A REVIEW ON PHARMACOLOGICAL ACTIVITIES OF PRENYLATED ALKALOIDS ISOLATED FROM NATURE

By

Faria Richee
19146075

A thesis submitted to the School of Pharmacy in partial fulfillment of the requirements for the degree of Bachelor of Pharmacy (Hons.)

School of Pharmacy
BRAC University
February 2023

Declaration

It is hereby declared that

1. The thesis submitted is my/our own original work while completing degree at Brac University.
2. The thesis does not contain material previously published or written by a third party, except where this is appropriately cited through full and accurate referencing.
3. The thesis does not contain material which has been accepted, or submitted, for any other degree or diploma at a university or other institution.
4. I/We have acknowledged all main sources of help.

Student's Full Name & Signature:

Faria Richee
19146075

Approval

The thesis titled "A review on pharmacological activities of prenylated alkaloids isolated from nature" submitted by Faria Richee (19146075) of Summer, 2022 has been accepted as satisfactory in partial fulfillment of the requirement for the degree of Bachelor of Pharmacy.

Supervise By:

Supervisor:

Sania Ashrafi
Lecturer
School of Pharmacy
BRAC University

Approved By:

Assistant Dean and
Program Coordinator:

Professor Dr. Hasina Yasmin
Program Director and Assistant Dean
School of Pharmacy
BRAC University

Dean:

Professor Dr. Eva Rahman Kabir
Dean
School of Pharmacy
BRAC University

Ethics Statement

No human or animal tests are involved in this study.

Abstract

Nature is a vast source of resources and has provided us with an abundance of natural products with various functional attributes. Prenylated alkaloids provides additional functionalities to natural products, including impressive pharmacological effects such as antioxidant, antiviral, anticancer, anti-inflammatory, antiallergic properties, and more. The prenylation of these alkaloids enhances their bioactivity and solubility, making them more effective as therapeutic agents for a range of diseases and conditions. Although the mechanism of action of these compounds is not yet fully understood, their potential as therapeutic agents cannot be ignored. The study of prenylated alkaloids underscores the importance of exploring natural compounds for the discovery of new treatments and the ever-growing need for new drugs. Further research is necessary to fully understand the pharmacological activity of prenylated alkaloids, including toxicity and pharmacokinetics.

Keywords: Prenylated alkaloids, Natural product, Anti-inflammatory, Antioxidant

Acknowledgement

First, all the praises to Allah for His blessings toward me.

After that, I would like to thank my faculty supervisor, Sania Ashrafi, Lecturer, School of Pharmacy, Brac University, her guidance, support, and direction during my thesis periods. This has been a great opportunity for me to work under her guidance. I thank her for her precious advice and patience whenever I faced difficulty and needed it. She has been a great help and mentor to me during this period.

Also, I would like to thank honorable Dr. Eva Rahman Kabir, Dean and Professor, School of Pharmacy, Brac University, for her devotion, dedication, contribution and direction to both the students and department.

Finally, I would be thankful to my family for their constant support and motivation.

Table of Contents

Declaration ..... **ii**

Approval ..... **iii**

Ethics Statement ..... **iv**

Abstract/ Executive Summary ..... **v**

Acknowledgement ..... **vi**

List of Tables ..... **ix**

List of Acronyms ..... **x**

Chapter 1 ..... **1**

Introduction **1**

1.1 Overview 1

1.2 Herbal drug 1

1.3 Conventional treatment 2

1.4 Necessity of complementary and alternative medicine 3

1.5 Examples of marketed herbal drugs 4

1.6 Conventional treatment and Herbal Drugs 5

Chapter 2 ..... **7**

Objective of the study **7**

Chapter 3 ..... **8**

Methods and Materials **8**

Chapter 4 ..... **9**

Pharmacological activity of Prenylated Alkaloids **9**

4.1 Alkaloids..... 9

4.2 Prenylated Alkaloids..... 10

4.3 Exploring the Therapeutic Potential of Prenylated Alkaloids: A Study on Their Pharmacological Activity 11

Discussion **1**

Chapter 6 ..... **2**

Future prospective **2**

Chapter 7 ..... **3**

Conclusion **3**

References..... **5**

List of Tables

Table 1: List of prenylated alkaloids isolated from nature …… 1

List of Acronyms

CAM Complementary and alternative medicine

PTases Prenyltransferase

DMAT Dimethylallyl tryptophan synthase

MRSA (Methicillin Resistant Staphylococcus Aureus

Chapter 1

Introduction

1.1 Overview

Natural substances have been used for their healing properties for centuries and have been an important part of human culture. They have served as food additives, aesthetics, and medicines. With the rise of antibiotic resistance, natural products are being considered as potential drugs. (Cheng et al., 2016). Herbal medicine has been used from the earliest civilizations. It involves employing medicinal plants to treat ailments and enhance people's general health and wellness. From minor aches and pains to chronic disorders, these plant-based treatments have been utilized to treat different kinds of illnesses. Herbal medications are getting more and more sure among those looking for alternative therapies as natural and holistic approaches to health gain popularity. Herbal medicines have consistently been shown to be efficient, secure, and affordable, from traditional Chinese herbs to Ayurvedic treatments.

Herbal medicines are the ideal means of achieving a healthier and happier life since they have the power to heal the body, mind, and spirit. Herbal medicines are the culmination of generations of practicing physicians of indigenous systems of medicine over many years of therapeutic experience. Due to effectiveness, safety, and lack of negative side effects, herbal medications are also much desired after for use in primary healthcare in the developed world. Additionally, they provide treatments for age-related illnesses including memory loss, osteoporosis, immunological problems, etc. for which there is no modern therapy. India has a pitiful market share due to the export of crude extracts and medications, while having a wealth of traditional knowledge, a long history of herbal remedies, and a vast amount of biodiversity. Guidelines for herbal drugs was developed by WHO in 1991. Even though nearly 80% of the world's population uses traditional medicines for early healthcare, WHO has not comprehensively reviewed them. (Oneschuk et al., 2011)

1.2 Herbal drug

Herbal medicines are natural substances derived from plants. These substances include combination of organic compounds that can originate from any refined part of a plant. Every civilization in the world has used herbal medicine at one time or another. There are many different types of traditional medicine, and each one's beliefs and practices are influenced by

factors such as society, environment, and location. However, all these systems share a comprehensive approach to health and life.

There should be a focus on health rather than disease, according to well-known herbal medicine systems as Traditional Chinese Medicine and Ayurvedic Medicine. By utilizing therapeutic herbs, individuals can concentrate on their overall well-being rather than just treating a particular ailment caused by an imbalance between the mind, body, and environment. The practice of using plants as medicine dates to ancient civilizations and involves the consumption or application of herbal materials for the purpose of curing illness and promoting health. Herbal remedies, which have been used for a variety of ailments like malaria, warts, intestinal issues, heart conditions, and chronic pain since antiquity, are a result of pharmacists and doctors learning about traditional knowledge. (Sam, 2019)

Natural medicines have been made from medicinal plants. There are several ways that plants have been discovered to be useful in medicine. For example, plant crude extracts is used because there is presence of natural chemical components like morphine, vincristine, berberine etc., and for the synthesis of drugs like colchicine, quinine, tubocurarine natural compounds are used. Medicinal plants contain natural compounds including willow bark (*Salix spp.*), madagascar periwinkle (*Vinca rosea*), quinine bark (*Cinchona officinalis*) and foxglove (*Digitalis purpurea*) were the source of many modern medications, including digitalis, vinblastine, aspirin, quinine, and paracetamol. Many plants are utilized therapeutically or preventatively in medicine. The active components found in medicinal plants, such as alkaloids, coumarins, glycosides, tannins and vitamins, are thought to be responsible for their therapeutic effects. (Mittal et al., 2014)

Along with allopathic medicines, herbal medications account for a sizeable portion of drug use. People from many cultures use local medicines to treat common illnesses. The use of oils derived from herbs and other plants in aromatherapy is used to treat or relieve sickness. In order to preserve optimum health, the ancient Indian and Chinese healing systems Ayurveda and Chinese herbal medicine place a strong emphasis on the mind-body connection. Ayurveda, naturopathy, homeopathy, and American medicine all use medicinal herbs. (Phair, 2021)

1.3 Conventional treatment

The most prevalent form of medicine in the Western world is conventional medicine. There are numerous supplementary medical practices that have existed for hundreds of years. When medical personnel use scientific research and therapies to diagnose and treat symptoms and

illnesses, this practice is referred to be conventional medicine, often known as Western medicine or modern medicine. Pharmaceutical drugs, physical therapy, psychotherapy, radiation therapy, and surgery are a few examples of traditional medicine. A system in which licensed healthcare practitioners use drugs and radiation to treat illnesses and associated symptoms, such as by writing prescriptions for medication. Based on thorough research and recommendations for the most severe illnesses and several problems that may even be treated by its resources, it suggests medications and medical treatments that are frequently successful. By using the tools that conventional medicine employs, which are supported by scientific research and put into practice by healthcare experts, certain human diseases and their symptoms may be treated and even cured.

Advanced diagnostic methods using effective and reliable technologies. The medications are known as synthetic drugs since they are created in laboratories using various approaches that are not found in nature. Even though natural remedies are less effective than synthetic drugs. The time required to discover a new medicine costs billions of dollars. using a contemporary technology that is only partially responsive. Most rural people prefer herbal medicinal plant or handmade solution for cure as they are not as expensive as synthetic pharmaceuticals. They are correct since they can use them to treat any condition without suffering any fatal adverse effects. Considering this, many chemists are now shifting their focus from the conventional drugs to the natural derived medicinal compounds to better understand nature. Synthetic medications have serious adverse effects on the human body in addition to curing disease. There are numerous examples linked to side effects mentioned in the literature. (Nisar et al., 2018)

1.4 Necessity of complementary and alternative medicine

Complementary and alternative medicine (CAM) indicates to a wide spectrum of therapeutic beliefs that teach, and practice mainstream medical treatment. But some of these are currently in institutions. The use of complementary medicine in healthcare is on the rise. The rising acceptance of CAM reflects the general shift in wants and values in contemporary society. This includes an increase in the prevalence of chronic diseases, a rise in public access to information about global health, a decline in the acceptance of paternalism, a rise in the sense of entitlement to a high quality of life, a decline in the belief that scientific advances will be relevant for the individual treatment of disease, and a rise in spiritualism.

The search for alternative approaches to sickness prevention and management is also being fueled by worries about the negative effects and increasing costs of traditional medical care. About 80% of consumers of complementary medicine report being happy with their care, according to surveys. It's interesting to note that this isn't necessarily reliant on their condition getting better at the same time. One study of cancer patients in the UK, for instance, revealed that even when the cancer did not progress, the participants reported feeling emotionally stronger and less nervous. Previous studies have shown that individuals who are more educated and in poorer health are more likely to use alternative medicine. Patients with chronic illnesses including cancer, AIDS, arthritis, asthma, diabetes, epilepsy, etc. are often drawn to CAM treatments. Alternative medicinal practices are used by cancer sufferers all over the world. Herbal preparations should only be used under the supervision of a CAM practitioner or herbalist who is knowledgeable on the appropriate conventional pharmacology. Serious negative consequences following the administration of herbal products have been documented in case reports. Most of the time, the herbs in question were self-prescribed, purchased without a prescription, or acquired from a source other than a licensed practitioner. The exact rate of adverse medication reactions is unknown due to the absence of a systematic reporting system, necessitating the need for more trustworthy data. One way to potentially reduce the risk is to encourage patients who are taking conventional medication to openly discuss their plans to use complementary therapies and only begin such treatments with a doctor's consent. A major influence is being felt on medical education because of the public's increasing interest in and usage of complementary and alternative medicines, which has gained ground in several medical campuses. Many medical students are interested in learning about complementary medicines. Medical educators are becoming more and more aware that the issue is not whether to address these problems in the training of future doctors, but rather how to handle these constant challenges. (Pal, 2002)

1.5 Examples of marketed herbal drugs

Medicines made from plants are known as herbal products. They might be utilized for different therapeutic purposes in addition to being taken as supplements to enhance health and wellbeing. The various forms of herbal goods include tablets, capsules, powders, extracts, teas, and more. There are herbal medications which received sign research attention but not enough clinical trials are conducted to demonstrate their efficacy and safety. For cardiovascular

diseases and CNS problems, *Ginkgo biloba* is used and St. John's wort (*Hypericum perforatum*), used as depressant. Both compounds are subjected to much clinical research.

Though clinical trials demonstrated that herbal medications are safe, they do not contain any side effects, further research is still needed to determine their clinical effectiveness. For treating cardiovascular disturbance and lowering low density protein garlic (*Allium sativum*) is used. As tonics herbs like (*Panax ginseng*) is used. As antispasmodic and carminative, chamomile (*Matricaria chamomilla*) is used. For repairment of liver function, milk thistle (*Silybium marianun*) and to function as sedative valerian (*Valeriana officinalis*) is used. The three herbal medications with the largest global markets are Arnica (*Arnica montana*), which is used to treat post-operative and post-traumatic conditions, as immunostimulant and to reduce inflammation, Echinacea(*Echinacea purpura*) is used. And lastly, Saw Palmetto (*Serenoa repens*), functions to treat benign prostatic hyperplasia. Despite their evaluation in various clinical trials, more appropriate and well-controlled randomized clinical trials are still required. (J.B., 2000)

1.6 Conventional treatment and Herbal Drugs

The best course of action depends on the individual and their unique demands. Both herbal medication and conventional treatment have benefits and drawbacks. Although many complementary and alternative medicine (CAM) methods place an emphasis on holistic approaches to health and wellness, some people believe that herbal medicine is superior to traditional treatment since it comes from natural sources. Compared to traditional treatments, which can have harmful side effects, herbal medications and CAM therapies are frequently seen to be safer and less toxic. Contrary to traditional treatments, which may be standardized, herbal medications and CAM therapies are frequently personalized to the individual and consider their own circumstances and preferences. For those without insurance or with limited coverage, herbal medications, and complementary and alternative medicine (CAM) therapies may be less expensive than traditional treatments.

The best way to proceed is always to consult with a healthcare professional before using any kind of herbal remedy or complementary and alternative medicine (CAM) therapy. It's important to note that herbal medicines can interact with conventional treatments and have their own risks and side effects. In addition, when illnesses are serious or life-threatening, traditional therapies shouldn't be ignored or disregarded. The most successful strategy frequently combines both traditional and CAM therapies. Herbal medicines often work to

support the body's natural healing capacities while synthetic pharmaceuticals typically target the symptoms of certain diseases as they are understood by scientific pathology. Herbal remedies typically have a mild effect, support inadequate systems and processes, or try to reduce excessive behavior.

The therapeutic uses of medicinal plants go well beyond simply relieving symptoms. For instance, steroid anti-inflammatory treatments are typically used to treat arthritis, but these medications have a variety of unsettling side effects. Herbs are used to treat these disorders in a variety of ways, including by moistening dry synovia, promoting circulation in the affected areas, facilitating excretion through the kidneys and hepatic/biliary channels, altering diet to improve metabolism, etc. It is uncommon and difficult to find evidence of teratogenicity in people caused by herbal treatments. Therefore, it is preferable to avoid it when pregnant. While synthetic medications aim to treat specific diseases as understood through scientific pathology by targeting the symptoms, herbal remedies aim to boost the body's innate healing capacities. Some medicinal plants can even enhance or act as alternatives for certain medications. Unlike synthetic drugs, herbal remedies usually lack potent effects or adverse side effects. In the United States, adverse reactions to synthetic drugs are responsible for around 8% of hospital admissions and an estimated 100,000 deaths each year. This means that prescription medications cause more deaths in the U.S. than drunk driving. Thousands of people also die annually from over-the-counter drugs. However, hospitalizations or fatalities related to herbal remedies are rare and hard to track. Herbal remedies are typically regarded as secure and efficient. (Karimi et al., 2015)

Chapter 2

Objective of the study

Drug discovery has benefited greatly from the use of natural ingredients. Natural alkaloids obtained from plants may be potent substances that are starting to gain appeal across the globe for enhancing health and preventing disease. They provide a wide variety of structurally unique bioactive compounds and have been a significant source of cutting-edge and potent medicinal medicines. The development of their natural resources and the use of alkaloids will be accelerated by in-depth research on the metabolic transformation, effectiveness, and safety of alkaloids. Additionally, the interactive collaboration of experts from several scientific fields and the biological screening of active alkaloids will become a research hotspot, presenting new and crucial healthcare potential. (Qiu et al., 2014)

Because of their relatively unexplored structural diversity, their significance in drug development has increased. Natural compounds with prenyl side chains constitute a unique class of their own. Prenylated natural compounds have been acknowledged as useful and intriguing biologically active phytochemicals for several decades. Prenylated alkaloids have demonstrated promising biological effects and could be used as starting points for the creation of new medications. These prenylated alkaloids with biological activity can interact with biological systems in distinctive ways, and exploring their interactions can offer valuable understanding into the underlying biological processes. With their intricate structures, studying the interactions of prenylated alkaloids with biological systems can offer insights into the biological mechanisms involved. Prenylated alkaloids are mainly produced by plants, and studying their chemistry and distribution can contribute to the understanding of biodiversity and conservation efforts. Prenylated alkaloids with biological activity have shown therapeutic potential for various diseases, such as cancer, inflammation, and cardiovascular disease, and further research can lead to new treatments for these conditions.

Chapter 3

Methods and Materials

This review study is constructed using current and relevant research papers and articles from high-impact journals. Peer-reviewed journals, government papers, and articles were all thoroughly searched. To enhance the review article, basic and supplementary information was gathered from numerous published journals. The main publications like Natural Products, ACS (American Chemistry Society) , Asian Natural Products Research, Royal Society of Chemistry, MDPI (Multidisciplinary Digital Publishing Institute), etc. are available in the following search engines: Elsevier, Google Scholar, ResearchGate, PubMed, Science Direct, etc. A thorough screening of journals was done to generate an ideal quality review on the prenylated alkaloids having pharmacological activity, and then the most recent and pertinent publications published from the year 2000 to the present were chosen. In order to find prenylated alkaloids containing pharmacological action, more than 70 Google Scholar journals were evaluated. Of these, 21 contained the correct information, and the remaining publications were disregarded because they were irrelevant or lacked adequate details.

Chapter 4

Pharmacological activity of Prenylated Alkaloids

4.1 Alkaloids

Alkaloids, which are derived from plants and mainly formed from amino acids, exhibit a variety of chemical structures. Approximately 20% of plant species contain some level of alkaloid, and ongoing research and development concentrate on improving the production, extraction, and processing of these compounds. For instance, the genetic manipulation of alkaloid biosynthesis pathways can be utilized to boost their production levels. Like inorganic alkalis, alkaloids can react with acids to form salts. In acid-base processes, these nitrogen atoms could serve as bases. Alkaloids are typically thought of as amines. They frequently taste harsh.

Currently, 4000 different plant species include more than 3000 different alkaloids. There are a few to as many as 30 different classes of structurally similar alkaloids found in plants. These alkaloids are members of the same class, but they differ in their structural makeup, with one typically making up the majority. Some plant families have many alkaloids. For instance, in the ergot fungus and plants like the opium poppy (*Papaver somniferum*) (Claviceps). Their use in plants is still mostly unknown. Alkaloids are naturally occurring substances that discourage herbivorous creatures because of their bitter taste. They serve as natural insecticides on some plants. Alkaloids in plants may serve to shield them from some insect species' harmful behavior, according to a theory.

Due to their extensive variety of effects on both human and animal systems, some of these compounds appear to have been known to humans for a very long time. Plant extracts with alkaloids is used as medicines from ancient times, and their potent effects can be attributed to the alkaloids' presence. Both human treatment and the natural defense mechanisms of organisms heavily rely on alkaloids. In plants among the secondary metabolites, 20% are alkaloids. Alkaloids are mainly used as medicine for having anti-inflammatory, anti-anesthetic, and cardioprotective properties. Some of the known used alkaloids in medical sector include strychnine ,nicotine, quinine , morphine and ephedrine. Recently, there is a growing interest in biologically active natural compounds having the possibility of discovering new drugs and the advancements in the field of traditional medicine (ethnopharmacology). (Heinrich et al., 2021)

Plant tissues typically contain aqueous solutions of alkaloids. Special extraction techniques for alkaloids with economic value were created. Alkaloid-containing mixtures should typically be dissolved using a solvent and reagents. Alkaloids in the solution can be recovered using the extraction method. Each alkaloid can then be extracted in pure form by being separated from the mixture. Alkaloids demonstrated a wide range of therapeutic effects. Although several of them have local anesthetic characteristics, their usefulness for clinical purposes is constrained. One of the most well-known alkaloids that has been utilized and is currently used for medical purposes is morphine. Although this alkaloid is a potent narcotic used to relieve pain, its usefulness is constrained by its propensity for addiction.

An alkaloid called tubocurarine is used as a muscle relaxant during surgery and is a component of the toxin curare. Many different cancer types are treated with the chemotherapeutic alkaloid's vincristine and vinblastine. An alkaloid, Cocaine is a powerful local anesthetic found in the plant *Erythroxylum coca*. Ephedrine (*Ephedra*) and ergonovine (*Claviceps purpurea*) are used as blood vessel constrictors. For treating bronchial asthma and for decreasing the pain with sinusitis, colds and fever, ephedrine is used. Alkaloids are essential substances for humans. Their extracts have been employed for ages as a remedy to relieve pain comparable to morphine and some ailments comparable to quinine for malaria and colchicine for gout. (Kurek, 2019)

4.2 Prenylated Alkaloids

Prenylation is the covalent attachment of hydrophobic moiety to chemical substance, mainly protein. In the case of proteins, it often involves adding of the C-terminal of a geranylgeranyl moietyor farnesyl or to the cysteine residue. Prenylated proteins are localized to the plasma membrane or organellar membranes because of the inclusion of the prenyl moiety, which endows proteins with unique hydrophobic characteristics. It has been demonstrated that most of the cell signal transduction pathways involve well-characterized prenylated proteins as key participants. Compared to the corresponding nonprenylated molecules, prenylation of natural products promotes different biological activities. The prenylated have more adaptable and promising pharmacological characteristics and good effects on multiple target tissues.

Prenylated natural products contains higher lipophilicity than nonprenylated counterparts, which results in cell membranes high affinity for and improved pharmacological and biological effects. These compounds expanded pharmacological investigation is justified by the wide range of biological functions they offer. Prenylated natural compounds have recently been the

subject of in-depth analysis, with the prenyl substituents plays a crucial role in it. As a result, potential anticancer, anti-inflammatory, antioxidant, and neuroprotective substances have been found. For catalyzing the prenylation of natural substances, different enzyme classes of prenyltransferases (PTases), which include bacterial and fungal ABBA-type, fungal dimethylallyl tryptophan synthase (DMATS)-type PTases and membrane-embedded UbiA-type.

Prenylated indole alkaloids having two tryptophan moieties and a bis (indolyl) benzoquinone structure are known as asterriquinones. They display impressive pharmacological effects as anticancer, antiviral, and antidiabetic capabilities. The prenyl moiety is attached to an aromatic nucleus at either C1 or C3 in prenylated indole alkaloids. A prenylated purine alkaloid glucoside known as locustoside has been found as a prenylated purine alkaloid extracted from the seeds of Gleditsia japonica. N6 -isopentenyladenine, a plant cytokinin. Prenylated alkaloids that have been isolated from fungi and plants show tremendous structural variety while only having a small number of structurally uninteresting starting materials. Selective C-H oxidation processes, which are catalyzed by enzymes, facilitate the construction of complex carbon skeletons. During the biogenesis of prenylated alkaloid, the heteroatom's ambivalent reactivity is utilized in a variety of condensation chemical processes. (Cheng et al., 2016)

4.3 Exploring the Therapeutic Potential of Prenylated Alkaloids: A Study on Their Pharmacological Activity

In search for novel compounds with bioactivity, we investigated some prominent prenylated alkaloids with their pharmacological activity.

Like prenylated indole alkaloids includes (1) Notoamides F, (2) Notoamide G,(3) Notoamide H, (4) Notoamide I, (5) Notoamide J, (6) Notoamides k, all of them were isolated from *Aspergillus sp*. with EtOH. They were tested MTT Cytotoxicity assay, compound 4 showed weak cytotoxicity against HeLa cells, containing IC50 value of 21 μg/mL, and compound 1,5,6 showed IC50 values more than 50 μg/mL. (Tsukamoto et al., 2008).

Then some more prenylated indole diketopiperazine alkaloids from *Aspergillus fumigatus* includes 3 spirotryprostatins C, 3 Spirotryprostains D, 3 Spirotryprostains E, 7-13-oxoverruculogen 2 derivatives of fumitremorgin B including another new compound (1) which has not been named yet were isolated with EtOAc. They were tested MTT Cytotoxicity assay, MTT and SRB Cytotoxicity assay. By employing the MTT method with the cell lines HL-60 and P388, and the SRB method with the cell lines BEL-7402 and A549, cytotoxic activities of

substances were assessed. 3 Spirotryprostains E, and 2 derivatives of fumitremorgin B (5 and 6) expressed better susceptivity to HL-60, MOLT-4, and A549 with IC50 value ranges from (3.1-11.6) micros compare to standard VP16 (0.003-1.4) micron than other 3 compounds. (F. Wang et al., 2008).

Further some more prenylated Indole Alkaloids named 1. Versicoamide F,2.versicoamide G, 3.Versicoamide H, 4.stephacidin Am5.Notoamide C, 6.Notoamide E 7.Notoamide O, 8.Notoamide Q, 9.Dehydronotoamide and E and 10.Deoxybrevianamide E from *Aspergillus tennesseensis* were isolated with EtOAc. Weak cytotoxicity ASSAY was done in them. The CCK8 method was used to evaluate the cytotoxic effects of various compounds on a limited number of tumor cell lines, including ASPC, H460, A549 and K562.Versicoamide F and versicoamide G demonstrated low cytotoxicity against H460 cells, with IC50 values of 83.4 and 95.5 μM, respectively. At a concentration of 200 μM, none of the compounds demonstrated any cytotoxic effects against ASPC, K562 and A549.(Liu et al., 2017).

After that, new prenylated carbazole alkaloids methyl-2,6,7-trimethoxy-8-(3-methyl-2-butenyl)carbazole-3-carboxylate and 2,6,7-trimethoxy-8-(3-methyl-2-butenyl)carbazole-3-carbaldehyde were isolated from *Zanthoxylum armatum* . The alkaloids were extracted with MeOH. DPPH radical scavenging Assay was assessed. Ascorbic acid (20 mg/ml) was used as a positive reference to assess the antioxidant properties of all the substances.. Prenylated alkaloids were found to show higher antioxidant property than ascorbic acid. (Samad et al., 2014).

Afterwards, new prenylated indole alkaloids, dihydrocarneamide A and iso-notoamide B were isolated *Paecilomyces variotii EN-291*. They were extracted with EtOAc. dihydrocarneamide A and iso-notoamide B were evaluated for their cytotoxic activities against human large cell lung carcinoma cell line (NCI-H460). These demonstrated weak activity containing IC50 values of 69.3 and 55.9 mmol/L, respectively. (Zhang et al., 2015).

Again linearly Fused Prenylated Indole Alkaloids Asperversiamides (A-H) were separated from *Aspergillus versicolor*. They were extracted with EtOAc. The ability of each substance to inhibit the generation of NO, RAW264.7, and iNOS was examined in comparison to the industry standard, MG132. In LPS-induced Raw264.7 cells, the compounds Asperversiamides B, C, F, and G showed potential iNOS inhibitory actions and decreased the production of NO. Of these compounds, seven had a significant inhibitory impact containing IC50 value of 5.39 M against iNOS. (H. Li et al., 2018)

More indole alkaloids (speramides A and speramides B) were extracted from fungus *Aspergillus ochraceus KM007*. They were extracted with MeOH. Cytotoxicity of compounds were examined on Lncap , DU145 and PC3 cell lines and no compounds showed IC50 > 40 μM. The four pathogens MRSA 92#, MRSA 98#, Staphylococcus aureus, and Pseudomonas aeruginosa were the targets of our antimicrobial evaluation. With a MIC value of 0.8 M in the 2-fold dilution procedure, only speramides A showed moderate antimicrobial activity against Pseudomonas aeruginosa, but none showed substantial activity having IC50 greater than 40 M. (Chang et al., 2016).

Moreover, four new prenylated indole alkaloids Mangrovamide D,Mangrovamide E, Mangrovamide F, Mangrovamide G were isolated from *Penicillium sp. SCSIO041218* with EtOAc. Against the positive control loratadine (20 g/mL), the bioactivity on IgE-mediated rat mast RBL-2H3 cells was used to test the anti-allergic potential of each of these substances. But these compounds did not show any activity. (Yang et al., 2018).

In addition to that, there were three indole alkaloids which were diprenylated named Mangrovamides A, Mangrovamide B and Mangrovamide C were exteacted *from Penicillium sp.* Fungus. They were extracted with acetone, and they were evaluated on anti-acetylcholinesterase activity and MTT cytotoxicity assay. Using the MTT technique, the cytotoxicity of each drug was evaluated in the HL60, H1975, Huh-7, U937, K562, MOLT-4, BGC823, MCF-7, A549, and Hela cell lines. All the compounds were not toxic to human tumor cell lines (BGC83, 2Huh-7, H1975, U937, K562, MOLT-4, A549, MCF-7, Hela, and HL60), and the anti-acetylcholinesterase activity was determined using Ell-coupled man's enzyme assay. Mangrovamide C demonstrated a moderate acetylcholinesterase inhibitory action with an IC50 value of 58.0 M. (Yang et al., 2014).

Likewise, two prenylated indole alkaloid dinotoamide J and di-6-hydroxydeoxybrevianamide E and were isolated from *Aspergillus austroafricanus Y32-2* with EtOAc. These compounds were evaluated by MTT Cytotoxicity, pro-angiogenic Activity, anti-inflammatory tests. All substances were tested using the MTT method for cytotoxicity against HepG2 human liver cancer cells, pro-angiogenic activity in a vatalanib (PTK787)-induced vascular damage zebrafish model, and anti-inflammatory activity in a CuSO4-induced zebrafish inflammation model. A dose-dependent pro-angiogenic action was demonstrated in dinotoamide J. (P. Li et al., 2021).

Moreover, Prenylated Guanidine Alkaloids Galegine, pterogynidine and alchorneine were extracted from *Pterogyne nitens Tul*. with ethanol. In vitro antibacterial study was performed against MRSA (Methicillin Resistant Staphylococcus Aureus) srains. Alkaloids showed action against EMRSA-16, S. aureus SA-1199B, and XU212 strains that was stronger than or comparable to norfloxacin, except for achorneine (MIC > 512 mg/L). For all studied strains, galegine and pterogynidine emerged as the most effective substances among some of the investigated natural guanidines. These substances were 32 times more effective than norfloxacin against the strongest resistant strain, EMRSA-16, and were 8 times more effective than norfloxacin against the multi-drug resistant strain, SA-1199B, which overexpresses the NorA efflux transporter. (Coqueiro et al., 2014).

After that, new compounds echinulin ,cristatumin F and dehydroechinulin were extracted from fungus *Eurotium cristatum*. They were extracted with MeOH. These substances were tested for their capacity to scavenge DPPH radicals. The IC50 values represent the sample concentration needed to neutralize 50% of the DPPH free radicals. Using 3T3L1 cells and the MTT assay, the impact of cristatumin F on cell viability was evaluated. Cristatumin F had mediocre radical scavenging action against DPPH with an IC50 value of 53.6 M where as a positive control, ascorbic acid is used with IC50 15 M), and when tested at 200 M, it showed mediocre cell prolification 20.6% inhibition. (Zou et al., 2014).

Then, utilizing CHCl3, ethyl acetate, and n-butanol, a new prenylated spiro-oxindole alkaloid known as Penioxalamine A was isolated from *Penicillium oxalicum TW01-1*. Penioxalamine A was investigated for its cytotoxic effects on the HL-60 cell line. The HL-60 cell line was moderately cytotoxic to penioxalamine A. The inhibitory impact of compound 1 was moderate, with an IC50 value around 28.12 M (the IC50 for 5-FU was 2.48 M). (Hu et al., 2014).

Some more prenylated indole alkaloids were extracted from *Tussilago farfara*. With EtOH. All the compoundswere screened for their α-glucosidase inhibitory. Acarbose having IC50 (503 1.5 M) was outperformed by compounds 1 and 2, whose IC50 values were 105 4.7 and 35.2 3.2 M, respectively. (Song et al., 2020).

Prenylated indole alkaloid named giluterrin was extracted from *Aspergillus terreus P63* with Hydromethanolic acid. Cell viability assay and clonogenic assay was done. Giluterrin's cytotoxic properties. after 48 hours of incubation, an assay on tumor cells from humans is conducted. U-251 glioma, MCF7 breast, 7860 kidney, NCI-H460 lung, PC-3 prostate, HT-29

colon, and HaCaT keratinocyte human non-tumor cell line are examples of human tumor lines. Giluterrin's cytotoxic potential was assessed in vitro using cancer cell lines and one non-tumor cell line. Not all cell lines were cytotoxic to giluterrin. Instead, it demonstrated specific cytotoxicity against PC-3 (prostate) and 786-0 (kidney) cancerous cells, with IC50 values of 22.93 M and 48.55 M, respectively. (Gubiani et al., 2019)

Additionally, isolation alkaloids, aspernidines F, G, and H, and aspoquinolones E and F. Using the MTT method and cis-Platin as a positive control, all the compounds were tested for their toxicity against the cancer cell linesA-549, HL-60, SMMC-7721, MCF-7, and SW480. Aspernidines E, G, and H showed moderate cytotoxic activity, with IC50 values that ranged from 3.50 to 33.03 M, when the inhibitory activity on five human cancer cells were evaluated in vitro. SW-480 cells and A-549 and were significantly inhibited by aspernidines E and H, having IC50 4.77 and 3.50M. (Q. Li et al., 2020).

Likewise, alkaloids which are glybomine B, glycoborinine and (E)-3-(3-hydroxymethyl-2-butenyl)-7-(3-methyl-2-butenyl)-1H-indole, extracted from *Glycosmis montana Pierre* (Rutaceae) with MeOH. Anti-HIV Assay, cytotoxicity assay, MTT colorimetric assay were done. In vitro inhibitory action against HIV replication were examined for each prenylated alkaloid in C8166 cells. With IC50 values of 4.47 and 9.73 lg/ml for Glycoborinine and Glybomine B, respectively, modest to moderate anti-HIV action was seen in both compounds. (E) -3-(3-hydroxymethyl-2-butenyl)-7-(3-methyl-2-butenyl) The strongest anti-HIV activity was demonstrated by -1H-indole, having IC50 =1.17 lg/ml and a SI value of 11.68. (J. Wang et al., 2005).

We have further seen that prenylated Indole Alkaloid named penipalines A, penipalines B and penipaline C were extracted from *Penicillium paneum SD-44* with AcOEt. Tumor cell linesHCT-116 and A-549 were used to investigate the cytotoxic effects of each substance. The MTT technique was used to assess the cytotoxic activity against the human cancer cell lines A-549 (lung cancer) and RKO (colon cancer). According to the findings, penipalines B and C were effective both against cell lines. Penipalines B and C had IC50 values of 20.44 and 21.54 mm against A-549 and 14.88 and 18.54 mm against HCT-116, respectively.(C. S. Li et al., 2014).

With the help of EtOAc, the p-enylated alkaloids asperpendoline and asperpenazine were extracted from *Penicillium sp. HUBU 0120 Aspergillus ochraceus MCCC 3A00521* , respectively. The substances underwent testing for cytotoxicity, CCK-8 assay, molecular

docking, ROS, and GSH ELISA. The CCK-8 assay was used to assess the compounds' cytotoxicities on SH-SY5Y cells. The interaction between 2 and Keap1 was demonstrated using molecular docking with dynamicsimulation studies (PDB ID: 1X2R). To harm SH-SY5Y cells, H2O2 (350 M) was used. No substances exhibit cytotoxic activity at a concentration of 50 M, although the positive control (TBHQ) did. When compounds' ability to protect cells from H2O2 damage was assessed, both metabolites showed cytoprotective action in a dose-dependent manner on H2O2-induced cells, while asperpendoline become more effective at concentrations of 50 M than TBHQ at 10 M. Asperpendoline was observed to enhance GSH concentration in H2O2-induced cells during ELISA experiment in a dose-dependent manner. (Xiao et al., 2022).

Later we observed that, when ethyl acetate was used to isolate prenylated indole diketopiperazine alkaloids, they were given the names dihydroneochinulin B, cryptoechinuline D (2a. cryptoechinuline + and 2b. cryptoechinuline -), dihydroechinulin B, neoechinulin B, and auroglaucin. There was an MTT Cytotoxicity assay. The compounds' cytotoxic effects were initially assessed on the cell lines P388, HL-60, BEL-7402, and A-549. As a check, doxorubicin was used. With IC50 values (3.43 and 2.50 lM) respectively, 2a(cryptoechinuline +) and cryptoechinuline D had substantial inhibitory action against the P388 cell line, whereas compound 2b(cryptoechinuline -) shown moderate intensity to P388 at IC50 values of 11.3 lM. A-549 and BEL-7402 were significantly inhibited by didehydroechinulin B, having IC50 values of (1.43 and 4.20 lM) respectively. (Gao et al., 2013).

At last, More prenylated indole alkaloids, such as 17-hydroxynotoamide D, 17-O-ethylnotoamide M, 10-O-acetylsclerotiamide, 10-O-ethylsclerotiamide, 10-O-ethylnotoamide R, ()-notoamide B, notoamide C, dehydronotoamide C, notoamide D, notoamide F, notoamide Q, 17 Both a colony formation assay and an MTT-based drug susceptibility assay were conducted. At doses up to 100 M, the MTT assay demonstrated that none of the chemicals tested were harmful to both benign (MRC-9 and HEK 293) and malignant (LNCaP, 22Rv1 and PC-3) cell lines. By using MTT method, (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) test, the in vitro cytotoxicity of several compounds was assessed. In a colony formation experiment, it was discovered that 17-O-ethylnotoamide M,.()-notoamide B, dehydronotoamide C, notoamide M, and sclerotiamide, at a concentrations of 100 M, reduced the bacterial population of 22Rv1 prostate carcinoma cells. At doses of 10 M, notoamide M and 17-O-ethylnotoamide M both considerably reduced colony formation by 25 and 55%, correspondingly. cells 22Rv1. (Afiyatullov et al., 2018)

In conclusion, the study of prenylated alkaloids has shown promising results in terms of their pharmacological activity. Additionally, the prenylation of these alkaloids has been found to enhance their bioactivity and solubility, making them more effective as therapeutic agents. However, further research is required to fully understand the potential of these compounds as therapeutic agents. This includes the exploration of their mechanism of action, their toxicity profile, and their pharmacokinetics. Overall, the study of prenylated alkaloids has demonstrated their potential as therapeutic agents and highlights the importance of exploring the vast diversity of natural compounds for the development of new and effective treatments for a range of diseases and conditions.

Table 1: Pharmacological Activities of Prenylated Alkaloids Isolated from Nature

No.	Compound	Source	Extraction process	Biological activity	Experimental detail	Result	Reference
1	Notoamides F, Notoamide G, Notoamide H, Notoamide I Notoamide j Notoamides k	*Aspergillus sp.*	EtOH	MTT Cytotoxicity assay	MTT Cytotoxicity assay, Cytotoxicity was evaluated in HeLa cells.	Against HeLa cells, Nitroamide I expressed weak cytotoxicity having an IC50 equals to 21 µg/mL, and notoamides F, J and K gave the IC50 values were more than 50 µg/mL.	Tsukamoto et al., 2008
2	1. New compound which has not been named yet. 2. 3 spirotryprostatins C, 3. 3 Spirotryprostains D, 4.3 Spirotryprostains E , 5. Derivatives of fumitremorgin B 6. Derivatives of fumitremorgin B 7.13-oxo verruculogen	*Aspergillus fumigatus*	EtOAc.	MTT Cytotoxicity assay, MTT and SRB Cytotoxicity method	Cytotoxic activities of compounds were assessed on HL-60 and P388 cell lines using MTT method using and and on BEL-7402 and A549 cell lines using SRB method.	3 Spirotryprostains E, and 2 derivatives of fumitremorgin B expressed better. susceptivity to A549, MOLT-4 and HL-60 with IC50 value ranges from (3.1-11.6) microm compared to standard VP16 (0.003-1.4) micron than other 3 compounds. VP16 was used as positive control.	F. Wang et al. 2008

3	1.Versicoamide F, 2.versicoamide G, 3.Versicoamide H, 4.stephacidin A 5.Notoamide C, 6.Notoamide E 7.Notoamide O, 8.Notoamide Q, 9.Dehydronotoamide E 10.Deoxybrevianamide E	*Aspergillus tennesseensis*.	EtOAc	Weak cytotoxicity	All the compounds were evaluated for their cytotoxic activities against a small panel of tumor cell lines including H460, A549, ASPC and K562, using the CCK8 method.	Isolates 1 and 2 demonstrated weak cytotoxicity against H460 cells with an IC50 of 83.4 and 95.5 μM,respectively. No isolates demonstrated cytotoxicities against ASPC, K562 and A549 at the concentration of 200 μM	Liu et al., 2017
4	1. 2,6,7-trimethoxy-8-(3-methyl-2-butenyl)carbazole-3-carbaldehyde, 2. Methyl-2,6,7-trimethoxy-8-(3-methyl-2-butenyl)carbazole-3-carboxylate	*Zanthoxylum armatum;*	MeOH	DPPH radical scavenging activity	Compounds were performed to assess the antioxidant property with positive reference (ascorbic acid (20 mg/ml))	Prenylated alkaloids were found to show higher antioxidant property than ascorbic acid, which is used as positive control.	Samad et al., 2014
5	1.Dihydrocarneamide A and 2.Iso-notoamide B	*Paecilomyces variotii EN-291.*	EtOAc	Cytotoxicity assay	Compounds were evaluated for their cytotoxic activities. against human large cell lung carcinoma cell line (NCI-H460	These compounds demonstrated weak activity containing IC50 values of 69.3 and 55.9 mmol/L, respectively	Zhang et al., 2015

6	1.Asperversiamides A 2.Asperversiamides B 3.Asperversiamides C 4.Asperversiamides D 5.Asperversiamides E 6.Asperversiamides F 7.Asperversiamides G 8.Asperversiamides H	*Asperg illus versico lor.*	EtOAc	Anti- inflammatory activity	All the compounds were tested for their inhibitory effects on iNOS, RAW264.7 and NO production against standard MG132	Compounds Asperversiamides B, C, F and G inhibited the release of NO in LPS-induced Raw264.7 cells and demonstrated potential iNOS inhibitory activities and of these compounds, Asperversiamides G exhibited a significant inhibitory effect against iNOS containing IC50 value 5.39 μM.	H. Li et al., 2018
7	Speramide A Speramide B	*Asperg illus ochrac eusKM 007*	MeOH	Antimicrobial activities,Cytotoxici ty	Cytotoxicity of compounds were examined on Lncap , DU145 and PC3 cell lines and no compounds showed IC50 > 40 μM. The four pathogens MRSA 92#, MRSA 98#, Staphylococcus aureus, and Pseudomonas aeruginosa were the targets of antimicrobial evaluation	Speramide A showed moderate antibacterial activity against Pseudomonas aeruginosa having MIC value of 0.8 M. But none of them demonstrated substantial activity with an IC50 value larger than 40M.	Chang et al., 2016
8	Mangrovamide D, Mangrovamide E Mangrovamide F Mangrovamide G	*Penicil lium sp. SCSIO 041218*	EtOAc	Antiallergic activity	Against the positive control loratadine (20 g/mL), the bioactivity on IgE-mediated rat mast RBL-2H3 cells was used to test the anti-allergic	Did not show any activity	Yang et al., 2018

					potential of each of these substances.		
9	Mangrovamides A Mangrovamide B Mangrovamide C	*Penicillium spp. SYFz-1*	Acetone	anti-acetylcholinesterase activity and MTT cytotoxicity	they were evaluated on anti-acetylcholinesterase activity and MTT cytotoxicity assay. Using the MTT technique, the cytotoxicity of each drug was evaluated in the HL60, H1975, Huh-7, U937, K562, MOLT-4, BGC823, MCF-7, A549, and Hela cell lines	Compounds were not toxic to human tumor cell lines (BGC83, 2Huh-7, H1975, U937, K562, MOLT-4, A549, MCF-7, Hela, and HL60), and the anti-acetylcholinesterase action was determined using Ell-coupled man's enzyme assay. Mangrovamide C demonstrated a moderate acetylcholinesterase inhibitory action with an IC50 value of 58.0 M.	Yang et al., 2018
10	1. Di-6-hydroxydeoxybrevianamide E, 2. Dinotoamide J	*Aspergillus austroafricanus Y32-2.*	EtOAc.	MTT Cytotoxicity,pro-angiogenic Activity, anti-inflammatory	All substances were tested using the MTT method for cytotoxicity against HepG2 human liver cancer cells, pro-angiogenic activity in a vatalanib (PTK787)-induced vascular damage zebrafish model, and anti-inflammatory activity in a CuSO4-induced zebrafish inflammation model	In a dose-dependent manner, Dinotoamide J exhibited pro-angiogenic activity.	P. Li et al., 2021
11	1.Galegine 2.pterogynidine 3.alchorneine	*Pterogyne*	Ethanol	MIC assays	In vitro antibacterial study was performed against MRSA (Methicillin	Alkaloids showed action against EMRSA-16, S. aureus SA-1199B, and XU212 strains that was	Coqueiro et al., 2014

		nitens Tul.,			Resistant Staphylococcus Aureus) srains	stronger than or comparable to norfloxacin, except for achorneine (MIC > 512 mg/L). For all studied strains, galegine and pterogynidine emerged as the most effective substances.These substances were 32 times more effective than norfloxacin against the strongest resistant strain, EMRSA-16, and were 8 times more effective than norfloxacin against the multi-drug resistant strain, SA-1199B, which overexpresses the NorA efflux transporter	
12	cristatumin F, echinulin, dehydroechinulin	*Eurotium cristatum*.	MeOH	radical scavenging activity against DPPH radicals,	The sample concentration needed to neutralize 50percent of total of the free radicals from DPPH is expressed by IC50 values. Using 3T3L1 cells and the MTT assay, the impact of cristatumin F upon cell viability was evaluated	Ascorbic acid, used as a positive control, had an IC50 value of 15 M for scavenging radicals against DPPH, while Cristatumin F had a modest IC50 value of 53.6 M and only moderately inhibited cell proliferation (20.6% inhibition) when evaluated at 200 M against 3T3L1 preadipocytes.	Zou et al., 2014
13	Penioxalamine A	*Penoxalicum*	CHCl3, ethyl	Cytotoxicity assay	The cytotoxic activity of Penioxalamine A against HL-60 (human promyelocytic leukemia cells) cell line was tested.	The HL-60 cell line was moderately cytotoxic to penioxalamine A. The inhibitory impact of compound 1 was moderate, with an IC50 value	Hu et al., 2014

		TW01-1	acetate and n-butanol,			28.12 M (the IC50 for 5-FU was 2.48 M).	
14	Four known compounds	*Tussilago farfara.*	EtOH	α-glucosidase inhibitory assay	All the compounds were screened for their α-glucosidase inhibitory.	With IC50 values of 105 4.7 and 35.2 3.2 M, respectively, compounds 1 and 2 demonstrated greater -glucosidase inhibitory action than acarbose (IC50 value as 503 1.5 M)	Song et al., 2020
15	giluterrin	*Aspergillus terreus P63*	Hydrometh anolic acid	Cell viability assay, clonogenic assay	Giluterrin's cytotoxic properties. test carried out using human tumor cells. 48 hours after incubation. U-251 glioma, MCF7 breast, 7860 kidney, NCI-H460 lung, PC-3 prostate, HT-29 colon, and HaCaT keratinocyte human non-tumor cell line are examples of human tumor lines.	cancer cell lines and non-tumor cell line were used to test the cytotoxic effect of giluterrin in vitro. Not all cell lines were cytotoxic to giluterrin. Instead, it demonstrated preferential cytotoxicity to the cancer cells 7860 (kidney) and PC-3 (prostate), with IC50 values of 22.93 M and 48.55 M, respectively.	Gubiani et al., 2019
16	aspoquinolones E, Aspoquinolones F aspernidines F, Aspernidines G , Aspernidines H	*Aspergillus nidulans.*	EtOAc	In vitro cytotoxicity, Inhibitory assay.	Using the MTT method and cis-Platin as a positive control, all the compounds were tested for their toxicity against the cancer cell lines MCF-7, HL-60, SMMC-7721, A-549 and SW-480. cancer cell lines	Having IC50 values varying from 3.50 to 33.03 M, aspoquinolones E, aspernidines G, and aspernidines H had moderate cytotoxic activity. SW-480 cells and A-549 cells were significantly inhibited by aspernidines E and	Q. Li et al., 2020

					were used to evaluate the inhibitory effects in vitro	H, having IC50 3.50 and 4.77 M, respectively.	
17	1. (E)-3-(3-hydroxymethyl-2-butenyl)-7-(3-methyl-2-butenyl)-1H-indole, 2. glybomine B and 3. glycoborinine	*Glycosmis montana Pierre* (Rutaceae).	MeOH	Anti-HIV Assay, cytotoxicity assay,MTT colorimetric assay	In vitro inhibitory action against HIV replication were examined for each prenylated alkaloid in C8166 cells. With an IC50 value of 4.47 and 9.73 lg/ml for glycoborinine and glycomine B, respectively, weak to moderate anti-HIV activity was seen in both compounds.	(E)-3-(3-hydroxymethyl-2-butenyl)-7-(3-methyl-2-butenyl) The strongest anti-HIV activity was demonstrated by -1H-indole, having IC50= 1.17 lg/ml, a SI = 11.68.	J. Wang et al., 2005
18	1.penipalines A 2.penipalines B 3. penipaline C	*Penicillium paneum SD-44*	AcOEt	Cytotoxicity Assay.	cell lines (tumor) HCT-116 and A-549 were used to investigate the cytotoxic effects of each substance. The MTT assay was used to assess the cytotoxic activity against the human cancer cell lines A-549 and RKO	According to the findings, penipalines B and C were effective against cell lines. Penipalines B and C had IC50 values of 20.44 and 21.54 mm against A-549 and 14.88 and 18.54 mm and 21.54 and 21.54 mm respectively against HCT-116.	C. S. Li et al., 2014
19	1.asperpenazine and 2.asperpendoline	*Aspergillus ochraceusMCCC*	EtOAc	Cytotoxicity assay, CCK-8 assay,Molecular Docking, ROS	Using the CCK-8 assay, the compounds' cytotoxicities on SH-SY5Y cells were initially assessed. Molecular docking and dynamic	No substances exhibit cytotoxic activity at a concentration of 50 M, whereas TBHQ, the positive control, did. When compounds' ability to protect cells from H2O2 damage was assessed, both	Xiao et al., 2022

		3A00521 and *Penicillium sp. HUBU 0120*.		assay,GSH ELISA assay	simulation investigations revealed that 2 connected to Keap1 (PDB ID: 1X2R). SH-SY5Y cells were subjected to injury with H2O2 (350 M).	metabolites showed cytoprotective action in a dose-dependent manner on Overexpression cells, while 2 being more effective at a concentration of 50 M than TBHQ at a concentration of 10 M. It was discovered during an ELISA assay that 2 increased GSH concentration in H2O2-induced cells in a dose-dependent manner	
20	1.dihydroneochinulin B 2.cryptoechinuline D (2a.cryptoechinuline + and 2b.cryptoechinuline -) 3.didehydroechinulin B 4.neoechinulin B 5.auroglaucin	*Aspergillus effuses H1-1*	ethyl acetate	MTT Cytotoxicity assay,	On the cell lines HL-60, P388, A-549 and BEL-7402, the compounds' preliminary cytotoxic activity was assessed. Doxorubicin was utilized as the control	With corresponding IC50 as 3.43 and 2.50 lM, compounds 2 and 2a significantly inhibited the growth of the P388 cell line, however compound 2b only demonstrated moderate inhibition at 11.3 lM. A-549 and BEL-7402 were significantly inhibited by compound 3 exhibiting IC50 as 1.43 and 4.20 lM, respectively	Gao et al., 2013
21	1. 17-hydroxynotoamide D , 2. 17-O-ethylnotoamide M , 3. 10-O-acetylscler-otiamide,	*Aspergillus sulphureus KMM 4640*	EtOAc	MTT-based drug sensitivity assay. Colony formation assay)	At doses up to 100 M, the MTT assay demonstrated that none of the chemicals tested were harmful to both benign (MRC-9 and HEK 293) and malignant	At a concentration of 100 M, compounds 2, 6, 8, 13, and 14 prevented the colony formation of 22Rv1 prostate carcinoma cells. At concentrations of 10 M, chemicals 2 and 13 considerably reduced colony development by	Afiyatullov et al., 2018

	4. 10-O ethylsclerotiamide , 5.10-O-ethylnotoamide R 6.(–)-notoamide B , 7.notoamide C , 8.dehydronotoamide C , 9.notoamide D , 10. notoamide F , 11.notoamide Q , 12.17-epi-notoamide Q, 13. notoamide M , and 14. sclerotiamide	and *Isaria felina KMM 4639.*			(PC-3, LNCaP and 22Rv1) cell lines. The MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) test was used to assess the in vitro cytotoxicity. A colony formation test was conducted.	25 and 55%, respectively on cells 22Rv1	

Chapter 5

Discussion

Natural products are used as medicines has a long history and has had a big influence on human society. They have been employed as medications, spices, colorants, and treatments. Due to rising antibiotic resistance, they are now being evaluated as possible medicines. When compared to synthetic approaches, natural chemicals have a distinctive structural diversity, which makes them desirable therapeutic candidates. Prenyl side chain-containing natural compounds constitute a unique class of their own. Prenylated natural compounds have been acknowledged for many years as fascinating because these phytochemicals physiologically active. Numerous aromatic compounds which are prenylated, have greater structural diversity, changed biological activity, and improved therapeutic potential are produced by straightforward biological or chemical changes. (Cheng et al., 2016).Compared to the corresponding nonprenylated molecules, prenylation of natural products promotes various biological activities. Prenylated natural compounds have recently been the subject of in-depth analysis as they acquire a crucial part in the molecular activity. As a result, potential anticancer, anti-inflammatory, antioxidant, and neuroprotective substances have been found. Prenylated alkaloids are worth studying for several reasons. First off, these substances have the potential to be used as lead compounds for the creation of novel medications to treat a variety of ailments. Prenylated alkaloids, for instance, are interesting candidates for cancer therapy because it has been discovered that they are effective against cancer cells.

Additionally, can provide insight into the mechanisms underlying various biological processes, which can inform the development of new therapeutic strategies. Another reason why we worked on prenylated alkaloids is that they are often obtained from plants with medicinal compounds, which are vastly used in traditional medicine. As a result, prenylated alkaloids have a long history of safe use and may one day replace synthetic medications. Furthermore, the study of these compounds can help to preserve traditional medicinal knowledge and promote the sustainable utilize of medicinal plants. In conclusion, the study of prenylated alkaloids is a rapidly growing field that has the potential to contribute to the development of new treatments for various diseases, preserve traditional medicinal knowledge, and promote the appropriate use of medicinal plants. There is emerging interest towards the utilization of natural products as alternative or supplementary treatments for diverse illnesses. This tendency is expected to persist in the future, and the demand for natural products, including prenylated alkaloids, is anticipated to rise. There has been a rising preference for investing in natural

product research, including the investigation of prenylated alkaloids. This preference is expected to persist in the future, and the resources available for this research is likely to grow.

Chapter 6

Future prospective

Although prenylated alkaloids showed a vast range of biological and physiological activity, the exact mechanisms underlying these activities are not well understood. Further research is needed to identify the specific targets and mechanisms of action of these compounds.

Also, there is a lack of standardized methods for testing the biological activity of prenylated alkaloids, which makes it difficult to compare results across studies. This hampers the ability to assess all biological activities of these compounds and to determine the most promising candidates for drug development. Also, the new compounds are not always named. Despite the potential of prenylated alkaloids as lead compounds for drug development, there is limited information available on their toxicity and safety profiles. Further research is needed to fully evaluate the potential risks and benefits of these compounds. Inadequate knowledge on the chemical diversity of prenylated alkaloids: Prenylated alkaloids are a diverse class of compounds, and there is a lack of knowledge about the chemical diversity of these compounds and the mechanism of their potential biological activities.

Working with prenylated alkaloids in the future is quite promising. Prenylated alkaloids have demonstrated promising pharmacological actions, such as anti-inflammatory, antioxidant, and anticancer effects, making them desirable targets for drug discovery and development. New medications based on these substances are likely to be found in the future. The development of analytical methods has made it simpler to isolate, recognize, and research prenylated alkaloids. This has made it possible for researchers to create novel processes for the synthesis and manufacture of these chemicals as well as to better understand their pharmacology and physical characteristics. The biological activity of prenylated alkaloids is currently understood, however there are still several gaps that require more study. To discover new prenylated alkaloids and completely comprehend their pharmacological characteristics, more investigation is required. The study of prenylated alkaloids with biological activity can advance the science of natural product chemistry by providing a new source of physiologically active natural products. These alkaloids may have intriguing medicinal, pharmacological, synthetic, and many other beneficial activities. (Kurek, 2019)

In conclusion, there are several gaps in the current understanding of the biological activity of prenylated alkaloids. Further research is needed to address these gaps and to fully realize the potential of these compounds as lead compounds for drug development.

Chapter 7

Conclusion

The discovery of drugs from natural products has been limited due to a misinterpretation of empirical rules and the use of computational designs that eliminate molecules with desired properties for therapeutic use. This narrow approach based solely on these rules and filters undermines the potential therapeutic properties of alkaloids and other natural products. Nevertheless, there is a growing trend towards exploring the potential of natural products, particularly alkaloids, as therapeutic agents. (Ernst, 2010)

The natural substances that have been prenylated display a wide range of intriguing chemical, biological, and pharmacological characteristics. The prenyl moiety broadens the chemical spectrum and boosts lipophilicity of the molecule, resulting in a strong affinity for cell membranes. Several natural chemicals' antibacterial, anti-inflammatory, antioxidant, cytotoxic, larvicidal, and estrogenic properties are improved by prenylation. Therefore, additional research will be needed in the future to fully examine the potential for enhancing health. The prenyl groups is essential to function as anticancer natural chemicals, potentially resulting in improved cell membrane targeting and subsequently higher intracellular activity. Finding and understanding dietary elements or natural products that have strong anti-cancer property and therapeutic activity, while also being lower toxic substance, is a highly encouraging area of experimentation as cancer prevention becomes a crucial societal concern.

In summary, the study of prenylated alkaloids holds a lot of potential and there are several indications that this field will continue to grow in the future. Additional studies will be required to fully understand the capabilities of promoting health. The prenyl groups contains the anti-cancer properties of natural substances, which leads to more targeted cell membrane interaction and stronger intracellular activity. Searching for and understanding dietary components or natural products that are effective in preventing cancer and potentially treating it, while also

being safe, is a promising area of research in light of the growing importance of cancer prevention in society. The future of this field appears promising, with the potential for new drug discoveries, the rising demand for natural drugs, the development of analytical techniques, and the increased investment in natural product research. (Cheng et al., 2016)

References

Afiyatullov, S. S., Zhuravleva, O. I., Antonov, A. S., Berdyshev, D. V., Pivkin, M. V., Denisenko, V. A., Popov, R. S., Gerasimenko, A. V., von Amsberg, G., Dyshlovoy, S. A., Leshchenko, E. V., & Yurchenko, A. N. (2018). Prenylated indole alkaloids from co-culture of marine-derived fungi Aspergillus sulphureus and Isaria felina. Journal of Antibiotics, 71(10), 846–853. https://doi.org/10.1038/s41429-018-0072-9

Afiyatullov, S. S., Zhuravleva, O. I., Antonov, A. S., Berdyshev, D. V., Pivkin, M. V., Denisenko, V. A., Popov, R. S., Gerasimenko, A. V., von Amsberg, G., Dyshlovoy, S. A., Leshchenko, E. V., & Yurchenko, A. N. (2018). Prenylated indole alkaloids from co-culture of marine-derived fungi Aspergillus sulphureus and Isaria felina. Journal of Antibiotics, 71(10), 846–853. https://doi.org/10.1038/s41429-018-0072-9

Chang, Y. W., Yuan, C. M., Zhang, J., Liu, S., Cao, P., Hua, H. M., Di, Y. T., & Hao, X. J. (2016). Speramides A–B, two new prenylated indole alkaloids from the freshwater-derived fungus Aspergillus ochraceus KM007. Tetrahedron Letters, 57(45), 4952–4955. https://doi.org/10.1016/j.tetlet.2016.09.071

Cheng, Y.-L., Lee, C.-Y., Huang, Y.-L., Buckner, C. A., Lafrenie, R. M., Dénommée, J.A., Caswell, J. M., Want, D. A., Gan, G. G., Leong, Y. C., Bee, P. C., Chin, E., Teh, A. K.H., Picco, S., Villegas, L., Tonelli, F., Merlo, M., Rigau, J., Diaz, D., … Mathijssen, R. H.

Cheng, Y.-L., Lee, C.-Y., Huang, Y.-L., Buckner, C. A., Lafrenie, R. M., Dénommée, J.A., Caswell, J. M., Want, D. A., Gan, G. G., Leong, Y. C., Bee, P. C., Chin, E., Teh, A. K.H., Picco, S., Villegas, L., Tonelli, F., Merlo, M., Rigau, J., Diaz, D., … Mathijssen, R. H.

Coqueiro, A., Regasini, L. O., Stapleton, P., Da Silva Bolzani, V., & Gibbons, S. (2014). In vitro antibacterial activity of prenylated guanidine alkaloids from Pterogyne nitens and synthetic analogues. Journal of Natural Products, 77(8), 1972–1975. https://doi.org/10.1021/np500281c

Ernst, E. (2010). ABC of Complementary Medicine. Focus on Alternative and Complementary Therapies, 5(3), 231–231. https://doi.org/10.1111/j.2042- 7166.2000.tb02553.x

Gao, H., Zhu, T., Li, D., Gu, Q., & Liu, W. (2013). Prenylated indole diketopiperazine alkaloids from a mangrove rhizosphere soil derived fungus Aspergillus effuses H1-1. Archives of Pharmacal Research, 36(8), 952–956. https://doi.org/10.1007/s12272-013- 0107-5

Gao, H., Zhu, T., Li, D., Gu, Q., & Liu, W. (2013). Prenylated indole diketopiperazine alkaloids from a mangrove rhizosphere soil derived fungus Aspergillus effuses H1-1. Archives of Pharmacal Research, 36(8), 952–956. https://doi.org/10.1007/s12272-013- 0107-5

Gubiani, J. R., Oliveira, M. C. S., Neponuceno, R. A. R., Camargo, M. J., Garcez, W. S.,Biz, A. R., Soares, M. A., Araujo, A. R., Bolzani, V. da S., Lisboa, H. C. F., de Sousa, P.T., de Vasconcelos, L. G., Ribeiro, T. A. N., de Oliveira, J. M., Banzato, T. P., Lima, C.A., Longato, G. B., Batista, J. M., Berlinck, R. G. S., & Teles, H. L. (2019). Cytotoxic prenylated indole alkaloid produced by the endophytic fungus Aspergillus terreus P63. Phytochemistry Letters, 32(June), 162–167. https://doi.org/10.1016/j.phytol.2019.06.003

Heinrich, M., Mah, J., & Amirkia, V. (2021). Alkaloids used as medicines: Structural phytochemistry meets biodiversity—An update and forward look. Molecules, 26(7), 1–18. https://doi.org/10.3390/molecules26071836

Hu, X. L., Bian, X. Q., Wu, X., Li, J. Y., Hua, H. M., Pei, Y. H., Han, A. H., & Bai, J.(2014). Penioxalamine A, a novel prenylated spiro-oxindole alkaloid from Penicillium oxalicum TW01-1. Tetrahedron Letters, 55(29),3864–3867. https://doi.org/10.1016/j.tetlet.2014.05.104

J. (2016). We are IntechOpen , the world ' s leading publisher of Open Access books Builtby scientists , for scientists TOP 1 %. Intech, 11(tourism), 13. https://www.intechopen.com/books/advanced-biometric-technologies/liveness-detection-in-biometrics /

Karimi, A., Majlesi, M., & Rafieian-Kopaei, M. (2015). Herbal Versus. Journal of

Nephropharmacology, 4(1), 27–30.

Kurek, J. (2019). Introductory Chapter: Alkaloids - Their Importance in Nature and for Human Life. Alkaloids - Their Importance in Nature and Human Life, 1–7. https://doi.org/10.5772/intechopen.85400

Li, C. S., Li, X. M., An, C. Y., & Wang, B. G. (2014). Prenylated Indole Alkaloid Derivatives from Marine Sediment-Derived Fungus Penicillium paneum SD-44 - Li – 2014 Helvetica Chimica Acta - Wiley Online Library. Helvetica Chimica Acta, 97, 1440–1444. http://onlinelibrary.wiley.com/doi/10.1002/hlca.201400035/abstract%5Cnpapers2://publication/uuid/70B9CC98-33B4-42E1-910A-EF97B5253154

Li, H., Sun, W., Deng, M., Zhou, Q., Wang, J., Liu, J., Chen, C., Qi, C., Luo, Z., Xue, Y., Zhu, H., & Zhang, Y. (2018). Asperversiamides, Linearly Fused Prenylated Indole Alkaloids from the Marine-Derived Fungus Aspergillus versicolor. Journal of Organic Chemistry, 83(15), 8483–8492. https://doi.org/10.1021/acs.joc.8b01087

Li, P., Zhang, M., Li, H., Wang, R., Hou, H., Li, X., Liu, K., & Chen, H. (2021). New Prenylated Indole Homodimeric and Pteridine Alkaloids from the Marine-Derived Fungus Aspergillus austroafricanus Y32-2. Marine Drugs, 19(2). https://doi.org/10.3390/MD19020098

Li, Q., Chen, C., He, Y., Wei, M., Cheng, L., Kang, X., Wang, J., Hao, X., Zhu, H., &Zhang, Y. (2020). Prenylated quinolinone alkaloids and prenylated isoindolinone alkaloidsfrom the fungus Aspergillus nidulans. Phytochemistry, 169(October 2019), 112177. https://doi.org/10.1016/j.phytochem.2019.112177

Liu, L., Wang, L., Bao, L., Ren, J., Bahadur Basnet, B., Liu, R., He, L., Han, J., Yin, W.B., & Liu, H. (2017). Versicoamides F-H, Prenylated Indole Alkaloids from Aspergillus tennesseensis. Organic Letters, 19(4), 942–945. https://doi.org/10.1021/acs.orglett.7b00145

Mittal, J., Sharma, M. M., & Batra, A. (2014). Tinospora cordifolia: a multipurpose medicinal plant-A. Review. Journal of Medicinal Plants Studies, 2, 32–47.

Oneschuk, D., Younus, J., & Boon, H. (2011). Herbal medicine. Enhancing Cancer Care: Complementary Therapy and Support, 78(1), 35–39. https://doi.org/10.1093/acprof:oso/9780199297559.003.0016

Pal, S. K. (2002). Complementary and alternative medicine: An overview. Current Science, 82(5), 518–524. J.B., C. (2000). Efficacy, safety, quality control, marketing and regulatory guidelines forherbal medicines (phytotherapeutic agents). Brazilian Journal of Medical and BiologicalResearch, 33(2), 179–189. http://ovidsp.ovid.com/ovidweb.cgi?T=JS&PAGE=reference&D=emed5&NEWS=N&AN=2000095062

Phair, M. (2021). iMedPub Journals The Ancient Use of Herbal Medicine. 9502. Nisar, B., Sultan, A., & Rubab, S. L. (2018). Comparison of Medicinally Important NaturalProducts versus Synthetic Drugs-A Short Commentary. Natural Products Chemistry & Research, 06(02). https://doi.org/10.4172/2329-6836.1000308

Qiu, S., Sun, H., Zhang, A. H., Xu, H. Y., Yan, G. L., Han, Y., & Wang, X. J. (2014).Natural alkaloids: Basic aspects, biological roles, and future perspectives. Chinese Journalof Natural Medicines, 12(6), 401–406. https://doi.org/10.1016/S1875-5364(14)60063-7

Sam, S. (2019). Importance and effectiveness of herbal medicines. Journal ofPharmacognosy and Phytochemistry, 8(2), 354–357

Samad, A., Badshah, S., Khan, D., Ali, F., Amanullah, M., & Hanrahan, J. (2014). New prenylated carbazole alkaloids from Zanthoxylum armatum. Journal of Asian Natural Products Research, 16(12), 1126–1131. https://doi.org/10.1080/10286020.2014.967228

Song, X. Q., Sun, J., Yu, J. H., Zhang, J. S., Bao, J., & Zhang, H. (2020). Prenylated indole alkaloids and lignans from the flower buds of Tussilago farfara. Fitoterapia, 146(August), 104729. https://doi.org/10.1016/j.fitote.2020.104729

Tsukamoto, S., Kato, H., Samizo, M., Nojiri, Y., Onuki, H., Hirota, H., & Ohta, T. (2008). Notoamides F-K, prenylated indole alkaloids isolated from a marine-derived Aspergillus sp. Journal of Natural Products, 71(12), 2064–2067. https://doi.org/10.1021/np800471y

Wang, F., Fang, Y., Zhu, T., Zhang, M., Lin, A., Gu, Q., & Zhu, W. (2008). Seven new prenylated indole diketopiperazine alkaloids from holothurian-derived fungus Aspergillus fumigatus. Tetrahedron, 64(34), 7986–7991. https://doi.org/10.1016/j.tet.2008.06.013

Wang, J., Zheng, Y., Efferth, T., Wang, R., Shen, Y., & Hao, X. (2005). Indole and carbazole alkaloids from Glycosmis montana with weak anti-HIV and cytotoxic activities. Phytochemistry, 66(6), 697–701. https://doi.org/10.1016/j.phytochem.2005.02.003

Xiao, X., Tong, Z., Zhang, Y., Zhou, H., Luo, M., Hu, T., Hu, P., Kong, L., Liu, Z., Yu, C.,Huang, Z., & Hu, L. (2022). Novel Prenylated Indole Alkaloids with Neuroprotection on SH-SY5Y Cells against Oxidative Stress Targeting Keap1–Nrf2. Marine Drugs, 20(3), 1–15. https://doi.org/10.3390/md20030191

Yang, B., Dong, J., Lin, X., Zhou, X., Zhang, Y., & Liu, Y. (2014). New prenylated indole alkaloids from fungus Penicillium sp. derived of mangrove soil sample. Tetrahedron, 70(25), 3859–3863. https://doi.org/10.1016/j.tet.2014.04.043

Yang, B., Tao, H., Lin, X., Wang, J., Liao, S., Dong, J., Zhou, X., & Liu, Y. (2018). Prenylated indole alkaloids and chromone derivatives from the fungus Penicillium sp. SCSIO041218. Tetrahedron, 74(1), 77–82. https://doi.org/10.1016/j.tet.2017.11.038

Zhang, P., Li, X. M., Wang, J. N., Li, X., & Wang, B. G. (2015). Prenylated indole alkaloidsfrom the marine-derived fungus Paecilomyces variotii. Chinese Chemical Letters, 26(3),313–316. https://doi.org/10.1016/j.cclet.2014.11.020

Zou, X., Li, Y., Zhang, X., Li, Q., Liu, X., Huang, Y., Tang, T., Zheng, S., Wang, W., & Tang, J. (2014). A new prenylated indole diketopiperazine alkaloid from Eurotium cristatum. Molecules, 19(11), 17839–17847. https://doi.org/10.3390/molecules191117839