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Review Article

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Novel Insights into Isoquinoline Alkaloids as Therapeutic Agents for Infectious and Non-Infectious Diseases

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Abstract

In recent years, traditional natural products have gained significant scientific interest, with ongoing research into their therapeutic potential. Isoquinoline alkaloids intrigue researchers due to their varied health effects. This review explores isoquinoline alkaloids from various plants. Among plant compounds, alkaloids are prominent, with isoquinoline alkaloids noted for their diverse biological activities, including anticancer, antineurodegenerative, antidiabetic, anti-inflammatory, and antimicrobial properties. Using plants for health conditions is a deeply rooted practice in traditional medicine. Modern therapeutics has encouraged global use of natural products for treating ailments. This review compiles information on isoquinoline alkaloids' potential in disease treatment and aims to guide future research on biologically active isoquinoline alkaloids and their plant sources. The authors acknowledge they could not cover the entire topic scope regarding isoquinoline alkaloids' biological activity. This review suggests avenues for further research and assists other researchers in future investigations.

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Introduction

Isoquinoline alkaloids are a class of naturally occurring bioactive compounds that are widely found in nature and play a crucial role in the secondary metabolism of many plant species. These alkaloids are among the most prevalent in the plant kingdom. They are typically found in families such as Papaveraceae, Berberidaceae, Fumariaceae, Menispermaceae, Rutaceae, Magnoliaeace, Cactaceae, Ranunculaceae, Amaryllidaceae, and Annonaceae. Essentially, they are synthesized from the precursor dopamine through various intermolecular reactions.

The Authors explored the structures, origins, and biological functions of certain isoquinoline N-oxides alkaloids, highlighting their significance for drug development. They discussed the chemistry, key biological activities, structure-activity relationships, and future applications of isoquinoline alkaloids, focusing on berberine [1]. The Authors noted challenges of berberine's low bioavailability and first-pass metabolism, as well as efforts to design molecules with drug-like properties. Deng et al. examined alkaloids in various medicinal plants of the Corydalis genus [2]. They concluded this genus is rich in alkaloids with diverse biological activities, making it valuable for research into potential treatments for numerous diseases. Bai et al. reviewed the discovery of natural anti-inflammatory alkaloids [3]. Authors reviewed research on natural alkaloids with anti-inflammatory properties and potential mechanisms. Li et al. examined isoquinoline alkaloids for ulcerative colitis treatment [4]. Rasouli et al. assessed plant alkaloids' anti-diabetic potential [5]. Efferth and Oesch evaluated alkaloids for repurposing in cancer treatment [6]. Plant-derived alkaloids as lead compounds for drug development and overcoming cancer multidrug resistance were highlighted [7]. Ti et al. reviewed plant medicine extracts and alkaloids with antiviral and anti-inflammatory properties [8]. Seteyen et al. reviewed isoquinoline, indole, and quinolizidine alkaloids as immunomodulators against arthritogenic alphavirus infection [9]. The activity of natural and semi-synthetic alkaloids against Trypanosoma cruzi has been reviewed [10]. Luo et al. studied alkaloids' anti-tumor properties and mechanisms in the tumor microenvironment [11]. Isoquinoline and related alkaloids' bioactivity as antiviral agents have been documented [12].

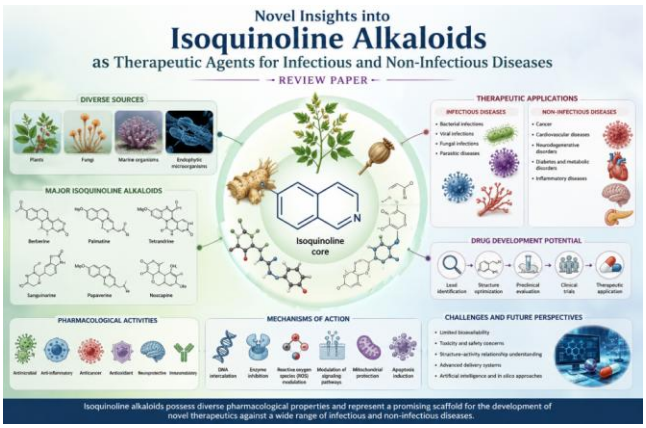

Fig 1. Isoquinoline Alkaloids as Therapeutic Agents

Pharmacological Activities

1. Anticancer activity

Cancer is a global health issue, influenced by factors like cell types in the tumor microenvironment, mutations affecting metabolism, immune evasion, inflammation, and oxygen diffusion creating hypoxic and necrotic areas [13]. Chemotherapy is a strategy used against cancer but faces challenges such as toxicity, severe side effects, and drug resistance.

Twenty-two isoquinoline alkaloids from Corydalis tomentella were tested for cytotoxicity on Hep-G2 and Hep-3B liver cancer cells [14]. The compound 3,4–2 H-tomentelline C showed significant cytotoxicity with IC_{50} of 7.42 µM for Hep-G2 and 9.67 µM for Hep-3B. Oxaliplatin, as a positive control, had IC_{50} values of 1.14 and 1.95, respectively.

Alkaloids like alangiifoliumines A-D, bharatamine, 10-demethylprotoemetinol, protoemetinol, ankorine, cepheline, isocepheline, deoxytubulosine, tubulosine, alangimarckine, and natalensine from Alangium salviifolium stems were evaluated for cytotoxic effects on A-549, HeLa, and SKOV-3 cell lines [15]. Deoxytubulosine showed the strongest cytotoxicity, with IC50 values of 0.09, 0.1, and 0.003µM for A-549, HeLa, and SKOV-3, respectively. Also, 10-demethylprotoemetinol had significant activity, with IC50 values of 0.3, 1.2, and 0.1 µM against A-549, HeLa, and SKOV-3, respectively.

2. Antibacterial activities

The rise in bacterial resistance to widely used antimicrobials poses a significant global health challenge. Consequently, finding new antimicrobials is crucial. Plant-derived molecules, which may operate through different mechanisms than those of existing antibiotics, could serve as a valuable source for developing new drugs.

Isoquinoline alkaloids derived from Corydalis tomentella demonstrated antibacterial activity against Staphylococcus aureus, Bacillus subtilis, Escherichia coli, and Pseudomonas aeruginosa using the microbroth dilution method [14]. Among them, (1′R, 2′ S)-coptichine B exhibited the most potent antibacterial effects, with a minimum inhibitory concentration (MIC) of 3.12 μg/mL against gram-positive bacteria and 6.25–12.5 μg/mL against gram-negative bacteria.

N-acetylanonaine from Monanthotaxis discolour root bark inhibited Staphylococcus aureus with an MIC of 0.17 mg/mL [16].

Alkaloids from Hypecoum ponticum, including hypepontine, N-methylcanadine, and N-methylstylopine, showed antibacterial effects against Staphylococcus aureus, Escherichia coli, and Pseudomonas aeruginosa [17]. Hypepontine had the strongest effect on Pseudomonas aeruginosa, with an MIC of 0.064 mg/mL. A crude extract with quaternary alkaloids was active against these bacteria, with MICs of 0.072, 0.036, and 0.036 mg/mL, respectively. The MIC for gentamicin, a positive control, was 0.032 mg/mL.

Extracts from Anabasis articulate stems, containing isoquinoline alkaloids, showed antimicrobial effects against gram-positive Micrococcus luteus and gram-negative Pseudomonas aeruginosa [18]. Minimum inhibitory concentrations (MICs) ranged from 0.781 to >100 mg/mL, with minimum bactericidal concentrations between 1.562 and >100 mg/mL.

3. Antiviral activity

Isoquinoline alkaloids such as dihydroglaziovine, laudanosine, 3-hydroxy-1-(6-methoxy-7-prenylisoquinolin-1-yl) propan-1-one, and 3-hydroxy-1-(2,2-dimethyl-2 H-pyrano[2,3-g] isoquinolin-6-yl) propan-1-one from Thalictrum cirrhosum were evaluated for antiviral properties [19]. 3-hydroxy-1-(2,2-dimethyl-2 H-pyrano[2,3-g] isoquinolin-6-yl) propan-1-one showed significant antirotavirus activity with a therapeutic index of 19.3, close to ribavirin's 20.4, used as a positive control.

Isoquinoline alkaloids like palmatine, berberine, jatrorrhizine, epiberberine, columbamine, and coptisine from Coptis chinensis interacted with influenza A virus neuraminidase, responsible for global flu transmission and mortality [20]. Molecular docking of these alkaloids into NA proteins of A/H1N1/1918, A/H1N1/2009pdm, H3N2/2010 wild type, H3N2/2010 D151G mutant, H5N1 wild type, and H5N1 H274Y mutant showed greater affinity than oseltamivir and zanamivir.

The COVID-19 pandemic remains a global issue despite vaccines, prompting a search for new treatments, including plant-derived isoquinoline alkaloids. In silico studies examined their inhibitory effects on SARS-CoV-2's main protease [21]. Molecular docking of nine alkaloids, including chelidonine, psychotrin, cephaeline, fumaricin, galanthamine, glaucine, boldine, drotaverine, coptisine, and hydrastine, revealed coptisine had the most favorable binding energy at −9.15 kcal/mol. Molecular dynamics simulations compared coptisine-main protease and inhibitor-main protease complexes, analyzing root mean square deviations, fluctuations, and radius of gyration. In silico studies suggest coptisine as a potential natural inhibitor of SARS-CoV-2 main protease.

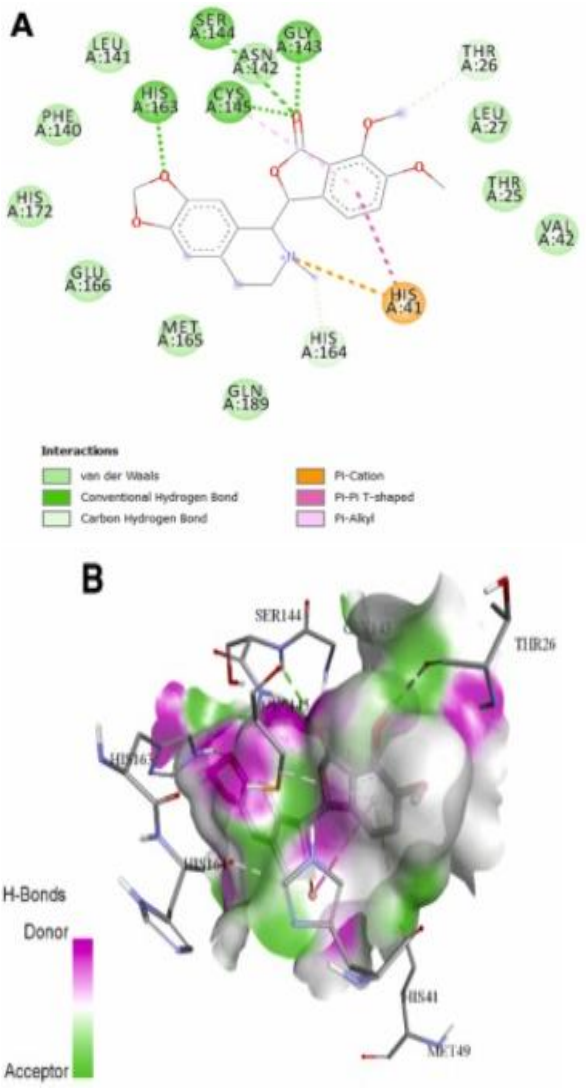

Fig 2. Illustration **A** shows the 2D interaction between Mpro and Coptisine. **B** visualizes the 3D interaction of the Coptisine-Mpro complex. **C** displays the 2D interaction of the N3-Mpro complex, and **D** shows the 3D interaction of the N3-Mpro complex [21].

4. Antifungal activity

Effective allylamine antifungal medications achieve a 70% success rate due to developing resistance [22]. New antifungal treatments are challenging since pathogenic fungi, like mammalian cells, are eukaryotic, and many antifungal drugs are nephrotoxic. Thus, identifying new antifungal compounds is urgently needed for drug development.

Ethanolic extracts from Annona coriacea bark and leaves were tested against Cryptococcus species and clinical yeast samples [23]. Both extracts inhibited all yeasts at 1.5 mg/mL. The lowest concentration with viable cells was 0.187 mg/mL. Extracts from bark and leaves also inhibited and reduced Cryptococcus gattii and Cryptococcus neoformans growth.

N-acetylanonaine from Monanthotaxis discolour root bark showed activity against Candida albicans and Aspergillus niger, with MICs of 0.13 mg/mL and 0.17 mg/mL, respectively [16].

Alkaloids hypepontine, N-methylcanadine, and N-methylstylopine from Hypecoum ponticum aerial parts, and crude extracts with tertiary or quaternary alkaloids, were tested against Candida albicans [17]. The quaternary alkaloid extract was most effective, with an MIC of 0.018 mg/mL, compared to amphotericin B's 0.064 mg/mL.

5. Alzheimer's disease

In developed nations, neurodegenerative diseases rank as the third leading cause of death, following cardiovascular diseases and cancer. Alzheimer's disease and Parkinson's disease are among the most prevalent neurodegenerative disorders. Key processes associated with the development of Alzheimer's disease include a deficiency in cholinergic function, oxidative stress, inflammatory pathways (notably NFκB), and the hyper-phosphorylation and aggregation of tau proteins, along with β and γ secretases that are crucial for APP processing.

Researchers identified potential anti-cholinesterase alkaloids in the Zanthoxylum genus by analyzing 41 alkaloid extracts from nine Colombian species using a modified Ellman's method [24]. They employed a multivariate statistical approach with the S-plot from the orthogonal partial least squares discriminant analysis model to select compounds with anti-cholinesterase activity. Berberine, chelerythrine, and columbamine from Zanthoxylum schreberi bark showed significant inhibitory effects on acetylcholinesterase and butyrylcholinesterase. The IC50 values ranged from 0.107 μM for berberine to 3.752 μM for columbamine against acetylcholinesterase, and from 2.048 μM for columbamine to 6.404 μM for berberine against butyrylcholinesterase.

Plazas et al. studied isoquinoline alkaloids from Zanthoxylum rigidum root extract, assessing their inhibition of acetylcholinesterase, butyrylcholinesterase, monoamine oxidase A, B, and Aβ aggregation. Nitidine and avicine were identified as promising candidates for Alzheimer's treatment. Nitidine and avicine exhibited IC_{50} values against acetylcholinesterase from Electric eel (0.65 and 0.15 μM), human recombinant acetylcholinesterase (1.25 and 0.52 μM), butyrylcholinesterase from Equine serum (5.73 and 0.88 μM), and monoamine oxidase A (1.89 and 0.41 μM), and against beta amyloid aggregation (1.89 and 5.56 μM). Both showed minimal activity against monoamine oxidase B. Kinetic analysis revealed they are reversible-mixed inhibitors, with avicine showing highest potency, having Ki values of 0.063 μM with acetylcholinesterase from Electric eel, 0.511 μM with human recombinant acetylcholinesterase, and 0.123 μM with butyrylcholinesterase from Equine serum.

6. Analgesic activity

Pain starts with harmful stimuli, traveling through neural pathways to the central nervous system, acting as a body shield. Similarly, inflammation from the immune system defends against infections and tissue damage. Untreated chronic pain leads to physical and psychological harm. Standard pain and inflammation medications manage these conditions but have side effects like gastric issues, kidney function changes, blood pressure impacts, liver damage, and bleeding risks.

Fifteen bisbenzyl isoquinoline alkaloids from *Menispermum dauricum* rhizome were assessed for analgesic properties on G-protein coupled receptors like dopamine D1, D2, opioid Mu, and muscarinic M3 receptors. The alkaloid (1 R, 1′ R)-daurisoline-2β-N-oxide showed high affinity and selective antagonistic activity on the M3 receptor with an IC_{50} of 2.2 μM. Another alkaloid, (1 R, 1′R)-espinin, exhibited the highest antagonistic affinity on the Mu receptor with an IC_{50} of 1.1 μM and acted as a D1 receptor antagonist with an IC_{50} of 8.8 μM [25].

7. Antidiabetic activity

Diabetes occurs when the pancreas produces insufficient insulin or the body cannot effectively use it. Insulin controls blood sugar. Prolonged high blood sugar can damage organs, especially urinary, nervous, and cardiovascular systems.

Isoquinoline alkaloids oleracein E and L from Portulaca oleracea show hypoglycemic and anti-diabetic effects by boosting insulin secretion and glucose absorption [26]. In β-TC6 cells, oleracein L reduced acid ceramidase activity, with IC_{50} values of 135.8 and 151.5 μM. At 200 μM or higher, these alkaloids significantly increased neutral sphingomyelinase activity.

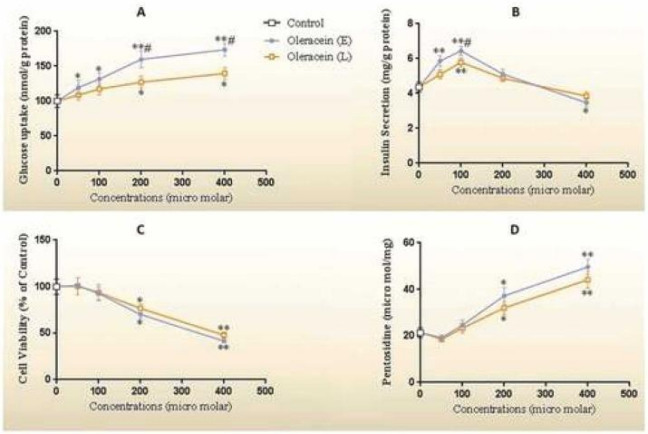

Fig 3. (A) The glucose uptake, (B) the insulin levels, (C) the cell viability as the percent of control, and (D) the pentosidine concentrations of β-TC6 pancreatic cells after 24 h treatment with different concentrations of OL-E and OL-L. The biological response of each substance was evaluated separately in cell lysate samples, and all data are presented as mean ± SD; n = 3 [26].

Dulic et al. documented the inhibitory effects of α-glucosidase and α-amylase from Berberis vulgaris root bark extract [27]. This extract showed greater activity than a 1 mg/mL acarbose solution.

The insulin-secretion-enhancing properties of isoquinoline alkaloids edulisines A–K and other alkaloids from Corydalis edulis were examined in HIT-T15 cells [28]. Edulisine B, E, J, hendersine B methyl ester, epi-coryximine, cheilanthifoline, dihydrosanguinarine, and 8-hydroxydihydrosanguinarine showed a significant insulinotropic effect at 40 μM.

Dimeric aporphine alkaloids, trivalcostatines A-J, and isoquinoline alkaloids trivalcostaisoquinoline, bidebiline A, B, heteropsine, and urabaine from Trivalvaria costata twigs were evaluated for α-glucosidase inhibitory activity [29]. Bidebilines A and B, heteropsine, and urabaine displayed inhibitory activities with IC_{50} values of 8.35, 9.84, 4.14, and 10.9 μM, respectively, significantly more active than acarbose (IC_{50} 185.7 μM).

8. Antioxidant activity

Plants contain bioactive compounds with antioxidant properties. The plant cell antioxidant system includes enzymatic and non-enzymatic components. Non-enzymatic molecules inhibit enzymes, chelate trace elements, capture reactive species, and enhance other defenses. Antioxidants prevent conditions like inflammation and cancer by neutralizing free radicals, binding metal ions, quenching •O2− ions, interrupting auto-oxidation, and reducing localized O2. Alkaloids' antioxidant activity is often assessed using DPPH radical scavenging, ferric reducing, trolox equivalent antioxidant capacity, and reducing power assays.

Alkaloids including iraqiine, kareemine, muniranine, kinabaline, O-methylmoschatoline, atherospermidine, and N-methylouregidione from Alphonsea cylindrica bark were tested for antioxidant properties using a DPPH assay [30]. Muniranine, iraqiine, and kinabaline showed significant antioxidant effects, with IC_{50} values of 44.51, 48.77, and 64.28 ± 0.93 μg/mL. Their superior activity may relate to hydroxyl groups in their structures.

Berberrubine, jatrorrhizine, and thalifendine from Berberis aristata root also showed antioxidant activity in the DPPH assay, with IC_{50} values of 9.8, 10, and 10.2 μg/mL [31]. These alkaloids protected human lymphocytes from free radicals, similar to gallic acid but at half the concentration, indicating higher efficiency.

Silver nanoparticles from Cucumis prophetarum fruit extract exhibited antioxidant activity, with IC_{50} values of 27.4 mg/mL in the DPPH assay and 23.7 mg/mL in the ABTS assay [32].

Research conducted in vitro has revealed that stem extracts from Anabasis articulate exhibit antioxidant capabilities, as confirmed by several assays [18]. The EC_{50} values for these extracts, as determined by the DPPH test, were found to range from 1.242 to 5.350

mg/mL, whereas the β-carotene test produced values between 0.372 and 2.313 mg/mL.

Extracts sourced from the entire plant and specific parts of Papaver somniferum demonstrated varying antioxidant activities [33]. The IC_{50} values from the DPPH radical assay ranged from 35.1 to 157.6 g/mL, while those from the ABTS•+ assay varied from 138.5 to 306.3 g/mL. Additionally, ferric reducing antioxidant power (FRAP) assay yield IC_{50} values ranging 59.75-1348.71 mM FeSO4/g extract.

9. Anti-depressant activity

Depression is characterized by ongoing feelings of sadness and a disinterest in performing everyday tasks. Common indicators of depression include a low mood, lack of enthusiasm, cognitive difficulties, and disruptions in daily habits such as altered sleep patterns, decreased energy, and changes in sexual desire. Medications that adjust the levels of monoamines noradrenaline, dopamine, and serotonin are employed to treat depression. Nonetheless, these drugs are only about 60% effective, highlighting the need to develop new antidepressant medications.

According to Baek et al., chelerythrine, which is extracted from Chelidonium majus, specifically inhibits a form of recombinant human monoamine oxidase A, with an IC50 value of 0.55 μM [34]. This inhibitory action of chelerythrine surpasses that of other plant-derived compounds like apigenin (IC_{50} 1.55 μM), alternariol monomethyl ether (IC_{50} 1.71 μM), decursin (IC_{50} 1.76 μM), and purpurin (IC_{50} 2.50 μM), but is less effective compared to hispidol (IC_{50} 0.26 μM) and acacetin (IC_{50} 0.19 μM).

10. Dopamine receptors antagonistic

Dopamine receptors play a crucial role in facilitating key physiological functions of dopamine, including movement, cognition, emotion, and memory. Substances known as dopamine receptor antagonists work by blocking these receptors through receptor antagonism. Many antipsychotic medications act as dopamine antagonists and are therefore used to treat conditions such as schizophrenia, stimulant-induced psychosis, and bipolar disorder.Menisperdaurines A-W, which was extracted from Menispermum dauricum, were evaluated for their D1 receptor antagonistic properties [35]. Among the alkaloids tested, five demonstrated strong D1 receptor antagonistic effects, with IC_{50} values ranging from 1.0 to 4.5 μM. Menisperdaurine A exhibited the highest level of antagonistic activity.

Certain isoquinoline alkaloids derived from Corydalis bungeana showed D2 receptor antagonistic effects. The alkaloid (R)-stephanine was the most potent, displaying significant antagonistic activity against the dopamine D2 receptor with an IC50 value of 0.85 μM, with IC50 values ranging from 5.20 to 26.07 μM [36].

Conclusions

Currently, new isoquinoline alkaloids are being extracted from plants and evaluated for their biological properties. Research shows that many plant-derived isoquinoline alkaloids hold promise for therapeutic applications, possessing activities such as cytotoxic, neuroprotective, anti-inflammatory, analgesic, antioxidant, and antidepressant effects. Several isoquinoline alkaloids exhibit multiple activities. This review highlights that developing new therapeutic agents is becoming more systematic. Most alkaloids discussed are structurally simple and modifiable, offering a practical foundation for new drug development.There is limited information on the precise molecular mechanisms of most isoquinoline alkaloids. Nonetheless, potential mechanisms require further research, and their effectiveness in patients needs validation through clinical trials. Efforts should focus on clarifying molecular mechanisms and assessing long-term efficacy and safety in trials.Pharmacokinetic studies should clarify processes within organisms, such as the absorption, distribution, metabolism, and excretion of alkaloids.

Future Perspectives

To thoroughly investigate isoquinoline alkaloids for long-term disease treatment and prevention, well-structured future studies, especially in vivo, are essential. Combining computational drug design and biophysical assays helps identify new medication candidates. Scarce safety and toxicity reports on isoquinoline alkaloids make comprehensive examinations crucial. Recent research addresses

limited in vivo activity and systemic toxicity by incorporating alkaloids into nanoparticle-based delivery systems. Advancements in techniques for identifying, isolating, and determining plant compound bioactivity create new opportunities for isoquinoline alkaloids, though further refinement is needed. Future structured in vitro, in vivo, and clinical tests are necessary to explore isoquinoline alkaloids and plant extracts for disease prevention and treatment. Investigating previously tested plants for new biological activities and targets is also important.

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Informed Consent

Not Applicable.

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Conflict of Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper. The authors declare no conflict of interest among themselves. The authors alone are responsible for the content and writing of this article.

Financial Interests

The authors declare they have no financial interests.

Human and Animal Rights

NA

Ethics approval and consent to participate

Not applicable.

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