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Chapter 1

Discovery, Development, and Regulation of Natural Products

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1. Introduction

Natural products have historically been an extremely productive source for new medicines in all cultures and continue to deliver a great variety of structural templates for drug discovery and development. Although products derived from natural sources may not necessarily represent active ingredients in their final form, the majority of all drugs in the market have their origin in nature [1, 2]. Therefore, the foremost emphasis in this chapter is given to aspects concerning the identification, properties, and development of potential drug candidates from natural products. It is the intention to give a high-level overview of the current status and developments in the field. Many important aspects in the arena of natural therapeutics including natural product sources, discovery, characterization, development and uses have been addressed and covered in depth in excellent recent reviews by extremely competent authors referenced in this contribution.

1.1. Definition of a natural product

The extent to which the term natural product has been characterized is both limited and debatable. Therefore, a common definition that is accepted by all involved disciplines will remain a moving target, but likely will evolve as researchers unveil the vast amount of compounds projected to be discovered in this field [3]. In the simplest of terms, a natural product is a small molecule that is produced by a biological source [3]. As a central theme of exploration bordering chemistry and biology, natural products research focuses on the chemical properties, biosynthesis and biological functions of secondary metabolites [3]. In this context, the task of defining "natural" is more straight forward and encompasses isolation from a native organism, synthesis in a laboratory, biosynthesis *in vitro*, or isolation from a metabolically engineered organism whereby the chemical structure has been determined and the resultant compound is chemically equivalent to the original natural product [3]. Thus, in summary, and for the purposes of this chapter, one can still agree with the refuted definition that a natural product is a pharmacologically or biologically active chemical compound or substance, which is found in nature and produced by a living organism and can even be considered as such if it can be prepared by a totally synthetic approach [4]. Albeit, we realize this definition can be challenged as many biosynthetic enzymes are nonspecific and may result in the production of multiple analogs combined with the fact that identifying the entirety of natural products is in the infant stage [5].

Generally the term "natural product" is regarded as being synonymous with "secondary metabolite" [6]. Secondary metabolites are organic compounds in the correct chiral configuration to exert biological activity, but have no "primary" function directly involved in the normal growth, development or reproduction of an organism [7]. Natural products are usually relatively small molecules with a molecular weight below 3,000 Daltons and exhibit considerable structural diversity [6]. The product categories in which natural compounds can be found as active ingredients include prescription and non-prescription drugs (pharmaceuticals), cosmetic ingredients (cosmeceuticals) and dietary supplements and natural health product ingredients (nutriceuticals) [8].

The respective studies leading to the identification, isolation, and characterization of natural products constitute an important part of the scientific field of pharmacognosy. The American Society of Pharmacognosy defines pharmacognosy as "*the study of natural product molecules (typically secondary metabolites) that are useful for their medicinal, ecological, gustatory, or other functional properties. The natural species that are the source of the compounds under study span all biological kingdoms, most notably marine invertebrates, plants, fungi, and bacteria*" [9]. Amongst the various assortments and exciting capacities that are being explored within the arena of pharmacognosy, this chapter will mostly address the study of health relevant medicinal properties of natural compounds for drug discovery and development.

1.2. History

Natural substances have evolved over a very long selection process to form optimal interactions with biological macromolecules [10] which have activity on a biological system that is relevant to the target disease. They have historically been the most productive source of active compounds and chemical lead structures for the discovery and development of new medicines [11]. Since ancient times, civilizations used plants and plant extracts to ameliorate diseases and foster healing. Early historic examples for medical treatments from natural sources include the discovery of the beneficial effects of *cardiotonic digitalis* extracts from foxglove for treating some manifestations of heart disease in the 18th century, the use of the bark of the willow and cinchona trees in treating fever and the effectiveness of poppy extracts in the treatment of

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dysenteries [12]. Morphine, largely reproducing the analgesic and sedative effect of opium, was isolated from opium obtained from the seed pots of the poppy plant in 1804 [12]. Throughout the century, purified bioactive natural products were extracted from the Peruvian bark cinchoa (quinine), from cocoa (cocaine), and from many other plants [12]. By 1829, scientists discovered that the compound salicin, in willow trees, was responsible for pain relief and in 1838 salicylic acid was isolated [13]. The problem was that salicylic acid was harsh on the stomach and in the second half of the 19th century acetylsalicylic acid was synthesized which served as a less-irritating replacement for standard common salicylate medicines [13]. A number of additional plants served as sources of natural product derived agents that are still used in current routine medical practice [14].

The discovery of valuable therapeutic agents from natural sources continued into the 20th century. Inspired by the discovery and benefits of penicillin, pharmaceutical research expanded after the Second World War into intensive screening of microorganisms for new antibiotics [12]. The study of new bacterial and fungal strains resulted in the expansion of the antibacterial arsenal with additional agents such as cephalosporins, tetracyclines, aminoglycosides, rifamycins, chloramphenicol, and lipopeptides [15, 16]. In the 1950's, two nucleosides isolated from Caribbean marine sponges paved the way for the synthesis of vidarabine, and the related compound cytarabine, which eventually received approval as therapeutics for clinical use in viral diseases and cancer, respectively [17]. A more recent example is the cancer therapeutic paclitaxel (Taxol®) derived from the Yew tree, which was discovered in the 1970s, but due to difficulties in obtaining commercial compound quantities only reached the market in late 1992 [18-20]. Overall, only 244 prototypic chemical structures (over 80% came from animal, plant, microbial or mineral origin) have been used as templates to produce medicines up to 1995, and relatively few new scaffolds have appeared since [21,22]. About half of the marketed agents in today's arsenal of drugs are derived from biological sources with the large majority being based on terrestrial natural product scaffolds [23]. Approximately 50% of the new drugs introduced since 1994 were either natural products or derivatives thereof [21, 23, 24].

2. Discovery and development

2.1. Discovery

Drug discovery involves the identification of new chemical entities (NCEs) of potential therapeutic value, which can be obtained through isolation from natural sources, through chemical synthesis or a combination of both. The field of natural products drug discovery, despite the success stories of penicillin, paclitaxel, etc., also had aspects that made it less attractive. In the traditional approach, drug targets were exposed to crude extracts, and in case of evidence of pharmacological activity the extract was fractionated and the active compound isolated and identified. This method was slow, labor intensive, inefficient, and provided no guarantee that a lead from the screening process would be chemically workable or even patentable [25, 26]. As natural products usually are molecules with more complex structures, it was more difficult to extract, purify or synthesize sufficient quantities of a NCE of interest for discovery and development activities [25]. Enriched or pure material is needed for the initial characterization of the chemical and biological properties as well as the elucidation of structure-activity relationships in drug discovery studies; furthermore, even larger quantities need to be supplied for potential later development activities and ultimately, the market [24, 27].

The pharmaceutical industry's interest in natural products diminished with the advent of such promising new technologies like combinatorial chemistry (CC) and high throughput screening (HTS) [28]. The prospect of such disciplines, aimed at accelerating drug discovery efforts for NCEs, led some companies to dismiss their natural product programs [28]. Combinatorial chemistry employs parallel synthesis techniques allowing the creation of libraries containing hundreds of thousands of compounds, whereas HTS allows rapid testing of large numbers of compounds [28]. High-throughput screening grew out of automated clinical analyzer technologies and miniaturization in the late 1980's, as drug companies focused on methods aiming to increase the pace of testing and lower the cost per sample [12]. As a result, large libraries of synthetic molecules could be exploited very quickly. These new synthetic libraries were also given preference because of the lack of compatibility of traditional natural product extract libraries with HTS assays [28-30]. Compounds obtained from commercial libraries, in-house collections of pharmaceutical companies containing hundreds of thousands of compounds and new libraries generated through CC could be now screened rapidly [21]. Although the initial hopes for such advances were high, they were not fulfilled by either of the improved technologies. To be successful, HTS needed appropriate therapeutic targets matched to collections of NCEs that are highly diverse in their structural and physicochemical properties. The approach to exclusively bank on synthetic compounds did not meet the initial expectations, as the newly created compound libraries had limited structural diversity and did not provide enough quality hits to be of value. For CC, the most valuable role of parallel synthesis therefore appears to be in expanding on an existing lead, rather than creating new screening libraries [12]. Consequently, the interest in natural sources experienced some renaissance; however, even if natural product extracts were tested first, the pace of their isolation made it difficult to keep up with the demand for testing candidates in high-throughput models [25, 26, 29]. Therefore, natural products, and derivatives thereof, are still under-represented in the typical screening decks of the pharmaceutical and biopharmaceutical industry [31]. Specifically, it has been noted that major pharmaceutical companies in the United States continue to favor approaches that do not enable the integration of natural products of marine origin into their screening libraries [32]. More risk friendly institutions like academic laboratories, research institutes and small biotech companies venturing in the natural products arena have now a greater role in drug discovery and feed candidates into the development pipelines of big pharmaceutical companies[32].

Overall, there are limited systematic approaches to exploring traditionally used natural products for compounds that could serve as drug leads. Additionally, the pharmaceutical industry has decreased their emphasis on natural product discovery from sources in various countries. Both of these facts may be based on possible uncertainties and concerns over expectations about benefits sharing resulting from the United Nations Convention on Biological Diversity (CBD) [21, 33, 34]. Countries are increasingly protective of their natural assets in flora and fauna and may not authorize the collection of sample species without prior approval [35]. In this context, potential handicaps may arise for companies as they develop and market new products from natural sources in the form of very difficult to negotiate agreements as well as significant intellectual property and royalty issues [25, 26, 28, 35].

Nonetheless, natural products continue to provide a valuable and rich pool for the discovery of templates and drug candidates and are suitable for further optimization by synthetic means because the chemical novelty associated with natural products is higher than that of structures from any other source [10]. This fact is of particular importance when seeking out lead molecules against newly discovered targets where no small molecule lead exists or in mechanistic and pathway studies when searching for chemical probes [24]. It is assumed that. in many cases, structures devised by nature and evolution are far superior to even the best synthetic moieties in terms of diversity, specificity, binding efficiency, and propensity to interact with biological targets [24]. In comparing a large number of natural products to compounds from CC and synthetic drugs derived from natural substances, it has become evident that drugs and products obtained from natural sources exhibited more diverse and chemically complex structures [36]. In fact, only a moderate structural overlap was found when comparing natural product scaffolds to drug collections with the natural product database containing a significantly larger number of scaffolds and exhibiting higher structural novelty [37]. The structural diversity of these naturally sourced compounds supports the belief that the assortment of natural products represents a greater variety and better exemplifies the 'chemical space' of drug-like scaffolds than those of synthetic origin [30, 38, 39]. As Newman and Cragg (2012) have stated, and demonstrated in their reviews for the 30-year period of 1981 to 2010, natural products do play a dominant role in the discovery of lead structures for the development of drugs for the treatment of human diseases [1]. We agree with these authors in their assumption that it is highly probable that in the near future totally synthetic variations of even complex natural products will be part of the arsenal of physicians [1].

In general, there is growing awareness of the limited structural diversity in existing compound collections. The historic focus of the pharmaceutical industry on a relatively small set of 'druggable' targets has resulted in the exploration of a very narrow chemical space appropriate for these targets [40]. The 207 human targets described for small-molecule drugs correspond to only about 1% of the human genome and half of all drugs target only four protein classes [41]. So called 'undruggable' targets, such as protein-protein interactions and phosphatases, still await the identification of lead structures with the required qualities for lead or development candidates [40]. Although the expectations in natural products for the future are still high, an analysis of the distinct biological network between the targets of natural products and disease genes revealed that natural products, as a group, may still not contain enough versatility to yield suitable treatments for all heritable human diseases [42]. Nevertheless, the importance of natural product related compound collections, as the most promising avenue to explore new bioactive chemical space for drug discovery, continues to be emphasized; consequently, efforts have been made over the last decade to generate CC libraries inspired by natural product scaffolds [31, 43, 44]. Those scaffolds, which have presumably undergone evolutionary selection over time, might possess favorable properties in terms of bioactivity and selectivity and therefore provide biologically validated valuable starting points for the design and generation of new combinatorial libraries [25, 26, 45, 46]. Thomas and Johannes state that the production of relatively small natural product like libraries have revealed biologically active compounds, while modification of natural products identified activity that is entirely unrelated to the parent molecules [31].

Libraries of small molecules of natural origin have already served as templates for the majority of approved therapeutics including important compounds for the treatment of life-threatening conditions. Moreover, these small molecule libraries are constantly growing through products extracted from various natural sources. Harvey *et al.* reviewed the current approaches for expansion of natural product based compound libraries and CBD compliant collections exist at the U.S. National Cancer Institute, academic institutions and commercial companies [11]. However, large collections of pure natural products are rare and the quantities of individual compounds that are isolated are typically small. A more recent strategy has been to use natural product scaffolds as templates for creating libraries of semi-synthetic and synthetic analogues [21, 28, 47]. Rosen *et al.* identified several hundred unique natural products which could serve as starting points in the search for novel leads with particular properties [48]. Based on the continuous efforts of researchers in the field of marine drug discovery, more potent bioactive lead structures are expected with new or unknown mechanisms of action [23, 48]. The progress made in the areas of cellular biology, genomics, and molecular mechanisms increased the number of druggable targets, allowing screening for candidates of natural compound libraries against an ever increasing number of potential molecular sites for therapeutic intervention. This increase in defined molecular targets combined with more automatization, more sensitive detection instruments, and faster data processing allows for high throughput assays, which can rapidly screen large existing libraries of new and specific biological targets.

In the last decade there has also been a major shift to technologically advanced and more complex screening assays conducted in cells, including those in which biological function is directly measured. These more complex approaches provide higher stringency which can mean lower hit rates. However, the specificity of such hits results in an increase in the quality of leads with more desired biological properties [12]. In this context, bioassays based on zebrafish embryos are noteworthy, as they can be used in 96-well plates and allow for *in vivo* bioactivity screening of crude extracts and natural substances at the microgram scale [49-52]. A further improvement, potentially leading to new secondary metabolites of interest for drug discovery, is based on the development of refined analytical and spectroscopic methods. This involves rapid identification and structural elucidation (dereplication) of natural products in complex mixtures (such as crude or pre-fractionated extracts) in parallel with profiling their bioactivity in information-rich bioassays [53]. In addition, stress can be applied to stimulate the number and levels of bioactive compounds in organisms. Wolfender and Queiroz presented examples of dynamic responses resulting from stress, which induced chemical defenses in elicitation experiments in both plants and microorganisms [30]. A significantly increased number of hits, including antibacterial, antifungal and anticancer agents were described for extracts from elicited plants [30]. New groups of microorganisms obtained through small scale, high-through-put cultivation methods and employing nutrient deficient media, specific nutrients and long cultivation times constitute another approach potentially leading to new secondary metabolites of interest for drug discovery [54]. Genome mining, the analyses of plant and microbial genome sequences for genes and gene clusters encoding proteins, is a further recent approach which has allowed the discovery of numerous novel natural products and also revealed gene clusters and novel pathways for the biosynthesis of several known natural compounds [55, 56].

Although plants are still the major source for many natural products and remedies, microbes and marine organisms also constitute promising, abundant, and valuable sources for bioactive natural compounds [57]. Like it is true for plants, also for these, only a very small fraction of structures of potential therapeutic relevance have been chemically analyzed or examined in a broad panel of screening models or bioassays. But even if discovered and identified, active substances from natural sources may not be readily available for further investigations, development or introduction to the market. A number of biologically relevant natural products can only be isolated in small amounts, consequently adding to efforts, timelines and costs by forcing the development of an economically viable synthesis [31].

2.2. Development

The time required to develop a pharmaceutical can range from only a few to as many as 20 years. For natural products, an additional challenge can be the provision of sufficient quantities from natural sources for development and consequently commercial market supplies. Early *in vitro* tests may only require microgram to milligram amounts but the demand for compound quantities will increase quickly when *in vivo* animal models, safety and toxicology studies, formulation development and ultimately clinical trials are initiated. As mentioned earlier, one of the more recent respective examples is the cancer drug paclitaxel (Taxol®), which was discovered in 1967 as the cytotoxic active ingredient in extracts of *Taxus brevifolia* but only approved for the market in 1992 [20]. From 1967 to 1993, almost all paclitaxel produced was derived from bark from the Pacific yew tree [18]. Harvesting of the bark kills the tree in the process, however, this production method was replaced by a more sustainable approach using a precursor of Taxol® isolated from the leaves and needles of cultivated yew tree species [18, 20].

The compounds in development today target a variety of indications, mainly cancer and infectious diseases (bacterial, viral, fungal, and parasitic), but also address other therapeutic areas such as cardiovascular diseases, neurological illnesses and depression, metabolic diseases (like diabetes and cholesterol management), and inflammatory diseases (like arthritis) [1, 15, 16, 25, 26]. The cytotoxic properties of many secondary metabolites from marine organisms and bacteria are of particular interest for the development of new anticancer treatments [58]. For infectious diseases, natural products are effective because most of these compounds evolved from microbial warfare and show activity against other microorganisms at low concentrations [25, 26, 29]. The renewed interest in natural drugs is determined by the urgent need to find and develop effective means to fight infections caused by viruses, like HIV (Human Immunodeficiency Virus) and so called “superbugs” (bacteria with multiple resistance against antibiotics) currently in use [29]. Pathogens having only limited and rather expensive treatment options include penicillin-resistant *Streptococcus pneumonia*, methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant *Enterococcus* (VRE), *Clostridium difficile*, and *Mycobacterium tuberculosis* [29]. However, some new structures identified from marine fungi exhibited activity against bacteria like MRSA [59].

Before the advent of high throughput screening and the post-genomic era, more than 80% of drug substances or active ingredients were natural products, semisynthetic analogs thereof, or were obtained using structures of natural compounds as templates for synthetic modification [60, 61]. Chin reported 23 drugs from natural sources being approved between 2000 and 2005 [2]. Between 1998 and 2007 a total of 34 natural products and natural product-derived drugs were approved in different international markets [15, 62, 63].

According to Brahmachari (2011), 38 natural product-derived drugs were approved in the decade from 2000 to 2010 for various indications including 15 for infectious diseases, 7 each for oncology, neurological diseases and cardiovascular disorders, 4 for metabolic disorders and 1 for diabetes [22]. It is therefore not surprising that by 2008 more than a hundred new drug candidates from natural sources like plants, bacteria, fungi and animals or those obtained semi-synthetically were reported to be in clinical development with a similar number in preclinical development [60]. Of those in clinical development, 91 were described to be plant-derived [63]. Although this was a lower number than in the years before, the interest in natural sources to obtain pharmacologically active compounds has recently been rekindled with improved access to a broader base of sources including those from new microbial and marine origins [23, 64]. Brahmachari (2011) reported 49 plant-derived, 54 microorganism-derived, 14 marine organism derived (including 2 from fish and 1 from a cone snail), and 1 terrestrial animal-derived (bovine neutrophils) drug candidate(s) in various phases of clinical evaluation [22].

Natural products have been the biggest single source of anti-cancer drugs as evidenced by the historical data reviewed by Newman and Cragg [1]. Of the 175 anti-cancer agents developed and approved over the seven decades from 1940 until 2010 in Western countries and Japan, 85 compounds representing 48.6%, were natural products or directly derived from natural products [1]. The four major structural classes of plant derived cancer treatments include Vinca alkaloids, Epipodophyllotoxin lignans, Taxane diterpenoids and Camptotectin quinolone alkaloid derivatives. Approximately 30 plant derived anti-cancer compounds have been reported to be clinically active against various types of tumors and are currently used in clinical trials [65].

A potential development candidate is typically isolated from its natural source only in milligram quantities [6]. Testing *in vitro* occurs in assays such as the U.S National Cancer Institute 60-cell-line panel, followed by human tumor-derived cell lines in primary culture and *in vivo* animal models such as the above mentioned zebrafish embryos, the hollow-fiber human tumor cell assay or human tumor xenografts in rodents [6, 50, 52, 66]. Harvey and Cree have recently reviewed current screening systems for anti-cancer activity suitable for use with collections of natural products. These include quantification of cell growth or cell death in standard cancer cell, three-dimensional and primary cell culture, as well as cell-based reporter and molecular assays [50]. The quantification of cell growth or cell death in culture using signals like caspase-3 as a marker for apoptosis come with the handicap that the artificial culture environment may not be suitable to predict activity in *in vivo* animal models or cancer patients [50]. Another concern raised is the fact that compounds which kill readily proliferating cancer cells in culture may not eliminate the tumor because of the persistence of cancer stem cells for which suitable screening assays with significant throughput are still lacking [50]. Cancer stem cells are only present in low abundance and remain in a quiescent state until receiving environmental cues such as overexpression of growth factors, cytokines, or chemokines resulting in recurrence of cancer after initially successful treatment and loss of efficacy of the initial treatment agent in the relapsed disease [67].

Dietary sources of compounds assumed to have anti-cancer benefits include fruits, vegetables and spices yielding biologically active components such as curcumin, resveratrol, cucurbitacins, isoflavones, saponins, phytosterols, lycopene, and many others [68]. A number of these are gaining importance as adjuvant anti-cancer agents with curcumin, resveratrol and cucurbitacins having activity reported against cancer stem cells [67]. Bhanot *et al* list 39 natural compounds from marine species, mostly invertebrates, and 10 from microorganisms, mostly from bacteria of the *Streptomyces* genus, as potential new anti-cancer agents [68]. It is assumed that many prokaryotic and eukaryotic natural product sources may still reveal a number of valuable anti-cancer compounds in the future and even ancient animal species have been suggested as a particularly valuable source [69].

Anti-virals constitute another important class of needed therapeutics. The HIV type-1 (HIV-1) is the cause of the Acquired Immune Deficiency Syndrome (AIDS), a major human viral disease with over 34 million people infected worldwide in 2012 and approximately 1.7 million dying per year [70]. Failure of anti-HIV therapy is observed due to the emergence of drug resistance and the significant side effect profile of existing therapies [71]. Hence, the quest for novel prospective drug candidates with fewer side effects and increased efficacy against various HIV strains also relies on natural products. Naturally derived anti-HIV compounds found to be most promising for the treatment HIV infections, with the potential to overcome drug-resistance of mutated HIV strains, were described to be flavonoids, coumarins, terpenoids, tannins, alkaloids, polyphenols, polysaccharides or proteins [72, 73]. Despite the need for affordable, effective, and better tolerated treatments, the vast majority of the potential natural anti-HIV compounds described have so far only been tested as *in vitro*, *ex vivo* or *in silico* approaches to identify activity; the findings have not yet been confirmed in relevant *in vivo* systems. Only a few of the many natural products that have been reported to exhibit anti-HIV activities have reached clinical trials and none of them made it on the list of conventional antiretroviral drugs [71, 72].

Antiviral agents from marine sources which demonstrated activity against HIV were recently reviewed by Vo and Kim (2010). These include phlorotannins from brown algae, sulfated derivatives of chitin from the shells of crabs and shrimps including chitosan (produced commercially by deacetylation of chitin), sulfated polysaccharides from marine algae, lectins or carbohydrate-binding proteins from a variety of different species (ranging from prokaryotes to corals, algae, fungi, plants, invertebrates and vertebrates) as well as bioactive peptides isolated by enzymatic hydrolysis of marine organisms [73]. Until now, most of the anti-HIV activities of these marine-derived inhibitors were also only observed in *in vitro* assays or in mouse model systems and still await confirmation of their value in clinical trials [73].

3. Natural product sources

Historically, the most important sources for biologically active natural products have been terrestrial plants and microorganisms such as fungi and bacteria. Terrestrial and aquatic species of plants and microorganisms, especially those of marine origin, produce unique bioactive substances yielding a large variety of valuable therapeutics and lead structures for potential new drugs. Even though natural products may not have coevolved with human proteins, they have emerged in nature to interact with biomolecules [74]. Natural products interact with a wide variety of proteins and other biological targets, acting also as modulators of cellular processes when they inhibit the difficult to target protein-protein interactions [27, 40].

Since the middle of the last century, marine species and microorganisms have consistently and increasingly raised interest as sources for new agents and scaffolds [75]. In recent years, other less conventional sources like alcoholic and non-alcoholic beverages, spices, animal and human excreta, and many more have generated interest for natural product researchers [75]. The more conventional sources for secondary metabolites like plants, marine organisms and microorganisms will be described in more detail in the following sections.

3.1. Plants

A significant number of drugs have been derived from plants that were traditionally employed in ethnomedicine or ethnobotany (the use of plants by humans as medicine as in Ayurvedic or Traditional Chinese Medicine), while others were discovered initially (through random screening of plant extracts in animals) or later, by determining their *in vitro* activity against HIV or cancer cell lines [6, 50, 71-73]. An avenue that may have influenced ethnopharmacology suggests that some traditionally used remedies may have arisen from observations of self-medication by animals [76]. Studies have shown that wild animals often consumed plants and other material for medical rather than nutritional reasons, treating parasitic infections and possible viral and bacterial diseases [11, 60, 76, 77]. For drug discovery, the chemical and pharmacologic investigation of ethnobotanical information offers a viable alternative to high-throughput screening and the body of existing ethnomedical knowledge has led to great developments in health care. It would appear that selection of plants, based on long-term human use in conjunction with appropriate biologic assays that correlate with the ethnobotanical uses, should be most successful [78]. Nevertheless, therapeutic approaches based on active principles from single plant and polyherbal formulations from traditional medicines, like the ones mentioned in Ayurvedic texts, still require scientific validation and sufficient pharmacoepidemiological evidence supporting their safety and efficacy [79]. This is evidenced by the example of aristolochic acid, a constituent of *Aristolochia* vines, which are used in complementary and alternative therapies. Aristolochic acid is a powerful nephrotoxin and a human carcinogen associated with chronic kidney disease and upper urinary tract urothelial carcinomas (UUC) [80]. These dual toxicities and the target tissues were revealed when a group of otherwise healthy Belgian women developed renal failure and UUC after ingesting *Aristolochia* herbs in conjunction with a weight-loss regime; subsequently, more cases were reported in Taiwan and countries throughout the world [80]. Importantly, the traditional practice of Chinese herbal medicine in Taiwan mirrors that in China and other Asian countries making it likely that these toxicities are also prevalent in these and in other countries where *Aristolochia* herbs have long been used for treatment and prevention of disease, thereby creating an international public health problem of considerable magnitude [80, 81].

In the early 1900's, 80% of all medicines were obtained from roots, barks and leaves and it is estimated is that approximately 25% of all drugs prescribed today still originate from plants [14, 19, 78]. The plant kingdom, with 300,000 to 400,000 higher species (estimated levels reach from 215,000 up to 500,000 [78], was always a key source of new chemical entities (NCEs) for active pharmaceutical ingredients and lead compounds [12]. It is estimated that only 5% to 15% of these terrestrial plants have been chemically and pharmacologically investigated in a systemic fashion [19]. Approximately 10,000 to 15,000 of the world's plants have documented medicinal uses and roughly 150-200 have been incorporated in western medicine [19, 82]. Marine plants like microalgae, macroalgae (seaweeds) and flowering plants (such as mangroves) have been studied to a much lesser extent and are mostly reported in connection with nutritional, supplemental or ethnopharmacological uses [83]. For over 20 years the U.S. National Cancer Institute has collected higher plants for screening, with the current collection composed of ~ 30,000 species [84]. Only a small percentage of these have reportedly been screened for biological or phytochemical activity until a decade ago and large numbers are constantly being tested for their possible pharmacological value today [35, 78]. Based on their research, the authors justify their assumption that the plant kingdom still holds many species containing substances of medicinal value and for potential pharmaceutical applications, which have yet to be discovered. However, such assumptions may be diminished as the loss of valuable natural sources increases due to factors such as deforestation, environmental pollution, and global warming [85].

Saslis-Lagoudakis *et al.* provided evidence through phylogenetic cross-cultural comparisons that related plants from different geographic regions are used to treat medical conditions in the same therapeutic areas [86]. Accordingly, there has been a recent surge in interest in the components of traditional Chinese medicines and Ayurvedic remedies [11]. Limitations of this approach include the fact that both of these ancient traditions use polyherbal preparations (botanicals) for the majority of prescriptions and that plants as biological systems have an inherent potential variability in their chemistry and resulting biological activity [12, 35]. Fabricant and Farnsworth reported that 25% of all plants showing biological activity in their assay system failed to reproduce the activity on sub-sequent recollections [35]. This may be caused by factors coming into play after the collection of a specimen, however, for plants it is common to dry the collected plant parts thoroughly in the field before extraction to assure that the material does not compose before reaching the laboratory [12].

Rout *et al.* describe the approaches for using individual plants as therapeutic agents as follows: (i) to isolate bioactive compounds for direct use as drugs, (ii) to produce bioactive derivatives of known compounds as new structures, (iii) to use substances as pharmacologic agents or tools, and (iv) to use a whole or partial plant as herbal remedy and provide examples for each category [78]. Mixtures of plant-derived products are known as botanicals, and the term is defined by the United States (US) Food and Drug Administration (FDA) to describe finished, labeled products that contain vegetable matter as ingredients which can include plant materials, algae, macroscopic fungi, and combinations thereof [87]. They can fall under the classification of a food (including a dietary supplement), a drug (including a biological drug), a medical device, or a cosmetic [87]. The vast majority of plant-derived treatments are based on synthetic, semisynthetic, or otherwise highly purified or chemically modified drugs [87, 88]. According to the most recent report by BCC Research, the global plant-derived drug market was valued at US$ 22.1 billion in 2012 and sales are projected to grow to US$ 26.6 billion by 2017 at a compound annual growth rate (CAGR) of 3.8% [89]. The botanicals subgroup currently has only one approved drug, Veregen, with an expected revenue increase from US $ 2.8 million in 2010 to 599 million in 2017 [89].

3.2. Marine life

Given the fact that oceans cover nearly 70% of the earth's surface and that life originated in the oceans with the first marine organisms evolving more than 3.5 billion years ago, the enormous diversity of organisms in the marine environment is not surprising and largely unexplored [90]. On some coral reefs, their density can reach up to 1,000 species per square meter, which is believed to be a higher biodiversity than observed in tropical rainforests and inspired researchers for decades to search for novel compounds from marine sources [57, 91]. As the greatest biodiversity is found in the oceans, it is estimated that between 250,000 and one million marine species could provide an immense resource to discover NCEs serving as unprecedented novel bioactive structures and scaffolds that have the potential to serve as medical treatments or templates for new therapeutics [23, 92].

The interest in novel chemical structures from marine organisms started in the 1950s as marine animal taxonomy advanced significantly, but progressed at a slow pace for the first two decades before it started to burgeon in the 1970s [91-94]. Since then, approximately 30,000 structurally diverse natural products with a vast array of bioactivities have been discovered from marine organisms including microbes, algae and invertebrates [92, 95]. Invertebrates alone comprise approximately 60% of all marine animals and were described as the source of almost 10,000 new natural products since 1990 with a pronounced increase to about 1,000 compounds per year in more recent years [23, 32, 93].

By the turn of the 21st century larger percentages of bioactive NCEs were reported for marine organisms in comparison to terrestrial organisms, but nevertheless, marine chemical ecology is still several decades behind its terrestrial counterpart with respect to the total number of characterized and documented natural products [93, 96]. Kong *et al.* specifically compared natural products from terrestrial and marine sources. They found that compounds from marine organisms exhibited a higher chemical novelty and that over 2/3 of those scaffolds were exclusively used by marine species, but alerted readers to concerns of the suitability of the new scaffolds as drug templates because of their unsuitably high hydrophobicity [96]. As is the case for plant derived natural compounds, the U.S. National Cancer Institute also plays an important role for establishing marine organism collections since the 1980s and has a vast National repository of invertebrate derived compounds and extracts from specimens rigorously identified by taxonomic experts [92].

Many marine natural products appear to arise from multi-functional enzymes that are also present in terrestrial systems, exhibiting a cross phylum activity with terrestrial biota [94, 95]. However, a large number of marine derived compounds also possess a substantial amount of functional groups, which were not previously described from terrestrial metabolites [91, 94, 95]. They range from derivatives of amino acids and nucleosides to macrolides, porphyrins, terpenoids, aliphatic cyclic peroxides, and sterols [91]. These secondary metabolites resulted from evolutionary pressure threatening many marine organisms, especially those which are soft bodied and have a sedentary life style, forcing them to develop the ability to synthetize toxic compounds which serve to deter predators, manage competitors or immobilize prey [57, 91, 93, 94]. The search for new drug candidates from marine species has expanded into circumpolar regions for cold-adapted species as well as harsh environments like deep-sea hydrothermal vents; these approaches have been particularly successful with filter-feeders such as sponges, tunicates and bryozoans [23, 97].

The fact that marine invertebrates contain astounding levels of microbial diversity and form highly complex microbial communities led to the assumption, followed by confirmation in recent examples, that microbial symbionts like bacteria are important producers of natural products derived from marine species [58]. In particular, these include polyketides and non-ribosomally synthesized peptides as well as unique biosynthetic enzymes which emerged as potent biocatalysts in medicinal chemistry [58, 97].

By 2010, four drugs of marine origin had obtained approval for the treatment of human disorders [98]. Cytarabine (Cytosar-U®; Upjohn/Pfizer) for the treatment of white blood cell cancers, vidarabine (Vira-A®; discontinued by distributor Monarch Pharmaceuticals) an ophtalmic antiviral, and ziconotide (Prialt®; Elan) for pain management were FDA approved and trabectedin (Yondelis®; Pharmamar), an anticancer compound against soft tissue and ovarian cancer was approved in Europe [98]. Vidarabine and cytarabine originate from marine sponges, ziconotide is the synthetic equivalent of a conopeptide originating from a marine cone snail, and trabectedin, now produced synthetically, originates from a bacterial symbiont of a tunicate or sea squirt [32, 99]. At the same time, 13 marine organism-derived drug candidates were listed to be in clinical development (3 in Phase III, 7 in Phase II, and 3 in Phase I) and hundreds are in pre-clinical testing as ion channel blockers, enzyme inhibitors, DNA-interactive and microtubule-interfering agents, with the majority of the latter compounds being tested for anti-tumor and cytotoxic properties [91, 94, 98]. Natural products of marine origin with biological activity of interest include, but are not limited to, curacin A, eleutherobin, discodermolide, bryostatins, dolostatins, cephalostatins [16].

3.3. Microorganisms

Microorganisms were identified early on as sources of valuable natural products as evidenced by the discovery of penicillin by from the fungus *Penicillium rubens* by Alexander Fleming in 1928 [100]. Historically, microorganisms (amongst them mostly bacteria and fungi) have played an important role in providing new structures, like antibiotics for drug discovery and development. The terrestrial microbial populations are immensely diverse which is also reflected in the number of compounds and metabolites isolated from these microorganisms. As mentioned above, the similarity of many compounds from marine invertebrates like sponges, ascidians, soft corals and bryozoans to those isolated from terrestrial microbes led to the hypothesis that associated microorganisms might be responsible for their production. Over time it became more and more evident, that a significant number of marine natural products are actually not produced by the originally assumed invertebrate but rather by microbes living in symbioses with their invertebrate host [92, 101]. In some instances it could indeed be demonstrated early on that the isolated marine microbes are the original source of the new compounds or secondary metabolites discovered and in recent years marine bacteria have emerged more and more as a source of NCEs [58, 91, 94, 95]. Besides bacteria, marine fungi and deep-sea hydrothermal vent microorganisms are reported to produce bioactive compounds and metabolites [91, 94]. Deep-sea vent sites offer harsh conditions in depth below 200 meters with complete absence of light, pressures in excess of 20 atmospheres, temperatures of up to 400°Celius, pH extremes and high sulfide concentrations and are populated by highly dense and unique, biologically diverse communities [91, 94, 102].

Unique microorganisms are abundant on land, in freshwater and all areas of the ocean. However, the enormous biological diversity of free-living and symbiotic marine microbes has so far only been explored to a very limited extent. The estimates extrapolate the number of marine species to at least a million, but for marine microbial species, including fungi and bacteria, the estimated numbers reach as high as tens or even hundreds of millions [23]. Over 74,000 known species of fungi are reported including around 3,000 aquatic species of which only about 465 are described as marine species, but a vast geographical area has not yet been sampled and estimates for the potential total number of species reach from 0.5 to 9.9 million with about 1.5 million considered as most realistic [103, 104]. The overlap is assumed to be relatively high between species in terrestrial and freshwater habitats, but not between these two and the marine habitat [104]. Nevertheless, a large percentage of the over 270 secondary metabolites isolated from marine fungi resembles analogues of compounds previously discovered from terrestrial fungi but some of the new substances identified exhibited potent activities against tumor cells, microbes or bacteria like methicillin-resistant *Staphylococcus aureus* (MRSA) or even antifouling properties [59, 105]. In comparison to bacteria, fungi appear to be rare in marine environments and few marine fungi isolates exist in culture [106]. Marine bacteria are assumed to constitute approximately 10% of the living biomass carbon and inhabit mainly sediments but can also be found in open oceans and in association with marine organisms [90, 91, 94]. Many marine invertebrates are associated with large amounts of epibiotic and endobiotic microorganisms and for many sponges bacteria can make up to 40% of the animal biomass and even resemble new species [97]. In fact it is assumed that almost all

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marine organisms host bacteria on their surface and that the vast majority bare epibiotic films of variable density and composition, which can affect the basibiont's physiology and interactions with its environment in beneficial, detrimental, or ambiguous manners [107]. This constitutes a vast pool for the discovery of new structures and scaffolds if the source can be unanimously established.

To identify the source of a compound, the determination of its mere presence in a certain organism is not sufficient, as this could be the result of active or passive accumulation and does not necessarily reflect the true site of its biosynthetic production. As Gulder and Moore further explain: *"An unambiguous assignment of the biosynthetic origin of a natural product derived from a complex assemblage of marine organisms thus has to originate at the genomic level. This is particularly true for bacterial symbionts, which have to date eluded cultivation"* [58]. These microbes generally organize their biosynthetic genes for each secondary metabolite in compact clusters, which will, following identification and sequencing of the cluster responsible for the respective pathways, allow the transfer of the respective bacterial genes into effective heterologous producers, like *Escherichia coli (E. coli)* [55, 58, 97]. In terms of microbial sources, culturing of the respective microorganism may generally be a viable approach to increase quantities. A major difference between microorganisms from terrestrial and marine sources is the fact that marine pelagic bacteria are much more difficult to grow in culture than the soil borne actinomycetes; therefore determining the conditions for replication, growth of sufficient quantities and induction of metabolite production can be a tedious challenge [12, 17]. This again may necessitate the production in a heterologous system like that observed for *E. coli.*

4. Challenges

Natural products, although a valuable and precious resource, also come with their fair share of challenges in a variety of aspects. As mentioned before, one of the major issues concerning the use of natural products are the difficulties associated with obtaining sufficient amounts of material pure enough for discovery and development activities. If a compound is derived from a plant growing only in small quantities or remote locations or a marine organism residing in great depth or difficult to access regions, re-supply becomes a problem.

The threat of losing potentially valuable natural sources of pharmacologically active ingredients is constantly increasing due to the threat of extinction by deforestation of large landmasses and environmental pollution in remote areas as well as global warming [85]. It is estimated that about 70% of the supply of herbal raw material for Ayurveda and other homeopathic medicines in India comes from the wild [82, 85]. To meet the increasing demand for raw material, to conserve wild resources, and to reduce the potential variability in the active ingredient content in medicinal plants from different collection areas, it is important to implement more controlled cultivation programs to ensure quality and to protect resources [82, 85].

Tissues of marine invertebrates present unique problems for extraction, because of their high water and salt content, and the promising compounds may be present only in low amounts and/or can be very difficult to isolate. Sponges and their microbial fauna are mostly not suitable for culture, and the compounds of interest need to be extracted and purified from specimens collected in the wild [17, 93]. Marine organisms and microbes constitute a valuable potential source of NCEs and structural templates for drug discovery in the future, but may necessitate tons of raw material to isolate milligram to gram amounts of the compound of interest [97]. This difficulty combined with the challenges for synthetic approaches to obtain significant quantities of potential new drug candidates, based on their often highly complex structures, are obstacles that can hamper their use in discovery and development [58, 97]. In some cases, supply issues could be resolved by semi-synthesis or total synthesis of the compound, the development of synthetic analogs with more manageable properties, or by design of a pharmacophore of reduced complexity, which can then be synthesized [17, 92, 97]. Fragments or synthetic analogs with simplified structures may retain bioactivity or even show improved activity towards the target [12].

Furthermore, environmental aspects can constitute significant hurdles for supplying material for discovery and development as the product may stem from an endangered species or the wild collection of the producing species may be detrimental to its originating terrestrial or marine ecosystem. Additionally, as mentioned above, because of their low abundance many compounds of interest from natural sources need to be extracted and purified from large quantities of specimen collected in the wild, which in turn carries the risks of over-exploitation and habitat destruction [17, 93]. Radjasa *et al.* provide a positive outlook for marine ecosystems and state "*There is optimism for the future because the international marine bioorganic community clearly recognizes that invertebrates must be harvested and studied in an environmentally sustainable manner*" [92]. Although aquaculture of marine species or culture of bacteria seem like logical alternative sources to obtain product, they are not viable avenues in most cases because it proves difficult to impossible to culture the source organisms (especially invertebrates and/or their microbial symbionts like bacteria etc.) or they may not produce the compound of interest under the given culture conditions [12, 17, 95, 97]. Findings indicate, that the bacterial composition on invertebrates is largely independent from sponge taxonomy or locality of collection and the bacteria most likely are contaminants from the ocean water rather than specific symbionts, which further exacerbates the cultivation problem [97, 108].

Another challenge can result from redundant activity determination in assay systems and the mixed composition of natural product extracts. With over 150,000 known small molecules characterized from natural sources, previously known natural products are often re-isolated in the course of bioassay-guided fractionation [84]. While this may be acceptable if the biological activity is new, it is frustrating to waste resources on the *de novo* structure elucidation of known compounds. Furthermore, not all compounds contained in natural product extracts are drug leads and it is extremely desirable to remove "nuisance compounds" like tannins, phorbol esters, saponins, and anionic polysaccharides; the latter, for instance, being highly active in cellular HIV bioassays [35].

Last, but not least, intellectual property rights can pose a significant hurdle that is difficult to manage. In general, patent protection can be obtained if the active principles derived from natural sources have novel structures and relevant biological activity. However, as mentioned before, additional handicaps may arise in the context of developing and marketing products from natural sources in the form of potentially significant intellectual property issues as well as, possibly, very difficult and costly negotiations to obtain agreements to collect and develop natural products from species collected in foreign countries [25, 26, 35].

5. Regulatory requirements and risks

The regulatory requirements for different product categories containing natural substances like pharmaceuticals, nutraceuticals, and cosmeceuticals vary from rather stringent to generous to non-existent at an International level. To exemplify regulatory approaches for the three aforementioned categories, an overview of the current situation in North America (U.S. and Canada) and the European Union is summarized. In many areas we have presented exact wording from the respective governing websites, as the phrasing of such represents the official context and any deviation thereof could be misleading.

5.1. Natural product-derived pharmaceuticals

Natural products constitute a key source of pharmacologically active ingredients in a variety of novel agents with therapeutic potential in a wide range of diseases. Pharmaceuticals containing natural products or compounds derived from natural product scaffolds or templates have to undergo the same stringent approval process as drugs obtained from purely synthetic origin.

5.1.1. North America

5.1.1.1. United States of America (U.S.)

The U.S. Government Office for the Control of Food and Drug Administration (FDA) oversees the regulatory control of pharmaceuticals including new treatments based on natural products [109]. The FDA's Center for Drug Evaluation and Research (CDER) role is to evaluate and approve new drugs before they can be sold ensuring that drugs are safe and effective for intended use and that their health benefits outweigh their known risks [109].

5.1.1.2. Canada

In Canada, Health Canada fulfills the same role as the US FDA according to the mandate under the authority of the Food and Drugs Act and the Food and Drug Regulations [110].

5.1.2. European Union

The European Medicines Agency (EMA) with headquarters in London/England regulates drugs and medicinal products in the European Union (EU) [111]. On April 30th, 2011 the EU entered into force the directive on herbal medicine products called Traditional Herbal Medicinal Products Directive 2004/24/EC, THMPD [111]. The regulation came as a sub-directive for the act on Human Medicinal Products Directive 2001/83/EC claiming a unique set of information on a herbal substance or herbal preparation for all EU Member States. Such could be used when evaluating marketing applications for herbal medicinal products from companies and covers medicinal products containing herbal substances/preparations [111]. To reach the market, these must fall within one of the following three categories, as outlined on the EMA website [111]:

1. a product can be classified under traditional medicinal use provisions ('traditional use') accepted on the basis of sufficient safety data and plausible efficacy: the product is granted a traditional use registration (simplified registration procedure) by a Member State,

2. a product can be classified under well-established medicinal use provisions ('well-established use'). This is demonstrated with the provision of scientific literature establishing that the active substances of the medicinal products have been in well-established medicinal use within the Union for at least ten years, with recognized efficacy and an acceptable level of safety. As a result the product is granted a marketing authorization usually by a Member State or by the European Medicines Agency. While both classifications have specific requirements, both regulatory paths involve the assessment of mostly bibliographic safety and efficacy data.

3. a product can be authorized after evaluation of a marketing authorization application consisting of only safety and efficacy data from the company's own development ('stand alone') or a combination of own studies and bibliographic data ('mixed application'). As a result the product is granted a marketing authorization by a Member State or by the Agency via the centralized procedure if all requirements are met.

In summary, while safety needs to be shown for products, proof of efficacy is not always a requirement and only the traditional indications in specified conditions must be plausible. Nonetheless, and irrespective of the regulatory pathway to access the market, the quality of the herbal medicinal product must always be demonstrated [111].

The Directive provides definitions for herbal medicinal products, herbal preparations and herbal substances, as follows [111]:

- *Herbal medicinal product:* Any medicinal product, exclusively containing as active ingredients one or more herbal substances or one or more herbal preparations, or one or more such herbal substances in combination with one or more such herbal preparations.

- *Herbal substances:* All mainly whole, fragmented or cut plants, plant parts, algae, fungi, lichen in an unprocessed, usually dried, form, but sometimes fresh. Certain exudates that have not been subjected to a specific treatment are also considered to be herbal substances. Herbal

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substances are precisely defined by the plant part used and the botanical name according to the binomial system (genus, species, variety and author).

- *Herbal preparations:* Preparations obtained by subjecting herbal substances to treatments such as extraction, distillation, expression, fractionation, purification, concentration or fermentation. These include comminuted or powdered herbal substances, tinctures, extracts, essential oils, expressed juices and processed exudates

Additionally, it has been noted that from a herbal substance (e.g. valerian root) different herbal preparations (e.g. a valerian root extract using 70% ethanol) can be made; in such cases, both can represent the active ingredient in an individual herbal medicinal product [111].

5.2. Nutraceuticals — Dietary supplements (U.S.)/Natural health products (Canada)

Even if natural health products (NHPs) or dietary supplements are considered as or expected to be safe, they may still carry potential risks in themselves or through interactions with prescription or Over The Counter (OTC) drugs. This is illustrated by the previously described example of *aristolochic acid*, a powerful nephrotoxin and a human carcinogen associated with chronic kidney disease and upper urinary tract urothelial carcinomas after ingesting *Aristolochia* herbs in conjunction with a weight-loss regime [80, 81]. Furthermore, interactions between NHPs and prescription medicines are of increasing concern and need to be considered by physicians and patients alike [112]. Mills *et al*, in their evaluation of 47 trials which examined drug interactions with 19 different herbal preparations, observed potentially clinically significant drug interactions with St. Johns Wort, garlic, and American ginseng [113].

5.2.1. North America

5.2.1.1. United States of America

In the U.S., biologically active food and dietary supplements are regulated by the FDA and are classified as food and nutrition, not drugs [88]. The FDA website provides a detailed overview of their regulatory approach concerning nutraceuticals. The following paragraphs reflect some core points as outlined on the FDA's respective website [88].

- The FDA regulates both finished dietary supplement products and dietary ingredients under a different set of regulations than those covering "conventional" foods and drug products (prescription and OTC). Under the Dietary Supplement Health and Education Act (DSHEA) of 1994, the dietary supplement or dietary ingredient manufacturer is responsible for ensuring that a dietary supplement or ingredient is safe before it is marketed. The FDA is responsible for taking action against any unsafe dietary supplement product after it reaches the market. Generally, manufacturers do not need to register their products with the FDA nor get FDA approval before producing or selling dietary supplements.

- The Federal Food, Drug, and Cosmetic Act requires that manufacturers and distributors who wish to market dietary supplements that contain "new dietary ingredients" notify the Food and Drug Administration about these ingredients, which must include information that is the basis on which manufacturers/distributors have concluded that a dietary supplement containing a new dietary ingredient will reasonably be expected to be safe under the conditions of use recommended or suggested in the labeling [87].

- The U.S. Congress defined the term "dietary supplement" and both of the terms "dietary ingredient" and "new dietary ingredient" as components of dietary supplements in the DSHEA. A dietary supplement is a product taken by mouth that contains a "dietary ingredient" intended to supplement the diet.
- In order to be a "dietary ingredient," it must be one or any combination of the following substances:
- A "new dietary ingredient" is one that meets the above definition for a "dietary ingredient" and was not sold in the U.S. in a dietary supplement before October 15, 1994.
- Dietary supplements can also be extracts or concentrates, and may be found in many forms such as tablets, capsules, softgels, gelcaps, liquids, or powders [88]. They can also be in other forms, such as a bar, but if they are, information on their label must not represent the product as a conventional food or a sole item of a meal or diet [88]. Whatever their form may be, the DSHEA places dietary supplements in a special category under the general umbrella of "foods," not drugs, and requires that every supplement be labeled a dietary supplement.

5.2.1.2. Canada

In Canada, the use and sale of natural health products (NHPs) is on the rise [8]. A 2010 Ipsos-Reid survey showed that 73% of Canadians regularly take natural health products (NHPs) like vitamins and minerals, herbal products, and homeopathic medicines [114]. Health Canada defines natural health products under the Natural Health Products Regulations as:

- Vitamins and minerals
- Herbal remedies
- Homeopathic medicines
- Traditional medicines such as traditional Chinese medicines
- Probiotics
- Other products like amino acids and essential fatty acids [115].

Natural Health Products must be safe to use as OTC products and not need a prescription to be sold [115]. Natural products, compounds and active ingredients derived from natural sources or totally synthesized and needing a prescription are regulated as drugs under the Food and Drug Regulations [115].

5.2.2. European Union

Herbal supplements and nutritional supplements are not regulated on a harmonized EU wide basis and remain under the control of the relevant medical institutions of the individual EU member states.

5.3. Cosmeceuticals

Although the term is not recognized by the US Food and Drug Administration (FDA) or by the European Medicines Agency (EMA), it has been widely adopted by the cosmetics industry, which is rapidly expanding in spite of global economic woes in recent years [116]. The global cosmeceuticals market references the seven most developed markets including the U.S. and the top five European countries, namely the UK, France, Germany, Italy and Spain; as well as Japan [116]. In 2011, the global cosmeceuticals market was estimated to be worth $30.9 billion (with the aforementioned European countries accounting for approximately 65% of overall revenues) and is expected to reach $42.4 billion by 2018 [116]. Three major categories have been noted in the cosmeceutical industry including skin care, hair care, and others, with the skin care segment accounting for the largest share of the market at 43% [117]. Dominated by anti-aging products, the skin-care market is expected to contribute significantly to future growth based on the aging populations in the top seven aforementioned markets [116].

Cosmeceuticals are topically applied and represent a hybrid of cosmetics and pharmaceuticals usually containing vitamins, herbs, various oils, and botanical extracts or a mixture thereof including antioxidants, growth factors, peptides, anti-inflammatories/botanicals, polysaccharides, and pigment-lightening agents [117, 118]. The combination of cosmetics and foods resulted in products termed nutricosmetics. Nutricosmetics are foods and supplements claiming cosmetic effects with major ingredients like soy isoflavone proteins, lutein, lycopene, vitamins (A, B_6, E), omega-3 fatty acids, beta-carotene probiotics, sterol esters, chondrotin and coenzyme Q10 [119, 120]. These compounds act as antioxidants and the respective nutricosmetics containing them are being promoted for their skin care properties as for instance in anti-aging by fighting free radicals generated as a by-product of biochemical reactions through skin exposure to the sun [119].

5.3.1. North America

5.3.1.1. United States of America

In the US, products that can be put in both the cosmetics and drugs category, such as cosmetic products with active ingredients which claim therapeutic use, require New Drug Application (NDA) approval or must comply with the appropriate monograph for an (OTC) drug. Moreover, the FDA also has specific guidelines for Good Manufacturing Practice (GMP) for cosmetics [116].

While the *Federal Food, Drug, and Cosmetic Act (FD&C Act)* does not recognize the term "cosmeceutical", the cosmetic industry uses this word to refer to cosmetic products that have medicinal or drug-like benefits [118]. The FD&C Act defines drugs as those products that cure, treat, mitigate or prevent disease or that affect the structure or function of the human body [121]. Under the FD&C Act, cosmetic products and ingredients, with the exception of color additives, do not require FDA approval before they go on the market [121]. Therefore, while drugs are subject to a review and approval process by the FDA, cosmetics are not approved by the FDA prior to sale. However, when a product makes a therapeutic claim (e.g. to prevent or treat disease), it is classified as a drug and therefore requires evaluation by the FDA's Center for Drug Evaluation and Research (CDER) and a drug identification number (DIN) before it can be sold.

5.3.1.2. Canada

In Canada, the term "cosmeceutical" (used to describe a cosmetic product with pharmaceutical-like benefits) is not employed by Health Canada [122]. Therefore cosmeceuticals fall under either cosmetics or drugs (depending on the claims made and/or the composition of the product) and are subject to the provisions of the Food and Drugs Act and its Cosmetic Regulations regarding composition, safety, labeling and advertising and they are subject to the provisions of the Consumer Packaging and Labeling Act and Regulations [122]. The three most significant features of the Canadian cosmetic regulatory system are mandatory notification of all cosmetic products, safety of ingredients and products, and product labeling [122]. According to Health Canada, a "cosmetic" is defined as *"any substance or mixture of substances, manufactured, sold or represented for use in cleansing, improving or altering the complexion, skin, hair or teeth and includes deodorants and perfumes"* [122].

5.3.2. European Union

In Europe, EMA guidelines place a clear demarcation between drugs and cosmetics, whereby a cosmetic is a product that is to be applied topically with an intended cosmetic function and products cannot fall under both categories, unlike in the US [116]. On November 30th (2009), the new Cosmetic Products Regulation, EU Regulation 1223/2009 was adopted, replacing the Cosmetics Directive [123]. With the new Cosmetics Regulation, Europe claims to have a robust, internationally recognized regime, which reinforces product safety taking into consideration the latest technological developments [123]. Most of the provisions of this new regulation will be applicable as of July 11th, 2013 [123].

6. Conclusion

A natural product or secondary metabolite is a pharmacologically or biologically active chemical compound or substance, which is found in nature and produced by a living organism. The lengthy process of natural products evolution has resulted in optimal interactions with biological macromolecules and targets. Historically, natural substances have been the most productive source of active compounds and chemical lead structures. Natural products have traditionally provided a large fraction of the drugs in use today and millions of terrestrial and marine plants, organisms and microorganisms provide an immense resource to discover unprecedented novel bioactive scaffolds. These have the potential to serve as medical treatments or templates for new therapeutics and may be suitable for production via a synthetic routes or in a heterologous system like *E. coli.* About half of the agents in today's arsenal of marketed drugs are derived from biological sources with the large majority being based on terrestrial natural product scaffolds. Approximately 50% of the new drugs introduced since 1994 were either natural products or derived from natural products. As of today, only a very small fraction of bioactive structures of potential therapeutic relevance from plants, microbes, and marine organisms have been chemically analyzed or examined in a broad panel of screening models or bioassays. The discovery of valuable therapeutic agents from natural sources continues in the 21th century by reaching into new and untapped terrestrial and marine source organisms as the chemical novelty associated with natural products is higher than that of structures from any other source.

There is growing awareness of the limited structural diversity in existing compound collections and the extreme chemical diversity, the high biological potency, and the potential to frequently discover drug-like characteristics in natural products. Therefore, they constitute a valuable platform for the development of new therapeutics for a variety of indications, although they may still not contain enough versatility to yield suitable treatments for all heritable human diseases.

As some major pharmaceutical companies terminated their natural product programs, the future role to discover and feed candidates into the development pipelines will reside increasingly with research institutes and small biotech companies. Over a hundred new drug candidates from natural sources like plants, bacteria, fungi and animals or obtained semi-synthetically are in clinical development with a similar number in preclinical development. They target a variety of indications, mainly cancer and infectious diseases (bacterial, viral, fungal, and parasitic) but also other therapeutic areas such as cardiovascular diseases, neurological illnesses and depression, metabolic diorders and inflammatory diseases.

Natural products, although a valuable and precious resource, also come with their fair share of challenges concerning the provision of sufficient amounts of pure enough material for discovery and development activities. As mentioned earlier, such apprehensions are based on the threat of losing potentially valuable natural sources through extinction resulting from deforestation of large landmasses, environmental pollution in remote areas as well as global warming. Countries are also increasingly protective of their natural assets in flora and fauna and may not authorize the collection of sample species without significant demands and very difficult negotiations. The regulatory requirements for different product categories containing natural substances like pharmaceuticals, nutraceuticals, and cosmeceuticals vary from rather stringent over generous to non-existent at an international level. Even if natural health products or dietary supplements are considered as or expected to be safe, they may still carry potential risks in themselves or through interactions with prescription or OTC drugs. Therefore, the discovery and development of natural products require cientific validation and sufficient pharmacoepidemiological evidence to support their safety and efficacy.

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