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Natural Products as Leads for Neglected Trophical Diseases (NTDs) Treatment; A Chemical and Biological - Review

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Abstract

Natural compounds are mostly found in medicinal plants that are used to treat various ailments. They are distinguished by their structural complexity and diversity, which span a wide chemical universe and present both benefits and shortcomings to the process of discovering novel drugs. Neglected tropical diseases (NTDs) are common tropical diseases that impact over one billion people globally. Numerous pathogens, such as bacteria, fungi, viruses, parasites, and poisons, are responsible for them. Natural products have always been important in the search for new drugs to treat differents diseases including NTDs. The purpose of this chapter is to provide an update on the evaluation of both the chemical and biological properties of natural compounds that have been extracted and identified from plant sources, and may be utilized as viable candidates for the development of new drugs treat NTDs with lower incidence such as: Buruli ulcer, dracunculiasis, echinococcosis, food-borne trematodiases, leprosy, lymphatic filariasis, parasitics, schistosomiasis, soil-transmitted helminthiases, taeniasis/cysticercosis, trachoma and yaws. This chapter also intends to make a

critical review on the chemical analysis of natural products' structure and classification, biological evaluation of natural products' antiparasitic, anti-inflammatory and immunomodulatory activities. In conclusion, Natural products continue to be a key source of fresh ideas for treating NTDs. Their distinct methods of action and variety of chemicals offer potential for the development of new treatments.

Keywords: Natural products, Neglected tropical disease (NTDs), Chemical and Biological activities

Introduction

Nigeria accounts for 25% of the entire burden of neglected tropical diseases (NTDs) in sub-Saharan Africa, making it the country with the highest NTD burden (FMH, 2013–1017). The World Health Organization (WHO) published an implementation roadmap in 2012 with the goal of expediting efforts to mitigate the worldwide effect of NTDs (WHO, 2012). Many endemic countries are working to control and/or eradicate NTDs by 20202, in accordance with the roadmap targets and national commitments made after the 2012 London Declaration (Uniting to Combat NTDs) (Hotez P.J. 2015). (WHO, 2005). The development of ulcerative colitis is regulated by a multitude of apoptotic signaling molecules. A family of five subunits known as nuclear factor-kB, or NF-ϰB, has a Rel homology domain (RHD) that facilitates dimerization and DNA binding. Along with other classical and non-classical cell pathways, it also impacts the immune response, apoptosis, proliferation, and cell migration and invasion (Wang et al., 2022; Wang and Shen, 2022). Research has demonstrated that NF-ϰB overactivation is necessary for the onset and progression of ulcerative colitis (UC) (Xiong et al., 2022). Using TNBS-induced UC rats, Arab et al. demonstrated that blocking the NF-ϰB pathway can significantly reduce inflammatory infiltration, stop cell death, and minimize colonic inflammatory damage.

Another crucial component of NTD prevention is increasing awareness among the population that is at risk. People can lower their risk by taking control of the environmental elements that encourage NTDs. One way to lower the risk of mosquito-borne diseases is to remove standing water from areas where mosquitoes like to nest. Another way to save money is to sleep under a treated bed net, which lowers the risk of diseases spread by night-dwelling flies. When visiting regions where non-transgenic diseases (NTDs) are

common, people should be careful to wear protective gear, use insect repellent, and sleep under a treated bed net. Ackley (2021) Significant strides have been achieved in the fight against and elimination of neglected tropical diseases. These accomplishments are the result of previously unheard-of funding from governments, private donors, and pharmaceutical firms. These achievements are based on unprecedented support from pharmaceutical companies, governments, and private donors. Nevertheless, challenges remain to achieve the London Declaration targets by 2020, and the ultimate elimination and eradication of these diseases remain uncertain. (Bodimeade, 2019)

Important of natural products in drug descovery

When compared to traditional synthetic compounds, natural products have unique properties that present both benefits and difficulties for the drug discovery process. Massive scaffold variety and structural complexity are characteristics of NPs. When compared to synthetic compound Libraries 1,6–9, they usually have higher molecular masses, more sp3 carbon and oxygen atoms but fewer nitrogen and halogen atoms, more H-bond acceptors and donors, lower calculated octanol–water partition coefficients (cLog P values, indicating higher hydrophilicity), and greater molecular rigidity. These variations may have benefits. For instance, the increased stiffness of NPs may be helpful in drug development when addressing protein–protein interactions.

The majority of oral drugs are really provided by NPs "beyond rule of five" (Doak, 2014). The increase in the molecular mass of approved oral medicines over the past 20 years (Shultz, 2019) indicates the increasing significance of medications that deviate from this recommendation. NPs are extremely relevant to cancer and infectious diseases because they have evolved to have particular biological activities, such as controlling endogenous defense mechanisms and interacting and occasionally competing with other species. Furthermore, their use in traditional medicine can provide insight on their safety and effectiveness.

Classification of natural products

Alkaloids:

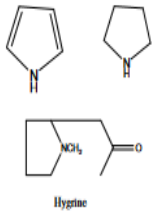
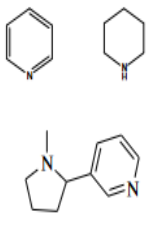
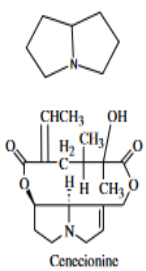
The primary property of alkaloids, a very large class of naturally occurring substances originating from secondary metabolism, is the presence of a basic nitrogen atom in any location within the molecule (does not include nitrogen in an amide bond or peptide). Although they have been discovered in animals, insects, marine invertebrates, and some

microbes, they are most frequently isolated from plants (Lu et al. 2012; 87 2013; Bribi 2018). They are present in many different cell organelles, such as mitochondria, vesicles, chloroplasts, and vacuoles. The majority of its precursors are amino acids, which are byproducts of metabolic processes like glycolysis. Alkaloid compounds were the original term for base-type substances containing nitrogen that interacted to form salts. The word comes from the alkaloid, which was first used to describe nitrogen-containing base-type substances that reacted with acids to generate salts. The word originally came from the Arabic word al-qali. When Sertürner extracted morphine (Fig. 5.2) from opium in 1806, the investigation of this class of metabolites got underway. Because of their alkaloid content, numerous plant extracts have since been employed as poisons and medications.

Chemically they are defined as crystalline, colorless substances with bitter taste that can form salts when being united to acids; in the plants, they can hide in free state, like salts or like N-oxides (Kutchan 1995; O'Connor 2010; Amirkia and Heinrich 2014; Encyclopædia Britannica 2018; Bribi 2018).

Classification of alkaloids

Different class of alkaloids are shown in table 1 below:

S.No.	Class	Basic ring	Example	Biological sources	References
1.	Pyrrole and Pyrrolidine	 Hygrine	Hygrine, nicotine, cuscohygrine, coca alkaloids	*Erythroxylum coca, Erythroxylum truxillense*	(Moor, 1994; Evans, 1981)
2.	Pyridine and Piperidine	 Nicotine	Piperine, coniine, trigonelline, arecaidine, guvacine, pilocarpine, cytisine, nicotine, sparteine, pelletierine, lobeline, arecoline, anabasine	*Piper nigrum, Areca catechu, Lobelia nicotianefolia*	(Parmar et al., 1997; Ravindran et al., 2000)
3.	Pyrrolizidine	 Cenecionine	Echimidine, senecionine, senesiphylline, symphitine	*Castanospermum australe, Senecio* sps.	(Molyneux, 1988; Hartmann and Witte, 1995)

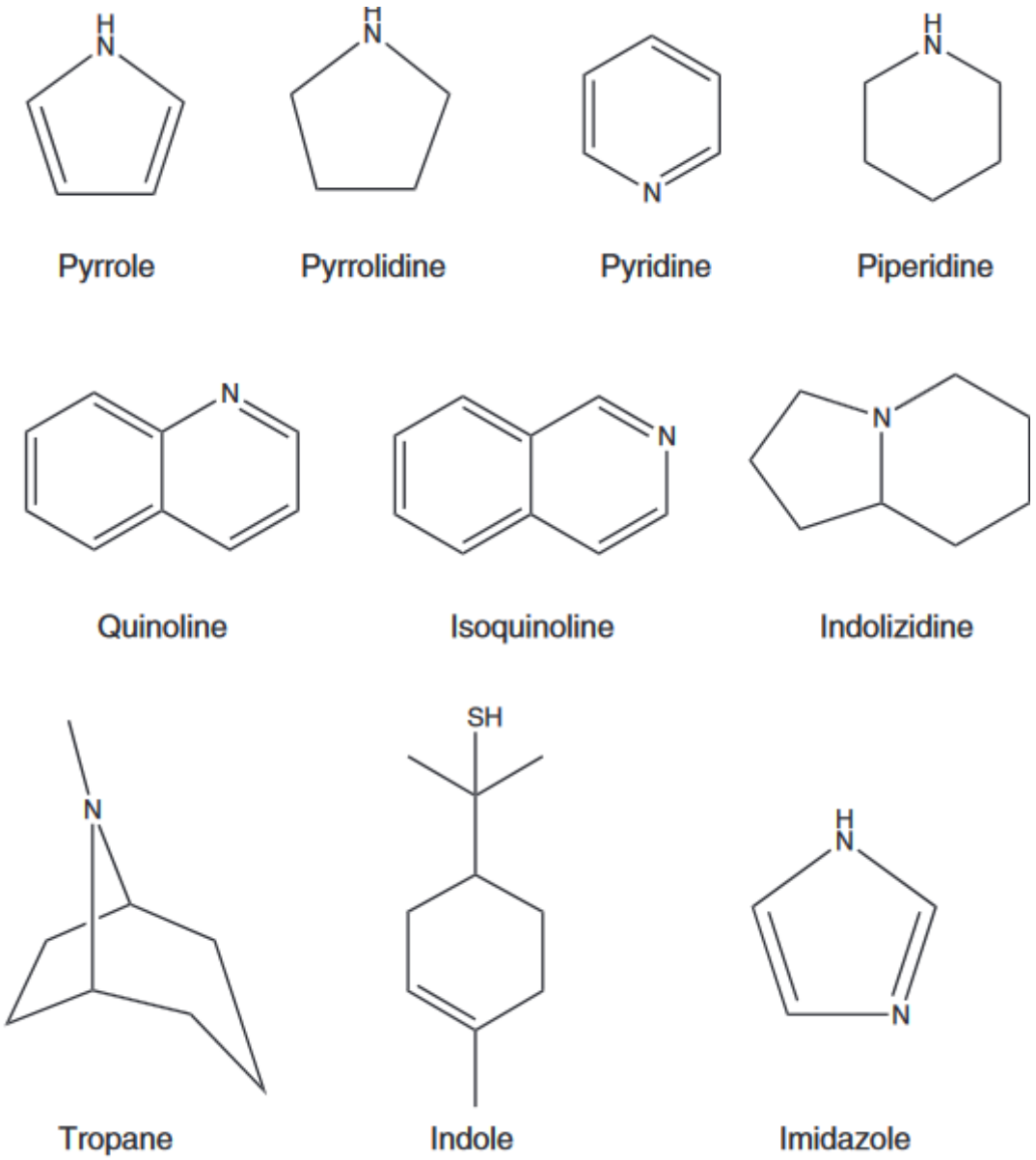
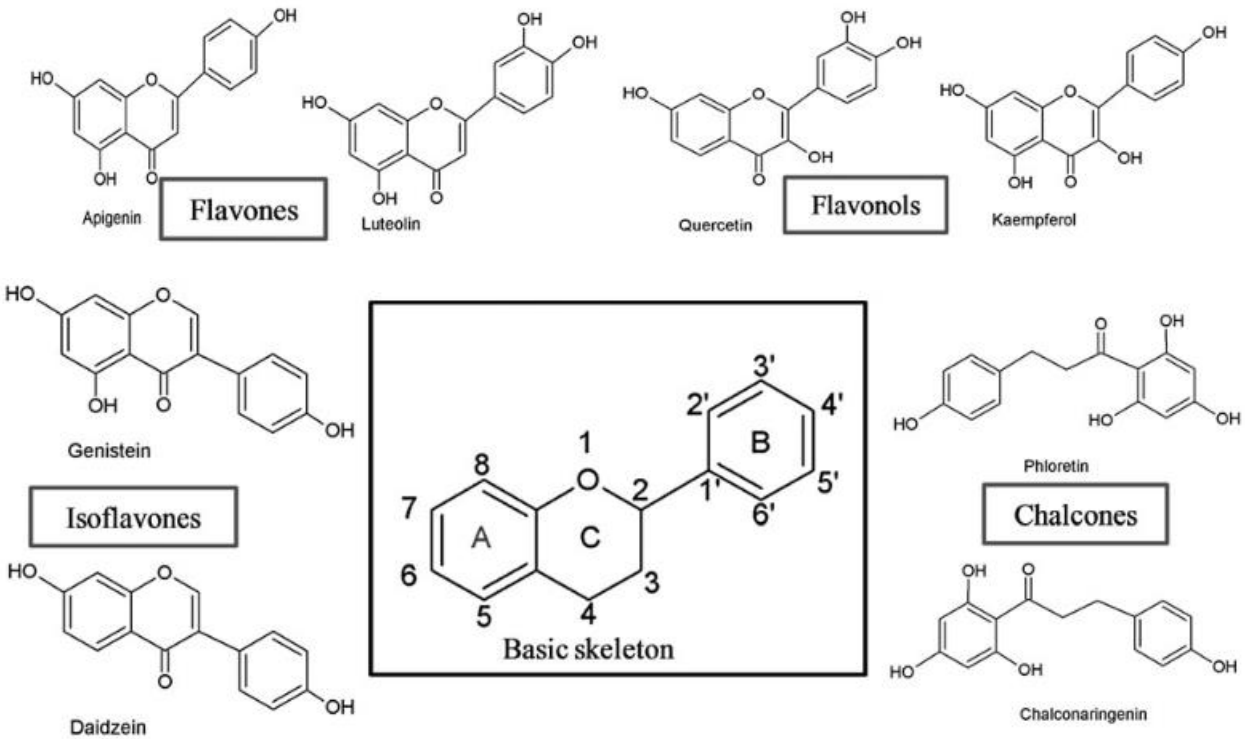


Figure 1: Skeletal structure of true alkaloids (Bisset, 1992)

Flavonoids:

Flavonoid chemicals are byproducts of plant extraction that are present in various plant sections. Vegetables use flavonoids for growth and defense against plaques (Havsteen B. 2002). They are a member of a group of phenolic compounds with low molecular weight that are found across the kingdom of plants. In higher plants, they make up one of the most distinctive types of chemicals. In most families of angiosperms, flavonoids are easily recognized as floral pigments. Nevertheless, they are present in all sections of plants and are not just found in flowers (Samanta A, 2011). Dietary flavonoids are so named because

they are plentiful in plant-based meals and beverages, including fruits, vegetables, tea, chocolate, and wine. These subgroups have unique major sources. For example, onions and tea are major dietary sources of flavonols and flavones. Flavonoids play a variety of biological activities in plants, animals and bacteria. In plants, flavonoids have long been known to be synthesised in particular sites and are responsible for the colour and aroma of flowers, and in fruits to attract pollinators and consequently fruit dispersion to help in seed and spore germination, and the growth and development of seedlings. In addition to acting as special UV filters, phytoalexins, signal molecules, allopathic substances, detoxifying agents, and antimicrobial defensive compounds, flavonoids shield plants from a variety of biotic and abiotic challenges. According to Samanta A. (2011), flavonoids have functions related to freezing tolerance, drought resistance, and heat acclimation of plants. Jorgensen has shown that functional gene silencing in plants was linked to flavonoid biosynthesis and has indicated that the early developments in floral genetics were mostly caused by mutation approaches having an effect on flavonoid produced flower colors. Flavonoids have been linked to improved health in both humans and animals, and there is currently interest in using them for chemoprevention and illness treatment. Nowadays, around 6000 flavonoids are responsible for the vibrant colors found in fruits, herbs, and vegetables.



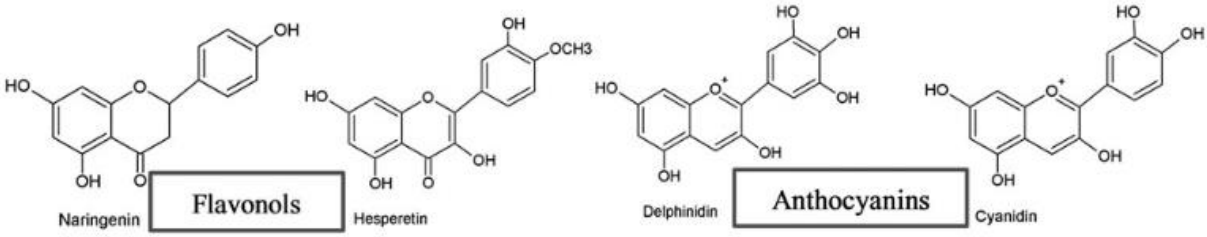


Figure 2 :Basic skeletal of flavonoids and their classes (Downloaded from https:/www.cambridge.org/core https://doi.org/10.1017/jns.2016.41)

Terpenes

Terpenoids are known to affect interactions between plants and insects, including pollinators, predators, parasitoids, and herbivores. In general, the interactions serve the interests of plants above those of herbivores. Although terpenoids make up a sizable portion of volatile organic compounds (VOC), it is hypothesized that these interactions are mediated by the emission of VOCs, including but not limited to terpenoids. It is thought that the identity and quantity of each component determines the properties of the mixture of volatile organic compounds (VOCs), and that herbivorous predators are susceptible to specific combinations of VOCs. A few that have poisonous, deterrent/repellent, or appealing qualities may be among the released volatile organic compounds. Important grain pest Sitophilus granaries is poisoned and repelled by essential oils of clove and cinnamon. FIn addition to these two essential oils, five hazardous terpenoids were proposed: caryophyllene oxide, α-pinene, α-humulene, α-phellandrene, and eugenol (which was classified as a terpenoid in that study but not in subsequent works). Eugenol displays Furthermore, it is recognized that terpenoids influence how plants and insects interact with pollinators, predators, parasitoids, and herbivores. Generally speaking, the interactions benefit plants more than herbivores. It is believed that these interactions are mediated via the emission of volatile organic compounds (VOCs), including but not limited to terpenoids, despite the fact that terpenoids constitute a significant fraction of VOCs.

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deterrent/repellent, or appealing qualities may be among the released volatile organic compounds. Important grain pest Sitophilus granaries is poisoned and repelled by essential oils of clove and cinnamon. Furthermore to these, both of which are proposed to cause impairment of aphid development and reproduction, increasing the defense ability of tomato against aphids Cascone,2015)

Plant Species	Terpenes	Targets	Effects	References
Tropical orchids	monoterpene: 1, 8-cineole	Male euglossine bees	an attractant and reward to pollinator	[62]
Dalechampia (Euphorbiaceae) epiphytes (*Clusia*)	terpenoid resins (oxygenated triterpenes)	Female euglossine (Apidae), female anthidiine (Megachilidae), or worker meliponine (Apidae) bees	reward to pollinators for use in nest construction	[63–65]
Kiwifruit (*Actinidia deliciosa*)	Sesquiterpene: α-farnesene, germacrene D, Monoterpenes: (*E*)-β-ocimene, (*Z*,*E*)-α-farnesene	Mainly honeybees (Apidae)	attract a variety of pollinators	[66]
White Campion (*Silene latifolia*)	lilac aldehydes	Noctuid moths (*Hadena bicruris*)	scent cue for pollinators to locate their specific host	[67]
Pineapple zamia (*Macrozamia lucida*)	β-myrcene, (E)-β ocimene and allo-ocimene	Thrips (*Cycadothrips chadwick*)	repel or attract pollinators to complete the pollination from male to female	[68]
Fig (*Ficus hispida*)	Monoterpenes: linalool, limonene and β-pinene	Wasp (*Ceratosolen solmsi marchali*)	signals for pollinators to identify floral stages	[69]
Monkeyflower (*Mimulus lewisii*)	D-limonene, β-myrcene and E-β-ocimene.	Bumblebee (Bombus vosnesenskii)	attract specific pollinators	[70]

Antiparasitic activities

Many parasitic infections are the cause of tropical diseases, such as malaria, trypanosomiasis, leishmaniasis, Chagas disease, schistosomiasis, onchocerciasis, lymphatic filariasis, and helminthiases. Parasites are responsible for probably more than 1–2 billion infections, which lead to several million deaths every year (Peters, 2007). In addition to these economically important parasitic diseases, a number of ectoparasites affect human health, which include mites (*Sarcoptesscabiei* causing scabies), lice (*Pediculus capitis*; *Phthirus pubis*), bed bugs (*Cimex lectularius*, *C. hemipterus*), fleas (*Pulex irritans*, *Tunga penetrans*), and several myiasis-producing HNB diptera (*Chrysomya*, *Cochliomya*, *Wohlfahrtia*, *Sarcophaga*, *Dermatobia*, *Cuterebra*, *Gasterophilus*, *Hypoderma*, Oestrus).

Medicinal chemists have created several medications that are effective against a variety of endoparasites, but not all of them. The fact that many of these medications were created decades ago and that certain parasite strains have developed resistance to them is a serious issue. Since many parasitic infections are found in developing nations where the populace cannot afford to pay high prescription prices, the pharmaceutical industry has not placed much emphasis on developing new antiparasitic drugs. Consequently, it is dangerous to invest in the development of drugs to treat parasite infections. Looking for anti-parasitic plant extracts or secondary metabolites obtained from them is an alternative to manufactured medications. Natural materials continue to be useful in therapy: between 1981 and 2006, 1,184 new drugs were registered of which 28% were natural products or their derivatives. Another 24% of the new drugs had pharmacophores (i.e., functional groups with pharmacological activity) derived from natural products [Newman,2007]. A good starting point to find antiparasitic natural products would be traditional medicinal plants, such as those known from Asia, Africa or America (Van Wyk, 2004) that have been employed to treat infections. Many promising results have been obtained so far to kill the parasites or their vectors *in vitro*, however a translation of these results into clinical practice is a neglected field. In this are provided. Furthermore, tropical diseases caused by viruses, bacteria and fungi will not be addressed in this review although plant-derived drugs can provide interesting candidates for therapy (Wink, 2010).

Anti-malaria Drugs

Human malaria is caused by unicellular sporozoa (Apicomplexa) of the genus *Plasmodium*, which are transmitted by various mosquito vectors . More than 250 million people are infected and more than a million deaths (mostly among children) are been recorded annually. The first drugs to treat malaria came from *Cinchona officinalis* and related *Cinchona* species (Rubiaceae) which naturally occur in Central and South America. Extracts from Cinchona bark contain quinoline alkaloids, such as quinine, quinidine, cinchonine, and cinchonidine (administered as "Quinimax" in malaria therapy). It was especially the bitter-tasting quinine which could be used to treat the blood stages of *Plasmodium* . Quinine served as a lead structure for the synthesis of several antimalarial drugs such as chloroquine, mefloquine, pyrimethamine, proguanil, atovaquone (sold together with proguanil as "Malarone"), or primaquine. Quinine (alone or in combination with

doxocycline, tetracycline or clindamycin) is still used today to treat acute cases of severe *P. falciparum* infections. Over the years *Plasmodium* (especially *P. falciparum* causing tropical malaria) has become resistant against many of the synthetic drugs. Among the mechanisms of drug resistance an enhanced expression of ABC transporters has been reported which can pump out any drug in an ATP dependent fashion that has entered the parasite (Wink,, 2012). A breakthrough for the development of antimalarial drugs was the identification of the sesquiterpene artemisinin from *Artemisia annua* (Asteraceae), which can even kill multidrug resistant strains of *P. falciparum* . Several semisynthetic derivatives of artemisinin (e.g., the water soluble artesunate) have been developed which are in clinical practice today (Kuhn, 2008)

Anti inflamation activities

Inflammation is a complex biological response against pathogens or tissue damage characterized by vasodilation, increased blood flow, vascular permeability, and cellular extravasation (C. N. Serhan, 2005). Macrophages, mast cells, and dendritic cells, resident in the tissues, are the first cells of innate immunity that detect and recognize the pathogen and initiate the inflammatory response (C. N. Serhan 2005). Acute inflammation is an early response in which innate immune cells such as polymorphonuclear cells and monocytes are recruited to the site of irritation and secrete inflammatory mediators (e.g., cytokines, chemokines, and free radicals), which amplify the response (C. N. Serhan, 2007). Chronic inflammation, in turn, is the long-term inflammatory process that occurs as a dysregulation of acute inflammation often due to extended exposure to the initial irritant, persistent injury, or autoimmune disease

According to B. Yang (2012), cembrane diterpenoids are a broad family of diterpenoids that have been isolated from both marine and terrestrial species. They have a variety of biological activities, such as antiviral, anticancer, antibacterial, and anti-inflammatory properties. A common 14-membered carbocyclic skeleton makes up the fundamental structure of cembrane diterpenoids, which typically have cyclic ether, lactone, or furan moieties surrounding this nucleus (reviewed by [W.-C. Wei,.2008]). There have also been reports of unconventional cembranoids with variations having 12, 13, or 14 members [Z. Xi, W, 2013, S.-K. Wang, 2013]. The majority of marine species' cembranoids are isolated from corals belonging to the genera Sarcophyton, Lobophytum, Eunicea, and Sinularia.

There have been reports of certain cembrane diterpenoids having anti-inflammatory properties.

Cembranoids such as gibberosenes, grandilobatin, querciformolides, sarcocrassocolides, crassumolides, crassarines, sinularolides, durumolides, and columnariols have shown a capacity to inhibit the expression of iNOS and/or COX-2 by LPS-stimulated RAW 264.7 cells [A. F. Ahmed2008–T.-H, 2015]

Table 2: Example of some important human endo parasites(Peters, 2007)

Parasite	Disease (estimated number of infections)	Vector (hosts); route of transmission	Distribution	Symptoms
Protozoa				
Apicomplexa				
Babesia spp.	Piroplasmosis (rare)	Ticks (*Ixodes*); bites	North America	Anaemia, damage of immune system
Plasmodium (*P. vivax*, *P. ovale*, *P. malariae*, *P. knowlesi*, *P. falciparum*)	Malaria (>250 million)	Mosquitos (*Anopheles*, *Nyssorhynchus*, *Cellia*, *Kerteszia*); bites	Tropics and subtropics	Anaemia, enlarged liver and spleen, high fever, jaundice, haemorrhage, haemoglobinuria ("blackwater fever"); blockage of cerebral capillaries (*P. falciparum*)
Toxoplasma gondii	Toxoplasmosis	Main host are cats; infection of humans from faeces	Worldwide	Flu-like symptoms; cysts in muscle and neural tissues; encephalitis, serious danger for developing foetus (abortion, malformations)

Immunomodulation

The human immune system can be modulated by the use of natural products, such as chemical ingredients and traditional medicinal plants. Natural products have been utilized for numerous ailments and disorders since ancient times. These days, immunomodulation refers to the immunological response that is administered through a shared therapy based on the patient's pathology and state of illness. This immunological response is brought on by the host defense mechanism, which generates an immune suppressor and results in a condition known as auto immune illnesses. According to Kaminsi (2008), immunity is the body's self-defense process that neutralizes antigens and safeguards the body. Immunomodulation is the process of repression being straightened out to highlight humoral immunity, cellular immunity, and non-specific protective components. These are

pharmaceutical drugs that, depending on their dosage, have immunomodulatory effects (Christmas S. 1984,1986) immunomodulator are worked as immunosuppression and immune-stimulators that shows reversible activity and they are biologically active (Bascones-Martinez,2014) both substances have special activity based on their sources and substances (Patwardhan B.1990)

The study of the immune system includes their properties and sources their function and structure in the first known about Immunity in ancient Time was a plague of Athens have infectious disease in 430 BC. Thucydides was an Athenian historian who noted the fact that individuals were getting recovered from the period of disease, were not getting sick from same disease another time. 18th-centuryFrench mathematician and philosopher Pierre Louis Maupertu is are researched scorpion venom and observed the immunity to this venom on dogs and mice [Saroj P,2012) after that observation, immunity developed by Louis Pasteur gives germ theory of disease and make the development of vaccination (Plotkin, 2004) after that determine the microorganism are show infectious disease virus determine for pathogens.

Enzyme inhibitors study

The majority of bioactive secondary metabolites known as enzyme inhibitors attach to an enzyme and reduce its bioactivity. In turn, many drug molecules are enzyme inhibitors, and primarily enzyme activators attach to different enzymes, increase their enzymatic actions, subtract link, and then distort to products in the catalytic cycle of the enzymes. As a result, blocking enzyme activity can eradicate a pathogen or correct a metabolic imbalance. Inhibitors can be linked together to remove a substrate from the enzyme's active site while maintaining the enzyme's ability to catalyze chemical reactions. Enzyme inhibition is a process that can be reversed or irreversible. By forming a covalent likening formation, the irreversible inhibitors react with the enzyme and modify it chemically. Then, these inhibitors adjust important amino acid remnants wanted from an enzymatic reversible inhibitors which are non - covalently bonded; different types of inhibition are shaped depending on whether inhibitors link non-covalently, and dissimilar types o inhibition are shaped depending on whether these inhibitors bind to the enzyme and produced enzyme substrate complex or both (Jump up,1991).

The discovery and development of enzyme inhibitors, which are found in many natural compounds, are exciting fields in pharmacology and biochemistry. Medicinal enzyme

inhibitors are often mediated by their specificity and efficacy, which identify the desired absorption to stop the enzyme. High potency and specificity ensure that a medication has minimal toxicity and few side effects. A lot of metabolic processes have guidelines that are influenced by natural enzyme inhibitors. Enzymes are really metabolic pathways that can be blocked by a variety of downstream outputs. These negative reactions significantly impair a cell's ability to maintain homeostasis and slow down the manufacturing process when the product activates.

An additional cellular enzyme inhibitor is protein which specially binds and inhibits an enzyme activities. Discovery of new drugs is actually the product of a very long drug growth procedure; the first step among which is the discovery of new enzyme inhibitors. In the past time, the only way to discover new drugs was a trial-and-error method, which proceeds to screen enormous libraries of chemical constituents against a marked enzyme and expect that maybe some valuable lead drugs will arise. This physical force method is still fruitful and has been lengthy by combinatorial chemistry methods that rapidly yield huge statistics of new, known, and novel

molecules and high-throughput screening expertise to quickly screen these enormous chemical libraries for valuable new inhibitors (Koppitz M 2006).

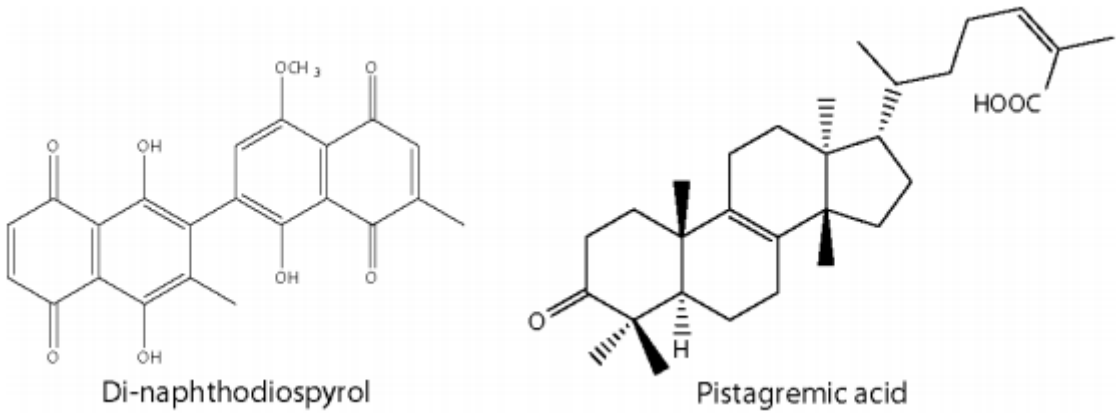

Figure 4: The chemical structure of natural enzyme inhibitor (Koppitz M 2006)

Cell signalling modulation

Several apoptotic signaling molecules are involved in controlling the process of UC formation. Five members make up the nuclear factor-kB (NF-ϰB) family; each subunit has a Rel homology domain (RHD), which facilitates dimerization and DNA binding and has biological effects via either classical or non-classical pathways in cells, including immune

defense, apoptosis, proliferation, and cell migration and invasion (Wang et al., 2022; Wang and Shen, 2022). Research has demonstrated that NF-ϰB overactivation is essential for the onset and progression of ulcerative colitis (UC) (Xiong et al., 2022). By using TNBS-induced UC animals in their research, Arab et al. demonstrated that blocking the NF-ϰB pathway can significantly minimize inflammatory infiltration, prevent cell death, and lessen colonic inflammatory damage.

BNumerous apoptotic signaling molecules have a role in regulating the genesis of UC. Nuclear factor-kB, or NF-ϰB, is a family of five subunits with a Rel homology domain (RHD) that aids in dimerization and DNA binding. It also affects immune response, apoptosis, proliferation, and cell migration and invasion, among other classical and non-classical pathways in cells (Wang et al., 2022; Wang and Shen, 2022). Studies have indicated that the initiation and advancement of ulcerative colitis (UC) are dependent on NF-ϰB overactivation (Xiong et al., 2022). Arab et al. showed that inhibiting the NF-ϰB pathway can considerably reduce inflammatory infiltration, prevent cell death, and limit colonic inflammatory damage by employing TNBS-induced UC rats in their study. It is not difficult to find that the pathogenic mechanism of UC is complex. In addition to the signaling pathways listed above, it also involves some other pathogenic mechanisms, such asextracellular signal-regulated kinase (ERK), PI3K/AKT/mTOR signaling pathways, etc. The above research results show that the occurrence and development of UC are closely related to apoptosis and are involved through multiple signaling pathways and targets.

Conclusion

Natural products continue to be a key source of fresh ideas for treating NTDs. Their distinct methods of action and variety of chemicals offer potential for the development of new treatments. Working together, biologists, chemists, and legislators will be necessary to address the issues surrounding their creation.

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