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Natural Products are a Precious Source of the New Bioactive Compounds

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Abstract

Cancer, microbial infections, and diabetes are the main causes of deaths globally. Curing these diseases have been the potential target for novel natural products by providing a huge diversity of chemical profiles. Half of the newly approved antitumor, antibacterial, and antifungal drugs between 2006 and 2010 were natural products or derived from natural products. As well as, from the thirteen natural products, derived drugs that were approved between 2005 and 2007, five of them were from a novel family of chemical classes. All this confirms the great role of natural products to provide new bioactive lead compounds for drug discovery. As mentioned before, natural source of chemical compounds is an attractive source of new therapeutic agents because of the huge diversity of these chemical compounds due to millions of species involved in the production of these compounds.

Keywords: *natural products, drug discovery, antibacterial, anticancer, antidiabetic.*

Introduction

Natural environments have been used as a source of many pharmacologically active compounds used as medicines from the old ages until now [1]. The information provided by research centres, educational institutions, and pharmaceutical manufacturers show that approximately half of the approved drugs between 1981 and 2007 are from natural source or derived from natural products [2]. Many of these compounds were isolated from plants, microbial or animal sources, such as elliptinium, galantamine and huperzine from plants, daptomycin from microbes, and exenatide as well as ziconotide from animals [1]. In addition, many synthetic and semi-synthetic compounds were produced based on natural compounds such as tigecycline, everolimus, telithromycin, micafungin and caspofungin [1].

As presented in Table 1, 255 drugs have been afforded directly or derived from a natural source [1]. As demonstrated in Table 1.1, plants and microbes are considered to be the most popular provider for natural lead compounds [3].

Advances provided by the improvements of existing chromatographic technologies such as counter-current chromatography and high-resolution analytical instruments in mass spectroscopy (MS), and nuclear magnetic resonance (NMR) aided the fractionation strategies and purification of natural compounds as well as the elucidation of chemical structures [4-6]. In addition, the high-throughput capability of screening mixtures of natural compounds or extracts has made the work with natural products less time-consuming and more successful [4]. Furthermore, these advances in analytical and chromatographic instrumentation have improved the duration of isolating target compounds to less than two weeks as well as from extracts obtained from a broth media [6]. Thus, research groups from around the globe working with natural products could currently produce and screen libraries of highly diverse compounds isolated from the natural sources. The Dictionary of Natural products (DNP) published by CRC Press, a member of the Taylor & Francis Group has provided evidence of the availability of highly diverse bioactive compounds and thereby has further aided drug discovery from the natural compounds [6]. Unfortunately, compound libraries as such have been facing some problems in their maintenance and curation especially from the cost-point of view [6].

Despite advancements toward computer-based or combinatorial drug discovery, Newman and Cragg stated in 2016 that over 34 years between 1981 and 2014, 44% of all new approved drugs in the market were either biological macromolecules, unaltered natural products, botanical natural products (define mixture) or natural products derivatives. As well as 21% of these new drugs were synthesised to mimic natural product (Figure 2). Furthermore, in spite of the essential role of combinatorial chemistry in drug discovery, natural product-like library is still of importance [2].

Anti-cancer compounds isolated from natural sources.

The first search of anti-cancer agents from natural source started in the beginning of 1950's [7]. The first active compounds, vinblastine and vincristine were isolated from the plant Madagascar periwinkle leaf (*Catharanthus roseus*) [8]. Due to the low yield production of vinblastine and vincristine by *C. roseus,* an endophytic *Fusarium oxysporum* was isolated from the plant and was found to produce both compounds in good yield to be available clinically [9]. On the other hand, another group of compounds (Taxol) exhibited bioactivity in various cancer cell lines like paclitaxel isolated from the bark of *Taxus brevifolia*. Paclitaxel was

found active against ovarian, breast and adenocarcinoma [10]. Another taxol compound was derived from the needles of *Taxus baccata*, docetaxel, which was used for the treatment of different types of cell carcinoma [10]. The advances in the analytical instrumentation resulted in the isolation of many compounds either from plants or marine environment. Some of these compounds have been introduced for clinical studies and/or approved for medicinal use as listed in Table 2 [11, 12].

Anti-diabetic compounds isolated from natural sources

Diabetes mellitus (DM) is a chronic disease that causes elevation in blood glucose level due to either a problem with insulin secretions from pancreas or the inability of insulin to work properly in the human body [18]. The number of patients with DM is more than 422 million to date, and this number will increase to be 592 million in 2035 [18]. Lifestyle and synthetic drugs are used to reduce the symptoms coupled with DM [19]. However, lifestyle and synthetic drugs are not enough to control DM due to the poor acceptability and compliance of diabetic patients [18]. Many evidences have been found to confirm the successful convenient management of DM with herbal medicines exhibiting high activity and low toxicity in patients [18]. Flavonoids, polyphenols, terpenoids, saponins, alkaloids, and quinones are different groups of compounds used to reduce the symptoms of DM. More specific examples include quercetin and rutin flavonoids, epigallocatechin gallate, resveratrol, abscisic acid, andrographolide, berberine, and jatrorrhizine [20-28].

Anti-bacterial compounds isolated from natural sources

Amongst the first type of antibacterial compounds were the sulpha-drugs, which was reported to be used in 1936, followed by the discovery of the β-lactam compound penicillin between 1929 and 1941, which was the golden age of antibiotic discovery [29]. However, the occurrence of multi-resistance microbes to the antimicrobial compound based on the β-lactam ring compelled scientists to isolate other antimicrobials, one of which were the phenylpropanoid compounds, such as chloramphenicol in 1946 [29]. The need of new type of antibiotics led to the discovery of the polyketides group, such as tetracycline in 1949, followed by the isolation of aminoglycosides like streptomycin between 1946 and 1950 [29]. While macrolides like erythromycin was discovered in 1952, followed by the isolation of glycopeptides, such as vancomycin between 1956 and 1975 [29]. Quinolones, 2nd generation β-lactams, streptogramins, 3rd generation β-lactams, oxazolidinones, and daptomycin have been discovered between 1960 and 2003 as represented in Figure 6 [29].

Acknowledgments

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insulinemia in rats and in humans. *The FASEB Journal* **2015,** *29* (12), 4783-4793.
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Table 1: Number of drugs based on natural sources in different developments stages.

Development stage	Plants	Bacteria	Fungi	Animals	Natural products-derived compounds	Total
Pre-clinical	46	12	7	7	27	99
Phase 1	14	5	0	3	8	30
Phase 2	41	4	0	10	11	66
Phase 3	5	4	0	4	13	26
Pre-registration	2	0	0	0	2	4
Total	108	25	7	24	61	225

Source: pharmaprojects database (dated: March 2008)

Table 2: Active anti-cancer agents derived from natural source [13-17].

Source	Compound
Plant source	
Catharanthus roseus	vincristine
Catharanthus roseus	vinblastine
Taxus brevifolia	paclitaxel
Taxus baccata	docetaxel
Camptotheca acuminata	topotecan
Camptotheca acuminata	irinotecan
Dysoxylum binectariferum	flavopiridol
Brucea antidysenterica	bruceantin
Scutellaria baicalensis	thalicarpin
Microbial source	
Streptomyces sp.	actinomycin D
Soil fungus Streptomyces	bleomycin
Streptomyces sp.	daunomycin
Streptomyces sp.	doxorubicin
Streptomyces sp.	epirubicin
Streptomyces sp.	streptazocin
Streptomyces sp.	mitomycin C

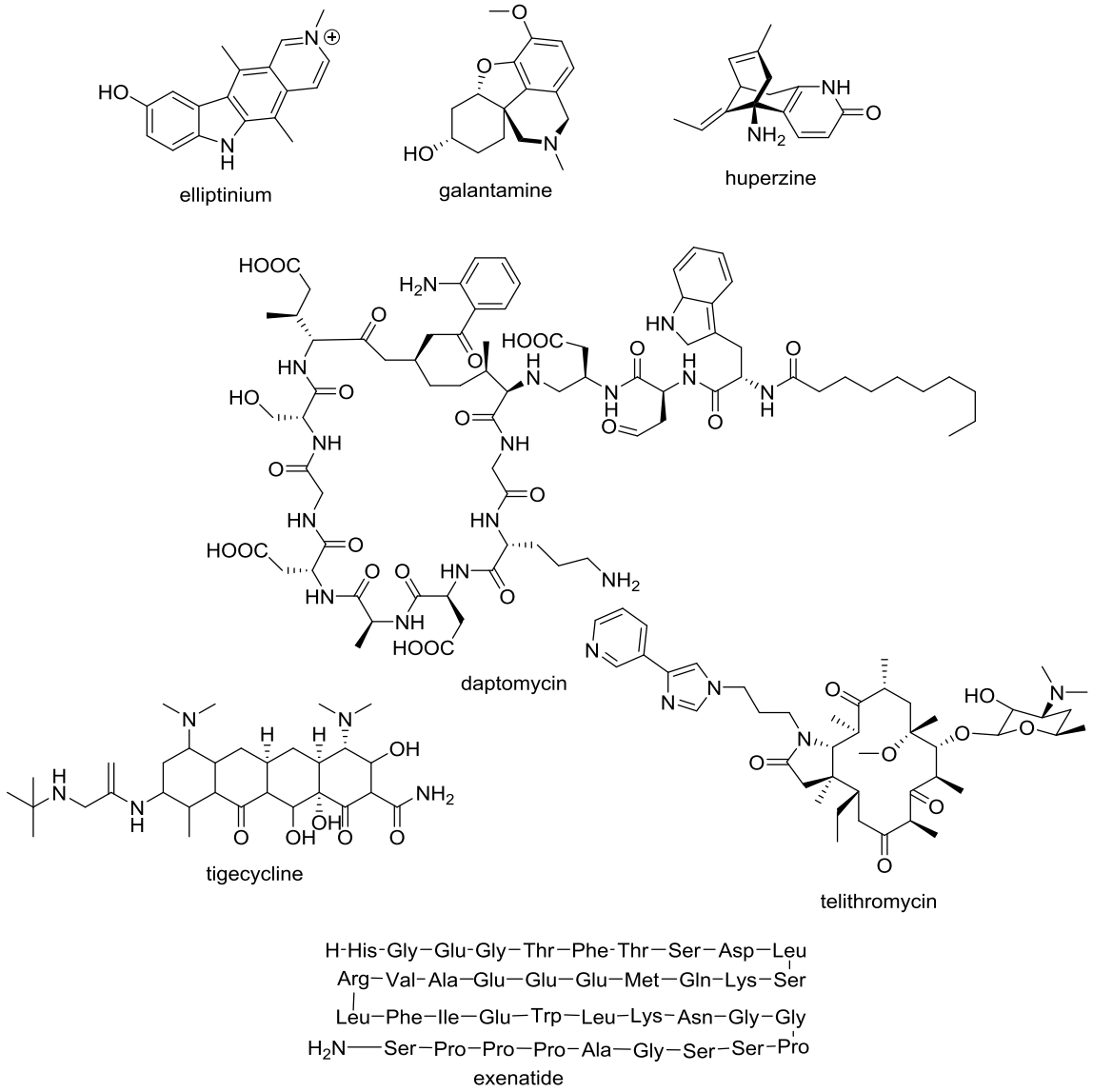
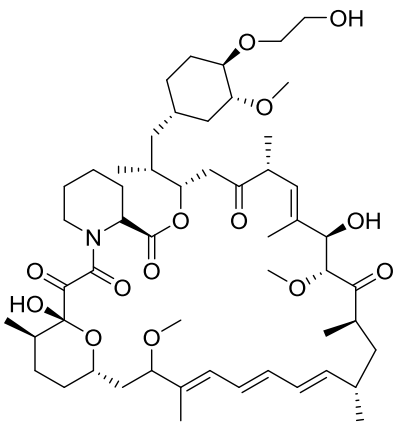
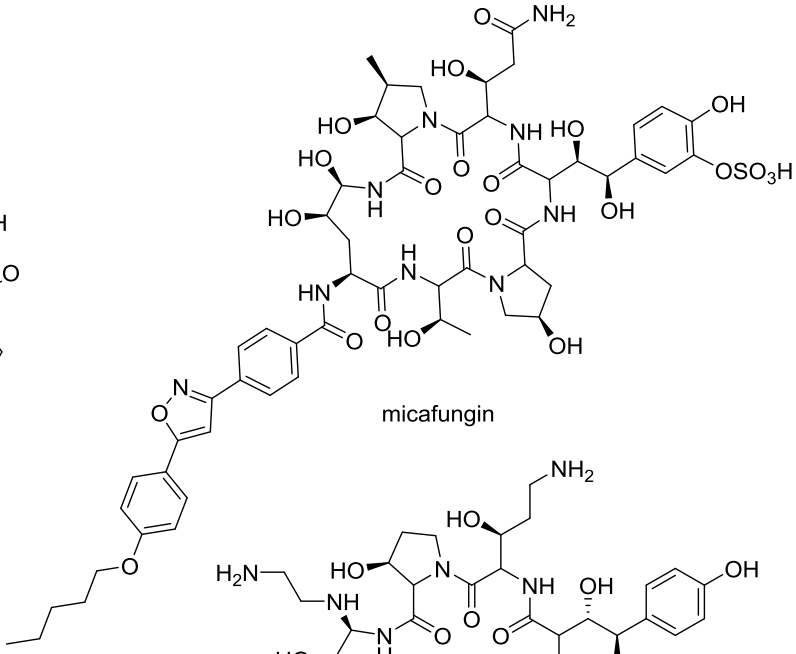


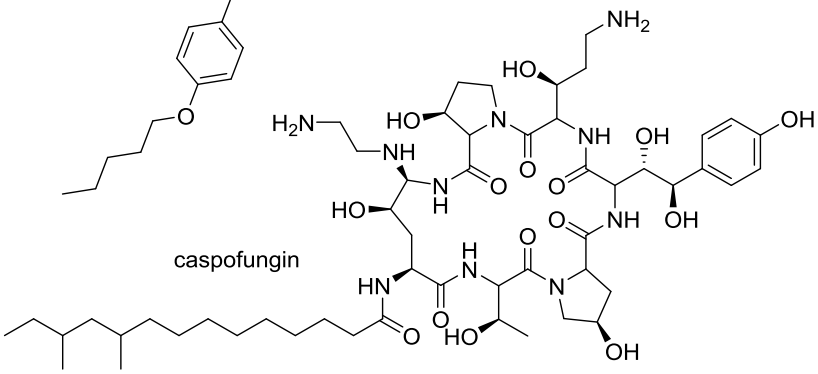
Figure 1 (A): Examples of natural products used or modified to be used as pharmaceutical preparations (Harvey, 2008).



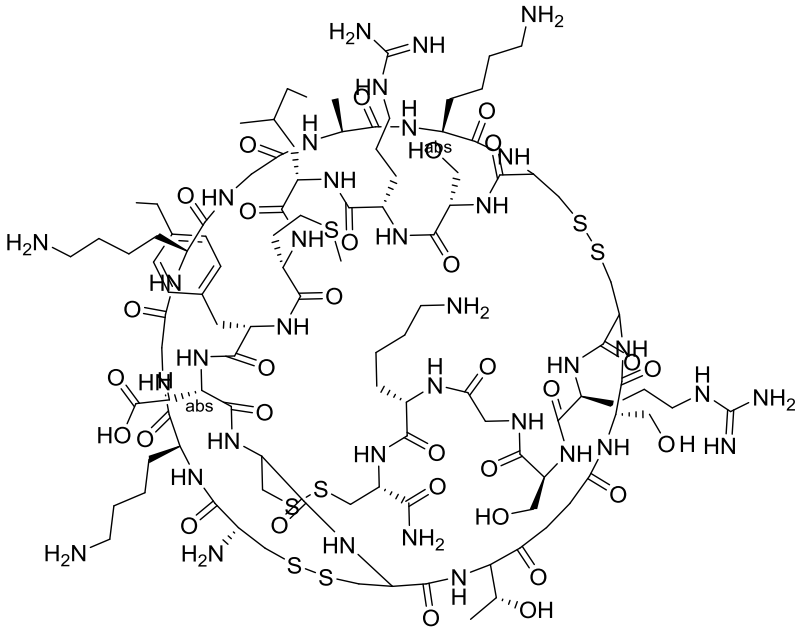
everolimus



micafungin



caspofungin



ziconotide

Figure 1 (B): Examples of natural products used or modified to be used as pharmaceutical preparations.

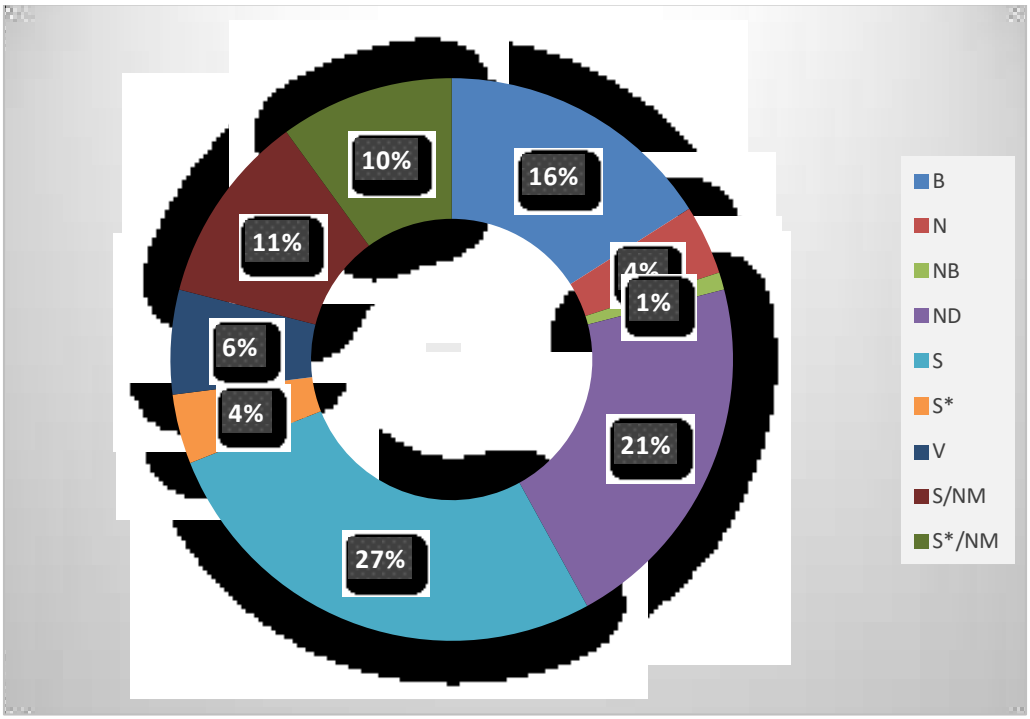
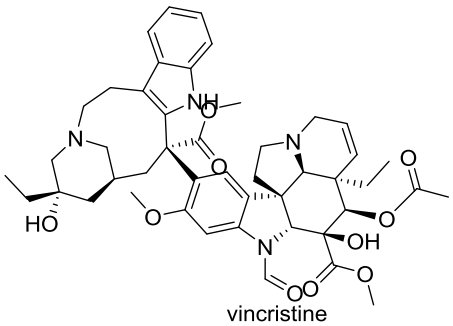
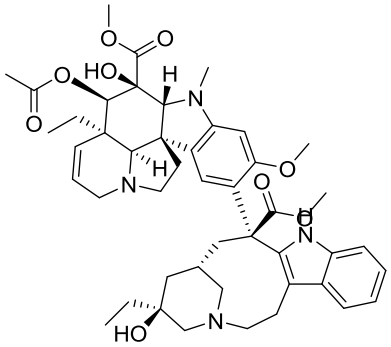


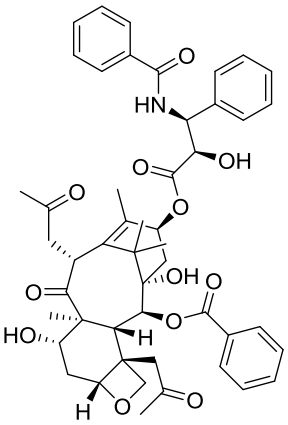
Figure 2: All new approved drugs 1981 – 2014; *n* = 1562, B: Biological macromolecule, 1997, N: Unaltered natural product, 1997, NB: Botanical drug (defined mixture), 2012, ND: Natural product derivative, 1997, S: Synthetic drug, 1997, S*: Synthetic drug (NP pharmacophore), 1997, V: Vaccine, 2003, /NM: Mimic of natural product, 2003 [2].



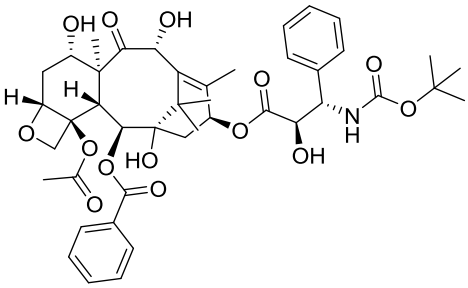
vincristine



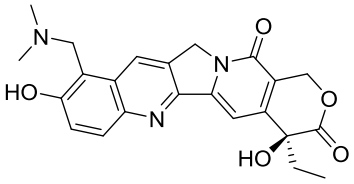
vinblastine



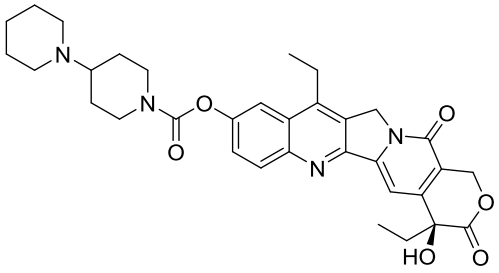
paclitaxel



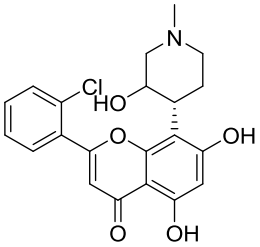
docetaxel



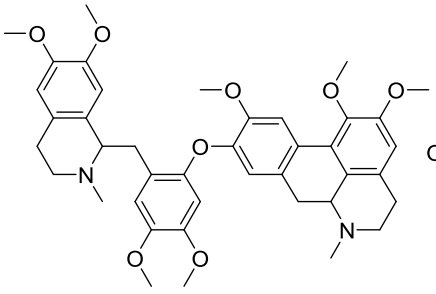
topotecan



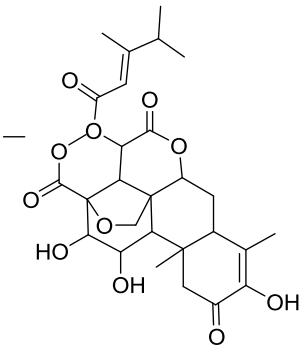
irinotecan



flavopiridol



thalicarpine



bruceantin

Figure 3: Anti-cancer chemical agents isolated from plants [13-17].

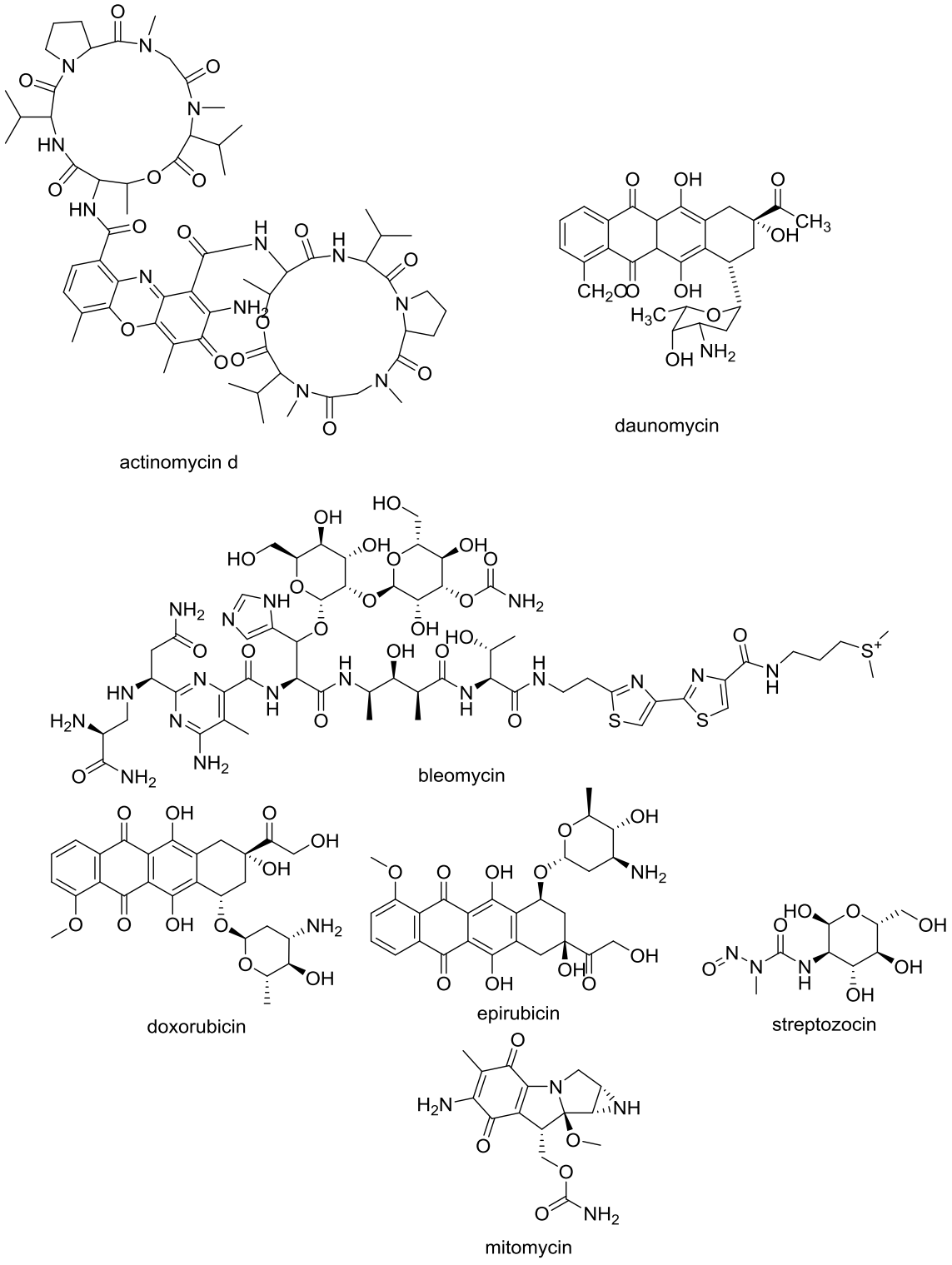


Figure 4: Anti-cancer chemical agents isolated from microorganism [13-17].

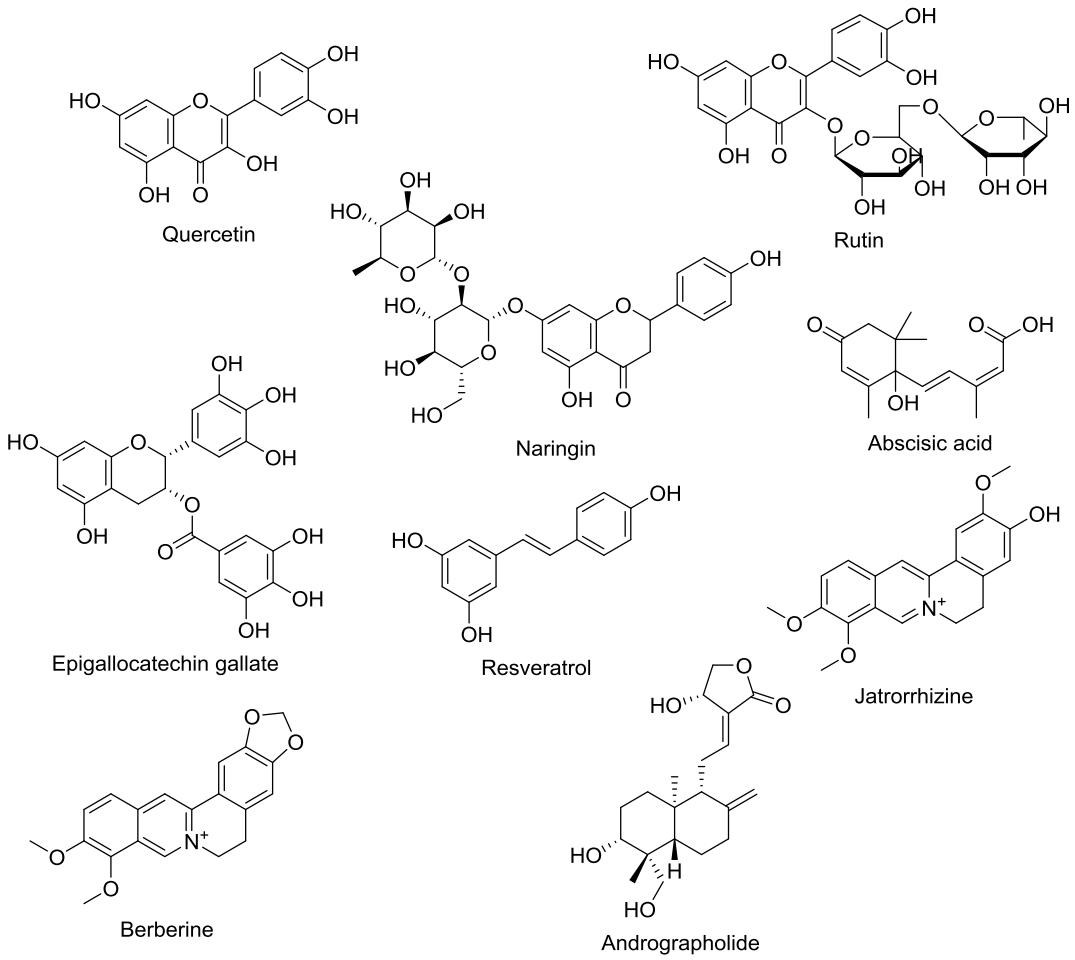


Figure 5: Chemical compounds isolated from natural sources used to reduce blood glucose level in DM patient.

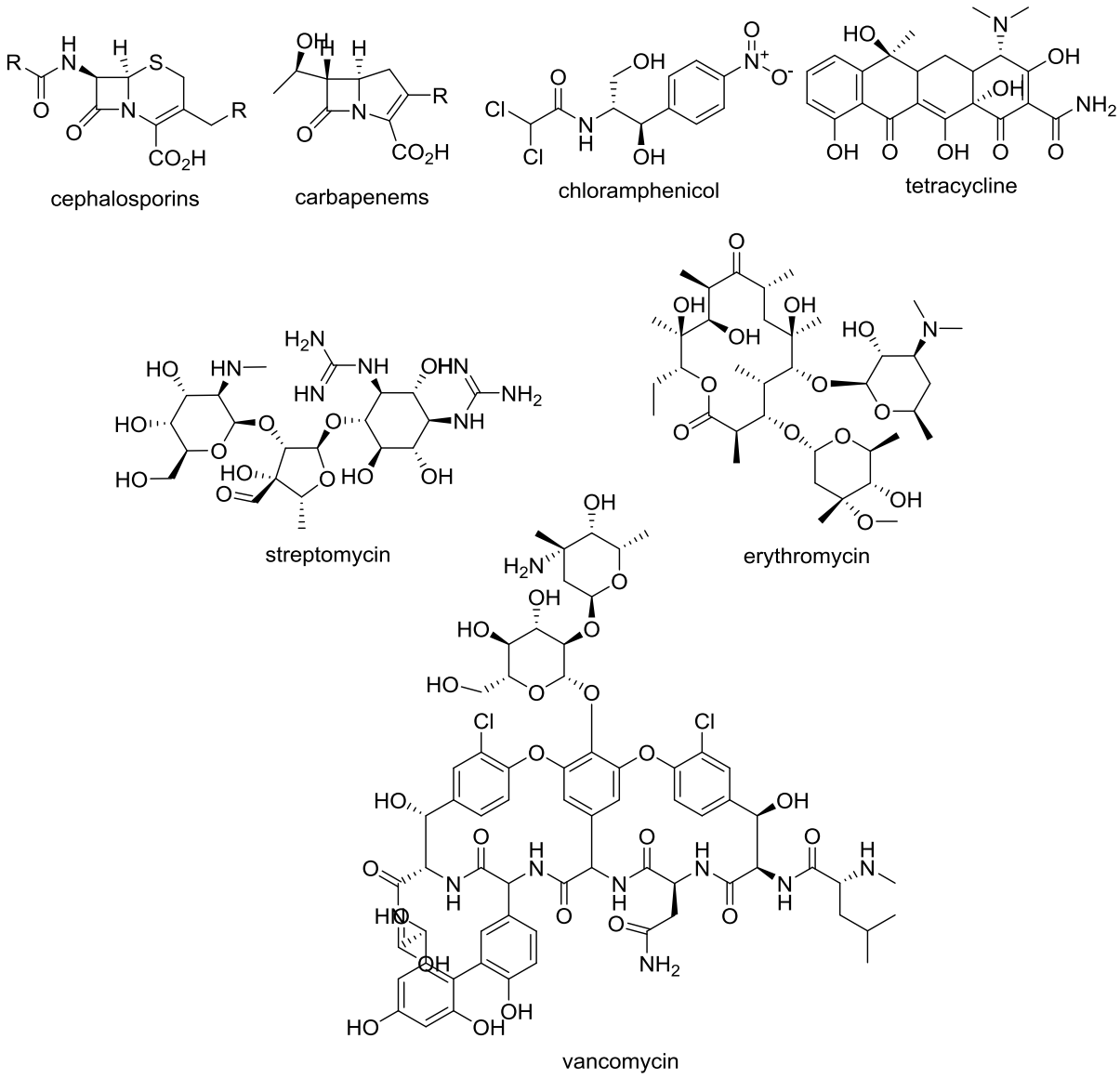
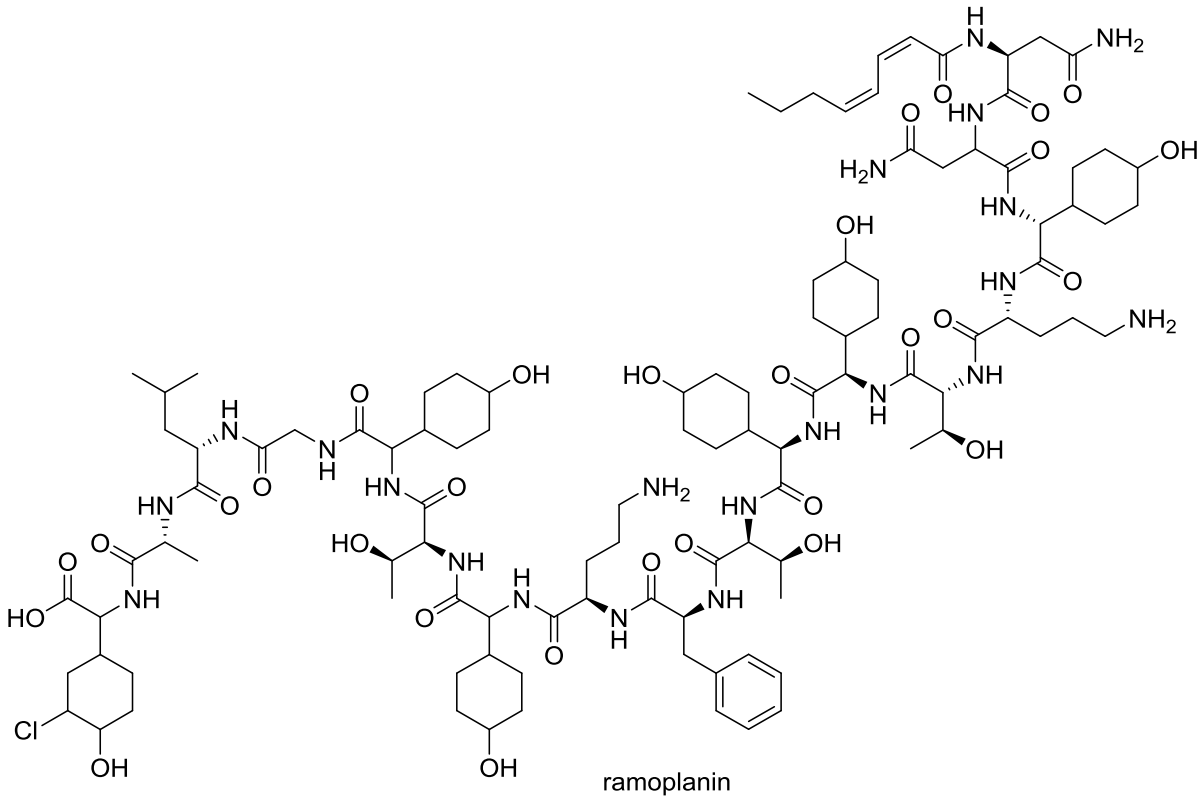


Figure 6 (A): Examples of antibiotic compounds isolated from natural sources.



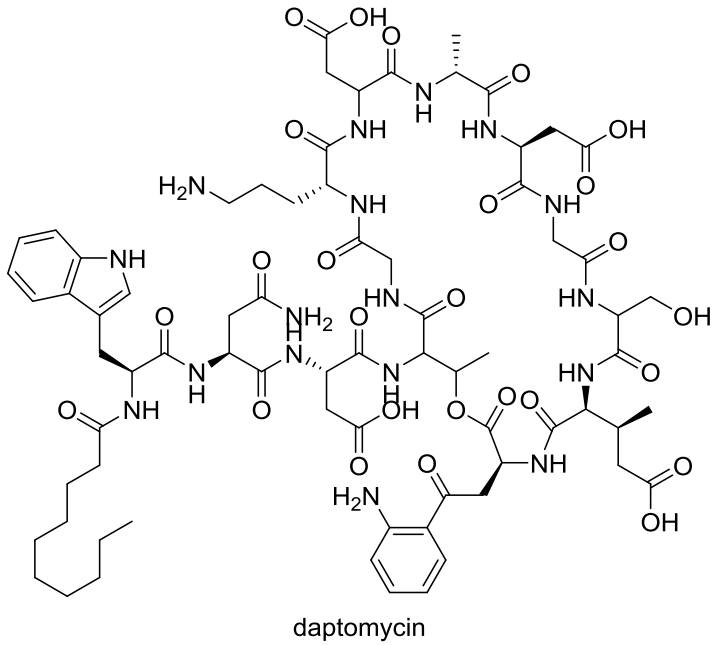


Figure 6 (B): Examples of antibiotic compounds isolated from natural sources.