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SHORT REVIEW

An Overview of Therapeutic Potential of Various Quinazoline Alkaloids and its Derivatives Containing Medicinal Plants

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Abstract

Medicinal plants have a wide range of therapeutic and pharmacological value with minimum side effects compared to synthetic drugs. Medicinal plants biosynthesis the secondary metabolites from the primary metabolites, such as alkaloids, glycosides, tannins, resins, etc. Alkaloids are abundantly naturally occurring secondary metabolites with high therapeutic value. Quinazoline alkaloids are two N-fused heterocyclic organic compounds with comparable therapeutic value. Quinazoline alkaloids such as vasicine and febrifugine showed valuable therapeutic effects such as anti-inflammatory, antibacterial, antioxidant and anti-malarial activities in both *in-vitro* and *in-vivo* studies. Medicinal plants such as *Adhatoda vasica*, *Dichroa febrifuga* and *Peganum harmala* have valuable therapeutic quinazoline alkaloids. This review article emphasises and explains the various biological sources and families of medicinal plants with quinazoline alkaloids and their therapeutic effects.

Major Findings: The present study highlights the key medicinal effects of plants containing quinazoline alkaloids. These plants exhibit diverse pharmacological properties, including bronchodilator, anticancer, antimicrobial, and anti-inflammatory activities. Understanding their therapeutic potential can contribute to developing new drugs and treatments for various diseases.

Keywords: Evadiamine, Febrifugine, Halofuginone, Vasicine

1. Introduction

Millions of diverse plants worldwide have undiscovered medicinal effects and researchers are still searching for information about the therapeutic potential of floras. Most of the synthetic drugs in this world have considerable adverse effects and they might cause tolerance and other harmful effects after repeated usage of them. Herbal medicines are a gift of nature with the most negligible side effects and comparable therapeutic actions, such as reserpine, an alkaloid from *Rauwolfia serpentina*, which acts as an anti-hypertensive agent. These phytochemical products are biosynthesised within the plant with the help of primary metabolites such as carbohydrates, amino acids, etc[1]. By utilising such primary metabolic initial components and via interference of biological catalyst enzymes, the plant's metabolic pathways produce secondary metabolites such as alkaloids, volatile oils, tannins, terpenes and resins[2]. Alkaloids are naturally occurring heterocyclic organic compounds produced within the plant and have broad therapeutic applications in medicine. In treating various diseases, quinine acts as an anti-malarial agent and quinidine acts as an anti-arrhythmic agent. Many alkaloids are still undiscovered and have intriguing medicinal potential.

Quinazoline alkaloids (Figure 1) and nitrogen-fused heterocyclic alkaloids have therapeutic applications

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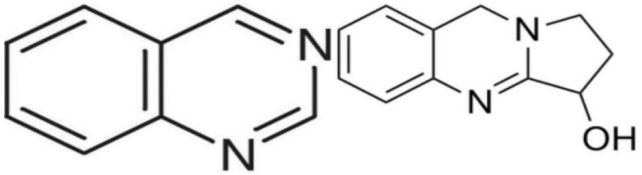


Figure 1. Structure of quinazoline and quinazoline alkaloid derivative vasicine**.**

like blood pressure decrease and anti-bacterial, anti-inflammatory and antioxidant potential. Researchers are exploring their undiscovered therapeutic effects in *in-vivo* and *in vitro* studies, and they offer comparable therapeutic effects in different plant species. This review article emphasises and explains the various biological sources and families of medicinal plants having quinazoline alkaloids and their therapeutic effects[4].

2. Materials and Methods

The information on the medicinal plants containing quinazoline alkaloids with immersed therapeutic potential was collected from several databases such as ScienceDirect, PubMed, NCBI, Springer, Google Scholar etc., from 1970 to 2024. The keyword used for searching was the therapeutic potential of Quinazoline Alkaloids, the therapeutic potential of *Adhatoda vasica*, the therapeutic potential of *Peganum harmala*, the therapeutic potential of *Evodia rutaecarpa* and the therapeutic potential of *D. febrifuga*.

2.1 Methodology

This review comprehensively searched the literature on three herbal plants: *A. vasica*, *P. harmala* and *E. rutaecarpa*. The review aimed to explore the recent progress in research on these plants, mainly focusing on articles published over the last five to ten years. A thorough search strategy was employed to identify and select the most pertinent articles on each of the plant species. For this search, databases used included PubMed, Scopus, Science Direct, PMC, Springer and Google Scholar. These databases were searched for articles directly related to these plants and their pharmacological properties.

2.2 *Adhatoda vasica*

A search to obtain information on *Adhatoda vasica* began with exploring several key academic databases. The PubMed database gave around 420 articles related to *A. vasica*. These articles were carefully reviewed and 144 studies published in the last five years were selected for inclusion in this review. This allowed for a more focused exploration of the most recent research developments. Moreover, the Scopus and Science Direct databases provided a total of 77 relevant articles, from which 36 articles published within the last five years were chosen. For the PubMed Central database, there were 49 articles, with 20 of these particularly relevant articles published within the last five years. Springer's database also assisted in this search with 54 articles. Of these, 11 studies published within the last two years were used for this analysis. In addition to this, a Google Scholar search yielded around 8,400 articles. After shortlisting the articles, in this review, around 1,600 articles have been considered, which were published after 2020. This multi-database searching strategy ensured that the most relevant and latest literature found across various scientific disciplines from different databases have been integrated into this review of the *A. vasica*, thus contributing to its well-rounded understanding of its current state of research work.

2.3 *Peganum harmala*

Similarly, the search for literature related to *Peganum harmala* was conducted across multiple academic databases. PubMed provided a total of 181 articles published over the last 10 years. From this set, approximately 110 articles were selected for inclusion based on their relevance to the review. The Science Direct database returned a much larger set of articles-1,089 in total, of which 636 were published in the last five years. From this list, 636 studies were selected in such a way that only the most recent work was considered for the review. Moreover, the database of PMC provided 1,039 articles, of which 180 articles were selected for review based on their relevance and regency. Springer's database contributed 206 articles, with only those articles published in the last two years being selected. Lastly, a Google Scholar search was done to identify about 13,000 articles on *P. harmala*,

of which 6,000 were relevant and published since 2020. This extensive search procedure has enabled a comprehensive understanding of the pharmacological and therapeutic properties of the plant, as well as its modern medicinal applications.

2.4 *Evodia rutaecarpa*

For the review of *Evodia rutaecarpa*, an equally intensive search procedure was followed. PubMed revealed 94 articles published in the last 10 years, with 50 of these studies being included in the review. This ensured that the most current and relevant research was incorporated. A search of the Science Direct database returned nearly 800 articles, from which 203 articles published in the last three years were selected for inclusion. The PMC database was also searched and 92 articles published in the last year were retrieved. All of these articles were relevant to the topic and were included in the review. Springer's database contributed 92 articles published over the last two years, all of which were incorporated into the review to ensure that the most recent studies were considered. In addition, a Google Scholar search retrieved about 1,500 articles published from 2020 onwards and were therefore included in this review. The methodology that was followed for this systematic review ensured the selection of the most relevant and recent articles about each species of plant. This review captures the current state of research on *Adhatoda vasica*, *P. harmala* and *E. rutaecarpa* by conducting thorough searches across multiple academic databases and including studies published in the last five to ten years.

3. Plants Containing Quinazoline Alkaloids and its Therapeutic Potential

3.1 *Adhatoda vasica*

The little, dense, evergreen shrub *A. vasica* (Figure 2) is found in many tropical Southeast Asian regions, including Singapore, Sri Lanka, Upper and Lower Myanmar and the Indonesian Peninsula. It is distinguished by long, broad leaves, a herbaceous, woody stem, large, dense flowers and a small, clavate fruit.

Adhatoda vasica, a plant native to India's lowlands, is known for its anti-inflammatory and antioxidant properties. Its essential alkaloids, vasicine, vasicinolone and vasicinol, are used in treating asthma, bronchitis, cough suppressants and tuberculosis. The plant's molecular mechanism of action is thought to be based on antioxidant properties and is hepatoprotective. *A. vasica* fruits are used in Pakistan for bronchitis, cold and spasmodics and are also used in herbal remedies like Fermiforte and Salus Tuss[5].

Vasicine (Figure 3) is also a uterine stimulant that can stimulate the uterus. It is commonly used in various forms, including decoctions, powders and juice. The Indian Pharmacopoeia mentions *vasaka* syrup and liquid extract. Vasicine has antibacterial efficacy against *Staphylococcus aureus*, *Staphylococcus epidermidis* and *Klebsiella pneumoniae*, with minimal inhibitory concentration values against *Micrococcus luteus*, *Enterobacter aerogenes*, *S. epidermidis*, and *Pseudomonas aeruginosa*.

Adhatoda vasica, a plant with anti-allergic properties, has been shown to reduce allergy reactions in mice, rats and guinea pigs. Its leaves and roots contain an alkaloid called vasicinone, which has anti-allergic effects on various organisms. The plant may also be a potent inhibitor of HIV-Protease and has antibacterial activity against various bacteria. Its powdered leaves have shown effective anti-ulcer action in rats, with the highest level of activity observed in the ethanol-induced ulceration model[6].

Within the separated guinea pig tracheal chain, an essential oil extracted from *A. vasica* leaves demonstrated the ability to relax smooth muscle. Although the paste of the plant *A. vasica* has been used to treat tuberculosis, diphtheria, malaria, leucorrhea and eye disorders, vasicine from the plant has stimulatory



Figure 2. *Adhatoda vasica.*

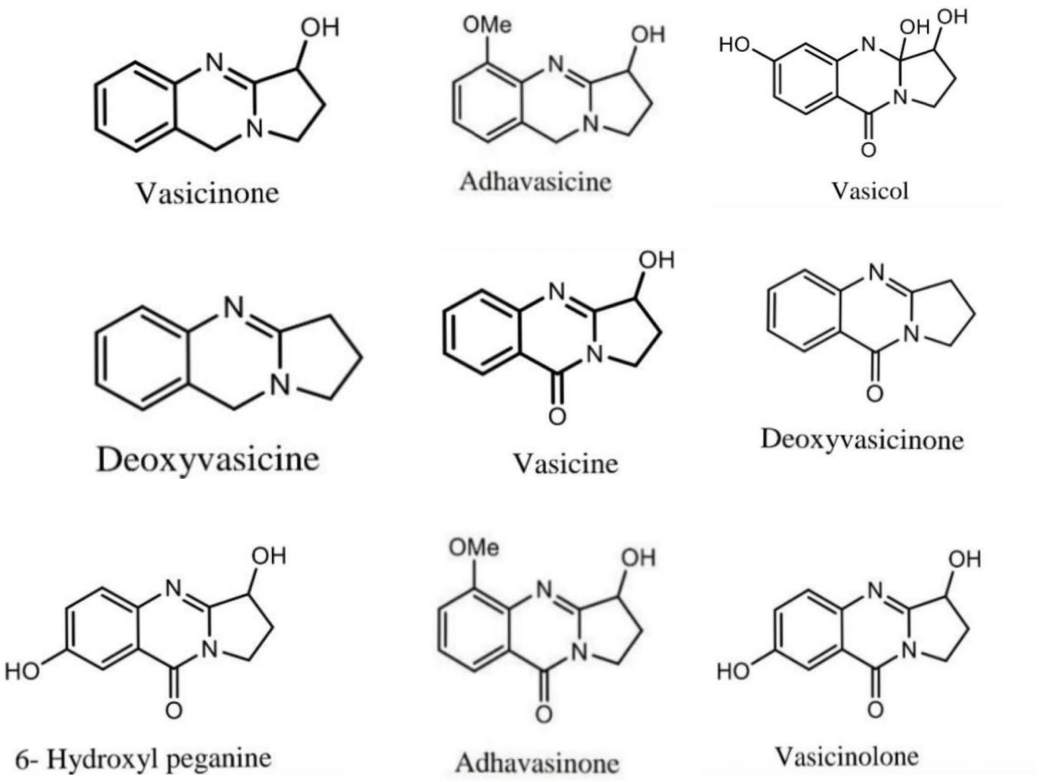


Figure 3. Chemical constituents of *Adhatoda vasica*.

effects on the uterine and tracheal muscle of rats and guinea pigs as well as other tissues[7].

3.2 *Dichroa febrifuga*

Dichroa febrifuga (Figure 4) is a crucial herb in Chinese medicine, known for its anti-malarial properties due to its alkaloids febrifugine and isofebrifugine. Halofuginone, a synthetic derivative of febrifugine, is used in veterinary medicine to reduce T helper 17 cell growth. Febrifugine, a natural anti-malarial chemical, has been studied for over 50 years. Halofuginone, a feed additive used in the chicken industry, inhibits collagen type I gene expression, treating conditions like pulmonary fibrosis[8].

Halofuginone (Figure 5), a derivative of febrifugine, is being investigated for its potential in treating liver cirrhosis, wound healing and injury-induced artery intimal hyperplasia. It has been shown to have anti-malarial activity, suppress Th17-driven autoimmune development and induce the resolution of existing fibrosis. Halofuginone's ability to decrease collagen production and boost collagenase activity makes it unique in its ability to induce the resolution of pre-existing fibrosis. It also has significant inhibitory effects on key events in the angiogenic cascade[9].

Dichroa febrifuga, a plant with potential health benefits, faces safety concerns due to its diverse chemical profile. Clinical trials are needed to establish safety, and sustainable harvesting methods are crucial for its availability. The plant's roots and shoots contain bioactive pollutants, including alkaloids and flavonoids, which can modify immune system reactions and counterbalance oxidative stress damage. Traditional medicine has praised *D. febrifuga*'s curative effects, but pharmacology is now investigating its chemical composition and potential applications[10]. Being infatuated stems from the expectation that understanding the particular systems of action and isolating compounds that act will pave avenues for pharmaceutical development. Arguably, those most noteworthy applications are in the ongoing battle against malaria. *D. febrifuga* has developed into a significant part of practitioners' anti-malarial arsenals in areas where this illness is endemic. People suffering from malaria have been treated by consuming the plant's roots and stems when prepared in highly



Figure 4. *Dichroa febrifuga.*

accurate formulations. *D. febrifuga's* anti-parasitic traits helped cement the plant's standing as a practical natural development for this life-threatening disorder[11].

3.3 *Peganum harmala*

Harmala (*Peganum harmala* L.) (Figure 6) is a noteworthy perennial herb in the *Zygophyllaceae* family for medical purposes. *Harmala*, Syria rue, a wild rue, harmal, and Africa rue are some of its common names. *P. harmala*, commonly called Syrian rue, is a recurrent plant with an extensive heritage and cultural importance over time[12]. This bare shrub, being native to the Middle East and South Asia, has been extensively utilised for an assortment of motives spanning from medicinal to ritualistic. The plant has become recognised for its hallucinogenic qualities, mainly because of the presence of harmala alkaloids, which have attracted mindfully in ethnobotany and pharmacology. *P. harmala* has been employed as traditional medicine solely due to its potential medicinal benefits[13].

Peganum harmala is a plant with a psychedelic effect and is important in religious and traditional parts of the world. It has Monoamine Oxidase (MAO) inhibitors, which have drug interactions and significant therapeutic activity. However, due to its physiological activity, it has some restrictions on use and safety. The plant grows in the Middle East and South Asia and requires good temperature preference for propagation[14]. It has been used to treat gastrointestinal and respiratory disorders in certain civilisations. *P. harmala* requires careful water management and pest management due to its exposure to certain insects. The plant's pharmacological and psychedelic properties are due to its harmala alkaloids, which include harmine, harmaline, tetrahydroharmine harmala alkaloid, and carboline derivatives. It is essential to approach the emergence of *P. harmala* with caution, considering its biological demands and legal ramifications[15].

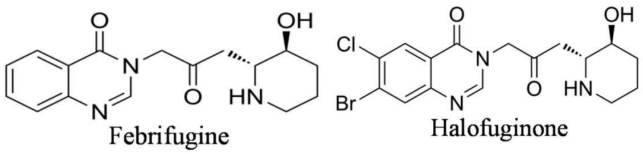


Figure 5. Chemical constituents of *Dichroa febrifuga*.

Peganum harmala is a plant with pharmacological and psychedelic properties, primarily due to its harmala alkaloids. Harmine, a beta-carboline alkaloid, reduces MAO enzymes, affecting neurotransmitter metabolism. Harmaline, another beta-carboline alkaloid, inhibits MAO enzymes and contributes to the plant's psychoactive qualities (Figure 7). Tetrahydroharmine harmala alkaloid is similar to harmine but has fewer inhibitory actions. Quinazoline alkaloids contribute to the plant's Chemical profile. Harmala alkaloids have potential therapeutic benefits and traditional ritual significance[16].

Harmala alkaloids, also known as harmine and harmonising, have been studied for their potential medicinal applications. They have been found to have anti-depressive effects, anti-inflammatory properties, antioxidant capabilities, and antibacterial properties. Harmala alkaloids are reversible monoamine oxidase inhibitors, potentially raising neurotransmitter levels, and have antioxidant properties, which could be beneficial for diseases causing oxidative damage, particularly neurodegenerative disorders[17].

Peganum harmala, a plant with cytotoxic and sedative properties, has been found to have antiviral properties due to its harmala alkaloids. These alkaloids alter cell death pathways, interact with drugs, and can cause adverse effects in drug interactions. Further research is needed to determine their medicinal properties[18].

3.4 *Evodia rutaecarpa*

The *Evodia rutaecarpa* (Figure 8) is a traditional Chinese plant that has some pharmacological effect on gastrointestinal disease and it improves the systemic circulation flow. It has some medicinally beneficial alkaloids namely Evodiamine which contains some anti-inflammatory and anti-obesity action. This plant is widely used to treat many Gastro-Intestinal Tract (GIT) diseases and is widely used in Chinese medicine. It also has tumor-suppressing action[19].



Figure 6. *Peganum harmala*.

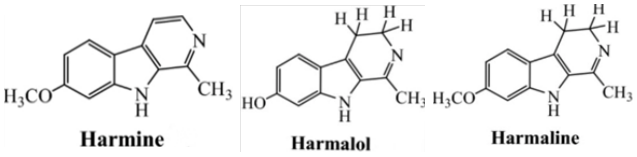


Figure 7. Chemical constituents of *Peganum harmala*.

Evodia fruit, native to China, has been researched as a fat burner, but no significant results have been found. It increases the sense of heat of animals, which is triggered by a diminished sense of cold and broadened heat metabolism. Although it doesn't significantly increase calorie expenditure, it may make one feel warmer. Evodia fruit has limited utility as a supplement and has potential as an anti-cancer agent. It is often used in medicine for warming bowel relaxation, treating stomach discomfort, injury and illness prevention. Rutaecarpine and evodiamine are found in the fruit, which is also found in Japan and Korea. *Evodia rutaecarpa* contains eighteen compounds, with 21 tested against human tumour cells[20].

3.4.1 Phytochemical Constituents of Evodia rutaecarpa

Evodiamine and rutaecarpine are the two primary components of *E. rutaecarpa*. Rutaecarpine is a pentacyclic indolopyridoquinazolinone first isolated from *E. rutaecarpa* by Asahina and Kashiwaki. *Rutaecarpa* is one of the most frequently utilised traditional Chinese herbs for treating many kinds of conditions, which include headaches, digestive disorders, postpartum haemorrhage, amenorrhea, issues with menstruation, and other diseases. Several potential therapeutic applications for rutaecarpine have been studied, including Vasodilatory actions that could help decrease blood pressure and improve blood



Figure 8. *Evodia rutaecarpa*.

circulation. According to specific research, it might have antiplatelet characteristics that prevent excessive blood clotting[21].

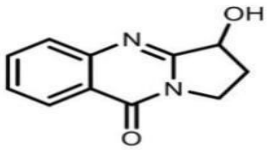
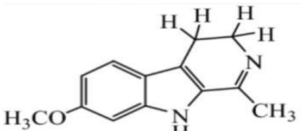
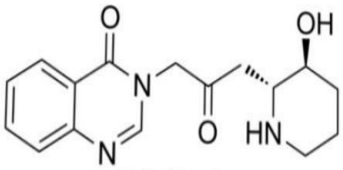
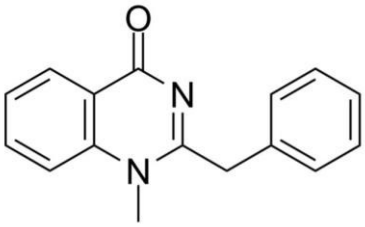
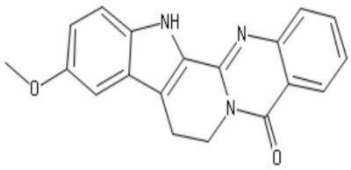
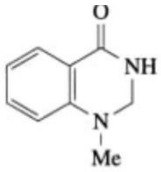
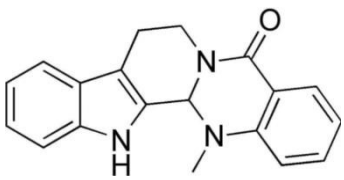
Rutaecarpine and evodiamine are two bioactive components of *Evodiae fructus*. Rutaecarpine affects lipid metabolism and caffeine metabolism, potentially impacting tolerance and susceptibility. However, its low effectiveness, cytotoxicity, and poor water solubility make it unsuitable for clinical application. Evodiamine, a naturally existing indole alkaloid, has beneficial effects on conditions like cancer, obesity, inflammation, cardiovascular disease, Alzheimer's disease and infectious diseases, and regulates its impact. Its enhanced binding ability makes it an excellent candidate for developing multi-target medications, inhibiting growth and dissemination in various tumour cells[22].

Evodiamine has potential therapeutic applications in weight management, obesity, inflammation-related disorders, cardiovascular benefits, and potential anti-cancer properties. However, adequate research on its safety, tolerance and pharmacokinetics is needed. Despite some studies supporting its clinical development as a modern cancer therapy, no clinical evaluation has been conducted. Evodiamine's soluble nature in acetone and aether makes it difficult to develop a suitable dosage form. Future research should focus on enhancing formulation and examining research working with evodiamine[23].

4. Other Quinazoline Alkaloids Containing Medicinal Plants

Research on the therapeutic applications and efficacy of alkaloids extracted from quinazoline alkaloids containing plant chemical constituents is limited. Arborine, derived from *Glycosmis arborea* and *Horti*

Table 1. Summary of phytochemical constituents and therapeutic uses of medicinal plants

S. No.	Plant Name	Chemical Constituents	Main Quinazoline Alkaloid Structure	Therapeutic Uses	References
1	*Adhatoda vasica*	Vasicine, Vasicinone, Vasicinol, deoxyvasicine.	 Vasicine	Expectorant, Anti-tussive, Antidiarrhoeal, Anti-bacterial, Antiinflammatory.	10
2	*Peganum harmala*	Harmaline, Harmol, Harmalol, Harmine, Beta Carboline.		Cardiovascular, neurologic, antimicrobial, insecticidal, antineoplasmic, antiproliferative, gastrointestinal, and anti-diabetic effects.	7
3	*Dichroa febrifuga*	Febrifugine and isofebrifugine	 Febrifugine	Anti-inflamatory, Anti–malarial.	23
4	*Glycosmis arborea*	Arborine.		Antiinflammatory, Anti-diabetic, Anti-bacterial, and Anti-fungal.	4
5	*Hortia arborea*	Hortiacine and hortiamine.	 hortiacine	Anti-inflammatory, Anti-microbial.	13
6	*Glycosmis pentaphylla*	Glycorine and glycosminine	 Glycorine	Hepatoprotective, Antiinflammatory, Anti-microbial.	11
7	*Evodia rutaecarpa*	Evodiamine and rutaecarpine.	 Evodiamine	Anti-ulcer, Anticancer, Antiinflammatory.	2

arboria, has anti-parasympathomimetic effects, anti-inflammatory, anti-fungal, and anti-bacterial properties. It may also help with blood sugar control, potentially mitigating diabetes symptoms. Other alkaloids from *G. pentaphylla* have anti-inflammatory, hepatoprotective, and anti-diabetic properties. Further study is needed to fully understand their medicinal properties[24].

Hormone and hortiacine were obtained from various species of *Hortia*, including *Hortia brasiliana*, *Hortia longifolia*, *Hortia superba* and *Hortia oreadica*. Hormones showed proarrhythmic and anti-inflammatory effects on dogs' cardiomyocytes. *Hortia* species have potential medical applications, including treating diseases like cancer and degenerative disorders. They also have larvicidal and repellent properties, potentially benefiting public health, agriculture, and the food and cosmetic industries[25] (Table 1).

5. Conclusion

Quinazoline alkaloids, a class of naturally occurring compounds, have drawn significant attention in medicinal chemistry due to their wide-ranging pharmacological activities. These alkaloids, found in various plant species, are particularly noted for their anti-malarial, anti-inflammatory, anti-tumour and neuroprotective effects. They play a crucial role in traditional medicine and continue to be the subject of modern research.

One of the most studied quinazoline alkaloids is harmaline, a β-carboline alkaloid isolated from *Peganum harmala* (Syrian rue). Harmaline exhibits various bioactivities, including its potential to treat neurodegenerative disorders, anxiety and depression, due to its ability to interact with the central nervous system. Harmaline and other similar compounds are being explored for their therapeutic potential in treating diseases like malaria, cancer and chronic inflammation.

The advantage of using plant-derived alkaloids like quinazoline derivatives lies in their enhanced medicinal properties with minimal side effects when compared to traditional allopathic drugs. While synthetic alkaloids can be designed to amplify the therapeutic effects and reduce toxicity, the reliance on natural sources remains vital for discovering novel and effective compounds.

In recent years, there has been a growing focus on secondary metabolites in plants for drug discovery. These compounds, which are not directly involved in the plant's primary metabolism but are often involved in defence mechanisms, hold promise for developing new medications. However, the challenge lies in the complexity of identifying and isolating new quinazoline alkaloids and understanding their full spectrum of pharmacological actions.

As more research is conducted, the search for quinazoline alkaloids in medicinal plants continues to expand, to identify additional plants rich in these compounds. These studies not only aim to uncover new potential therapies but also provide a better understanding of how these compounds can be used safely and effectively in modern medicine.

In conclusion, quinazoline alkaloids represent a promising frontier in pharmacology, offering a wealth of therapeutic potential. Ongoing research is crucial for discovering new alkaloid-rich plants, improving extraction and synthesis techniques, and ensuring that these natural compounds can be integrated into modern medical treatments with minimal adverse effects.

6. Author Contribution

H. Mohamed Ishaq: Data curation, writing original draft, Resources, Validation; Nanthakumar Lingam: Validation, Review and writing; R. Rathika: Data Curation, Resources, writing original draft, Methodology; Thirumalaikumaran Rathinam and Manimegalai: Supervision, Review and writing.

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