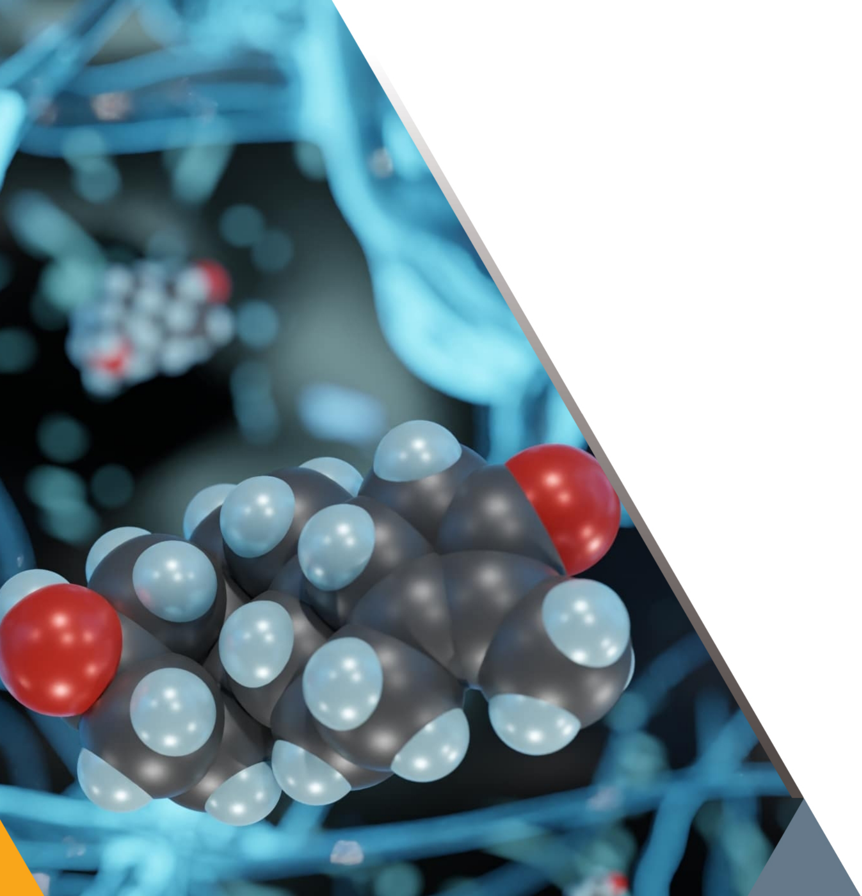
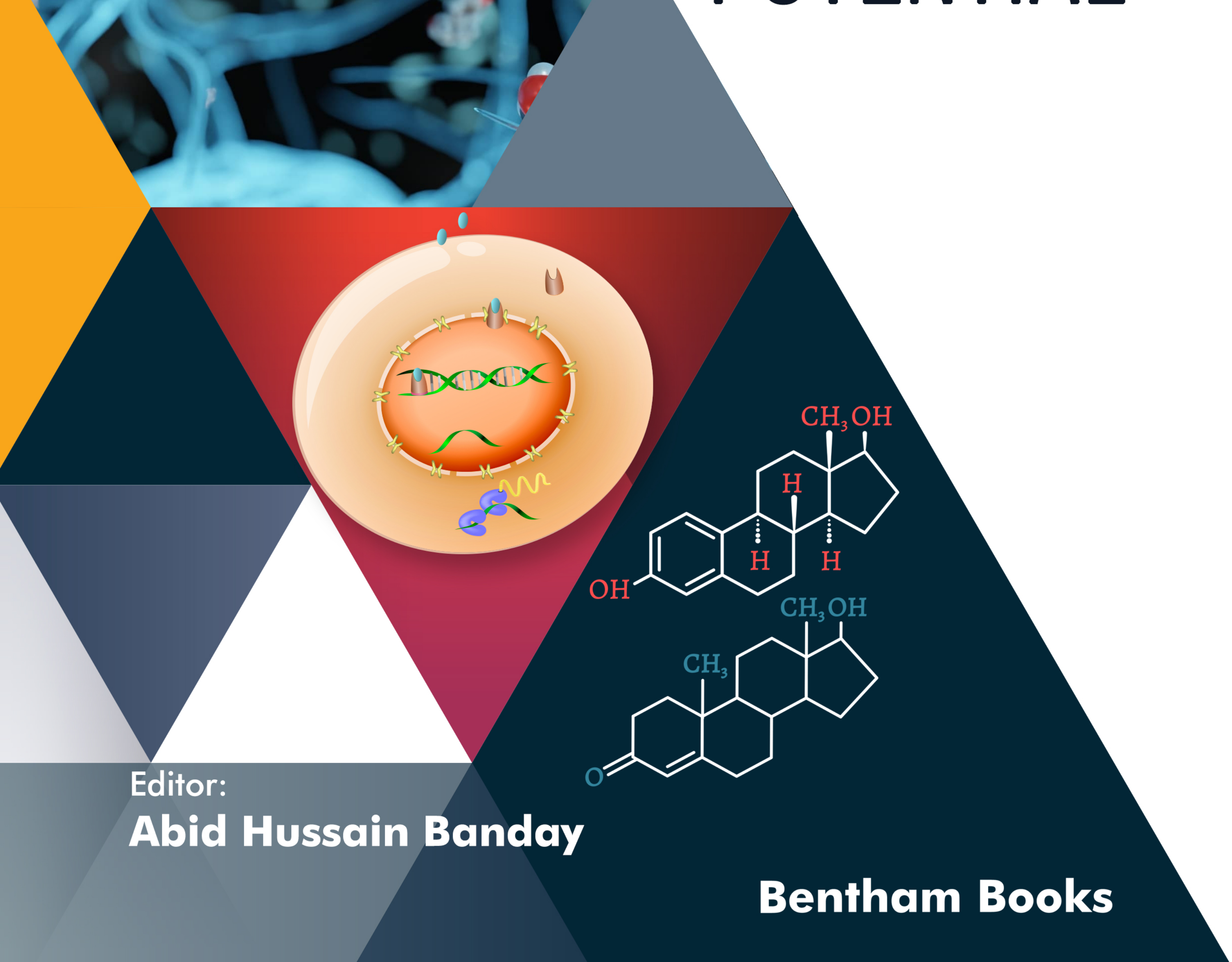


STEROIDS AND THEIR MEDICINAL POTENTIAL



Editor:
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Steroids and their Medicinal Potential

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PREFACE

Steroids represent a fundamental class of biomolecules with diverse roles and functions. In the human body, steroids act as structural constituents of the cell membrane, signaling molecules controlling metabolism, hormones inducing sexual functions, regulators of electrolyte balance of body fluids, immunomodulatos *etc.* Steroids also have key roles in nervous system and many disorders including malignancies like prostate cancer, breast cancer *etc.* Besides the immense potential of regulating key biological processes, steroids also have tremendous medicinal potential. Typically steroids are considered as potent immunomodulators as they work by decreasing inflammation and suppressing the immune system. However, the latest research has shown that these molecules hold promise against numerous disorders including cardiovascular conditions, cancer, inflammation, autoimmune disorders *etc.* Besides, there are several reported investigations where a non-steroidal pharmacophore has been attached to a steroidal framework in order that the latter may provide lipid solubility, receptor selectivity or membrane binding properties.

The proposed book titled "Steroids and their Medicinal Potential" contains chapters covering the classification, distribution, biosynthesis, chemical synthesis and semi-synthesis of different steroids. The medicinal potential of each class has been exhaustively discussed in different chapters. The latest advances and developments in steroid based drug discovery have been discussed thoroughly and care has been taken to make it a useful resource for the readers. Few chapters have been dedicated to anabolic steroids and their abuse. There is, till date, no such book available that provides a comprehensive coverage of all aspects of steroid chemistry, biochemistry, medicinal potential, drug discovery and advances in target binding interactions of steroid based drugs. The present volume is the first volume of the book series and its contents are of introductory nature wherein the introduction and biological significance of Steroids has been discussed in an elaborative manner. Topics like introduction to steroids, classification, biosynthesis, semi-synthesis and total synthesis in addition to sources of steroids, characterization and breakthroughs in steroid research have also been included and discussed thoroughly from academic and research perspective. We hope the present book shall be an indispensable learning resource for students, teachers and researchers, both in academia and industry.

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CHAPTER 1

Terpenes, Terpenoids and Steroids: Properties, Biosynthesis and Functions

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Abstract: Terpenes belong to the largest class of secondary metabolites consisting of five carbon isoprene units which are assembled through innumerable patterns generating diverse structural motifs. Terpenes are linear or cyclic hydrocarbons, whereas terpenoids are oxygen-containing terpene analogues found in all living organisms. Steroids are a subclass of terpenoids that are biosynthesized from terpene precursors. Terpenes, terpenoids and steroids are all derived from five-carbon isoprene units assembled and arranged in different ways generating thousands of structurally varied molecules. Terpenes and terpenoids are widely explored as biomaterials and biofuels while steroids are used as drugs to increase protein synthesis in animals besides their anti-inflammatory, anticancer and other properties. In this chapter, we discuss the properties, functions and biosynthesis of terpenes and terpenoids in general and steroids in particular to better understand their functions and prospective applications.

Keywords: Terpenes, Terpenoids, Steroids, Biosynthesis, Hormones, Essential oil, Cosmetics, Epoxidation.

INTRODUCTION

The terpenes are a structurally diverse and widely distributed family of natural products containing well over 40,000 defined compounds identified from all kingdoms of life. The majority of terpenes have been isolated from plants where they serve a broad range of roles in primary metabolism (including several plant hormones and the most abundant plant terpenoid, phytol, which forms the side chain of the photosynthetic pigment chlorophyll) and in ecological interactions (as chemical defenses against herbivores and pathogens, pollinator attractants, allelopathic agents, *etc*). Terpenes have been known for hundreds of years as

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components of essential oils and are widely used in flavors, fragrances and medicinal formulations [1]. They are a varied class of hydrocarbons with structural diversity but a simple unifying feature which represent the isoprene rule. Terpenes are extensively found in almost all organisms, mostly in higher plants. In crude and pure form, these are widely used in perfumes and cosmetics [2]. Besides having tremendous medicinal value, terpenes are used as precursors in the synthesis of vitamins, insecticides and steroids [2]. They are also widely used as solvents and diluting agents in paints and varnishes [1]. Acyclic to pentacyclic derivatives of terpenes with alcohols, ether, ester, aldehyde or ketone groups and/or oxidized methyl group at various positions are called terpenoids. Terpenoids are also a biologically active class of compounds. Terpenes and terpenoids are volatile, odoriferous, complex natural classes of secondary metabolites generated usually by aromatic plants having intense smell and flavor. They represent traditional pharmacopeia besides being used by the plants to attract insects for pollination and to deter predator animals. The consumer demand for better food quality, cosmetics and other pharmaceutical products free of artificial and synthetic additives and preservatives in addition to maintaining long shelf-life has diverted the present research towards the exploration of terpenes and terpenoids for numerous food, cosmetic and medicinal applications. Steroids are biologically active organic molecules functioning as important constituents of cell membranes and represent the main signaling molecules. These are found widely distributed in plants, animals and fungi. Steroids, terpenoids and terpenes are used in almost all living organisms including humans as growth regulators for communication and signaling. All these three classes of compounds are active at low concentrations in the natural form, inexpensive and do not change the smell or taste of products in a bitter/harmful way. They do not change the composition of food products owing to their antimicrobial activity and thus inhibit the spoilage caused by pathogenic microorganisms. These are nontoxic at low to moderate concentrations. The structural and functional diversity of terpenes, terpenoids and steroids in nature pertains to their diverse biological activities which render them as interesting molecules for traditional and modern drug exploration. These compounds have been improving the quality of life since ancient times. These natural compounds are remarkably explored for their potential medicinal values, health benefits, flavoring properties, fragrances in food, pharmaceutical and cosmetic industries.

TERPENES

Terpenes, also called as isoprenoids, is a miscellaneous class of naturally occurring organic compounds widely distributed in plants and animals. Terpenes are composed of isoprene units (C_5H_8) and are classified on the basis of the number and organization of these units. Monoterpenes are the smallest terpenes containing ten carbon atoms ($C_{10}H_{16}$). Examples include α-pinene (pine trees) and limonene (citrus plants). Monoterpenes are the most fragrant class of terpenes and are usually purified by fractional distillation. Sesquiterpenes contain 15 carbon atoms ($C_{15}H_{24}$) and are more stable than monoterpenes. Sesquiterpenes are naturally found in plants, fungi, insects, *etc*. where these molecules play important roles as plant growth hormones and in signaling mechanism in response to environmental stress. Diterpenes ($C_{20}H_{32}$) *e.g.* phytol, capestol, kahweol, *etc*. regulate germination, control flowering in plants and contain antitumour, cytotoxic and anti-inflammatory therapeutic effects. Sesterpenes contain 25 carbon atoms ($C_{25}H_{40}$) and occur naturally in fungi, insects, sponges, lichens and waxes of plants. Triterpenes ($C_{30}H_{48}$) are precursors of steroids and sterols, *e.g.* saponins. Triterpenes have wound-healing properties and act as diuretics. Tetraterpenes (carotenoids) have the molecular formula ($C_{40}H_{56}$), *e.g.* β-carotene. They are found in fungi, bacteria, plants, and animals usually as fat-soluble pigments.

Properties of Terpenes

The fragrance of flowers, taste of fruits and vegetables, and pigmentation in plants are due to terpenes [3]. Terpenes are used in defense mechanisms by certain plants as a scent or imparting bitter taste to the foliage so as to defend against grazing animals [3]. Terpenes are reported to have thermoprotective and signaling functions in plants [4]. Many living organisms like microorganisms, animals and plants use terpenes to protect themselves from abiotic and biotic stresses [5]. Terpenes are also used to ward off pathogens, predators and competitors and to communicate about food, mates or enemies [3]. Terpenes depict potential medicinal values and are reported to exhibit anti-cancer, anti-microbial, anti-fungal, anti-viral, anti-hyperglycemic, analgesic, anti-inflammatory and anti-parasitic properties [6]. Terpenes are also widely used in ointments and various cosmetic creams to enhance skin penetration [5]. The main sources of terpenes are plants like tea, thyme, cannabis, citrus fruits, *etc*. Most common terpenes, their source and their main properties are listed in the below (Table **1**).

CHAPTER 2

An Overview of Natural Steroid Sources and their Therapeutic Profile

Mahalakshmi Krishnan[1], **Livya Catherene Martin**[1], **Parimalanandhini Duraisamy**[1], **Sangeetha Ravi**[1], **Beulaja Manikandan**[2], **Janarthanan Sundaram**[1] and **Ramar Manikandan**[1,*]

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Abstract: Natural steroids are organic compounds that play important physiological roles in various organisms. They are the key components of a cell, which act as important signalling molecules engaging in stress response, metabolic activities, reproduction, inflammation, and behavioural uniformities. Naturally, the human body embraces a cluster of steroids in the form of biological hormones, namely, sex hormones, adrenal cortical hormones and bile acids. Steroidal derivatives can imitate human hormones and exhibit their activities by boosting enzymes that the body lacks. Clinically, it is evident that the distribution of synthetic steroids is high in pharmaceutical use for hormonal anomalies, but they provide adverse side effects over long term usage. Steroids work as immunosuppressants to control many autoimmune disorders concerned with inflammation, but they also reduce the activity of the immune system, which is the body's natural defence against infection and illness. Replacement of natural steroids sourced from herbal plants, marine invertebrates, bacteria, algae, and fungi has a medicinal value that aids in the treatment of various ailments. Apart from hormonal functions, bio-derived steroids also display a safe and copious pharmacological profile for anti-oxidant, anti-inflammatory, anti-carcinogenic, anti-neoplastic, neuroprotective, and cardioprotective activities. This chapter discusses the prevalence of various naturally available steroids in different entities and their suitable applications in various fields.

Keywords: Anti-inflammatory, Hormones, Natural steroids, Pharmacology, Signaling molecules.

INTRODUCTION

Steroids are typical organic lipid molecules with a hydrophobic nature and remarkable differences in structure. Steroids are basically the gonanes, steranes,

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or cyclopentanoperhydrophenanthrene (the nucleus of steroids), which hold the seventeen carbon atoms bonded in tetracyclic rings with an alkyl side chain arranged as three six-membered rings (cyclohexane) and one five-membered ring (cyclopentane) (Fig. **1**). The biotic functions of steroids vary according to the changes in the functional group attachment, modified structure, and oxidation state of the steroid rings [1].

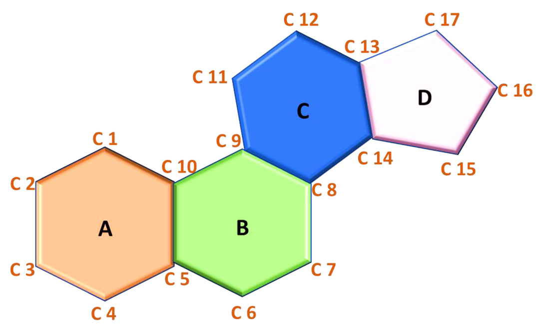

Fig. (1). Structure of a steroid nucleus.

Altered chemical composition in the nucleus of steroids results in their classification (Table **1**) [2].

Table 1. Classification of steroids based on number of carbon atoms.

Steroids	Carbon Atoms Present	Example
Cholestanes	27	Cholesterol
Cholanes	24	Cholic acid
Pregnanes	21	Progesterone
Androtanes	19	Testosterone
Estranes	18	Estradiol

Secosteroids

Secosteroids are a class of steroids with broken rings as a result of cleavage or chain scission taking place in the C-9 and C-10 carbon atoms of their parent steroids [3]. The class of secosteroids includes cholecalciferol and vitamin D3, as they are the derivatives of cleaved C-9 and C-10 carbon atoms of the steroid nucleus [4]. Vitamin D is the most commonly available secosteroid and is of utmost physiological importance, as vitamin D deficiency causes osteomalacia and rickets and significantly increases the risk of osteoporosis, autoimmune disease, infections, various cancers, and cardiovascular disease.

Sterols

Sterols are a subgroup of steroids possessing a hydroxyl group at the third carbon position of the A ring [5]. They are found in plants such as vegetable oils, nuts, and seeds and are known as phytosterols. They are commonly used to lower cholesterol levels.

ROLE OF STEROIDS IN THE HUMAN BODY

Steroids are the essential molecules produced in most eukaryotic organisms that accomplish diverse functions. They play an important role in cell membranes and regulate metabolism. Cholesterol, the predominant sterol present in our body, is metabolised by the liver into bile acid and toil as precursor of endocrine hormones [6]. Such steroid hormones carry out communication between cell intermediaries and organ tissues [7]. And these endogenous steroidal hormones released into the bloodstream interact with the receptors and regulate various physiological functions like development, growth, and homeostasis through the regulation of specific genes [8].

STEROID BIOSYNTHESIS

In humans, there are distinct classes of steroids synthesised in the steroidogenic adrenal glands, testes, and ovary, which are further structurally modified in various tissues and organs [8]. In the adrenal cortex and gonadal organs, the side chains of cholesterol are cleaved by the cytochrome P450 enzyme and form a pregnenolone [9], where it initiates the synthesis of other hormonal steroids through the biosynthetic enzymes, cytochrome P450 or specialised hydroxysteroid dehydrogenase (HSD) (Fig. **2**) [10].

CORTICOSTEROIDS

The adrenal cortex produces adrenal cortical hormones, or corticosteroids. They include glucocorticoids, mineralocorticoids, and androgenic steroids.

The hypothalamic pituitary adrenal gland (HPA) stimulates the production of adrenocorticotrophic hormones (ACTH) in response to physiological stress and signals, where the ACTH hormone activates the corticotropic cells of the adrenal glands to synthesise corticosteroids [11]. The site and the enzyme involved in the production of corticosteroids and their functions are as follows (Table **2**) [10, 12]:

CHAPTER 3

Synthesis of Steroids

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Abstract: The term steroid pertains to a broad spectrum of molecules with varying physiological roles. More explicitly, they are a class of compounds that are naturally produced in the body of living organisms as well synthetic or semi-synthetic molecules. They have tremendous effects on biochemical processes and thus any aberration from the required physiological range can have potential effects. Moreover, due to the therapeutic potential of steroids for the treatment of a wide range of diseases, many synthetic approaches have been made available to the organic chemist for their synthesis. Most of the steroids that are in use as drugs are still prepared by modifying naturally occurring steroids (partial synthesis). This chapter highlights the biosynthetic pathways of steroids and the approaches to chemically synthesize them because of their biological and synthetic relevance.

Keywords: Biotransformation, Partial Synthesis, Steroidogenesis, Total Synthesis.

INTRODUCTION

Steroids are the vital secondary metabolites that are characterized by a tetracyclic ring structure, out of which, three rings are six-membered while as one ring is five-membered [1]. They are associated with a myriad of physiological functions in the cells such as the modulation of cell membrane fluidity [2]. Cholesterol, as an example, is the parent steroid molecule and the substrate for steroidogenesis [3].

Biosynthesis of Steroids in Mammals

The steroid hormones are classified into six families based on their structure and biology. These are glucocorticoids, progestins, vitamin D mineralocorticoids,

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estrogens and androgens. Furthermore, the bile acids can constitute the seventh member of steroid family as they are structurally related to cholesterol. All the mammalian steroid hormones are biologically derived from cholesterol and this biosynthesis of biologically important steroid hormones from cholesterol is referred to as Steroidogenesis [4]. Earlier it was known that the biosynthesis of steroid hormones happened *via* steroidogenic glands, but researchers have now suggested that in addition to steroidogenic glands, various other organs known as intracrine tissues such as adipose tissues and the brain are involved in the biosynthesis of active steroid hormones. These intracrine tissues convert inactive precursors of steroid hormones into an active form thereby modulating the activation and deactivation of steroid hormones as per the requirement of the cell [5].

Cholesterol and its Derivates

Cholesterol is a chief constituent of the cell membrane and exists in the blood in the esterified or unesterified form [6]. It is essentially not soluble in water and thus is transported with proteins in the bloodstream [7]. It plays a significant role in various physiological processes and is necessary for regulating the homeostasis of the body. Almost 60% of the daily biosynthesis of cholesterol occurs in the liver and intestine from acetate *via* an intricate pathway that occurs in the endoplasmic reticulum, however, circulating lipoproteins are the main sources of steroidogenic cholesterol. Cholesterol is intercalated between phospholipids of the polar bilayer and can be distinguished from active cholesterol kinetically. The active membrane cholesterol or free cholesterol is the moveable cholesterol that is in excess than phospholipids and is the major substrate for steroidogenesis [8]. The interaction between cholesterol and the polar bilayer depends on: A) the polar head group of lipids (the larger the head group more is the umbrella of protection.) B) Unsaturation level in case of phospholipid's acyl chain. C), The cholesterol which is weakly protected has high chemical activity coefficient (Fig. **1**) [9].

The biosynthesis of cholesterol is controlled by sterol regulatory-element binding proteins which have three isomeric forms (SREBP-1a, SREBP-1c, and SREBP-2) in mammals. These proteins convey information to the nucleus about the content of sterol in the membranes [10]. SREBP-1c preferably activates genes involved in the biosynthesis of fatty acids. SREBP-2 targets genes that are responsible for cholesterologenesis whereas SREBP-1a activates all SREBP-responsive genes, including those which facilitate the biosynthesis of triglycerides, fatty acids and cholesterol [11]. The sterol regulatory-element binding proteins are processed by SREBP cleavage–activating protein (SCAP), Site- 1 protease (S1P) and Site-2 protease (S2P) so that they act as transcription factors. SREBP cleavage–

activating protein also acts to sense the concentration of sterols in addition to escorting it to the golgi complex where S1P and S2P are present. When the level of cholesterol in the cells is high, then the SREBP is confined in the membranes of the endoplasmic reticulum where it binds to SCAP leading to a change in its conformation. The SCAP-SREBP complex then interacts with Insig proteins which acts as an inhibitor for the transfer of the SCAP-SREBP complex to golgi complex from ER. However, when the concentration of cholesterol in the cells decreases, SREBP is escorted by SCAP from the ER to the Golgi apparatus, where the two proteases are present. In the Golgi complex, S1P divides the SREBP molecule into half followed by the second cleavage by S2P which leads to the release of the NH2-terminal bHLH-Zip from the membrane. The NH2-terminal domain binds to nonpalindromic sterol response elements (SREs), activating their transcription [12].

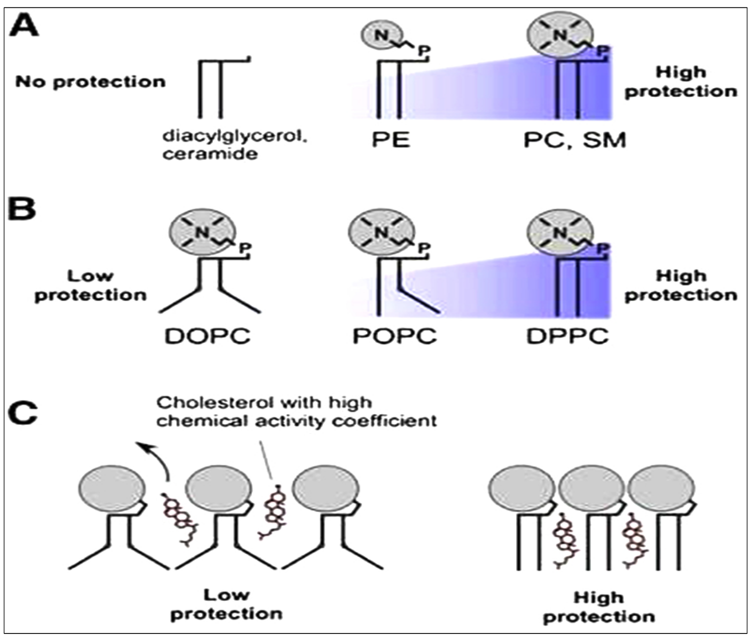

Fig. (1). (A) Lipids having a larger polar head group (N) provide more protection. With increase in the size of head group in case of lipids the level of protection increases. (B) Unsaturation level in case of phospholipid's acyl chain (As the degree of unsaturation decreases the level of protection increases.) (C) The weakly protected cholesterol can easily leave the membrane, whereas highly protected cholesterol is not readily available and thus has low chemical activity [Adapted from Ref. 9].

The circulating lipoproteins which are the major sources of the steroidogenic substrate are divided on the basis of hydrated density into five major classes: Chylomicrons, very low density (VLDL), intermediate density (IDL), low density (LDL), and high-density lipoproteins (HDL). The physiological function of

CHAPTER 4

Biotransformation of Steroids: Accelerating Discovery of New Drugs in the Pharmaceutical Industry

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Abstract: Natural products account for 60% of the total market, making them a major source of drug discovery. Some of these are sourced from the cultivation of microorganisms. Microbial transformation is an example of the application of the cultivation of microorganisms. It is a method of modifying the chemical structure of compounds such as steroids by microorganisms. The diversity of the possible reaction types in microbial transformation includes the process of oxidation, hydroxylation, esterification, isomerization, reduction, acetylation, hydrogenation and glycosylation. Therefore, screening of new microbial strains for specific bioconversions is essential for bioprospecting. This chapter reviews a range of previous studies that have used fungi for biotransformation.

Keywords: Drug Discovery, Ethynodiol Diacetate, Finasteride, Fungi, Microbial Transformation, Microorganisms, Medroxyprogesterone, Medrysone, Psychrotolerant Fungus, Steroids.

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INTRODUCTION

Natural products account for 60% of the total market, making them a significant source of drug discovery [1]. Some of these are sourced from the cultivation of microorganisms. This approach started with Fleming's serendipitous discovery of penicillin from the filamentous fungi, *Penicillium notatum* in 1929. His findings have raised the intensive probe of nature as a source of novel bioactive agents. The broad chemical diversity of natural products in addition to a strong correlation to biological functionality is the justification for the necessity to constantly nurture natural products in today's discovery efforts [2].

Natural products (NPs) including biologicals play a major role as active substances and model molecules for the discovery and validation of drug targets. Natural products have been the source of the majority of FDA-approved agents and significant sources of inspiration for future drug discovery. About 60% of the drugs that have been introduced to the market during the last 25 years are derived directly or indirectly from small biogenic molecules [3]. The recent development and implementation of new technologies offer unique opportunities for the screening of secondary metabolites, and NPs are likely to be re-established as a major source for drug discovery. In this chapter, we have presented a brief introduction to the biotransformation of steroids and their applications in drug discovery.

Steroids

The steroid is a compound with four-membered hydrocarbon core, where all steroids are derivatives of this core. The oxidation state of the rings apart from the number, type, regio/stereo position of the functional groups attached to the core affects the physiological activity of steroids [4]. The idea is consistent with the past review [5] on the activity after modifications of the parent compounds: introduction of a double bond at C-14/C-15 and the addition of 7α-methyl group to testosterone have increased the activity of the product by 100 times. The addition of the 6β-methyl group to 5α-dihydrotestosterone (5α-DHT) resulted in a product with higher anabolic activity than testosterone.

FUNGI

Fungi are known as eukaryotic microorganisms due to having a distinct nucleus or other membrane-bound organelles. They are entirely different from bacteria, which are prokaryotes of nature. Fungi obtain their nutrients from the degradation of organic compounds (heterotrophic nature where they are not able to make their food), and acquiring energy *via* this method is termed chemoorganotrophs.

Climates, geographical location, substrate type and microhabitat are among the factors that affect the distribution of fungi globally [6]. These results in a broad range of their physiologies and metabolic assortments. Therefore, bioprospection of other less established settings such as the Antarctic continent offers a unique source of microorganisms and their metabolites, presenting a vast capacity for biotechnological applications [7].

MICROBIAL TRANSFORMATION

One of the most studied whole-cell systems for microbial natural product isolation and also for biotransformation are systems in fungi [8]. That being said, the most active ingredients in the medicine are inspired by the natural products and findings of this study would help improve current understanding in developing bioactive metabolites, providing the basis for more potent drugs *via* microbial transformation.

Microbial biotransformations are also described as unique and inexpensive resources of bioactive natural products. Microbial transformation involves an array of possible reactions namely oxidation, hydroxylation, esterification, isomerization, reduction, acetylation, hydrogenation and glycosylation [9].

Studies on the subject of microbial transformation of diverse compounds provide a foundation for the roles of fungi in modifying the chemical structure. Libraries of analogue compounds with unique structural modifications can be generated by microbial biotransformation. This is due to the fungal transformation of parent drugs, or starting materials may result in the production of metabolites with structural similarities to the parent drugs. It is also noted that sustainable uses of resources under defined culture conditions are feasible *via* microbial transformation: unconstrained by seasonal fluctuations and pathological restrictions [10 - 12]. These metabolites might be giving various metabolites from a single substrate with enhanced pharmacological, pharmacokinetic, and toxicological properties on top of having comparable biological activities as parent drugs.

CURRENT AND FUTURE TRENDS OF MICROBIAL TRANSFORMATION OF STEROIDS IN INDUSTRIAL APPLICATIONS

Isolation and screening of new microbial strains which can carry out specific bioconversions is an essential area of research and development. Genetically engineered microorganisms have a diversity of adapted or non-native enzymes which can be used for the manufacturing of novel steroidal metabolites. A successful example of an industrial application of this technology is by utilizing recombinant *Escherichia coli* method in the hydroxylation process to convert

CHAPTER 5

Biological Significance of Steroids

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Abstract: Steroids display varied biological functions and play a crucial role in the fascinating fields of biology, chemistry, and medicine.Steroids encompass wide-ranging natural products which are abundantly encountered in eukaryotic organisms. These exhibit a pivotal role in regulating the cellular functions of animals, plants, and fungi. Furthermore, they act as chemical messengers in the human body and get secreted in the systemic circulation and extracellular fluids, where they regulate metabolic, immune, and reproductive functions. Steroids are the fundamental components of cell membranes and serve primarily as signalling molecules. This chapter gives a comprehensive overview of physiologically active steroids in various organisms.The biological activities of various steroid classes have been discussed in detail. Glucocorticoids are a class of steroid hormones that regulate the metabolic processes involving the formation of glucose from amino acids and fatty acid deposition of glycogen in the liver. Another important group of hormones, called mineralocorticoids, helps in balancing water and electrolyte content in the body and primarily affects the kidney. The principal class of steroids *viz*. the sex hormones are essentially crucial for the development and maintenance of reproductive function and cause stimulation of secondary sexual characteristics in humans. To summarize, steroids stabilize and regulate the structure and functions of cellular membranes and play a crucial role in regulating growth and development.

Keywords: Steroids, Natural products, Hormones, Sterols, Therapeutic steroids.

INTRODUCTION

Steroids are biologically active organic compounds consisting of four rings arranged in a particular pattern generating specific molecular configurations. Steroids carry out two principal biological functions, *i.e*., alter cell membrane fluidity because of being an important constituent of the cell membrane and act as signalling molecules. A number of steroids present in plants, animals, and fungi

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are manufactured in the cells from sterols-lanosterols in opisthokonts and cycloartenol in plants. In early 1935, steroids were isolated and identified from the adrenal gland and were supposed to be used only for treating Addison's disorder but later these were used in a broad range of treatments for various ailments and also as supplements [1]. One must say that steroids are a large group of molecules exhibiting several biological functions and physical characteristics. Steroids are present naturally in numerous dietary products, produced from plants, animals, and microorganisms as their secondary metabolites [2]. Steroids display diverse clinical applications like potent anti-inflammatory and immune-modulating actions but at the same time produce side effects ranging from minor acne to significant problems like Cushing syndrome. Over dosage of steroids or a longer intake sometimes results in diabetes mellitus and potentially life-threatening heart disease if untreated [3].

Steroids are secondary plant metabolites which are distributed in various classes like cardiac aglycones, steroidal alkaloids, and alkylamines, each limited to specific plant families. However, it is also studied that almost every plant has a particular type of steroid that is important for the cell constitution [4].

Steroids are categorized as lipids due to their hydrophobic property, *i.e*., being non-polar and thus insoluble in water.Still, they are structurally not similar to lipids as they consist of four fused rings unlike most of the common lipids. The most common example of steroids is cholesterol, a precursor of Vitamin D, testosterone, progesterone, aldosterone, cortisol, and bile salts. Steroids are also present in the brain. They alter the electrical action of nerve cells by toning down the receptors that help communicate messages from neurotransmitters and are often used as anaesthetic drugs during surgery [5]. As steroids originate from two different cyclic precursor processes, it was found in some studies that a small amount of cholesterol is obtained from plant sources as well [6].

Presently, steroids are widely used as drugs for anaesthesia, muscle building, contraception, *etc*. The steroid derivatives like corticosteroids and their synthetic analogs, *i.e*., glucocorticoids and mineralocorticoids, help in metabolic and electrolyte-regulation. There are side effects associated with the use of steroids which depend upon the dose taken, dose duration and route of administration [7 - 9]. Steroids have beneficial biological actions if used in the right manner as per prescription. They are present naturally in plants, fungi, deposits of karst, microorganism, and marine invertebrates. A diverse range of steroids areobtained from all these sources. Mono, di, and tri aromatic steroids are highly effective in biological functions particularly depicting anti-tumour, anti-inflammatory, and neuroprotective action that can treat up to 78-92% of these disorders [4].

In this chapter, we summarize the biological uses of common categories of steroids (Fig. **1**).

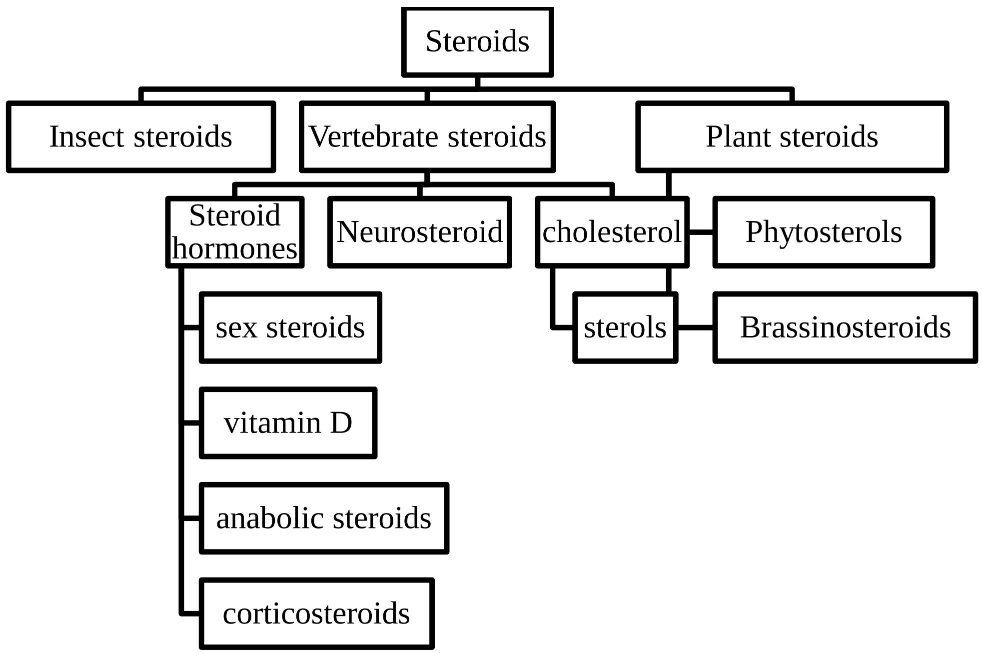

Fig. (1). Common categories of steroids.

Insect Steroids

The insect steroid, also termed as ecdysteroid, is a naturally occurring hormone in the form of 20-hydroxyecdysone in specific plants. Chemically these are polyhydroxy steroids with cis-AB ring junction. Such steroids are produced in a plant named *Cyanotis vaga* for which insects are taken up as feed. These steroids have immense biological potential in muscle growth, fat loss and in lowering the adverse effects related to anabolic steroids [10 - 11]. In numerous studies, these steroids have been shown to exhibit potential immunomodulatory activities [12, 13]. Ecdysteroids are hormones known to control the morphogenesis and development of insects. These hormones are also found in crustaceans and spiders.

Vertebrate Steroids

Steroid Hormones

Steroid hormones display numerous biological actions besides primarily acting as chemical messengers.Steroid hormones are mainly classified as sex steroids, anabolic steroids, corticosteroids and vitamin D (Fig. **2**). All of these steroid types

CHAPTER 6

A Comprehensive Overview of Estrogen: Physiological and Pathological Insights

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Abstract: Estrogens (estrone, estriol, and estradiol) are a class of steroidal hormones produced by developing ovarian follicles. These hormones induce various cyclic events in the uterine endothelium and vaginal epithelium and make the female body competent for conception and ultimately for motherly care. While estrogen is primarily produced by ovaries from cholesterol, the non-reproductive tissues including the brain, liver, and heart also produce a considerable amount of it. Apart from its important role in controlling sexual behavior and reproductive function, estrogen also functions in the regulation of various physiological functions including reproduction, skin physiology, cardiovascular health, skeletal homeostasis, bone integrity, electrolyte balance, cognition, and behavior. These biological functions are regulated by diffusion through the plasma membrane *in vitro* signaling through specific binding to nuclear receptors such as estrogen receptors (ERα and ERβ) or binding to cell membrane receptors such as GPR30 and ER-X. The signaling mechanism can be genomic (change in gene expression) or non-genomic (activation of various signaling cascades). Disruption in estrogen functioning has a pivotal role in the pathogenesis of many diseases such as osteoporosis, insulin resistance, neurodegenerative disease, obesity, and endometriosis. Also, dysregulation in the levels of estrogen has been linked to the development of many cancers such as breast cancer, *etc*. This chapter aims to summarize the complete insight of estrogen by providing a clear understanding of its synthesis, receptor binding, signaling, regulation of physiological functions, and role in various diseases.

Keywords: Breast cancer, Endometriosis, Estradiol, Estrogen, Estrogen receptors, Estrogen signaling, Estrogen synthesis, Lymphangioleiomyomatosis, Prostate cancer, Sex hormones, Steroidal hormones.

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INTRODUCTION

Estrogen is a steroidal class of hormones and is an aggregate term for the number of female hormones such as estrone, estriol, and estradiol. Estrogen is mainly synthesized in ovaries, but other tissues like adipose tissue, cardiac tissue, *etc*. are also able to synthesize a significant amount of estrogen [1]. The term estrogen is derived from the Greek words oistros (frenzy in heat) and gennan (to produce). Estrogen was discovered at the beginning of the 1900s when it was observed that the administration of the ovarian extract (liquor folliculi) obtained from the hogs and cattle in rodents induced the sexual behavior that is "estrous" [1].

Structure of Estrogen

Estrogens are affiliated to the steroidal class of organic compounds with "estrane steroidal nucleus", and this core structure is present in all the estrogens viz, estrone, 17- estradiol, and estriols (Fig. **1**). The core steroidal nucleus comprises 18 carbon atoms ($C_{18}H_24O_2$) and is also called the C-18 steroid and is organized into 4 rings. It consists of an aromatic benzene ring having phenolic hydroxyl moiety positioned at the C3 and one hydroxyl group at C17 in 17β-estradiol, two hydroxyl groups in estriol (C16 & C17), and a ketonic group in estrone at C17. The benzene ring with -OH group at C3 and the availability of oxygen either as a hydroxyl group or as a ketonic group at C17 are crucial for the estrogens to exhibit hormonal activity [1].

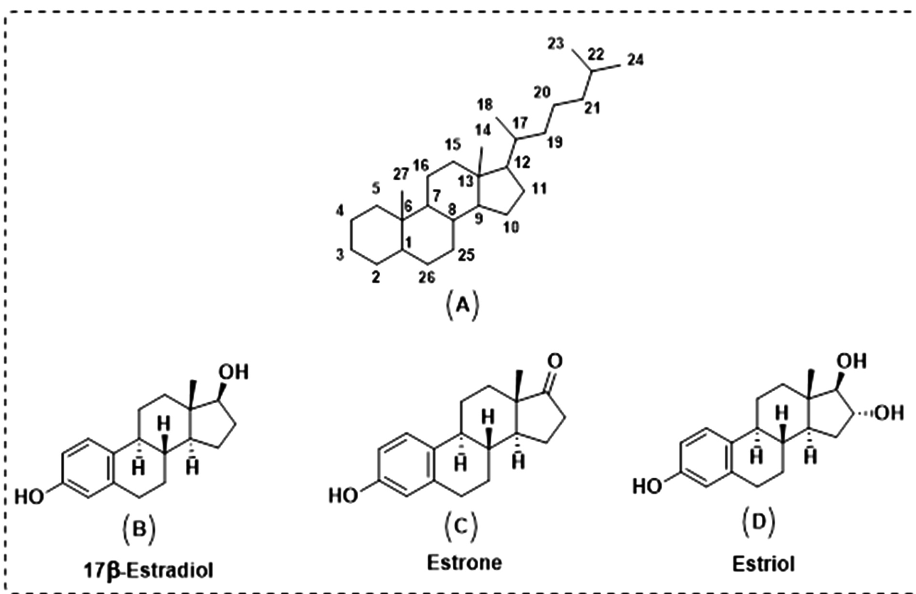

Fig. (1). Structure of estrogen.

Structure of Estrogen Receptors

Estrogen receptors are ligand-activated transcription factors and members of the steroidal hormone family of nuclear receptors [2]. There are three types of estrogen receptors that mediate various functions of estrogen, ERα, Erβ, and GPER1 (Fig. **2**). These receptors are encoded by different genes and showed varied expression levels in tissues [3]. The ERα and Erβ are encoded by genes ESR1 (located on chromosome 9) and ESR2 (located on chromosome 14) respectively. The full-length ERα protein has 595 amino acids and a molecular size of 66 kDa whereas ERβ has 530 amino acids and a size of 60 kDa [3, 4]. Structurally the estrogen receptors are comprised of many structural domains that include A/B, C, D, E/F. The N-terminal region (A/B) plays a role in the activation of transcription genes and facilitates the binding with the target sequence. The B domain is the DNA binding domain and enables the ER receptor dimerization and subsequently facilitates the binding with a specific sequence at the estrogen receptor element. The Hinge region (D region) can bind to chaperone proteins and links the C and E regions. The D domain also has a nuclear location signal, which is exposed following estrogen binding and enables the translocation of receptor-ligand complexes into the nucleus. The E/F region or C terminal or Ligand binding region has a binding sequence for coactivators and corepressors apart from estrogen [1, 4, 5]. Moreover, the activation factors AF-1 and AF-2 present in A/B and E/F region regulate the transcriptional activity of estrogen receptors [1, 4]. Further, the percentage homology shared between two estrogen receptors include A/ B (17%), C domain (97%), D region (36%), and E/F region (56%) [3].

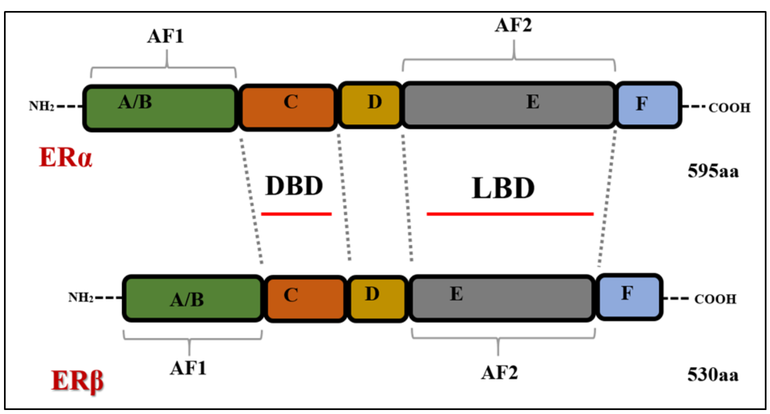

Fig. (2). Structure of estrogen receptors.

The estrogen can also mediate actions through GPER1 receptors. GPER1, a membrane-bound receptor was previously defined as an orphan G protein-coupled receptor 30 (GPR30). It is structurally dissimilar to ERα and Erβ and its gene is

CHAPTER 7

Plant Cardenolides: Multifunctional Medicinal Agents

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Abstract: Cardenolides are a class of compounds steroidal in nature, belonging to the cardiac glycoside group of secondary metabolites. They consist of a sugar part and a non-sugar part consisting of a steroidal cyclopentanoperhydrophenanthrene ring with lactone substitution at the β-17 position. Cardenolides are found in angiosperm plant families like Plantiginaceae, Asclepiadaceae, Apocynaceae, Brassicaceae, Cruciferae, Liliaceae, Moraceae, Ranunculaceae, and Scrophulariaceae. These include some important glycosides, such as digitoxin, digoxin, Ouabain, Calotropin, *etc.* with profound pharmacological potential. Moreover, cardenolides have toxic effects for which these have been used in poison arrows and for self-harm purposes. Traditionally, these were used to treat congestive heart failure. However, recently they have emerged as promising agents to exhibit anticancer, antiviral, anti-inflammatory, neuroprotective, and various other therapeutic roles. Cardenolides like Digoxin and Digitoxin have been used in the treatment of heart failure and atrial fibrillation. Toxicarioside A, and Calotropin have been reported to suppress tumor growth and are used as anticancer agents, Strophalloside and Oubain are reported to be involved in apoptosis. Oleandrin is an antiproliferative agent and can inhibit IL-8 which is responsible for cystic fibrosis.

Keywords: Anticancer, Cardiac Glycosides, Cardenolides, Digitoxin, Neuroprotective.

INTRODUCTION

Plants are chemical factories which synthesize magical compounds with profound medicinal properties. These phytocompounds are considered to be much safer than synthetic compounds for the treatment of various ailments. Alkaloids,

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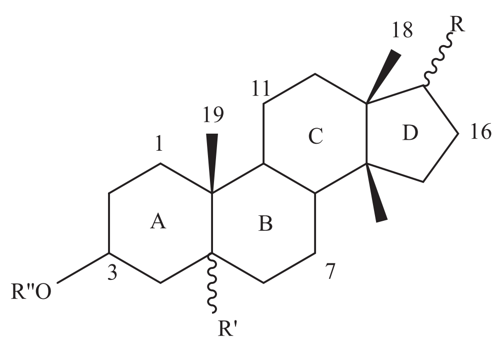
flavonoids, saponins, terpenoids *etc.* are common plant secondary metabolites with intense physiological effects on human bodies. Steroidal glycosides or cardiac glycosides are a special class of secondary metabolites derived from triterpenoids, mainly synthesized for defense purpose in response to biotic stress [1]. Traditionally, they have been used as arrow poisons, abortifacients, and emetics but for more than 200 years, they have been in use for the treatment of heart disorders. Cardiac glycosides possess a positive inotropic effect on heart *via* the dose-dependent inhibition of the Na+/K+-ATPase enzyme [2]. This enzyme is responsible for the movement of Na+ and K+ ions across the cell membrane as well as receives signals for the important cellular events. Thus, they are also known as cardiotonic steroids for use as cardioprotective drugs.

Structurally, they consist of two parts: an aglycone fragment (non-sugar) and a sugar fragment [3, 4]. The aglycone portion, also known as the steroidal or "genin" moiety, has a steroidal skeleton, namely, a cyclopentano-perhydrophenanthrene ring, that has a unique and structurally distinct fused ring system [5 - 7] (Fig. **1**). On the basis of types of sugar fragments and lactone rings, Cardiac Glycosides have been classified as Cardenolides and Bufadienolides [8, 9]. Both the groups of compounds Cardenolides and Bufadienolides share a common structural scaffold but the former possess a five-membered unsaturated butyrolactone ring while the latter Consists of six-membered pyrone ring (Table **1**, Fig. **2**) and are found in the plants of the genus *Urginea* and *Bufonidae* family of toads where these possess defensive role against predators. While Cardenolides produced solely by plants, are a miraculous group of compounds useful in the treatment of various fatal ailments.



R = unsaturated lactone or pyrone ring system
R' = H or OH
R'' = Sugar moiety

Fig. (1). Structure of cardiac glycosides.

From a long time in history, Cardenolides are being used as a remedy for various health issues but there was a lack of systematic scientific study of their medicinal potential. It was found that *Digitalis purpurea* plant extract containing cardenolides could be used for the treatment of dropsy [10]. Later, first pure exogenous cardiotonic steroid which was a cardenolide digitoxin was isolated from it. Various other species of *Digitalis* were extracted and identified and some of them are used in therapeutics of heart failure and atrial fibrillation such as digoxin which was isolated from *Digitalis lanata* in the year 1930. The two most important endogenous cardenolides identified are Ouabain [11 - 13] and Digoxin [14]. There are several cardenolides like oleandrin, oleandrigenin, digitalis, digoxin, digitoxin, calotropin, ouabain, *etc.* used in the treatment of various ailments like heart disorder, cancer, neurodegenerative disorders, and viral infections and as a HIV therapeutic. This chapter presents a comprehensive account of the latest studies on the occurrence, properties, toxicity and various pharmacological potentials of natural plant cardenolides.

Table 1. Showing difference between Cardenolides and Bufadienolides (El-Seedi *et al.* [9]).

Character	Cardenolides	Bufadienolides
Lactone ring substituent	Unsaturated 5-membered butyrolactone ring (but-2-en-4-olide ring)	Unsaturated 6-membered pyrone ring (penta-2,4-dien-5- olide ring)
Common occurrence	Generally found in plants	Mostly obtained from animal sources and few plants
Carbon number	C_{23} steroid	C_{24} steroid

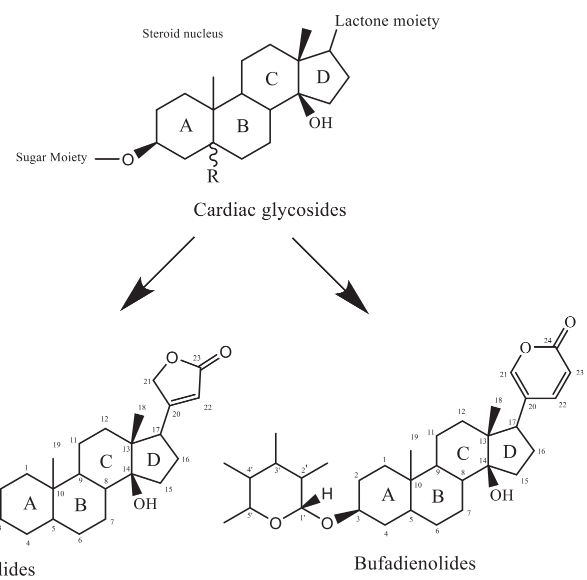


Fig. (2). Structure differences in types of cardiac glycosides (Redrawn from El-Seedi *et al.* [9]).

CHAPTER 8

Immunological Significance of Steroids and Implications for Immune Related Diseases

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Abstract: This book chapter compiles a general idea of steroids and their overall biological significance in immunity and immune-associated diseases. Steroids chemically comprise a group of cyclical organic compounds constituted by seventeen carbon atoms that consist of four fused rings called sterane, and cyclopentanoperhydrophenanthrene. The four-ringed structures are mainly synthesized by mitochondria and smooth endoplasmic reticulum through the cyclization of thirty-carbon chain squalene into lanosterol or cycloartenol. Steroid hormones differ only in number of oxygen and carbon atoms, but all are derived from cholesterol. The biological significance of steroids and their derivatives range from energy metabolism, and body growth to the control of reproductive activities. However, deficiency or malfunctioning of steroids can lead to direct effects on body salt/sugar levels, sexual differentiation and immunity. As far as immune responses are concerned, a lot of research works have emerged which show the importance of steroids in immune regulation, and in extreme cases, they are also known to result in immune-related diseases. Most of these effects are mediated by the influence of steroids on gene expression in cells and this could in turn prove to be novel drug targets as well. We have made an attempt in this chapter to update and highlight the role of steroids in immune regulation and immune-related diseases, which we hope would open up therapeutic options for diseases.

Keywords: Steroids, Immune System, Macrophages, Cytokines, inflammation.

INTRODUCTION

The immune system is a major defence system which is crucial for defending the host body from invading pathogenic organisms. It provides a flexible and dyna-

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mic response against a wide range of antigens. Immune system exceedingly exhibits activities like recognition and response towards antigens and it is mainly divided into two main categories like innate and adaptive immune system greatly based on the speed and specificity of the immune reactions produced [1]. Innate immunity or non-adaptive immune system includes the first line barriers which help in eliminating the pathogens entering the body by instant response with the help of natural killer cells but it lacks specificity and memory towards antigens, whereas the adaptive immune system is specific and protects the body by producing antigen-specific responses [2].

Cells and molecules produced by adaptive immune system influence various tissues and organs by patrolling throughout the body. Adaptive immune system discriminates self and nonself-antigens by pattern recognition process to exhibit an immune reaction and it possesses immunological memory upon second exposure to a previously exposed antigen [3]. In adaptive immune system, immune reactions are performed by mobile, active cellular and soluble elements produced by the immune system with the help of T and B lymphocytes as well as T cell subsets like T helper (Th1 and Th2) cells [4, 5]. These lymphocytes produce immunoglobulins or antibody molecules which are lytic to target cells. Further, the secreted antibody molecules by immune cells possess paratopes and recognize specific patterns called epitopes on antigenic molecules to carry out immunological reactions. Various molecules like protein, enzymes and hormones perform their functions by pattern recognition process [6].

Homo sapiens being the most developed and evolved living beings on earth have a complicated biological system comprising cells, tissues and complex organs. To maintain a homeostatic system, the body undergoes various physiological and immunological functions with the aid of chemical signals or messenger molecules called hormones. Hormones contribute to a vast extent in maintaining the physiological and immunological functions in the body. Organs are being distributed at distant regions in the body and in order to coordinate various functions, hormones come in play and exhibit their role [7]. These hormones are secreted in distinct exocrine and endocrine glands where they exhibit major physiological roles such as growth, development, digestion and reproduction. In addition, immune system is predominantly supported by the neuroendocrine system in protecting the host organism by producing various steroidal hormones based on several stimuli encountered by the organism [8].

Steroids are tremendously incorporated with functions of the immune system and they interact bi-directionally in various processes to maintain homeostasis. Steroid hormones help in physiological functions like growth, differentiation and metabolism that are present in all eukaryotic organisms. Steroids are highly lipophilic cholesterol molecules which are metabolized by bile acids in the liver and serve as the initiator for the synthesis of steroidal hormones [9]. These hormones are further subdivided into progestins, mineralocorticoids, glucocorticoids, androgens, and estrogens based on their function [10, 11]. Glucocorticoid is one of the chief steroids that have an imperative role in immune functions. It has an ability to directly interact with a wide range of transcription factors involved in immune responses. A substantial number of glucocorticoids are produced under the stimulation of the immune system through the neuro-endocrine immune network. Glucocorticoids in broad-spectrum are immunosuppressive in nature and play a key role in ameliorating inflammation as well as autoimmune responses. In addition, they induce apoptosis in immature thymocytes. Endogenous glucocorticoids are intricate modulators of immune functions toward enhancing and inhibiting host immune responses that in turn also influence disease progression along with its susceptibility [12].

Gonadal steroid sex hormones are the prime factors in humans that influence immune functions. Sex hormones like estrogen and testosterone can cause an impact on various immune organs and the immune system directly [13]. The testosterone hormone exhibits anabolic activity along with various immunological functions. It down-regulates immune functions by dampening T-lymphocyte activities and also acts as an immunosuppressive agent. Analogues of testosterone hormone exhibit trivial immune functions when abused [14]. The estrogen hormone in females performs critically complex functions during pregnancy and in reproduction. Estrogen benefits females by exhibiting a strong immune function when compared to males even though estrogen exhibits immunosuppressive effects [15]. This hormone plays a central role in immune functions and in immune-mediated diseases. Autoimmune diseases have prevalence both in males and females, whereas females predominantly exhibit a higher range of humoral and cell-mediated immunity. It has been reported that sex-hormones influence the onset and severity of immune-related diseases by modulating the lymphocytes in all stages of life. Autoimmune diseases like systemic lupus erythematosus (SLE), multiple sclerosis and rheumatoid arthritis have an incorporated relationship with the estrogen hormone. The occurrence of lupus erythematosus and Hashimoto's thyroiditis in female-to-male susceptibility is reported to be 9:1 and 50:1, respectively. It has been reported that sex chromosomes have been a major factor linked to the expression of immune-mediated diseases [16, 17].

In addition to this, recent studies and research have gained limelight on steroidal hormones and their incorporation with immune functions as well as their related diseases. An attempt has been made to focus on the immunological functions of

CHAPTER 9

Heterocyclic Steroids

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Abstract: Steroids are organic compounds with four rings arranged in a precise molecular configuration and are involved in many biological functions displaying a wide spectrum of biological activities and diverse chemical reactivities. Structural modifications of the steroidal rings have attracted a considerable amount of attention recently. Steroids of natural origin have been modified in several ways, particularly in the cyclopentanophenanthrene ring system with heteroatoms such as nitrogen, oxygen, and/or sulfur or with the heterocyclic ring to obtain more active compounds with less or no harmful side effects and are termed as heterosteroids or heterocyclic steroids. Heterocyclic steroids are enticing as the minor modifications to the steroidal molecules, produce remarkable differences in their biological activities. The introduction of the heteroatom in the skeleton of a steroidal molecule often poses challenges to organic chemists, demanding the exploration of new synthetic reactions and new synthetic routes. In this article, the overview of the various synthetic strategies employed to synthesize azasteroids, oxasteroids, thiasteroids, and steroids modified by the introduction of the heterocyclic ring is broadly covered along with its biological significance.

Keywords: Steroids, Heterocyclic Steroids, Azasteroids, Oxasteroids, Thiasteroids.

INTRODUCTION

Steroids are an important class of biologically active compounds known to possess a wide spectrum of biological activities and diverse chemical reactivities. The synthesis of modified steroids is gaining a lot of attention in recent years. Attaching the heterogeneous ring with the steroid molecule significantly improves the biological activity of the overall molecule. The introduction of the heterocyclic ring in the basic structure of the steroidal ring or the replacement of

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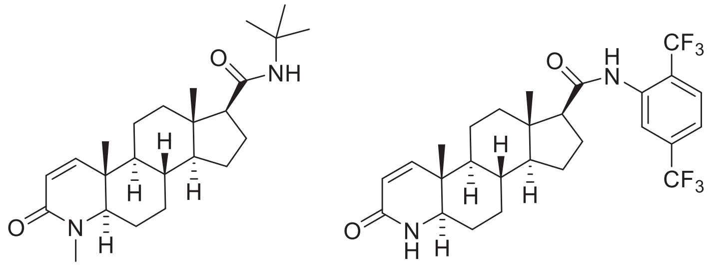
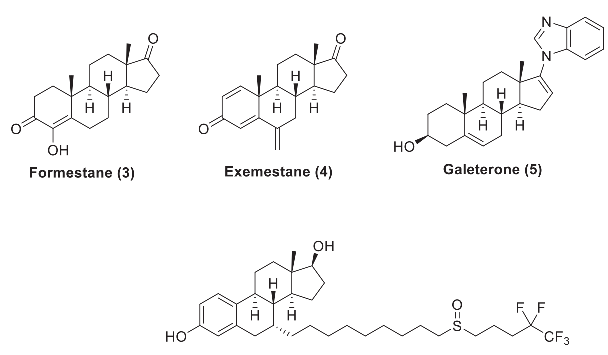
one or more of the carbon atoms with the heteroatoms produces remarkable differences in their biological activities [1]. Azasteroids are obtained by the replacement of one of the carbon atoms by nitrogen atoms in the steroid ring system. Finasteride (**1**) and dutasteride (**2**) are two azasteroids approved for clinical use as 5α-reductase inhibitors (Fig. **1**).



Finasteride (1) **Dutasteride (2)**

Fig. (1). Biologically active azasteroids.

The replacement of one or more of the carbon atoms in the cyclopentanophenanthrene skeleton at any position from 1-17 with oxygen atoms gives oxasteroids. Similarly, thiasteroids are obtained by the replacement of one or more of the carbon atoms in the cyclopentanophenanthrene skeleton at any position from 1-17 with sulfur atoms. However, thiasteroids are less explored compared to azasteroids and oxasteroids. Synthetically prepared steroids such as Formestane (**3**), Exemestane (**4**), Galeterone (**5**), and Fulvestrant (**6**) are effective anticancer agents (Fig. **2**). Formestane and Exemestane showed potent antiproliferative activity and are used for the treatment of breast cancer [2], whereas Galeterone inhibits the androgen signaling and serve as an effective regimen for prostate cancer [3]. Fulvestrant serve as selective estrogen receptor degrader (SERD) and is used to treat the metastatic breast cancer [4].

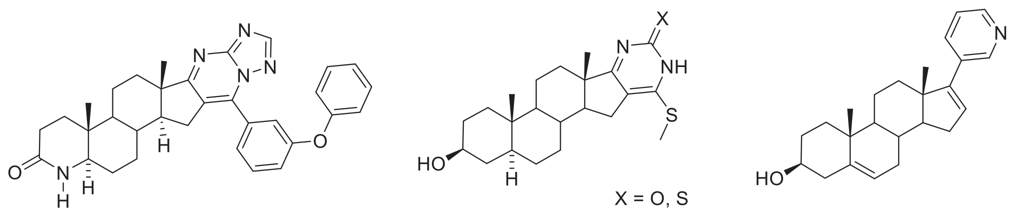


Formestane (3) **Exemestane (4)** **Galeterone (5)**

Fulvestrant (6)

Fig. (2). Synthetically prepared anticancer steroids.

Incorporation of the heterocyclic ring in the skeleton of the steroidal ring causes significant improvement in biological activities. Steroidal ring fused with triazolo-pyrimidine at ring-D (**7**) showed cytotoxic activity [5]. Steroids fused with pyrimidine ring at ring-D (**8**) demonstrated antibacterial activity [6]. Abiraterone (**9**) is used to treat prostate cancer (Fig. **3**) [3].



Cytotoxic (7) Antibactrial (8) Abiraterone (9)

Fig. (3). Biologically active hetersteroids obtained by fusion of an extra heterocyclic ring with steroidal ring skeleton.

Azasteroids

Azasteroids possess a wide range of biological activities and received more attention compared to other structurally modified steroids. Azasteroids are reported to possess anti-atherogenicity, anti-carcinogenicity, antifungal, antilipidemic, local anesthetic, and neuromuscular blocking activities, and are mostly free from harmful side effects [7 - 12]. Based on the position of the heteroatoms in the steroidal skeleton, azasteroids are classified into two main categories, endocyclic and exocyclic azasteroids. Replacement of carbon atom with the nitrogen atom at the positions 1-17 gives endocyclic azasteroids, whereas exocyclic azasteroids are obtained by the replacement of carbons in the side chain or the added rings. The endocyclic azasteroids are further classified based on the position of the heteroatom in the steroidal ring or by the ring (A-D) of the steroidal skeleton, for example, finasteride (**1**) and dutasteride (**2**) are synthetic A-ring-4-azasteroids [13, 14].

Synthetic Approaches

Replacement of carbon atom with the nitrogen atom at position 1 in the cyclopentanophenanthrene skeleton gives 1-azasteroid. Reissig and coworkers reported the synthesis of 1-azasteroid using samarium diiodide (Scheme **1**) [15]. Treatment of precursor **10** with sodium hydride followed by treatment with nonafluorobutanesulfonyl fluoride afforded **11** [16]. Heck reaction of **11** with various homoallylic alcohols (**12**, **13**, and **14**) in the presence of palladium diacetate in DMF gave unsaturated alcohols **15**, **16**, and **17**, in good yield.

CHAPTER 10

Spectroscopic Analysis of Steroids

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Abstract: All the steroids are basically made of seventeen carbon atom skeletons bonded in four fused rings: three six-membered cyclohexane rings and one five-membered cyclopentane ring, they vary from each other by having different functional groups. Recent modifications have added heteroatoms like nitrogen, oxygen, sulphur, selenium, *etc* in the basic structure of naturally occurring steroids. Heterocyclic steroids have always been a field of interest for researchers due to their diverse biological performances. The biological activity of steroids and heterocyclic steroids is based on the structure they possess. Spectroscopy plays a key role in the determination of distinct properties of numerous compounds by their interaction with electromagnetic radiation and the sort of interactions that may occur in different regions. The structure of different steroids and heterocyclic steroids may be established through various spectroscopic techniques viz. Infrared spectroscopy (IR), Nuclear Magnetic Spectroscopy (NMR), Ultraviolet spectroscopy (UV) and mass spectrometry (MS).

Keywords: Absorbance, Beer-Lambert law, Cholesterol, Electromagnetic radiation, Fourier Transform (FT), Fragmentation, Hook's law, hypsochromic effect, Infrared spectroscopy, Larmor precession, Mass spectrometry, McLafferty rearrangement, nuclear spin, Nuclear magnetic resonance spectroscopy, Nuclear overhauser effect, Pascal's triangle, rotational and vibrational energy levels, Steroids, U.V. spectroscopy.

INTRODUCTION

An Insight into Organic Spectroscopy

Molecular spectroscopy deals with the study of the interaction of electromagnetic waves and matter that can give us a lot of information about the matter, depending upon the nature of electromagnetic radiation and sort of their interaction. When a beam of electromagnetic radiation is passed through an organic molecule, some of the radiation is absorbed *i.e.* some of the wavelengths (frequencies) are absorbed

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giving the spectra and the rest is unaffected. The main concern of organic chemists lies in the absorption from three or four regions *viz*. UV visible, infrared, microwave and radiofrequency regions. Apart from this, in mass spectrometry, the molecule is bombarded with high energy electrons (≈ 70 eV or 6000 $KJmol^{-1}$) that cause the molecule first to ionize and then to disperse into the spectrum of fragment ions of different masses (Table **1**).

Table 1. Different regions of the spectrum and information obtained from each region [1].

Region of the Spectrum	Effect on the Molecule (Deduced Information)
UV-visible region $\nu = 3x10^{14} - 3x10^{16}$ Hz $\lambda = 1\ \mu m - 10$ nm	Changes in electronic energy levels within the molecule (detection of π-electron systems, presence of conjugation and unsaturation)
Infrared region $\nu = 3x10^{12} - 3x10^{14}$ Hz $\lambda = 100\ \mu m - 1\ \mu m$	Changes in the vibration and rotational movements of the molecule (detection of functional groups by specific vibrational frequency of each group like C=O, -OH, *etc*)
Microwave region $\nu = 3x10^{10} - 3x10^{12}$ Hz $\lambda = 1$ cm $- 100\ \mu m$	Electron spin resonance or electron paramagnetic resonance ; induces changes in the magnetic properties of unpaired electrons (detection of free radicals and their interaction with electrons)
Radiofrequency region $\nu = 3x10^{6} - 3x10^{10}$ Hz $\lambda = 10$ m $- 1$ cm	Nuclear magnetic resonance; induces changes in the magnetic properties of certain atomic nuclei (hydrogen and carbon atoms in different environments can be detected and counted *etc*)
Electron-beam impact 70 eV or 6000 $KJmol^{-1}$	Ionization and fragmentation of the molecule into a spectrum of fragment ions (determination of relative molar mass and deduction of molecular structures from the fragments produced)

In 1900, Max Planck suggested that the energy of an oscillator is discontinuous and that any change in its energy content can occur only by means of a jump between two different energy states. A molecule in space may have many sorts of energy *i.e.* it may have rotational, vibrational and electronic energy. Many researchers believe that an electron can exist in one of several discrete energy levels and the energy in each level is quantized. In other words, a molecule may exist in a variety of rotational and vibrational energy levels and can jump from one level to another only by absorbing a finite amount of energy. Amount of energy, $\Delta E = E_2 - E_1$, the frequency involved in the transition has the simple form:

$$\nu = \Delta E/h \text{ Hz}$$

i.e. $$\Delta E = h\nu \text{ Joules}$$

where, $$h = 6.63 \times 10^{-34} \text{ joules s molecule}^{-1}$$

Thus, an electronic transition between energy levels in an atom or molecule may absorb or emit radiation of different frequencies to appear as a spectra which is further used for the analysis and identification of different chemical compounds [1, 2]. Modern chemical laboratories are equipped with instruments capable of measuring many physical properties of a chemical compound and mixtures of compounds. Spectroscopy can provide information, about both structure (of a compound) and composition (of mixtures) if interpreted correctly [3]. The main focus of this study was to establish methods of analysis of steroids based on spectroscopic techniques involving infrared spectroscopy (IR), UV-visible spectroscopy (UV-Vis), Nuclear magnetic resonance (NMR), and mass spectrometry (MS).

Steroids: An Introduction

All the steroidal compounds possess a similar tetra-cyclic structure consisting of four fused carbocyclic rings. The unsubstituted carbohydrate scaffold with a total of 17 carbon atoms has been baptized gonane (Fig. **1**). It is a hypothetical structure that forms the chemical class of the steroid molecules (Table **2**). The substituent on the gonane scaffold constitutes the steroid sub-class including cholestane (with 27 Carbon atoms), pregnanes (with 21 Carbon atoms), androstane (with 19 Carbon atoms) and estranes (with 18 Carbon atoms). In parallel to this chemical classification, a nomenclature is also used for the steroids, which is based on the origin of the compound or its main natural source: progestagens, androgens, oestrogens, glucocorticoids and mineralocorticoids. Surprisingly, within these classes, the number of carbon atoms remains unchanged (Fig. **1**).

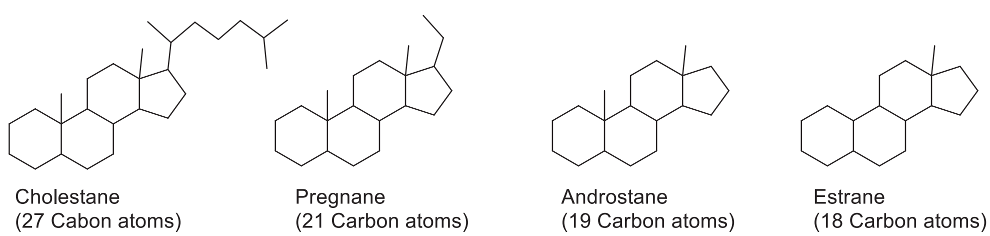

Fig. (1). Sub-classes of Gonane (basic steroid skeleton).

CHAPTER 11

Destructive Effects of Steroidal Drug Abuse and their Immunological Impact

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Abstract: Steroidal drugs are synthetic in nature that are closely identical to naturally produced hormones in our body such as cortisol and testosterone. They are lifesavers for several threatening medical conditions. They are currently in wide use for the treatment of various inflammatory diseases since they are known to involve in suppressing the immune system resulting in a reduced inflammatory process. They are produced in different forms and do not cause any major side effects when consumed at low doses. However, occasionally they lead to perilous side effects when taken in appropriate doses that lead to mental health problems, high blood pressure, diabetes, osteoporosis, *etc.* Practices such as the uptake of illicit anabolic steroids and corticosteroid drugs without an appropriate prescription can potentially lead to fatal side effects. Anabolic steroids are performance and image-enhancing drugs that were once viewed as predicament associated with bodybuilders and have now become a widespread problem throughout our society including children. Dietary supplements which act as steroidal precursors also promote medical consequences that are similar to steroids and the absence of such awareness in our society leads to varied difficulties in our current lifestyle. The increasing concern about possible health hazards in association with abusive steroid drug uptake should be addressed with strict measures. It is important to educate our society about the hazardous effects of steroidal drug abuse and the precautions that need to be carried out while using them. This chapter highlights different types of steroid drugs that are currently in use and the deleterious side effects caused by their abusive use. Potential treatments for their withdrawal and preventive measures will also be addressed in detail.

Keywords: Anabolic steroids, Corticosteroids, Drug abuse, Inflammation, Steroidal drugs.

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INTRODUCTION

Steroidal drugs have been a boon to a wide range of pharmacological uses since their identification in 1935. In the beginning, these adrenal gland isolates were thought to be utilized only for treating Addison's disease [1]. Now, they have been found to play significant clinical roles due to their potential anti-inflammatory as well as immunomodulatory properties. Steroids are four-ringed complex lipophilic molecules that are found in all eukaryotic organisms and mainly involved in various biological functions like the regulation of cells, tissues and organ systems of the body. The presence of cholesterol in the body is the key molecule for steroid synthesis. Metabolized cholesterol in the liver by the bile acids serves as an initiator molecule for steroid hormone synthesis. A steroid remains a structural component of cell membranes and its incorporation therein helps in fluidity and averts the development of crystalline substructures [2]. A highly synchronized biosynthetic enzymatic pathway that particularly operates in specific endocrine organs like adrenal gland, ovary and testis helps in the derivation of steroids [3].

This modified cholesterol form of steroids is called endocrine hormones which play a key role in carrying signaling information in blood stream and provide communication among cells and organs located by large distances. The steroids are further identified and named as hydrophilic or hydrophobic based on their affinity with water molecules. Hydrophilic steroids or hormones are found to act primarily with protein receptors on cell surfaces, whereas, hydrophobic steroids diffuse through cell membranes and trigger certain intracellular hormone receptors [4]. Predominantly, in all multicellular organisms, physiological functions like growth, development, reproduction and systemic homeostasis are maintained by certain recognized endogenous endocrine hormones. The physiological steroid hormones are produced by specific endocrine glands. The major endocrine hormones produced by the adrenal gland, ovary and testis are cortisol or corticosterone, aldosterone, estradiol, progesterone, and testosterone.

Aldosterone synthesized by the adrenal cortex helps in the balance of Na^+ concentration in the body. Low concentration of Na^+ or low blood pressure instigates the release of aldosterone from the kidney and influences Na^+ concentration which in turn indirectly regulates water in cells [5]. Essential sex hormones like progesterone, estrone and estradiol produced in ovaries help in the preparation of uterine endometrium for the implantation of fertilized egg and maintenance of pregnancy [6]. Androgen hormones like testosterone and stanolone produced by the testis in males help in the development of sexual characteristics [7]. Bile acid like cholic acid belongs to other members of the steroid family and they contribute to equally important biological functions like digestion in the intestine.

The physiological functions of these hormones are mainly exhibited by signal transduction and binding process. The transported hormones bind to their active specific site called the receptor site either in the nucleus or cytoplasm to carry out further processes [8]. The binding of hormones to its receptor alters the conformation of the receptor site and leads to its dimerization, which is essential for the association of hormone-responsive for a particular target gene. Thus, all biological processes exhibited by steroids ultimately lie in the molecular recognition of various steroids by specific receptors. Despite their useful functions, they are considered problematic and potentially life-threatening due to their side effects. Therefore, this review emphasizes the recent status of different types of steroidal drug abuse and their immunological perilous side effects. The current trend in their preventive and curative therapies along with some of their future aspects is also highlighted.

STEROIDAL DRUGS AND THEIR CLASSIFICATION

Recent steroidal drug therapies play prominent and varying physiological as well as immunological functions. They are either synthetically produced in laboratories or isolated from natural resources [9]. In general, steroidal drugs can be classified as catabolic and anabolic steroids.

Catabolic Steroids and their Applications

Catabolic steroids comprise corticosteroids which are primary stress hormones secreted by the cortex of the adrenal gland and are responsible for a multitude of physiological functions in the body. Hormones such as glucocorticoids and mineralocorticoids are produced rapidly and released into circulation, which are known for their metabolic and electrolyte regulating activities. The effect of corticosteroids on the body is widespread. They perform functions like alterations in carbohydrates, proteins and lipid metabolism. They aid in maintaining fluid and electrolyte balance as well as contribute to preserving the normal functions of the cardiovascular, immune, kidney, skeletal, endocrine and nervous systems. These hormones are also beneficial to the organisms by endowing the capacity to resist stressful circumstances, noxious stimuli and environmental changes. These corticosteroids are synthetically manufactured and prescribed to patients at a physiological dose as a replacement therapy when endogenous production of corticosteroids is impaired. These corticosteroids are very much effective in dampening inflammation by inhibiting various aspects of the inflammatory process by enhancing or subduing gene transcription. Due to their vast beneficial effects, principal glucocorticoids like cortisol are synthetically produced and

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Dr. Abid Hussain Banday is presently working as an Associate Professor at the Department of Chemistry, ICSC, Srinagar, India. His research interests include medicinal chemistry, cancer biology, cancer immunotherapy, and the design of biologically relevant heterocyclic scaffolds. Dr. Abid has published highly cited research articles, review articles and monographs, book chapters, and books in many reputed international journals and has patented many of his research works. Dr. Abid has been awarded many prestigious fellowships like the Singh-Obama postdoctoral fellowship by The University Grants Commission, India at the Department of Chemistry and Biochemistry, University of Arizona, Tucson, USA. He was awarded the Fulbright Academic and Professional Excellence Award by United States-India Education Foundation (USIEF) at the Department of Chemistry and Biochemistry, Auburn University, Alabama, USA in 2020. Dr. Abid has delivered a number of lectures internationally and has been on the review and editorial panel of many prestigious journals.