepG2 cells

Compounds (5 μM)	Fold of control (DMSO)
Cryptolepine	0.78 ± 0.02
Isocryptolepine	1.85 ± 0.01
Neocryptolepine	1.00 ± 0.03
Cryptolepinone	0.96 ± 0.01
Quinoline	0.97 ± 0.01
Nagilactone B	1.44 ± 0.01

Table No. 5: IC_{50} of the examined compounds on two different cancer types

Compound Code	IC50 (μM) ± SD	
	MDA-MB-231	HepG-2
9a	37.7 ± 3.9	27.7± 3.8
9b	30.0 ± 3.8	36.1 ± 4.2
11c	22.7 ± 3.1	35.6 ± 4.1
11d	25.3 ± 3.1	25.4± 3.3
14	29.9 ± 3.6	23.6 ± 3.8
16a	38.8 ± 4.3	24.6± 3.3
16b	31.9 ± 3.8	25.6 ± 3.1
5-Fluorouracil	12.0 ± 2.5	28.0 ± 2.3

CONCLUSION

The aim of conducting the review on *Cryptolepis sanguinolenta* is to identify, and analyse its pharmacological characteristics and evaluate its potential therapeutic applications. Scientists can find chemical compounds with better properties by looking at cryptolepine derivatives; these compounds have better selectivity, solubility, assurance, and less toxicity. The potential optimization of the pharmacological properties of cryptolepine may require structural modifications or the complete synthesis of novel derivatives. The primary objective of investigating cryptolepine, and isocryptolepine-like derivatives is to develop novel modified compounds with enhanced therapeutic efficacy and reduced side effects for the treatment of various diseases, including malaria, fungal infections, cancer, and inflammatory disorders. These modified agents aim to surpass the effectiveness of currently available treatments through the optimization of alkaloid-based derivatives from *Cryptolepis sanguinolenta* (Lindl.) Schltr., scientists have been able to enhance activity against specific targets, minimize toxicity, and expand pharmacokinetics. This has led to the creation of more reliable and safer individuals for human use by examining cryptolepine focusing on understanding its molecular level mechanisms, its interactions with tissues, proteins, and amino acids, and how it can be further improved for therapeutic purposes. To fully understand their safety and effectiveness, it is necessary to do a lot of experiments on the cryptolepis alkaloids and their related derivatives using animals as test subjects.

ABBREVIATIONS

Cells known as **A549**, which are derived from human alveolar basal epithelial cells and have adenocarcinoma properties, **CQR** refers to a strain that is resistant to chloroquine, while **CQS** indicates a strain that is sensitive to chloroquine. **EAC-** Ehrlich cites carcinoma, exploring the fascinating world of **FtsZ-** Filamenting temperature-sensitive mutant Z, Human colorectal carcinoma, specifically **HCT116, IC50** is the concentration at which a response is reduced by half. **SI-** Selectivity index, **LDL,** also known as low-density lipoprotein, Unable to determine, Plasmodium berghei and Plasmodium falciparum are two types of malaria parasites. **RI-** Resistance indices, there are two types of topoisomerases involved in DNA manipulation. **Topoisomerase I** is responsible for single-strand DNA breaks, while **Topoisomerase II** is involved in transient double-strand DNA breaks.

CREDIT AUTHORSHIP CONTRIBUTION STATEMENT

Shourya Pratap: Conceptualization, Methodology, Investigation, Data curation, Writing- Original draft, Supervision; **Abhilasha Mittal:** Writing-reviewing and editing; **Sambit Kumar Parida:** Writing-reviewing and editing; **Vipin Kumar Pandey:** Writing-reviewing and editing.

DECLARATION OF COMPETING INTEREST

The authors assert that no competing interest exists.

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