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RARE PHYTOCHEMICALS FOUND IN NATURE WITH SUBSTANTIVE MEDICINAL POTENTIAL

Maria Siddika Mim, Majedul Hoque, M.S.K. Choudhuri and Iftear Kazim Rafi*

Department of Pharmacy
Jahangirnagar University, Dhaka, Bangladesh

**Corresponding author*: iftearrafi4@gmail.com

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Abstract: The use of medicinal herbs continues to be essential source of bioactive substances with a variety of structures with extensive therapeutic potential. Natural products made from plants are abundant in bioactive substances that are crucial for the development of new drugs. These substances have intricate metabolite combinations that give them their pharmacological activities. Rare phytochemicals, which are found in a small number of plant or marine species and are produced through complex biosynthetic pathways, provide remarkable scaffolds for contemporary drug discovery. They are very appealing as a therapeutic leads because of their therapeutic effectiveness, structural diversity, and low abundance or identified in nature. This article provides a succinct discussion of rare phytochemicals with substantive medicinal potential. Ten substances *namely* maytansine, silvestrol, homoharringtonine, thapsigargin, conophylline, brusatol, salvinorin A, phyllanthin, rohitukine and pseudopterosins are thoroughly analyzed and summarized.

Keywords: Lead compound, Maytansine, Medicinal herbs, Pharmacological effect, Rohitukine.

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INTRODUCTION

Numerous natural products with a variety of medicinal qualities can be found in plants, and these products are constantly being investigated to create new medications (Singh *et al.,* 2012). These natural materials have long been used in traditional medicine to treat a wide range of illnesses. These natural compounds are now used to make the majority of pharmaceutical drugs. Numerous bioactive chemicals make up natural goods. These bioactive substances provide biological activity against a number of pathogens. Many secondary metabolites from plants have been discovered so far, each having a unique structure and set of pharmacological activities (Fig. 1) (Gad *et al.,* 2013). The continuous investigation of a number of medicinal plants for the production of pharmaceuticals has been made possible by the knowledge upheld by the conventional medical system (Mushtaq *et al.,* 2018). Over 85-90% of people on the planet rely on traditional medicine to treat a variety of illnesses (Wangchuk, 2018).

While many common plant-derived compounds have been well researched (Rao, 2021), an increasing amount of research is currently concentrated on rare and emergent phytochemicals that exhibit great therapeutic promise. These lesser-known compounds, which are often found in tiny amounts or in

uncommon, poorly understood species, have strong antioxidant, anti-inflammatory, antibacterial, and anticancer activities. As advances in analytical chemistry and biotechnology continue to uncover new molecular structures and mechanisms of action, these rare phytochemicals present an intriguing new path for drug discovery and quality health innovation.

NATURAL PRODUCT DEVELOPMENT

Natural products and their derivatives, known as secondary metabolites, have been used in the evolution of new medicinal drugs since ancient times (Muhammad *et al.,* 2024). Even though natural compounds have been employed for centuries, their uses in contemporary drug discovery have greatly increased because to recent technological developments in genomics, bioinformatics, and extraction methods. These developments have made it possible to isolate and characterize bioactive chemicals with previously unheard-of accuracy, creating new opportunities for the creation of innovative treatments.

Before the 20th century, raw or partially processed extracts from a variety of sources were used to cure both humans and animals. Drug development was revolutionized by the introduction of receptor theory in the 20th century, which emphasized the significance of drug-chemical interactions with biological molecules like proteins, DNA, and RNA. This idea has led researchers to focus on the chemical characteristics of natural product for therapeutic use (Pereira, 2019). A new era in pharmacology is being launched by isolated naturally occurring compounds, which are the vital therapy approach for various diseases in their pure forms. Previous research has clarified the molecular structures of various bioactive substances that give the medication extracts their effects (Kobayashi, 2016). Synthetic approaches can be used to improve natural-source based medications, which can also been utilized as drug leads.

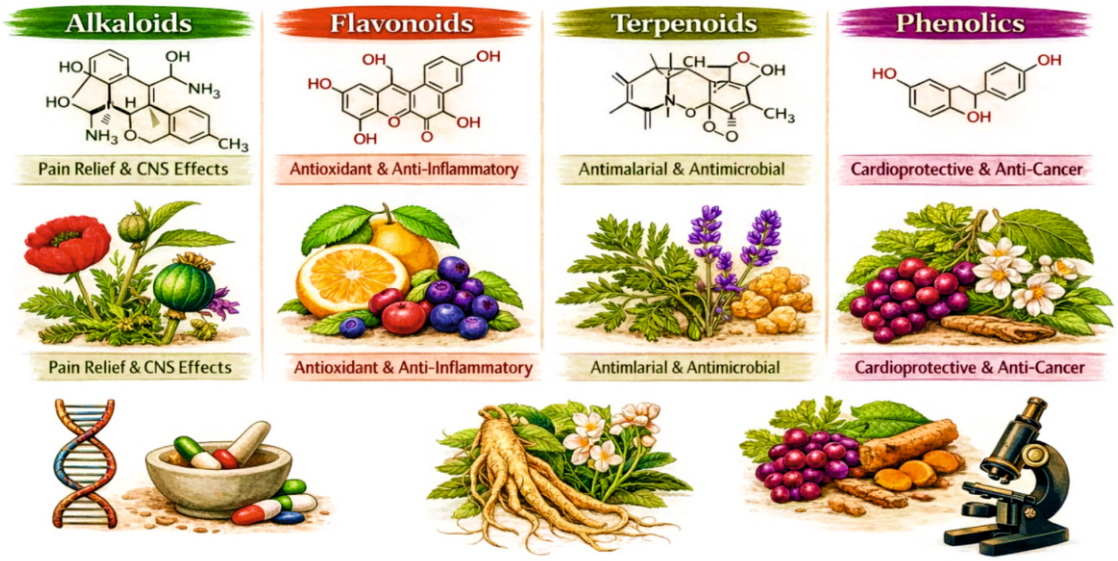


Fig. 1: Secondary plant metabolites possess pharmacological properties.

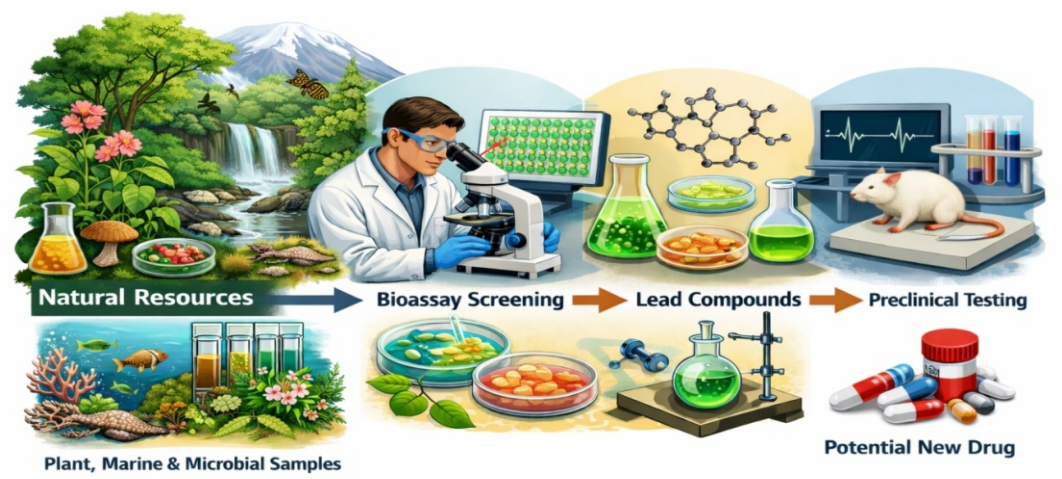


Fig. 2. Drug lead compounds are discovered and processed from natural resources.

Need for production of plant-based drugs

The pharmaceutical business has long been drawn to natural products, with interest in alternative therapies and medications produced from plants for a variety of diseases. Even though synthetic medications offer immediate relief, they come with a number of negative side effects. Because of its manufacturing process and lots of excipient, synthetic medication is expensive and may not be available to a significant portion of the global population.

Conversely, traditional medications are often safe, more effective, have less adverse effects, and are readily absorbed and digested by the body. They are broadly accepted, reasonably priced, and readily available to individuals because of their cultural and social beliefs. Evidence-based medications have been made possible by an increase in scientific research and clinical trials conducted by several scientists and pharmaceutical corporations (Nasim *et al.,* 2022; Hoque, 2024). Additionally, it is easier to standardize and purify a single chemical, which makes it easier to use in the contemporary medication delivery system.

Drug lead compounds often come from natural resources like plants, microbes, and marine organisms. These sources have various bioactive molecules that are extracted and tested through bioassays to find biological activity. Promising substances are isolated, characterized, and improved as lead compounds. Finally, the chosen leads go through preclinical testing to assess their safety and effectiveness before drug development (Fig. 2) (Najmi *et al.*, 2022; Karthikeyan *et al.*, 2022).

Details of rare phytochemicals

Rare phytochemicals are found only in a limited geographic area, produced in amounts ranging from micrograms to milligrams per kilogram of plant material, known to have complex and lengthy criteria for extraction or purification (Table 1). They have little clinical research or literature and possess distinct pharmacological or chemical properties. Their sources, molecular weight and chemical formulae are shown in table 2. Such 10 phytochemicals are:

1. Maytansine: The maytansine belongs to the maytansinoid family of compounds and is a potent antimitotic. It was first isolated from the Ethiopian shrub *Maytenus ovatus* in the early 1970s (Kupchan *et al.,* 1972). Its exceptional cytotoxicity, which was several orders of magnitude higher than that of conventional chemotherapeutic medications like vincristine, immediately, raised interest in its potential as an anti-cancer treatment. However, high systemic toxicity limits maytansine's therapeutic window by impeding early clinical trials. Maytansine derivatives were therefore studied and, more importantly, employed as a payload in antibody-drug conjugates (ADCs), which reduce off-target effects and allow targeted drug delivery to cancer cells (Sun *et al.,* 2011; Perra *et al.,* 2025). The complicated chemical structure of maytansine is defined by a macrolide ring system with 19 members. Important structural elements consist of: Macrolide Ring: The molecule's core is formed by the central 19-membered ring. Chlorine Atom: The C-9 position contains a chlorine atom. Ester Linkage: An N-methyl-L-alanine moiety and the macrolide ring are joined by an ester linkage. Aromatic Ring: The alanine moiety is joined to an aromatic ring.

Microtubules are vital parts of the cytoskeleton and are involved in cell division, intracellular transport, and cell motility. Maytansine binds to tubulin, the protein subunit of microtubules, at the same location as vinca alkaloids like vincristine and vinblastine does, that is how it exhibits its cytotoxic effect (Prota *et al.,* 2013; Prota *et al.,* 2014). Maytansine's intricate structure has made chemical synthesis extremely difficult. Although there have been a number of documented total syntheses of maytansine, they are typically intricate, rendering them unsuitable for large-scale manufacturing. For the production of maytansine and its derivatives, semi-synthetic methods have proven more feasible, beginning with naturally occurring maytansinoids. These methods usually entail modifying the naturally occurring compounds chemically in order to enhance their pharmacological qualities or add desired functionalities (Taplin *et al.,* 2018; Perra *et al.,* 2025).

2. Silvestrol: This is a potent rocaglate isolated from *Aglaia* species, has emerged as one of the most promising phytochemicals in modern phytomedicine due to its strong anticancer and antiviral activities. Its primary mechanism is the selective suppression of the eukaryotic initiation factor eIF4A, an essential RNA helicase required for cap-dependent translation, to decrease the synthesis of oncogenic and survival-related proteins.

The focused action causes substantial cytotoxicity against a range of malignancies, including pancreatic, breast, and leukemia tumors (Fig. 3), frequently at nanomolar concentrations. Outside of oncology, silvestrol has demonstrated remarkable antiviral activity by disrupting viral protein synthesis, particularly against recently discovered RNA viruses. Despite its medicinal potential, challenges such as its complicated structure, restricted natural availability,

and bioavailability issues have hindered its clinical advancement. Further studies on synthetic analogs, improved delivery systems, and sustainable production practices are needed to fully fulfill silvestrol's promise as a next generation phyto- medicine contender (Hwang *et al.*, 2004; Kim *et al.*, 2007).

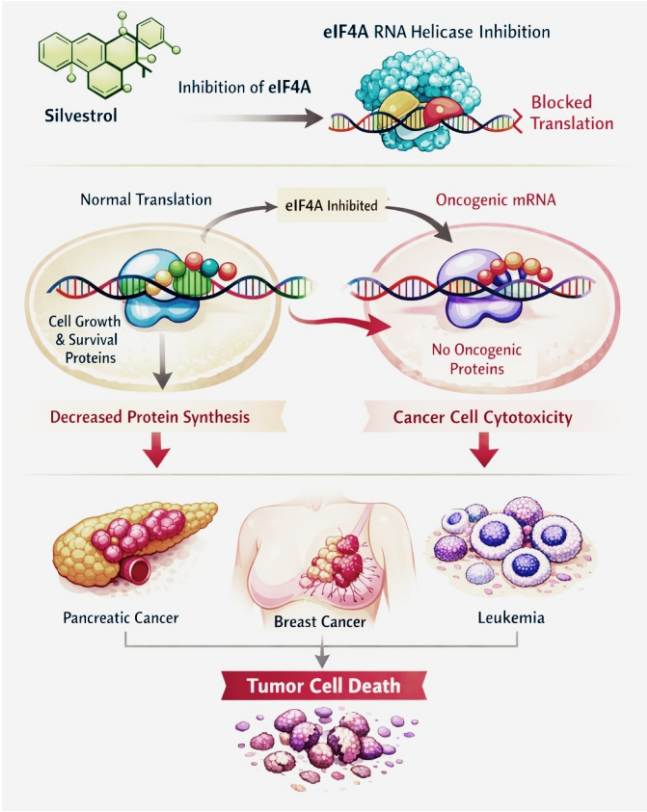


Fig. 3: Suggested anticancer mechanism of silvestrol.

3. Homoharringtonine (HHT): This is a cephalotaxine ester first isolated from *Cephalotaxus* species, is an uncommon but therapeutically most significant phytomedicine with a long history of traditional use and a present significance in anticancer therapy. Its primary mechanism, which prevents protein synthesis by interfering with the early elongation step of translation, causes the rapid depletion of short-lived oncogenic proteins. Omacetaxine mepesuccinate, its semi-synthetic version, has been approved by regulators to treat some forms of chronic myeloid leukemia that are resistant to tyrosine kinase inhibitors. In hematological malignancies, this distinct method of action has proven effective (Khatua *et al.,* 2024; Wang *et al.,* 2025). Interest in HHT has increased due to its preclinical effectiveness against a range of tumors and viral infections. Despite its potential, the chemical is nevertheless limited by narrow therapeutic windows, challenging extraction techniques, and low natural prevalence. Further mechanistic study, improved delivery modalities, and advancements in total synthesis have elevated homoharringtonine as a helpful indication of how unusual plant-derived chemicals can influence phytomedicine in the future (Eswaran and Kasthuri, 2024; Hai-Jun *et al.*, 2024).

4. Thapsigargin: This a potent sesquiterpene lactone isolated from a plant *Thapsia garganica*, is a rare phytochemical of remarkable biomedical importance. Its primary mechanism is the permanent blockage of the sarco/endoplasmic reticulum Ca^{++}-ATPase pump, which causes endoplasmic reticulum stress-mediated apoptosis and disturbs intracellular calcium homeostasis. Thapsigargin has become a helpful framework for the development of targeted prodrugs that release the active ingredient solely within the tumor microenvironment, despite the fact that its severe cytotoxicity prevents direct therapeutic usage (Andersen *et al.,* 2015; Jaskulska *et al.,* 2020). This approach has resulted in the development of novel treatments that seek to maximize thapsigargin's effectiveness while reducing systemic toxicity, such as PSA-activated prodrugs for prostate cancer. Its distinct mechanism has made it an essential molecular tool for researching ER stress pathways and calcium signaling outside of oncology. Thapsigargin remains a prime example of how uncommon plant-derived metabolites can motivate sophisticated and highly targeted approaches in contemporary phytomedicine, despite issues with safety, natural scarcity, and complicated synthesis (Denmeade *et al.,* 2003; Mahalingam *et al.,* 2016).

5. Conophylline: Because of its distinct biological characteristics and potential for therapeutic application, the incredibly rare bisindole alkaloid conophylline, isolated from *Tabernaemontana divaricata* and related Apocynaceae species-has attracted growing attention in phytomedicine. Since its ability to induce differentiation in pancreatic β-cells, conophylline has been studied for its broader cytomodulatory effects, which include anti-inflammatory, anticancer, and antifibrotic properties (Kam *et al.,* 2003; Sim *et al.,* 2019). It is a promising lead compound for diseases marked by excessive proliferation or impaired cell function because of its ability to modulate important signaling pathways, including those involved in metabolic regulation and cellular differentiation. However, its low natural abundance, structural complexity, and limited accessibility have posed significant challenges to pharmacological development.

The conophylline is a promising but little-studied example of how uncommon plant metabolites can push the boundaries of contemporary phytomedicine.

Recent advancements in semi-synthesis, total synthesis, and tissue-culture-based production have started to outweigh these obstacles.

6. Brusatol: The quassinoidbrusatol, which is mostly extracted from *Brucea javanica*, is a rare and structurally distinct phytochemical that has garnered significant attention due to its strong anti-inflammatory and anticancer properties. Although the therapeutic benefits of brusatol have long been recognized in traditional medicine, recent research has concentrated on its ability to alter cellular stress responses, particularly by momentarily blocking the Nrf2 signaling pathway (Fig. 4), which increases the susceptibility of cancer cells to oxidative stress and chemotherapy (Ren *et al.,* 2011; Yu *et al.,* 2020; He *et al.,* 2023). Brusatol has become a promising chemosensitizer that can boost the efficacy of conventional anticancer treatments in preclinical animals due to this mechanism. In addition to cancer, brusatol's action against a range of inflammatory diseases and certain viral infections further expands its biological importance. However, issues like poor solubility, limited natural availability, and nonspecific toxicity still prevent it from being used in clinical settings. The promise of brusatol as a helpful but underutilized rare phytomedicine is being highlighted by current efforts in structural modification, targeted delivery, and sustainable manufacturing (Ren *et al.,* 2011; Xi *et al.,* 2024).

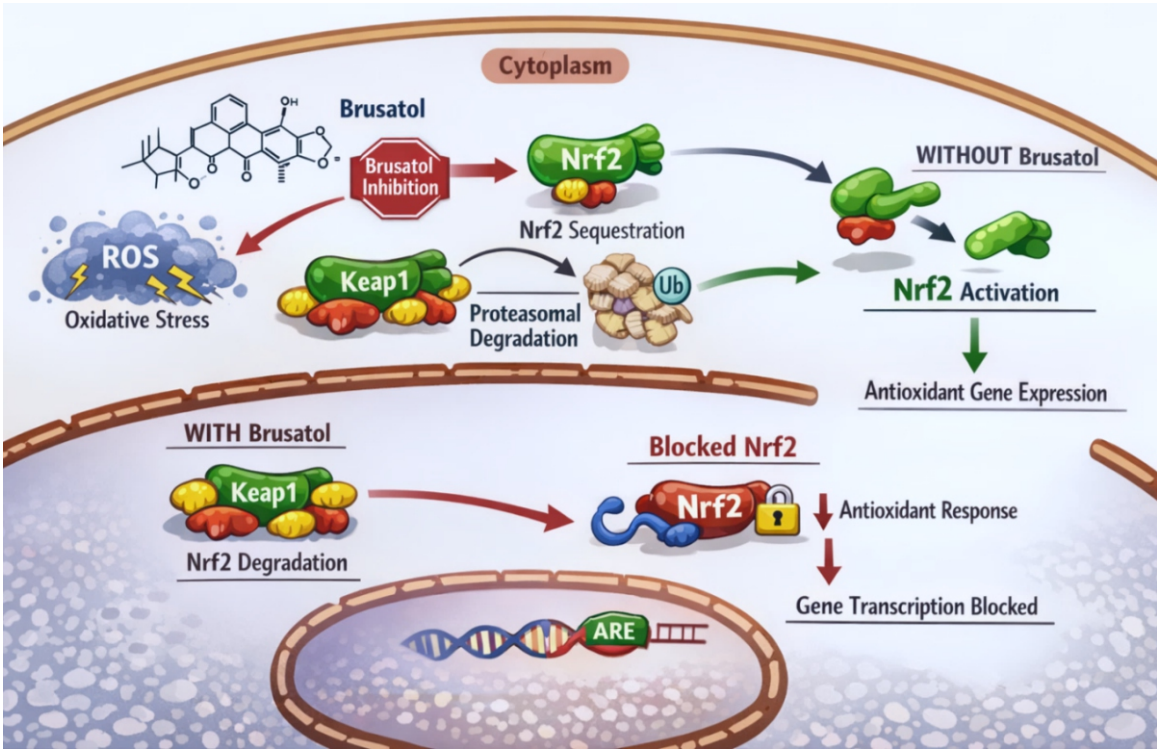


Fig. 4: Possible mechanism of Nrf2 pathway blocking by brusatol.

7. Salvinorin A: This is a rare neoclerodanediterpene, isolated from *Salvia divinorum*, is noteworthy in phytomedicine due to its unique pharmacological profile and structural properties. One of the most powerful naturally occurring kappa-opioid receptor (KOR) ligands is salvinorin A, a non-nitrogenous compound with potent and selective agonist action at the KOR. This is not the case for most naturally occurring psychotropic substances. Its exceptional selectivity has generated a great deal of interest in its potential therapeutic applications, particularly in areas including pain modulation, treatment-resistant depression, addiction, and neuropsychiatric diseases where KOR pathways are crucial regulators (Chavkin *et al.,* 2004; Ansonoff *et al.,* 2006). Its short duration of action and rapid start also provide a helpful framework for developing future neuromodulatory medications with controlled effects.

However, problems including its potent psychotropic qualities, regulatory limitations, and low oral bioavailability have hindered conventional drug-development processes. A rare but important phytochemical in science, salvinorin A has substantial implications for the development of new neurotherapies. Research focused on structural analogs, formulation improvements, and tailored delivery systems further emphasize this (Cichon *et al.,* 2022; Nammas, 2025).

Table 1: Suitable parameters for phytochemical extraction using several extraction techniques.

Extraction method	Solvent	Temperature	Time	Pressure	References
Soxhlet extraction	Organic solvent	65-100^{0}C	6-24 hours	Atmospheric pressure	(Sulaiman *et al.*, 2017; Kumar *et al.*, 2023)
Pressurized liquid extraction	Water, aqueous and non-aqueous solvent	50-200^{0}C	5-20 minutes	50-300 psi	(Mustafa *et al.*, 2012; Calderón-Oliver and Ponce-Alquicira, 2021)
Maceration	Water, aqueous and non-aqueous solvent	Room temp. or cold method (4-15^{0}C)	3-7 days	Atmospheric pressure	(Cvetanović *et al.*, 2020)
High hydrostatic pressure extraction	Water, ethanol, glycerol, silicon oil, or a mixture of solvents	Below 45^{0}C	3-15 minutes	100-1000 MPa	(Moreira *et al.*, 2020; Kumar *et al.*, 2023)
Natural deep eutectic solvent extraction	Deep eutectic solvents such as reline, ethaline, glycerine	25-105^{0}C	30-60 minutes	Atmospheric pressure	(Zissi *et al.*, 2025)
Decoction	Water	65-70^{0}C	1-2 hour	Atmospheric pressure	(Ennaifer *et al.*, 2018)
Supercritical fluid extraction	Supercritical Fluids such as S-CO_2, S-H_2O	40-80^{0}C	10-60 minutes	35-70 MPa	(Volcho and Anikeev, 2014; Ahangari *et al.*, 2021)

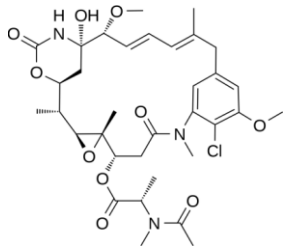
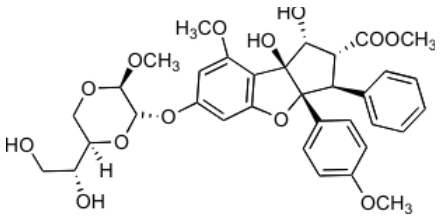
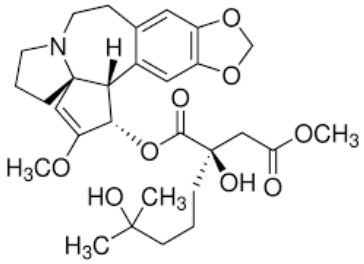
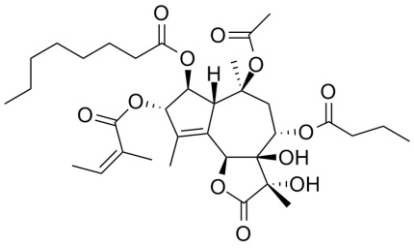
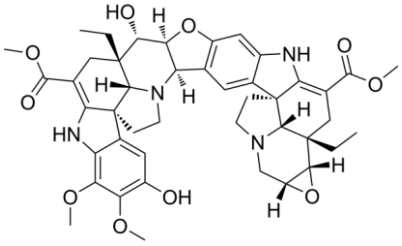
8. Phyllanthin: This is a lignan mostly isolated from *Phyllanthus amarus* and related species, is considered a rare and pharmacologically useful phytochemical due to its wide spectrum of bioactivities and very low natural abundance. Phyllanthin, which has long been associated with hepatoprotective effects, is largely responsible for the well-known liver-protective properties of *Phyllanthus* plants. It has been shown to retain the cellular antioxidant defenses, modify inflammatory pathways, and combat oxidative stress. The substance contains antiviral, anti-inflammatory, and anticancer qualities in addition to hepato-protection. Lipid peroxidation attenuation, cellular detoxification enzyme increase, and NF-κB signaling regulation facilitate these effects (Hanh *et al.,* 2014; Hanh *et al.,* 2015). Despite these promising outcomes, phyllanthin's development as a therapeutic candidate is still limited by its scarcity in nature, trace amount in plant, and challenges in achieving optimal bioavailability. Developments in plant cell culture, extraction methods, and synthetic analog design are addressing these issues, underscoring phyllanthin's status as an exciting but little-researched uncommon phytomedicine (Pagliano *et al.,* 2021; Badawy *et al.,* 2025).

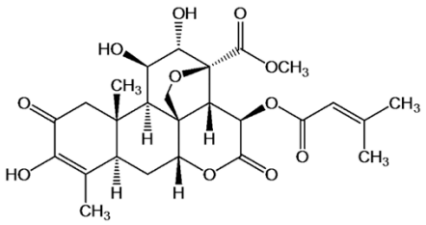
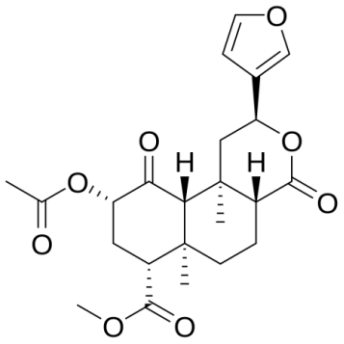
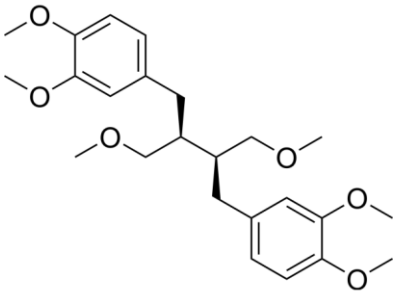
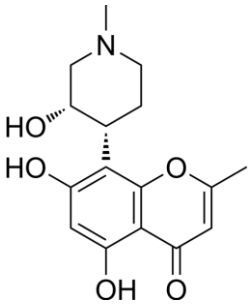
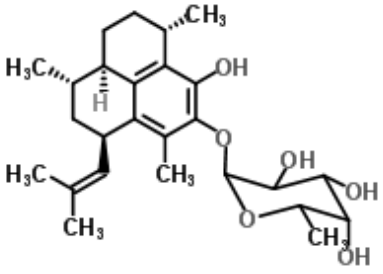
9. Rohitukine: *Amoora rohituka* and *Dysoxylum binectariferum* are the sources of rohitukine, a chromone-alkaloid that is a rare and structurally distinct phytochemical. It has been crucial candidate to the development of modern anticancer medications. The most well-known effects of rohitukine are its cytotoxic, anti-inflammatory, and immuno-modulatory effect. It is also the natural precursor of the clinically used cyclin-dependent kinase (CDK) inhibitors P-27600 and flavopiridol. Its suppression of NF-κB signaling, blockage of CDK-mediated cell-cycle progression, and manipulation of apoptotic pathways are the main causes of its antiproliferative actions in a range of tumor types (Kumara *et al.,* 2014; Mahajan *et al.,* 2015). As new research suggests potential roles in immune response control and oxidative damage mitigation, its therapeutic importance has extended beyond oncology. However, the compound's narrow distribution among plant species, complicated stereochemistry and scarcity in nature has hindered large-scale development.

10. Pseudopterosins: This is an unique class of diterpene glycosides isolated from the Caribbean

gorgonian coral *Pseudopterogorgia elisabethae*, is an uncommon and highly potent class of marine-derived phytomedicinal chemical. The powerful anti-inflammatory and wound-healing properties of pseudopterosins are attributed to their dual modulation of eicosanoid pathways and suppression of key inflammatory mediators like PLA_2 and COX enzymes. They are now included in high-end dermatological formulations due to their remarkable ability to promote tissue regeneration and reduce inflammation. This has sparked interest in a wider range of therapeutic purposes, from chronic inflammatory illnesses to neuroinflammation (Look *et al.,* 1986; Puyana *et al.,* 2004; Correa *et al.,* 2009). Additionally, because of their structural complexity and range of analogs, efforts in medicinal chemistry to improve stability, potency, and bioavailability have been successful. Notwithstanding their potential, obstacles like ecological sustainability, scarce natural resources, and the requirement for effective synthetic or semisynthetic production methods continue to be major obstacles. As demonstrated by continuous advancements in aquaculture, biosynthesis, and structural optimization, pseudopterosins are a rare but incredibly important class of marine phytomedicines with expanding biological promise.

Table 2: Molecular weight and structure of ten rare phytochemicals.

Phytochemicals	Molecular weight	Molecular structure'
Maytansine	692.2 g/mol	
Silvestrol	654.66 g/mol	
Homoharringtonine	545.62 g/mol	
Thapsigargin	650.76 g/mol	
Conophylline	794.9 g/mol	

Brusatol	520.5 g/mol	
Salvinorin A	432.4636 g/mol	
Phyllanthin	418.53 g/mol	
Rohitukine	305.32 g/mol	
Pseudopterosins	446.6 g/mol	

FUTURE DIRECTIONS

Future research on these ten less common and pharmacologically important natural compounds such as maytansine, silvestrol, homoharringtonine, thapsigargin, conophylline, brusatol, salvinorin A, phyllanthin, rohitukine, and pseudopterosins should focus on utilizing advancements in modern drug-development technologies to overcome supply, specificity, and safety limitations. Sustainable production methods including metabolic engineering, plant and microbial biomanufacturing, and complete or semi-synthesis will be essential for ensuring steady access to these structurally complicated compounds (Fig. 5). Mechanistically, more comprehensive multi-

omics profiling and systems-level investigations are needed to better identify the molecular targets and off-target liabilities of safer prodrugs and analogs. Particularly for potent cytotoxins like thapsigargin and maytansine, targeted delivery advances including antibody–drug conjugates, nanoparticle systems, and microenvironment-activated prodrugs provide intriguing strategies to lower toxicity and boost therapeutic efficacy. Additionally, investigations into the non-oncological applications of these compounds, such as their antiviral, neuropharmacological, hepatoprotective, and anti-inflammatory qualities, may lead to the development of novel treatment approaches. Understanding and combining these uncommon phytocompound with natural-product chemistry, synthetic biology, structure-guided drug design, and precision-medicine frameworks will ultimately determine how well they translate into next-generation treatments.

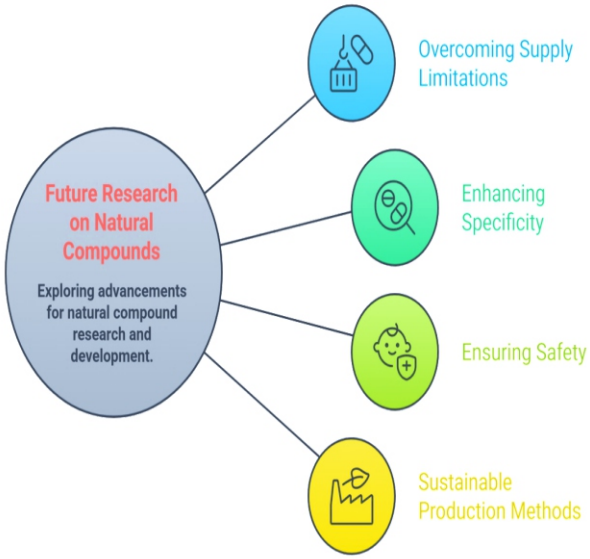


Fig. 5: Future research prospect and development.

CONCLUSION

Rarely found medicinal plants contain drug-like molecules with substantial bioactivity and exceptional structural diversity. Neural modulation, ER stress induction, β-cell regeneration, translation suppression, and microtubule inhibition are their mechanisms. Despite their restricted availability and challenging chemistry, their medicinal promise is rapidly being unlocked by modern biosynthetic technologies and formulation advances. The comprehensive study of these rare molecules is expected to yield novel therapeutics for neurological illnesses, metabolic disorders, cancer, and viral infections.

CONFLICTS OF INTEREST

Authors declare that they have no conflict of interest.

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