Frontiers in Natural Product Chemistry

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Frontiers in Natural Product Chemistry

(Volume 7)

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PREFACE

Frontiers in Natural Product Chemistry presents recent advances in the chemistry and biochemistry of naturally occurring compounds. The book is a valuable resource for pharmaceutical scientists and postgraduate students seeking updated and critically important information on bioactive natural products. The chapters in this volume are written by eminent authorities in the field.

In Chapter 1, Abrahamse *et al* present the progress made in the field of plant-derived anticancer agents in the treatment of cancer, as well as their mechanism of action and the limitations associated with current therapeutic options. Ernesto *et al*., in the second chapter of the book, have reviewed benanomicin-pradimicin antibiotics (BPAs) with respect to structural, functional, mechanistic and synthetic aspects. Chapter 3 by Pérez-Gutiérrez *et al* provides interesting information regarding the numerous pharmacological activities of the different parts and extracts of *Bixa Orellana*.

Chapter 4 of the book by Sharma *et al* focuses on the distribution, cultivation, traditional uses, phytochemistry, pharmacological potential and future prospective of *Nilakanthi* (*Ajuga bracteosa* Wall. ex Benth.). Buarque *et al*., in chapter 5, discuss the synthesis of benzocarbazoles, mostly benzo[a]carbazoles (including the dihydro and tetrahydro derivatives), with interesting properties. Chapter 6 of the book by Aksoz deals with the anti-inflammatory, anti-diabetic, and anti-depressant activities of chalcones. In the last chapter by Ajduković, an overview of the new steroid compounds isolated from marine sponges, macroalgae and cucumbers, is presented.

I hope that the readers will find these reviews valuable and thought-provoking so that they may trigger further research in the quest for new and novel natural therapies against various diseases. I am grateful for the timely efforts made by the editorial personnel, especially Mr. Mahmood Alam (Director Publications), and Miss Asma Ahmed (Senior Manager Publications) at Bentham Science Publishers in bringing this volume to fruition.

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CHAPTER 1

Plant-Derived Anticancer Compounds Used in Cancer Therapies

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Abstract: Cancer is a serious public health problem that affects both men and women. Globally cancer is one of the leading causes of death. The risk factors associated with cancer development are categorized into intrinsic and extrinsic. The treatment modalities used in the treatment of cancer, such as chemotherapy, radiotherapy, surgery, and targeted therapies have adverse effects either during or after therapy. Currently, plant-derived anticancer compounds are being used in the treatment of various cancers. The variation of these compounds is according to their origin, general classification, and mechanism of action. Various studies have shown that anticancer agents of natural origin have fewer side effects when compared to traditional therapies. Anticancer agents of natural origins are a revolution in the field of cancer research and treatment as they are easy to isolate, cost-effective, and reliable to use. The advantage of anticancer agents of natural origin over synthetic ones and conventional therapeutic options is that their functions are selective and specific to a tumor undergoing treatment. This article is aimed at covering the success of plant-derived anticancer agents in the treatment of cancer, as well as their mechanism of action and the limitations associated with current therapeutic options.

Keywords: Ayurvedic system, Cancer, Plant-derived anticancer agents, Treatment.

INTRODUCTION

Globally, cancer is a very serious health problem. In the United States, it has been identified as the second leading cause of death [1]. Through its metastatic abilities, cancer can spread to other parts of the body, and its incidence rate differs across geographical locations and gender [2]. In 2018, the GLOBOCAN report showed an estimated number of new cancer cases to be 18.1 million and 9.6 million cancer-related deaths [3]. In Sub-Saharan Africa (SSA), the number of

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cancer cases is expected to double in the next 20 years [4]. Out of all cancers, lung cancer has been identified as the leading cause of death among men. This is because of the arising transformational changes of normal cells into cancerous cells. The transformation of these cells is due to the interaction between genetic materials with three different categories of carcinogenic agents such as chemical, biological and physical carcinogens. These carcinogens are well known to induce mutation through activation and inactivation of various signaling pathways [5]. Breast cancer has been identified as the most frequently diagnosed type of cancer among women [2].

Various factors contribute to the development of cancer. These factors may further be divided into intrinsic and extrinsic. Intrinsic risk factors are any mutations that arise randomly. They could be inherited or be caused by random errors during replication. These types of risk factors cannot be controlled. Extrinsic risk factors are carcinogens from the environment that can cause DNA damage, leading to mutations. These risk factors are further divided into two categories; endogenous or exogenous risk factors. Extrinsic endogenous risk factors are genetic factors that are related to an individual's characteristics. These include biological aging, diet, hormones, DNA repair mechanisms, inflammation, genetic susceptibility, while extrinsic exogenous risk factors include radiation, chemicals, viruses, and smoking. Several biological and epidemiological studies have pointed out some of the exogenous risk factors such as tobacco smoking to be associated with lung cancer, ultraviolet radiation (UV) with skin cancer, and viral infections to be associated with the development of both liver and cervical cancer [6, 7]. In the following paragraphs, this review is aimed at highlighting the significance of some plant-derived anticancer compounds used in the treatment of cancer, their origin and history, mechanisms of action, current cancer treatment options, and their limitation as well as their potential application in drug development.

Current Cancer Treatment Options and Their Limitations

There are various traditional modalities used in the treatment of cancer. Therapeutic options used are dependent on the type of tumor and the stage of cancer [8]. Traditional therapeutic modalities used in the treatment of cancer are divided into two classes localized and systemic therapies. Localized treatment options include; radiation therapy and surgery, while systemic options include chemotherapy, immunotherapy, gene therapy, and other targeted therapies such as clustered regularly interspaced short palindromic repeats (CRISPER) [9]. Radiotherapy (RT) is a non-invasive medical technique used in the treatment of cancer. Unlike other cancer therapies, radiotherapy uses ionizing radiation to kill tumor cells. The adverse effects associated with RT include genetic mutations,

infertility, hair loss, and the development of secondary malignancies [10]. Surgery is an invasive procedure that is used in the diagnosis and treatment of various cancers, such as breast cancer. It is often combined with other therapies such as RT and chemotherapy. The side effects experienced during or after this type of treatment include pain, bleeding, infections, and loss of organ function [11].

Chemotherapy is a type of cancer therapy that one or more anticancer drugs that target fast-growing tumor cells. It was believed that chemotherapeutic drugs were specific to targeting only cancer cells, but it is now reviewed that it can also damage normal cells leading to dose-dependent adverse effects such as hair loss, nausea, fatigue, and vomiting [12]. On the other hand, other systemic treatment approaches such as immunotherapy are the type of cancer treatment that uses components of the immune system to suppress tumor cells. There are different types of immunotherapy, among them are vaccines and monoclonal antibodies such as rituximab, trastuzumab, cetuximab, and bevacizumab [9]. Side effects related to immunotherapy do not occur immediately but are mostly observed after a few weeks of treatment, and these include fever, chills, fatigue, diarrhea, and dermatitis [13].

Gene therapy and other targeted therapies such as CRISPER involve the modification of genes to treat or prevent the spread of disease. In 1990, the first gene therapy for a patient with combined immunodeficiency disorders was approved by the Food and Drug Administration (FDA). Ever since, several clinical trials involving different approaches in gene therapy have been conducted with successful outcomes in cancers such as leukemia, lymphocytic leukemia, and brain cancers [14]. Some of the common side effects of gene therapy include inflammation and less genotoxicity which could be due to self-inactivating vectors [15]. Apart from these traditional modalities, there are novel promising therapies with good specificities, such as photodynamic therapy (PDT) [16].

Origin/History of Plant-derived Agents in Cancer Therapies

For many years, medicinal plants have been used in the treatment of many diseases. African and Asian populations have consumed several plant derivatives for medicinal purposes [17]. Over 5000 years, plants have been utilized for various medicinal purposes, foods, and spices. During these olden times, medicinal plants were administered without knowing the active biochemical constituents contained within the plant and their mechanisms of action. Not only in the 18th century when Anton Von Störck conducted research that focussed on the investigation of poisons contained in some herbs. The research laid a principal baseline for clinical investigations [18, 19]. Two ancient cultures have provided current medicinal plant-related knowledge, Traditional Chinese medicine (TCM)

CHAPTER 2

Pradimicin and Benanomicin Antibiotics: From Antifungal Polyketide Natural Products to Antiviral Agents with a Unique Carbohydrate-Binding Mode of Action

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Abstract: The family of benanomicin-pradimicin antibiotics (BPAs) is reviewed exhaustively with respect to its structural, functional, mechanistic and synthetic aspects. BPAs can be considered a unique class of compounds from the structural point of view due to the presence of a 5,6-dihydro-benzo[α]naphthacenequinone (DHBNQ) scaffold attached to a glycan moiety. The mechanism of action is 'lectin-like' and related to the selective recognition and binding to specific mannoside residues located at the surface of the membrane of fungal and viral pathogens. BPAs are prototype structures of non-peptidic small-size carbohydrate-binding agents (CBAs).

Keywords: 5,6-dihydro-benzo[α]naphthacenequinone (DHBNQ), Antibiotics, Antifungal, Antiviral, Aromatic Polyketides, Atropisomerism, Benanomicin, Benanomicin-Pradimicin Antibiotics (BPAs), Biosynthesis, Carbohydrate-Binding Agents (CBAs), Natural products, Pradimicin, Total Synthesis.

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INTRODUCTION

Nature is the main and irreplaceable source of bioactive compounds. The scientific community has devoted historically notable efforts to searching for naturally occurring products endowed with both original structures and interesting activities. As a result, many families of substances from diverse origins have been discovered, structurally characterised and tested as chemotherapeutics.

In the late 80s of the last century, a novel class of secondary metabolites, denominated benanomicins and pradimicins antibiotics (BPAs), emerged from screening programs searching for antifungal drugs. The BPA family currently encompasses a large number of congeners isolated from natural sources as well as many semisynthetic derivatives. They share a common structure based on a molecular construction that confers a unique mechanism of action on these compounds.

This chapter will be devoted to an exhaustive description and in-depth critical analysis from all aspects of this class of compounds. It will be organised in thematic sections focused on the isolation, structural characterisation and chemical modifications (Section 2), the biological activity (Section 3), mechanistic considerations (Section 4), and finally, will be unraveling the biosynthesis procedure and the different strategies of total chemical synthesis that have been attempted (Section 5).

DISCOVERY, STRUCTURAL CHARACTERISATION AND CHEMICAL MODIFICATIONS

The first references regarding BPAs appeared almost simultaneously in 1988 from two different research groups. Takeuchi described benanomicin A (**1**) and B (**2**) as metabolites isolated from unspecified *Actinomycete sp.* bacteria related to *Actinomadura* or *Microtetraspora* (strain MH193-16F4) [1, 2]. In a parallel and independent way, Oki described pradimicins A (**3**) and B (**4**) isolated from the *Actinomycete* bacteria *Actinomadura hibisca* (strain P157-2) obtained from soil collected from Fiji [3, 4]. The structures of the first BPAs obtained by fermentation of bacterial strains are shown in Fig. (**1**).

The promising biological activities exhibited by these BPAs have made them valuable candidates for chemotherapeutic intervention. They are active *in vitro* and *in vivo*, protecting cell cultures and murine animal models from infections caused by fungi. Apart from exhibiting remarkable antifungal activity, **1**, **2** and **3** proved to be efficient inhibitors of the human immune deficiency virus (HIV), the causative agent of the acquired immunodeficiency syndrome (AIDS) [5, 6],

attracting amplified interest. This circumstance must be particularly emphasised due to the severe AIDS pandemic context at the time of the discovery of the first BPAs and the urgent search for antiretroviral agents to treat this fatal disease.

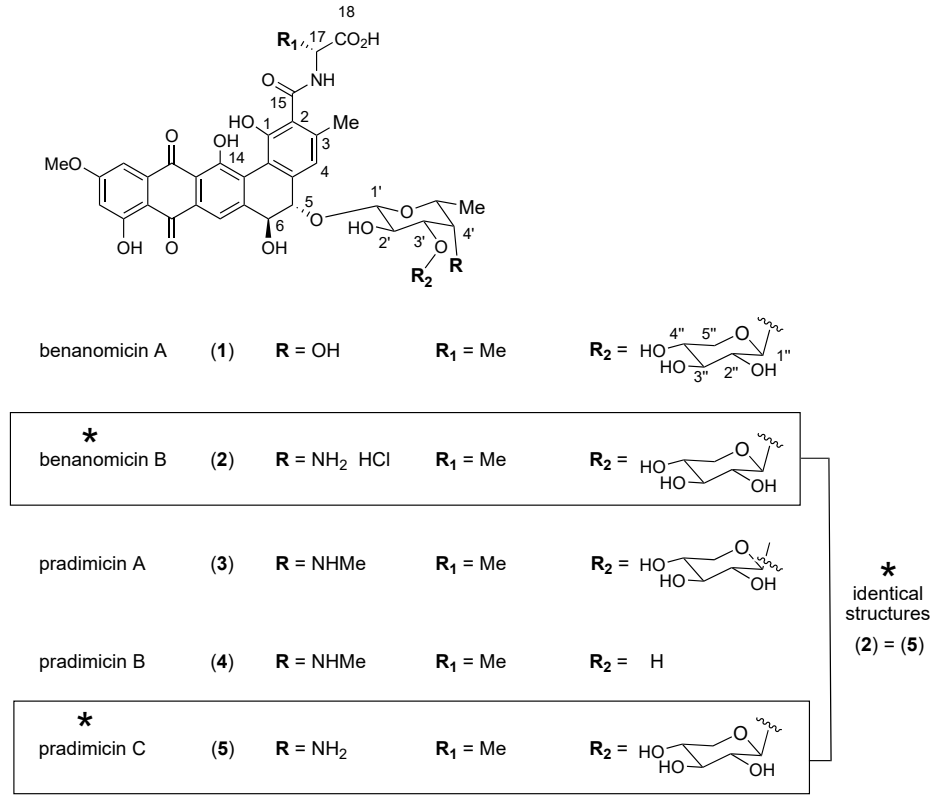

Fig. (1). First members of the BPA family, benanomicins A-B (**1**-**2**) and pradimicins A-C (**3**-**5**) [1 - 4].

The members of the family increased in 1989 with the incorporation of pradimicin C (**5**) [7, 8]. As can be observed in Fig. (**1**), pradimicin C has the same structure as benanomicin B**(2)**. Although they were believed originally to be different molecules, a detailed analysis confirmed both as structurally identical. Despite this circumstance, we have preferred to list both denominations of the molecule to keep the rigour of the original description while stressing that **2** and **5** are the same compound isolated independently by different research groups and published separately. It was also speculated that pradimicin B (**4**) could not be a proper metabolite but a derivative obtained *in situ* by partial hydrolysis during the isolation process, although this point has never been corroborated experimentally.

The first studies on BPAs explored their chemical degradation and analysed the identity of the different fragments of the molecule (Scheme **1**). Thus, pradimicin

CHAPTER 3

The Chemical Compositions of *Bixa orellana* and their Pharmacological Activities

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Abstract: For many years, natural products have been exploited to obtain extracts and pure substances, especially to treat various diseases and conditions. *Bixa orellana*, the seasoning and colouring known as "Achiote", is used in several countries in traditional medicine to treat a variety of health needs, mainly using the dried pulp of the fruit, the seeds, the leaves and the roots. The objective of this review is to provide information regarding the numerous pharmacological activities of the different parts and extracts of *B. orellana,* such as the anti-inflammatory, anti-bacterial and anti-parasitic activity, as well as the hypoglycaemic, cytotoxic, antioxidant, bronchodilator, diuretic and hepatoprotective effects. This information will promote the development of further research regarding this plant and its various benefits, either in the form of an extract or pure substance, such as bixin and norbixin. Similarly, it will allow the discovery of its various mechanisms of action for each disease, which will promote the development of new active compounds.

Keywords: Antimicrobial activity, Antioxidant activity, Bixin, *Bixa orellana*, Cytotoxic activity, Norbixin, Phytochemistry.

INTRODUCTION

Throughout the years, humans have used plants to meet basic needs, such as clothing, food and medicine, among others. At the beginning of civilization, plants were employed in traditional medicine, mainly as tea, powders, tinctures and poultices [1].

The World Health Organization (WHO) has indicated that, currently, approximately 80% of the population in developing countries depends on traditional medicines for the treatment of various health problems [2], such as fever, malaria and diarrhea [3].

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Plants produce different metabolites to ward off animals and microorganisms, as well as to attract pollinators. These metabolites are responsible for the fragrances, colours and toxicity of plants. The plants used in traditional medicines are a good source for the discovery of innovative drugs, as these plants often contain natural products with therapeutic properties, such as antiviral, anti-inflammatory, antimicrobial, antitumor and analgesic effects.

Starting from the purification of morphine in the nineteenth century, up to present day, many additional active plant metabolites have been isolated, including terpenoids, phenolics, flavonoids, alkaloids, *etc.,* [4], leading to the discovery of drugs such as codeine, quinine, paclitaxel and vincristine. Over the last 20 years, one-third of the drugs approved by the Food and Drug Administration (FDA) has been based on natural products or their semi-synthetic derivatives [5], a fact which further indicates the utility of natural products in drug discovery.

The biological activities of plant extracts often involve synergistic effects from the simultaneous action of several components [6]; for this reason, in some cases, the single compound is less effective than the extract. Therefore, research aimed at plant-based drug discovery must draw on novel technologies, such as computational biology methods and quantum computing.

Bixa orellana has been used in traditional medicine to treat a variety of health needs. All parts of the plant are used for various reasons, comprising the dried pulp of the fruit, the seeds, the leaves and the roots.

B. orellana belongs to the Bixaceae family, commonly known as “Achiote”, and is a shrub or small tree that grows up to 6 m high. This plant is native to Central and South America, but is also cultivated in Southeastern Asia and East Africa. *B. orellana* was named in honour of the Spanish conquistador Franciso Orellana who first explored the Amazon river [7]. The fruits of the shrub are found at the end of the branches, and a fruit contains between 10 to 50 small seeds. Through transmission and scanning electron microscopy, it has been determined that the secretory process of the pigment glands in the vegetative and reproductive organs of *B. orellana* has characteristics such as anastomosed articulated laticifers that produce the reddish latex, rich in carotenoids [8]. The seeds are covered with a thin bright crimson layer; the extract obtained from these outer layers is a colouring agent named annatto, which is widely used in the food, cosmetic and pharmaceutical industries. Additionally, many countries have permitted the use of annatto as a condiment, as well as a food additive for colouring [9]. Thus, the seeds of *B. orellana* are a part of the plant that has commercial importance. Annatto is obtained from the pericarp, which is treated with hot water or steam and then extracted with vegetable oil, chemical bases or supercritical CO_2 [10].

USE IN TRADITIONAL MEDICINE

Table **1** shows all the parts of *B. orellana* that have been used for many years in different countries, especially South America, Mexico and the Caribbean, for the treatment of diabetes mellitus, constipation, hypertension, infections, mild indigestion, fevers, skin problems and dysentery. This plant has also been used as an aphrodisiac, insect repellent and snake antivenom.

Table 1. Traditional uses of *B. orellana*.

Country	Plant Part	Uses	References
Argentina	Seeds	Antidiarrheal, cardiotonic, antipyretic	[11]
Brazil	Leaves	Relief from heartburn, indigestión, antipyretic, antimalaria, laxatives, chemopreventive of cancer	[12 - 14]
Colombia	Leaves and Seeds Roots	Antivenin for snakebites, aphrodisiac, expectorant digestive	[15 - 16]
Cuba	Seeds	Aphrodisiac	[17]
Guatemala	Leaves Roots	Hepatitis, gonorrhea, dysentery To treat Diabetes mellitus	[18 - 19]
Honduras	Leaves	Dysentery, digestive, analgesic	[20]
Jamaica	Seeds	To treat diabetes mellitus	[21 - 22]
Malaysia	Leaves	Postpartum medicine, treatment of gastric ulcers	[23 - 25]
Nicaragua	Leaves Seeds	Diuretic, antidiarrheal, respiratory diseases, analgesic	[26]
Peru	Leaves Fruits Seeds Roots	Anti-inflammatory, antipyretic, skin problems, to treat indigestion For epilepsy, aphrodisiac, diuretic Astringent, hepatitis	[12 - 16]
Trinidad and Tobago	Leaves Roots Inside of Pods	Diuretic Diabetes Treatment of mange in dogs	[27 - 29]

The objectives of the present review are to present the phytochemistry and pharmaceutical studies of *B. orellana* conducted in the last ten years and to suggest that this plant has potential as a source of pharmacologically active compounds.

PHYTOCHEMISTRY

From all the different parts of this plant species, a wide variety of compounds have been isolated: mainly carotenes, such as bixin, norbixin, lutein,

CHAPTER 4

Overview of Phytochemistry and Pharmacology of Nilakanthi (*Ajuga bracteosa* Wall. ex Benth.)

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Abstract: Human beings from prehistoric period are mainly dependent on mother nature for the fulfilment of their elementary needs, such as medicines, foodstuffs, shelters, clothing, flavors and fragrances, *etc.* From ancient times, medicinal plants are known to act as a source of a variety therapeutic agents which are widely used in traditional medicine system to cure the various deteriorative diseases and ailments. The wide range of therapeutic applications of various medicinal plants is largely attributed to the presence of a variety of bioactive secondary metabolites (SMs), such as alkaloids, terpenoids, steroids, flavonoids, polyphenolic acids, saponins, tannins, glycosides and essential oils *etc.* Apart from a variety of traditional uses, medicinal plants are also well known for their notable pharmacological potential like anticancer, antiperiodic, antimicrobial, analgesic, antiemetic, antitumor, antioxidant, anti-inflammatory, antiarthritic, *etc. Ajuga bracteosa* Wall. ex Benth (*A. bracteosa*), commonly known as Nilakanthi in Ayurveda belongs to the family Lamiaceae, is an important endangered medicinal plant of Himalayan origin. *A. bracteosa* is a good source of flavanol, glycosides, ergosterol, neo-clerodane diterpenoids, iridoid glycosides, 8-endoperoxide and phyto-ecdysones, which shows numerous biological and pharmacological activities *viz.* antiviral, antitumor, antimicrobial, antiplasmodial, anti-inflammatory, antiarthritic, antioxidant, *etc.* Further, variety of *A. bracteosa* leaves uses had been elaborately described in Ayurveda, Unani and Chinese medicine text, for the treatment of numerous ailments like agues, dysentery, vomiting *etc.* The plant is also known for its antivenom potential against snake bite. *A. bracteosa* is an endangered and medicinally high valued Himalayan species that why it is very significant to reveal its full potency. Therefore, the present article mainly focuses on the distribution, cultivation, traditional uses, phytochemistry, pharmacological potential and future prospective of this versatile Himalayan plant.

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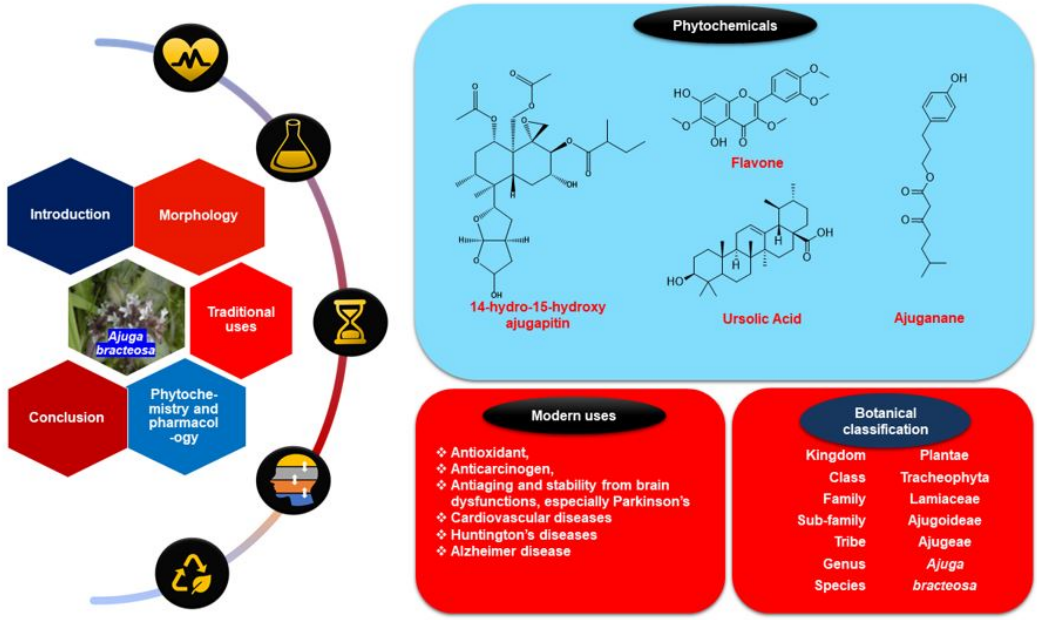
Keywords: *Ajuga bracteosa*, Himalayas, Medicinal plant, Pharmacology, Phytochemistry, Secondary metabolites, Traditional uses.

GRAPHICAL ABSTRACT



INTRODUCTION

The usage of medicinal herbs for the treatment of illnesses is as old as human history and is in vogue since ancient times [1]. It is assumed that about 25-30% of all modern day drugs are natural product derived either directly or indirectly [2]. Though the medicinal plants are distributed worldwide but they are more abundant in tropical areas due to the more favorable environmental conditions. Medicinal plants contain a variety of bioactive compounds with different chemical structures; as a result, they show different modes of action in the biological system. Therefore, single plant extracts or combination of different plant extracts hold great opportunity for the discovery of novel medicine against various human diseases [3]. Medicinal plants (rich in various secondary metabolites (SMs), sources of achiral systems to develop modern medicines, nutraceuticals, food supplements and traditional medicines) naturally synthesize and contain biologically active SMs, like alkaloids, quinines, flavonoids, sterols, terpenes, anthraquinones, glycosides, tannins, saponins, resins, lactones, volatile oils *etc*. Such important bioactive leads are extracted and used in numerous ways, such as injections, syrups, concoctions, decoctions, essential oils, ointments,

infused oil and creams, throughout people's daily lives. Traditional sources of knowledge in medicine such as Ayurveda, Unani, homoeopathy, natural pathology and Siddha are as old as the human origin that is reported to be popular with more than 2/3 of the world's primary healthcare population, especially in developing countries (World Health Organization~ 80%) [4, 5]. The SMs present in the plants are also used in modern clinical studies such as hemorrhoids, osteoporosis, memory loss, cancer, AIDS, malaria, *etc*. because of their long biogenic action in the biological system [6].

There are many families of flowering plants belonging to the Himalayan region, which have high medicinal values. Among them, **Lamiaceae** is the most important family used for medicinal purposes. It is commonly known as the mint or deadnettle or sage family. Plants belonging to this family are mainly aromatic in nature and easy to cultivate through the vegetative propagation method. The family contains 236 genera and 6,900-7,200 species worldwide, which are mainly used for food, ornamental, perfumes and dyes and also used in medicinal purposes [7]. The geographical distribution of this family is from the Mediterranean region to central Asia, also found in tropical and temperate regions. Out of 236 genera, Ajuga is the most studied genus due to its high medicinal value. This genus is native to Central Asia, and Eastern Himalayan region to North East India [8].

A. bracteosa Wall. ex Benth. is an evergreen perennial growing up to 0.2 m tall, is chiefly found in Eastern Asia to Himalayan region from Kashmir to Nepal and China, also in the wide tropical belt of Assam. The plant is regarded as a high valued medicinal herb in the traditional Chinese, Nepalese and Indian medicine systems. Research conducted on *A. bracteosa* over the last few decades implies the presence of many novel components that have notable bio activity such as anti-viral, anti-depressant, antiplasmodial, diuretic activity, *etc*. Recent studies revealed that *ex-situ* conservation of many wild plants is ignored. Lack of awareness and mismanagement by the people leads to the extinction of many important species causing problems in sustainable cultivation and use [9]. Many literatures reported about its threatened status and declared it as an endangered species by following the guidelines provided by the International Union for Conservation of Nature (IUCN) [10]. Among the various threatened causes, overexploitation by the local people and land degradation are of great concern. Due to its high medicinal properties, it is important to cultivate this plant by traditional and modern biotechnological methods for its conservation [11]. It is recommended to follow a multidimensional approach to select better quality genotype and *ex-situ* as well as *in-situ* conservation techniques [12]. The main objective of this chapter is to provide a brief summary and detailed study on traditional uses, phytochemistry, pharmacology, toxicology of *A. bracteosa*. This chapter also addressed the theoretically advantageous way in the immediate future

CHAPTER 5

Tetracyclic Benzocarbazoles and Derivatives: Synthesis and Applications

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Abstract: Tetracyclic benzocarbazoles are examples of nitrogen-containing heterocycles, which display interesting pharmacological activities and physicochemical properties. This chapter aims to bring some examples about the synthesis of bezocarbazoles, mostly benzo[a]carbazoles (including the dihydro and tetrahydro derivatives), with interesting properties. This chapter also includes aza-pterocarpans and aza-coumestans, which are structurally similar to benzo [*a*] carbazoles, although their analogous natural products are formed through different biosynthetic pathways. Being aware of the potential interest of these compounds, many efforts have been made for the development of new methodologies to carry out their synthesis and will be discussed below.

Keywords: Azaarylation, Aza-coumestans, Aza-pterocarpans, Azaspirodecanes, Benzocarbazoles, Chromanones, Chromene, Dihydronaphtalene, Fischer indol, Harmicine, Indole, *N-tert*-butanesulfinyl imine, Tetralone.

INTRODUCTION

Indole alkaloids occur widespread in many natural products ranging from fungus as psilocybin mushrooms and *Claviceps purpurea* to plants as *Rauvolfia serpentina*, and *Robinia pseudoacacia* [1 - 3]. When the indole system is fused with a naphthalene moiety, it is denominated benzo [*a*] carbazoles, benzo [*b*] carbazoles, or benzo [*c*] carbazoles, depending on the position of the fused rings.

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Benzocarbazoles (BCs) are part of an indoline carboline system and are scarcely found in natural products. The synthetic compounds frequently present a variety of biological activities [4 - 13] and are present in functional organic materials [14 - 16]. Benzo [*a*] carbazoles **1**, dihydobenzo [*a*] carbazoles **2** and **3**, tetrahydrobenzo[a]carbazoles **4**, aza-pterocarpan **5**, and aza-coumestan **6** (Fig. **1**) are the most significant related examples highlighted in this chapter due to their interesting properties and activities, although they do not present a unified synthetic pathway. Being aware of their importance, many efforts have been made to develop new methods for obtaining them in a cheaper, greener, and more attractive fashion, allowing for different patterns of substitution to be presented, thus modulating their properties [17, 18]. Initially, the first synthetic approach towards the benzo [*a*] carbazoles relied on the Fischer indole reaction [19] and in the last fifty years, several different methods have been published [5, 20, 21]. The present work will comprehensively cover the most pertinent contributions to this research. We regret in advance that some contributions are excluded to maintain a concise format.

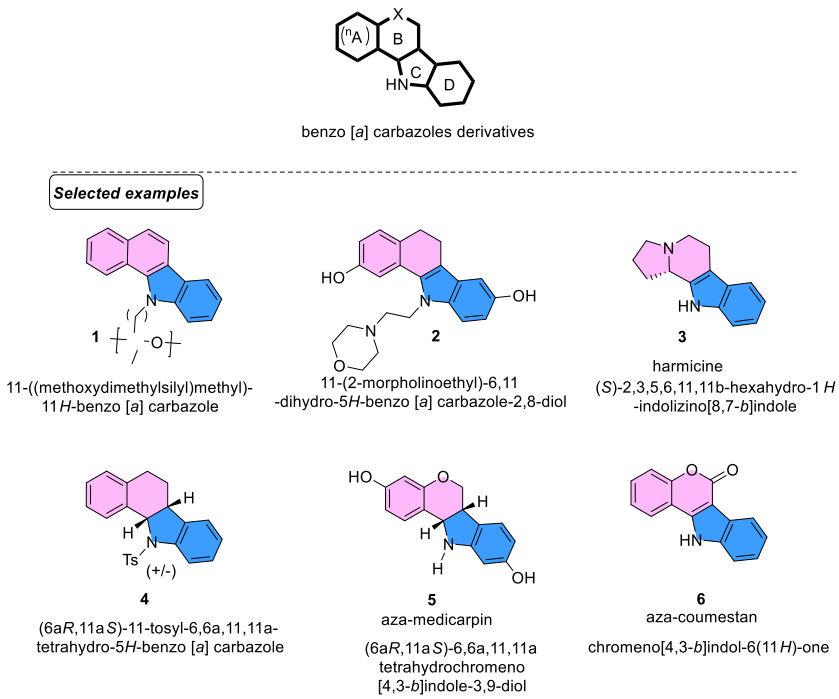
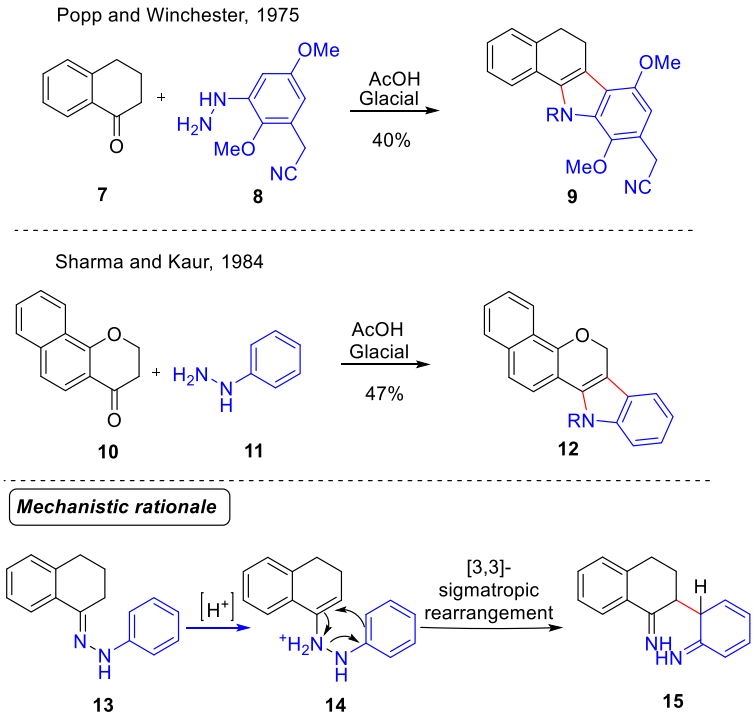


Fig. (1). Some important benzo [*a*] carbazole derivatives.

Early Methodologies and Modern [3, 3]-sigmatropic Rearrangement

In 1883, Fischer`s indole synthesis was one of the first approaches towards C2-C3

substituted indoles [22] and was subsequently employed in the synthesis of 1,2,3,4-tetrahydrocarbazoles [17]. One of the first reactions between α-tetralone or α-chromanone and phenylhydrazines dates back to 1975 by Popp and Winchester aiming to prepare ellipticine alkaloids analogs [23]. They effectively employed α-tetralone **7** with phenylhydrazine **8** in glacial acetic acid, obtaining the dihydrobenzocarbazole **9** Scheme **1**. Later, a similar methodology was implemented in 1984 by Sharma and Kaur [24]. They reacted benzochromanone **10** with phenylhydrazine **11**, satisfactorily obtaining dihydrochromenoindole **12** Scheme **1**. However, the use of chromanones in those conditions is scarcely reported compared to the ones employing tetralones, probably due to the chemical challenge in the preparation of functionalized chromanones and their intrinsic instability in acidic conditions. Nevertheless, this methodology is one of the best routes for obtaining polyoxygenated tetracyclic compounds to date.



Scheme 1. First uses of Fischer indole synthesis with α-tetralone and α-chromanones.

Angerer and Prekajac described the first study aiming to establish a structure and activity relationship for dihydrobenzo [*a*] carbazoles and tetrahydrobenzo [*a*] carbazoles in 1986 employing Fischer indole methodology Scheme **2**. They showed that dihydrobenzo [*a*] carbazoles **17** and benzo [*a*] carbazoles **18** substituted by hydroxyl groups at the A and D rings displayed estrogen receptor

CHAPTER 6

Chalcones as Anti-inflammatory, Anti-diabetic, and Anti-depressant Agents

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Abstract: Flavonoids are naturally sourced compounds found in many substances consumed as food and have beneficial effects on human health. Chalcones, essential members of the flavonoid family, have also attracted many researchers' attention due to their wide range of pharmacological effects. In this chapter, the antiinflammatory, antidiabetic, and antidepressant activities of the natural compounds in the structure of chalcones and the compounds synthesized with the help these compounds will be discussed. It has been written after a literature review of the articles published between 2000 and 2020 and aims to be a guide for designing new active drug ingredients.

Keywords: Aldose reductase, Alpha glucosidase, Antidepressant, Antidiabetic, Antiinflammatory, Butein, Chalcones, Cyclooxygenase, Dipeptidyl peptidase-IV, Heme oxygenase-1, Interleukins, Isoliquiritigenin, Kinases, 5-Lipoxygenase, Monoamine oxidase, Noradrenalin, Protein tyrosine phosphatase 1B, Serotonin, Sodium-glucose cotransporter 2, Tumour necrosis factor-alpha.

INTRODUCTION

Diabetes and depression are diseases increasing in frequency with each passing day [1, 2]. While untreated diabetes can cause organ loss and death [3], untreated depression can significantly reduce both quality of life and work performance initially and may result in suicide at a later stage [4].

The incidence of depression and depressive symptoms is twice as high in patients with type 2 diabetes, and the mortality rate is higher than in the general population. Some inflammatory markers, such as interleukin (IL)-1β, IL-1

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receptor antagonist (IL-1RA), monocyte chemoattractant protein (MCP-1), and triglyceride (TG), increase in depression [5]. Inflammation is related to diabetes. Overproduction of an inflammatory mediator, tumour necrosis factor-alpha (TNF-α), enhances insulin resistance and beta-cell death in pancreatic islets [6]. Inflammation plays a role in the pathogenesis of depression [5, 7] and diabetes [6]. Treatment with antiinflammatory drugs causes antidepressant effects [8], whereas some antidiabetic drugs show antiinflammatory effects [1]. The treatment of these three diseases may be interrelated.

Chalcones, members of the flavonoid family, found in many natural products, draw attention due to their easy synthesis and many pharmacological effects. Chalcones have antiinflammatory [9], antidiabetic [10], and antidepressant activities [11]. When the relationship between inflammation, diabetes, and depression is studied in more detail, chalcones containing these three effects can be a ray of hope in treating these three diseases.

This chapter presents natural and synthetic chalcones with antiinflammatory, antidiabetic, and antidepressant activities and the targets of these compounds while showing their effects.

ANTI-INFLAMMATORY CHALCONES

Inflammation is the immune system's response to infection and injury. Cells of the immune system move to the infection/injury area to repair tissue and heal the wound. Firstly, mediator molecules are released from injured tissue. Thus, it is ensured that the protective and healing components reach the damaged tissue. After that, either the disease can be treated and the stimuli are cleared, or the disease may progress [12]. If the condition continues to advance, chronic inflammation occurs. Excessive amounts of superoxide radicals, proteases, chemokines, and cytokines continue to be released due to periodic signals in chronic inflammation, which can cause subsequent tissue damage [13]. Reducing inflammatory mediators in the macrophages is a critical treatment approach for inflammation.

Anti-inflammatory Targets for Chalcones

Chalcones exert their anti-inflammatory effects by acting on different parts of inflammatory mechanisms. They exhibit their effects through different targets, such as an enzyme, a gene, a receptor, or a chemical released in inflammation. Some targets for chalcones are as follows:

Heme Oxygenase-1

The anti-inflammatory activity of heme oxygenase-1 (HO-1) is related to its activity in mononuclear phagocytes (monocytes and macrophages) and endothelial cells. Macrophages are activated by cytokines or products of microorganisms and provide the first immune response. Thus activated macrophages initiate the inflammatory response [14]. The induction of HO-1 in macrophages transforms these cells into anti-inflammatory phenotypes [15]. HO-1 inhibits adhesion molecule expression, decreases oxidative stress, and protects the cell from inflammation [16].

Nuclear Factor-κB and Histone Deacetylases

Nuclear factor κB (NF-κB) is a transcription factor that controls the release of iNOS and cytokines, such as TNF-α and IL-1β, and is found in macrophages [17]. It is a dimer that is composed of two similar subunits. NF-κB is mainly found complexed with the inhibitory molecules of the inhibitory kappa B (IκB) family. IκB proteins must be degraded for NF-κB to be activated after a stimulus. Phosphorylation of IκB molecules is necessary for this degradation [18]. NF-κB inhibition is an important target to stop the release of proinflammatory mediators.

Histone deacetylases (HDACs) are enzymes that remove the acetyl group from lysine and impact inflammatory gene expression [19]. Since the NF-κB pathway is a significant adjuster of the expression of many inflammatory genes, acetylation plays a vital role in adjusting many responses of NF-κB. Histone deacetylases play a role in regulating the NF-κB signalling pathway, therefore, inhibitors of HDACs are targets for decreasing the inflammatory response [20].

Kinases and Activator Protein-1

Kinases are enzymes that transfer phosphate groups from high-energy donor molecules, such as ATP, to particular substrates *via* phosphorylation [13]. The main pathway that controls the part of inflammation involved in gene expression is the activation of the NF-κB. Mitogen-activated protein kinases (MAPKs) are responsible for the expression of pro-inflammatory cytokines, such as interleukin-1 and TNF [21]. The c-Jun amino-terminal kinases (JNKs) are a group of MAP kinases [22]. IκB kinases (IKKs) play a critical role in regulating the NF-κB cascade [23]. Activator protein-1 (AP-1) is a transcription factor that induces pro-inflammatory cytokine expression [24].

CHAPTER 7

Bioactive Steroids from Marine Organisms

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Abstract: Natural products have played a key role in cancer drug discovery, as well in other therapeutic fields. In the past decades, marine organisms have proven to be a primary source of new potentially bioactive natural products for drug discovery. By reviewing the literature describing marine organisms and isolated metabolites, we can notice a large increase in the number of studies today compared to the end of the 20th century. The number of structures isolated each year has almost doubled over the past 20 years. Because of their topicality, we have focused on natural bioactive steroids isolated from marine organisms. In the chapter 'Bioactive Steroids from Marine Organisms', an overview of the new steroid compounds isolated from marine sponges, macroalgae and cucumbers, described in the relevant literature in the period from 2011 to 2020, is given. To provide a comprehensive introduction in the field of marine bioactive steroids, we highlighted typical molecules grouped according to their structural characteristics with additional reference to their biological activity. The structures of the new compounds, their natural origin (species of the organism) and their rich biological activities are presented and described in detail. In addition, biological tests performed on known compounds during this time period are also described. Some of the compounds possess multiple activities and have been tested only in a limited number of biological assays, which means that the full potential and significance of these compounds may only be discovered in the future.

Keywords: Bioactivity, Biosynthetic origin, Marine cucumber, Marine macroalgae, Marine sponges, Natural steroids, Structural characterization.

INTRODUCTION

The American, Werner Bergmann, was one of the first scientists who started the chemical investigation of marine organisms. He reported the isolation of unusual nucleosides from the sponge *Cryptotethia crypta* collected near the coast of Florida [1] and his discovery was followed by the development of the very first marine-derived drug, Cytarabine, which destroys cancer cells by blocking DNA

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polymerase function [2]. In 1969, the U.S. Food and Drug Administration (FDA) approved this drug for the treatment of leukemia. Currently, there are six FDA-approved marine-derived drugs in the market and several compounds in different phases of the clinical trials [3].

Steroids are a major class of natural compounds with an important biological role. They have attracted great attention over the years from medicinal chemists in the search for new drugs. Their function involves the constitution of the membrane, hormonal function, protective functions and many others. Steroid-based compounds are widely used in medicine as drugs with anti-inflammatory, anabolic, contraceptive or anticancer activities [4].

The term ‘steroid’ covers a wide variety of compounds based on a partially cyclized isoprenoid skeleton. These molecules are structurally defined by their 17-carbon tetracyclic (cyclopentanoperhydrophenanthrene) core containing three cyclohexane rings (A, B, and C) and one cyclopentane (D ring). The numbering of the steroid nucleus is presented in the example of a cholestane-type compound, which is structurally the most representative (Fig. **1**).

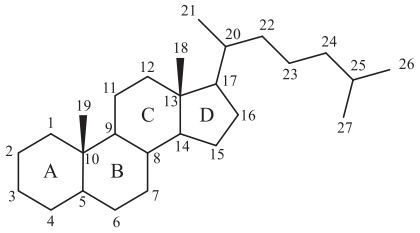

Fig. (1). The structure and the numbering of a cholestane-type compound.

The chapter ‘Bioactive Steroids from Marine Organisms’ covers the literature published in the period from 2011 to 2020 relating to the new steroid compounds isolated from marine sponges, macroalgae and cucumbers. The chapter contains three subchapters, each relating to one of the groups of marine organisms. Within these subchapters, steroid compounds are grouped according to their common structural characteristics, while their biological activity is additionally described, as well as their biosynthetic origin. Also, new biological activity for known steroid compounds is described.

BIOACTIVE STEROIDS FROM MARINE SPONGES

The sponges are the simplest and probably oldest group of animals that have separated from other metazoans. They are sessile organisms that do not possess true tissues, organs or nerve structures [5]. Sponges are important within the fields

of marine biotechnology and marine pharmacology. They are considered the best resources for highly active therapeutic molecules amongst other marine invertebrates.

Marine sponges are the source of a large number of compounds with unusual carbon frameworks and functionalities. Various compounds with a unique structure, such as secosteroids or steroids with sugar moiety on the side chains of steroid compounds, are often present [6, 7].

In the literature, novel compounds, particularly steroids with a diverse range of conventional and unconventional side chains and nuclei with various biological activities have been described as secondary metabolites of sea sponges [8]. Due to their significant potential, steroid compounds isolated from sponges will be described in this subchapter.

A-Norsteroids

A-Norsteroids are a class of steroids with unusual A-nor skeleton, in which carbon was biosynthetically or synthetically removed from the A-ring of steroid compound. Such unusual compounds have also been isolated from sponges and described in the literature (Fig. **2**) [9, 10].

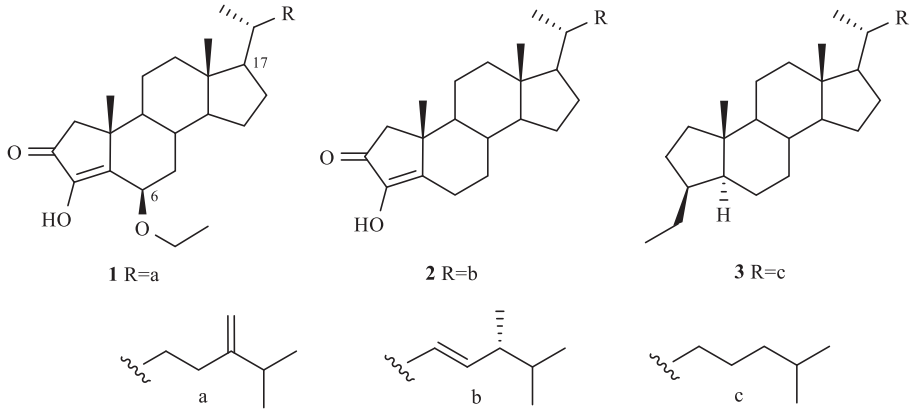

Fig. (2). A-Norsteroids.

Ragini *et al.* [9] have isolated two new steroids, crellasterones A (**1**) and B (**2**) (Fig. **2**), with the previously reported compounds from the sponge *Crella incrustans*, collected in New Caledonia. The structures of the new compounds revealed unprecedented marine natural products with a ring-contracted A-norsterone nucleus and 2-hydroxycyclopentenone chromophore. Crellasterones A (**1**) and B (**2**) have an identical steroid skeleton, but differ in the side chain at the

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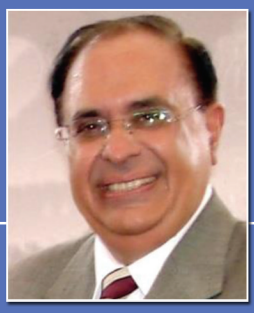

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Prof. Atta-ur-Rahman, Ph.D. in Organic Chemistry from Cambridge University (1968) has 1,232 international publications (45 international patents and 341 books). He received the following awards: Fellow Royal Society (FRS) London (2006), UNESCO Science Prize (1999), Honorary Life Fellow Kings College, Cambridge University (2007), Academician (Foreign Member) Chinese Academy of Sciences (2015), Highest Civil Award for Foreigners of China (Friendship Award, 2014), High Civil Award Austria ("Grosse Goldene Ehrenzeischen am Bande") (2007), Foreign Fellow Chinese Chemical Society (2013), Sc.D. Cambridge University (UK) (1987), TWAS (Italy) Prize (2009). He was the President of Network of Academies of Sciences of Islamic Countries (NASIC), Vice President TWAS (Italy), Foreign Fellow Korean Academy of Science & Technology, President Pakistan Academy of Sciences (2003-2006) and (2011 – 2014). He was the Federal Minister for Science and Technology of Pakistan (2000 – 2002), Federal Minister of Education (2002) and Chairman Higher Education Commission/Federal Minister (2002-2008), Coordinator General of COMSTECH (OIC Ministerial Committee) (1996-2012), and the Editor-in-Chief of Current Medicinal Chemistry.