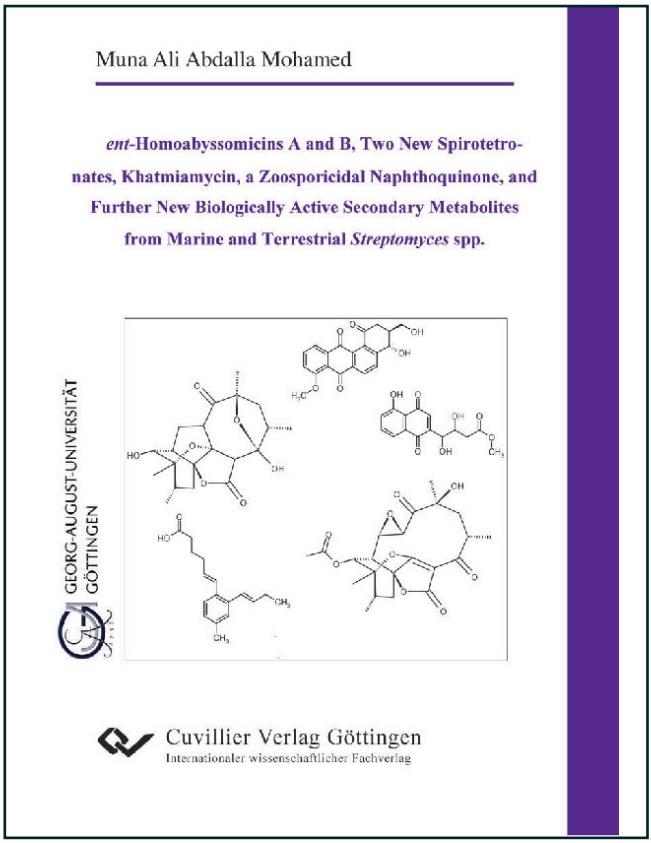
Muna Ali Abdalla Mohamed (Autor)

"ent-Homoabyssomicins A and B, Two New Spirotetronates, Khatmiamycin, a Zoosporicidal Naphthoquinone, and Further New Biologically Active Secondary



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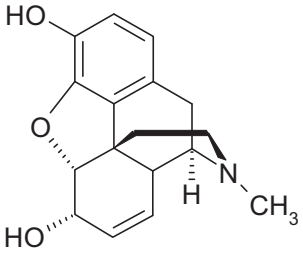
1 Introduction

1.1 Short History of Plant-derived Drugs and Traditional Medicine

In Africa and Asia, the majority of the population lives in rural areas and relies on plant materials to treat their illnesses. The plants are used in different forms such as extracts or decoctions to treat cancer, tuberculosis, HIV, malaria and many other diseases. Accordingly, these drugs, which are referred to as 'traditional herbal medicines' play an important role in improving the health status of the population and preventing endemic and acute diseases.[1] Also in developed countries traditional herbal medicine has attracted great interest,[2] enforced by the green movements and an increasing aversion to synthetic materials. Scientifically, plant metabolites have provided important ideas for discovery and industrial development of therapeutics.[3]

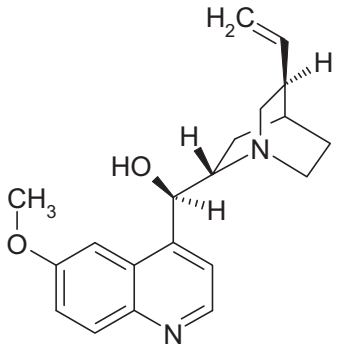
The beginning of this development dates more than 200 years back. The young German pharmacist Friedrich Sertürner (1783-1841) isolated at an age of 21 one of the first pharmacologically active compounds in a pure state: He obtained morphine (**1**) from opium, the latex produced by cutting the seed pods of poppy, *Papaver somniferum.*[4,5] Morphin (**1**) was the first commercially produced plant product with a guarantee for it's purity. Since then the idea to isolate pure compounds from plants began a rapid development, and the plant-focussed traditional medicine was set on a scientific basis.



1

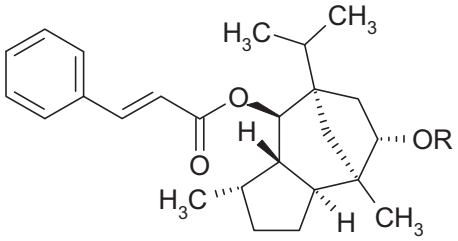
Quinine (**2**) from the *Cinchona* tree[6] was the first effective antimalarial drug used until the 1940s. In the 17th century, Jesuit Missionaries in the Andes (western South America) discovered that the extract of the *Cinchona* tree can treat fever, and the tree was known as "Jesuits' bark" at that time. In 1820 the French chemist Pierre-Joseph Pelletier (1788-1842) together with Joseph-Bienaime Caventou (1795-1877) succeeded to isolate quinine (**2**) from *Cinchona* bark. The structure was confirmed

later by the American organic chemist Robert Burns Woodward (1917-1989) by synthesis.[7]



2

Englerin A (**3a**) and englerin B (**3b**) have been isolated from the stem bark of *Phyllanthus engleri* (Euphorbiaceae) on the basis of ethnomedical reports about their toxicity. Englerin A (**3a**), the major compound of this species, showed indeed a 1000-fold higher selectivity against six renal cancer cell lines, with GI_{50} values ranging from 1–87 nM compared with taxol.[8]

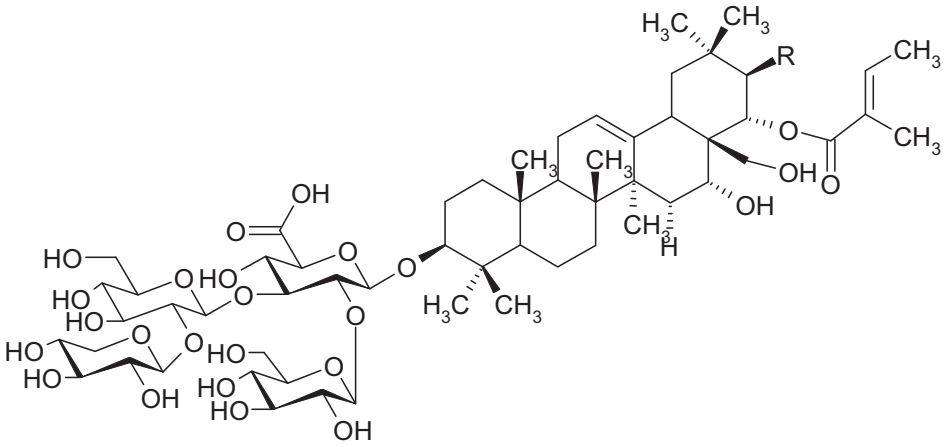


3a: R = $COCH_2OH$

3b: R = H

Recently the methanolic extract of the stem bark of the medicinal plant *Antonia ovata* afforded four highly cytotoxic triterpenoid saponins: Compounds **4a** and **4b** exhibited the most potent cytotoxic activity of all isolated and tested metabolites.[9]

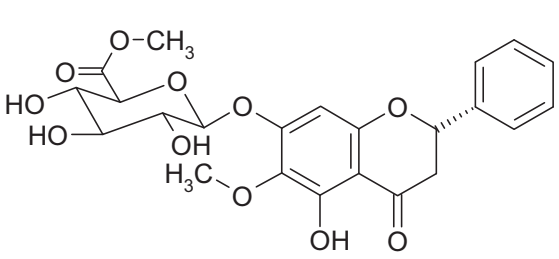
Flavonoids are a group of naturally occurring compounds present in fruits and vegetables. Recent studies indicated that flavonoids play a role in the prevention of cancer. The mechanism is not yet clear, but there are many hypotheses suggesting that these compounds may act as antioxidants or as phytoestrogens and interfere with estrogen metabolism. Another suggestion is that these compounds act by affecting the cell signalling or the regulation of genes involved with carcinogenesis.[10]



4a: R = H

4b: R = $OCOCH_3$

New flavonoid glycosides **5** and **6** were isolated recently from the stem bark of the medicinal plant *Oroxylum indicum* and tested for their ulcer protective effects against various gastric ulceritis inducing models in rats. Compound **5** with a free phenyl ring (ring B) together with a glucuronide linkage afforded the most potent gastroprotective activities.[3]



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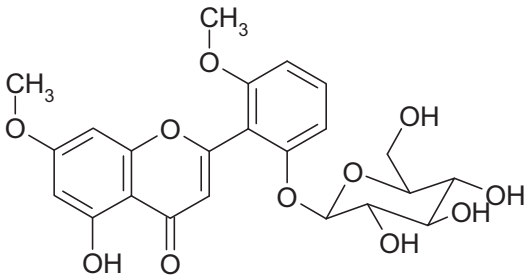
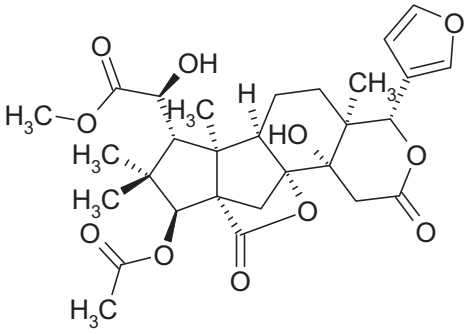


6

Plants are still a source of novel and interesting structures: A recent example is the new limonoid grandifotane A (**7**), which has been isolated from the stem bark of *Khaya grandifoliola* (Meliaceae). The structure was confirmed by X-ray crystallography. This plant has been used traditionally in Africa as antimalarial remedy.[11]



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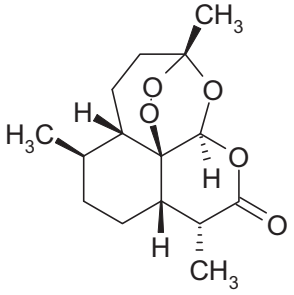
The most important example of the recent development in plant therapeutics is certainly artemisinin (**8**) from *Artemisia annua*.[12] It has been found to be up to 97% effective against malaria and is globally distributed, especially in Africa where one child dies from malaria every 30 seconds.[13]



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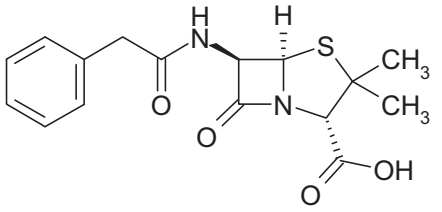
1.2 Natural Products in Modern Medicine

While the traditional medicine is mainly based on plants (and to a lesser extend on animals), the "modern" nature-derived medicine relies additionally on microbial metabolites: In 1928, the biologist and pharmacologist Alexander Fleming (1881-1955) discovered that colonies of *Staphylococcus aureus* could be destroyed by the mould *Penicillium notatum* proving the existence of antibacterial agents produced by other microorganisms and assessing the principle that certain drugs could kill pathogenic bacteria inside the body.[14,15] In the 1940s, the use of penicillin (**9**) as an antibiotic was initiated by the contributions of Howard Florey (1898-1968) and Ernst Chain (1906-1979), who purified and characterized the effective ingredient, penicillin.[16] The discovery of penicillin paved the road for the birth of β-lactam antibiotics such as the many modified penicillins and cephalosporins (cephalosporin C, **10**).[17,18] After the Second World War pharmaceutical research was intensified, and the success of penicillins encouraged the scientists to search for further antibiotics from microorganisms. In 1990, nearly 80% of the newly discovered drugs were derived from natural

products. These natural drugs included antibiotics such as tetracycline (from *Streptomyces rimosus*),[19] erythromycin (**11**) (from *Saccharopolyspora erythrea*)[20] as well as antiparasitic drugs like avermectin (avermectin B1a, **12**) (from *Actinomyces* sp.).[21]



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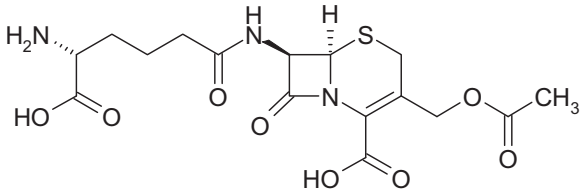

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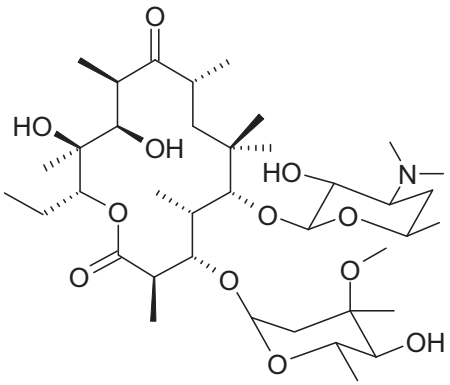

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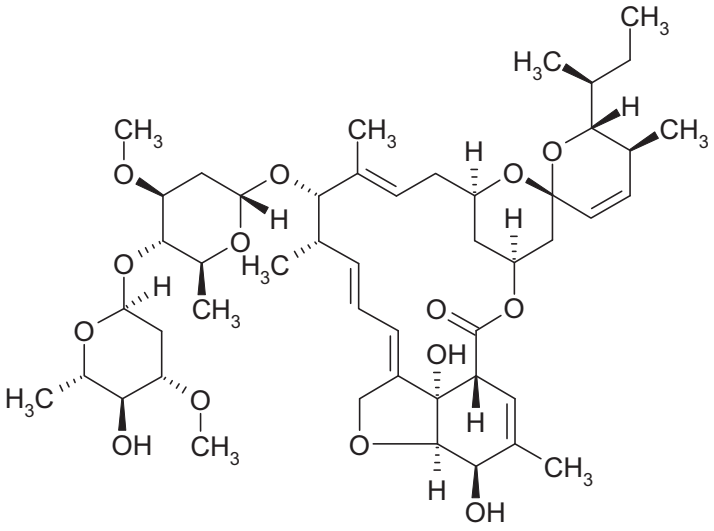

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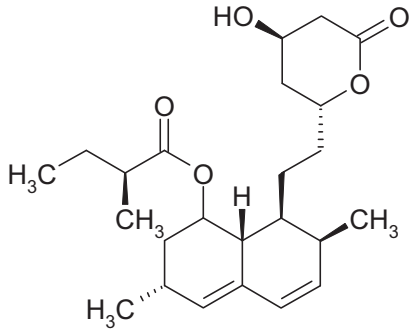

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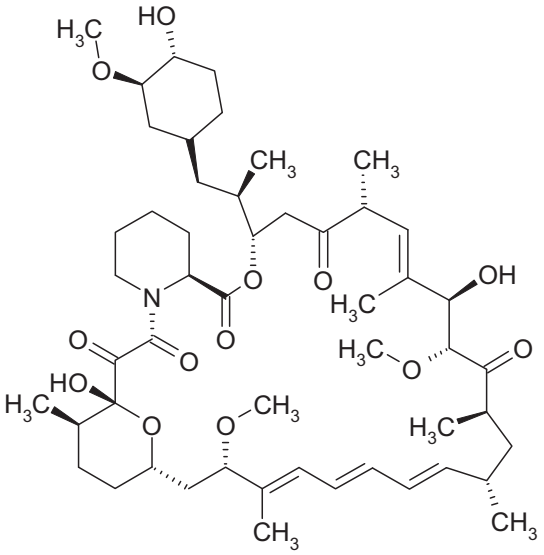
Additionally, lipid control agents like lovastatin (**13**) (from the fungus *Aspergillus terreus*),[22] immunosuppressants for organ transplants like cyclosporine,[23,24] (from the fungus *Beauveria nivea*) and rapamycin (**14**)[25] (from *Streptomyces hygroscopicus*) and anticancer drugs such as doxorubicin[26] (from *Streptomyces peucetius*) were discovered. These drugs revolutionised the medicinal industry during the late fifty years in the 20th century till today. Medicinal chemistry developed increasingly new drugs on the bases of natural products.[27]

Stimulated by the successes in medicine, natural products were also applied in agriculture: An important success was the discovery of leading fungicides like strobilurin and synthetic derivatives (e.g. azoxystrobin, *β*-methoxyacrylate) and the insecticide spinosad (a tetracyclic macrolide).[28]



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