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THE ROLE OF NATURAL PRODUCTS IN DRUG DISCOVERY AND DEVELOPMENT

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ABSTRACT

The principle objective of this review was initially to document the use of medicinal plants throughout the history of the humans and the distinct eras during which the so called "Rationoal ethnopharmacology" or the home- remedy based medicine evolved eventually to become what we currently know as the age of " high throughout put technique".

KEYWORDS: Medicinal plants, Phytochemicals, Drug discovery.

1. Medicinal plants' journey across history

Medicinal plants have always been a key cornerstone in the process of healing on both the physical and the spiritual levels, not to mention that they recently gained a sky rocketingly increased popularity in the western societies as a suitable complementary source of nutrients alongside the orthodox medicine.[1]

Since antiquity, medicinal plants uses were mentioned in several archeological evidences from different civilizations around the globe. The earliest known medical document is a 4000-year-old Sumerian clay tablet, that recorded plant remedies for various illnesses.[2] These tablets were unearthed and subsequently considered to be one of the oldest evidences in history.[1] The Egyptian civilization is another wealthy source. Ancient Egyptains used Garlic (*Allium sativum*) as a treatment for cardiac and circulatory disorders, a fact which has been scientifically proven only very recently.[3] They also treated pain with mandrake (*Mandragora officinarum).*[1]

During almost the same period, ancient Chinese developed their system of medicine. The Traditional Chines Medicine, or wildly known as TCM, is known to harbor more than 5000 plants. This wealth of plants was schematized and structured in the Chinese *Materia Medica* which was published in 1977.[4] Well known examples include cinnamon (*Cinnamomum zeylanicum*) to treat gastro intestinal upset, Astragalus (*Astragalus membranaceus*) as adaptogen i.e., relief stress and Rhubarb (*Rheum rhabarbarum*) as a cathartic. Ginseng (*Panax ginseng*) is the most famous one, of course, even though there has been a dispute among researches about its origin.[5]

Ayurvedic medicine (also known as Traditional Indian Medicine) represents a highly reputable, independent school with its own criteria, profundity and complexity. This school represented a key point in transferring knowledge to the subsequent Greek and Muslim civilizations. The concept of the "Four bodily humors": health being a result of their harmony and illness of their imbalance that shaped Galenical Medicine was adapted from the Ayurveda.[4] The neuropsychiatric combined with antihypertensive activity of *Rauwolfia serpentina,* an ayurvedic herb used in India, was clinically assessed and ultimately marketed worldwide, saving millions of lives.[6] Shamans in North America enjoyed a high religious, spiritual and social standard within the tribal settings. The so called "shamanistic Rituals" targeted to cure the insane and alleviate the burden of mental and physical illness amid the tribe members.[4]

The effect of the Greeks is no less than prominent. Name such as Theophratus, Dioscorides and Galen emerged during the course of the Greek (and Roman) civilizations as medicines men, practioners, teachers and most importantly, authors of books which impacted in a multitude of ways the Arabs and the medieval medicobotanical practice.[7]

The climax of the previous evolution in Herbal medicine was during the Islamic civilization. In addition to the ibn al- baitar's Pharmacoepia of *Kitāb Al-jāmi fi-mufradāt al-adwiya wa al-aghdhiya* registering more than 1400 medicinal plants,[8] Other Arab Scientist were pioneers in developing modern pharmacy and chemistry practice. They introduced novel methods of extraction and coined new scientific terminologies.[9]

2. From whole plant's extracts to area of active constituents

So far, plants were used as a whole and "Medical Herbalism" remained as a practice largely based on observation and transmission from generation to another with no solid scientific

foundations. The next 'leap'in the field could have not been possible had there were not remarkable advances in a closely related science: Chemistry. Chemists all over the 18th-19th century Europe were preoccupied developing methods to purify, isolate and elucidate the structures of organic compounds. A new concept has evolved: the pharmacological activities of medicinal plants observed since antiquity can be attributed to chemical compounds that can be detected and identified. The first recorded breakthrough in the field came from Friedrich Serturnern in 1806, who was isolated morphine from opium poppy (*Papaver somniferum).*[1] Subsequent success stories echoed all over Europe by the isolation of Quinine, atropine, Caffiene, Coiine, Emetine, Strychnine, Tubocurarine and Acetylsalicylic acid (Aspirin). However, the discovery of Aspirin represents a dilemma in the history of modern science.[10] The investigation done by Walter Sneader revolutionized our view and understanding of the history of science and more importantly noted that scientists should not succumb to quixotic chronicles without thoroughly investigating them with an eye keen on details and the relations underlying chronological events.[10]

By the 20th century, the pure bioactive compounds isolated from medicinal herbs where formulated into suitable pharmaceutical dosage forms on a large scale. This was the time when business and science collaborated to produce quantities sufficient to cover the need of the market: millions of people. And this was the time when giant pharmaceutical companies emerged, for example: Bayer's and Co. and Boehringer Ingelheim. The process of isolation and purification of bioactive compounds not only took place in the laboratories of universities, but also in these companies' labs. It is worth mentioning that in certain cases, it would've not been possible to carry out the drug discovery process without the equipped, state-of-the-art laboratories (at that time, of course) of such companies.

3. Importance of plants in Modern Medicine

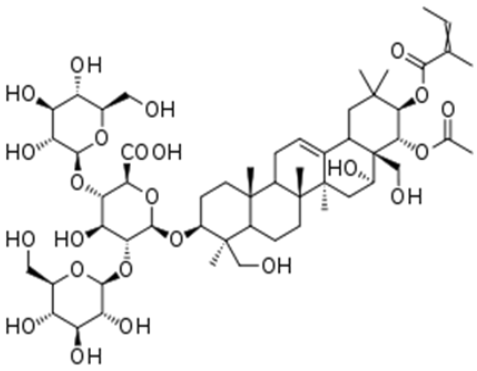
Plants can be serving as source of bioactive compounds with new chemical entities of wide structural diversity, which can be used: directly as bioactive compounds, as drug precursors, as drug prototypes, as pharmacological tools and as marker compounds for standardization of extracts.[11]

I- Plant secondary metabolites as drugs

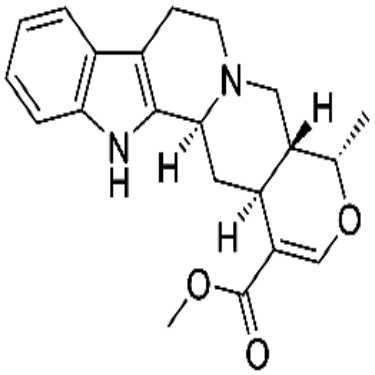
The second half of the twentieth century witnessed a rapid development in the methods and instruments in the process of plant's secondary metabolites isolation. In addition to that, the potential activities of the isolated compounds were understood at a molecular level.[11]

Thousands of secondary metabolites were isolated and used as drug such as: Digoxin which used as cardiotonic is isolated from *Digitalis purpurea* (purple or common foxglove), Aescin which used as anti-inflammatory, venotonic, and as anti-eadematous drug is isolated from *Aesculus hippocastanum* (horse chestnut).[12] While Ajmalicine the indole alkaloids used for treatment of circulatory disorders was first isolated from *Rauwolfia sepentina* by Siddiqi in 1931.[11]

Cragg and associates conducted an analysis and found out that 30% of the approved drugs by the FDA (Food and Drugs administration) between 1983-1992 were of natural origin.[13]



Aescin



Ajmalicine

II. Plant secondary metabolites as drug precursors

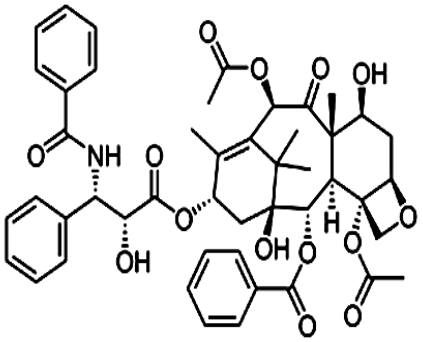
The semi-synthetic approach is usually used to resolve the shortage of supply due to the low yield of compounds from plants and/or the high cost of total synthesis. Drug precursors can be converted into the compound of interest by chemical modification or fermentation methods. The following examples indicate some secondary metabolites from plants are useful drug precursors, although they are not necessarily pharmacologically active in their original naturally occurring forms:

Paclitaxel (well-known potent anticancer compound) was semi-synthesized by Bristol-Myers Squibb method since 2002 from 10-deacetylbaccatin III which isolated from *Taxus baccata*. (Family: Taxaceae).[14]

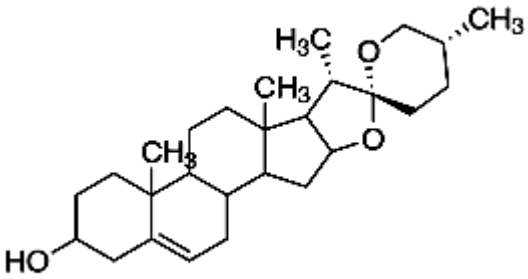
Diosgenin, a steroidal sapogenin obtained from the tubers of various *Dioscorea* species can be converted chemically in several steps into progesterone.[15]

Oseltamivir phosphate (Tamiflu)® is developed for the treatment and prophylaxis of influenza viruses A and B.[16] The starting material for the oseltamivir synthesis is (−) shikimic acid.

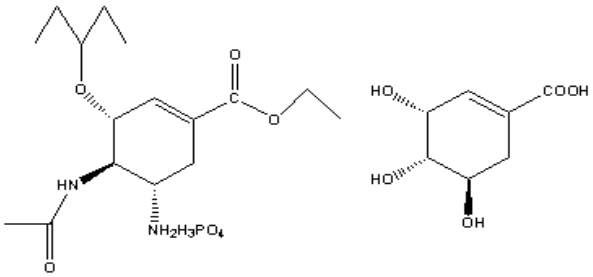
Currently, Roche, the drug manufacturer, still relies on both extraction and fermentation methods to obtain ton quantities of shikimic acid.[17]



Paclitaxel



Diosgenin



Shikimic acid

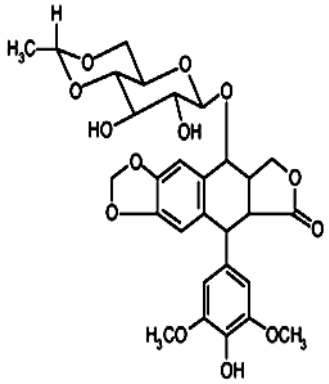
III. Plant secondary metabolites as drug prototypes

Drug prototype is the first compound discovered in a series of chemically related therapeutic agents.[18] In 1996, from a total of 244 drug prototypes identified in one analysis from minerals, plants, animals, microbes, and chemical sources, plant secondary metabolites contributed 56 of these (23 %). With advances in organic chemistry, medicinal chemists started preparing analogs from these drug prototypes to provide safer and more potent drugs[18] such as:

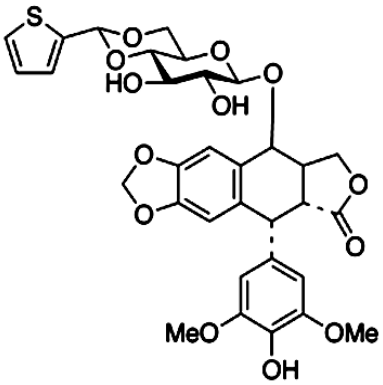
Several anti-neoplastic compounds isolated from plants, such as podophyllotoxin and camptothecin, were too toxic and not water soluble enough for clinical application, and analogs with higher therapeutic indices such as etoposide (Vepesid)® and topotecan (Hycamtin)® have been developed in consequence.[19]

Guanidine is a natural product with good hypoglycemic activity isolated from *Galega officinalis* L., but it was too toxic for clinical use. Many derivatives of guanidine have been

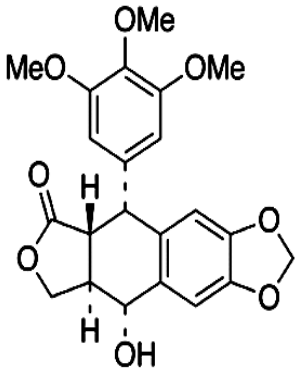
synthesized, metformin (dimethylbiguanide) was later found to be clinically suitable for treatment of type II diabetes.[20]



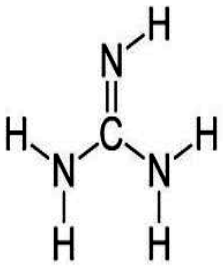
Etoposide



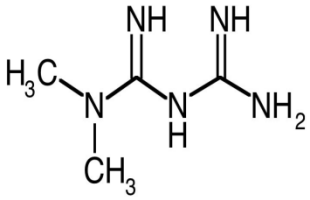
Topotecan



Podophyllotoxin



Guanidine



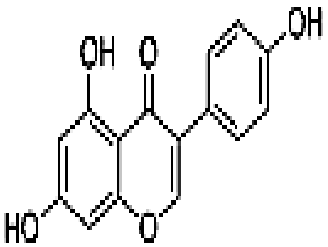
Metformin

IV. Plant secondary metabolites as pharmacological probes

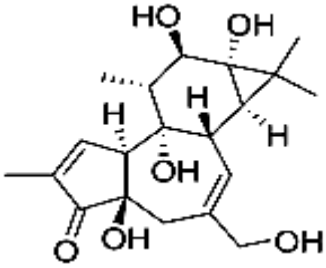
Pharmacological probes help researchers to understand the mechanism of action of intracellular signal transductions and biological mechanisms related to human disease, which can aid the design of better drugs.[21]

Genistein, an isoflavone found naturally in soybean (*Glycine max Merr.*), is an inhibitor of various protein tyrosine kinases (PTK), which are essential enzymes involved in intracellular signal transduction. Genistein is used to probe the interaction between PTK and cyclic nucleotide-gated (CNG) channels, which are important in mammalian olfactory and visual systems.[21]

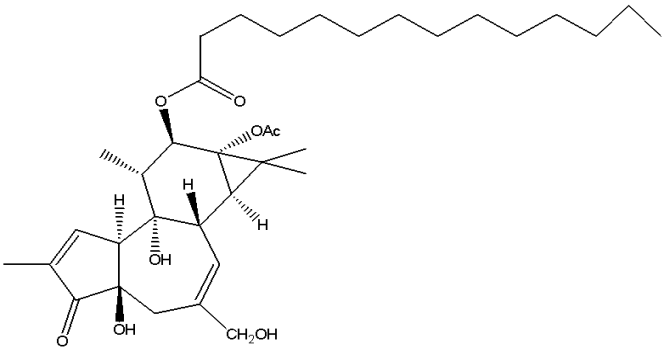
Phorbol is a tetracyclic diterpenoid plant secondary metabolite isolated as a hydrolysis product of croton oil from the seeds of *Croton tiglium* L. Various 12, 13-diesters of phorbol have the capacity to act as tumor promoters.[22]



Genistein



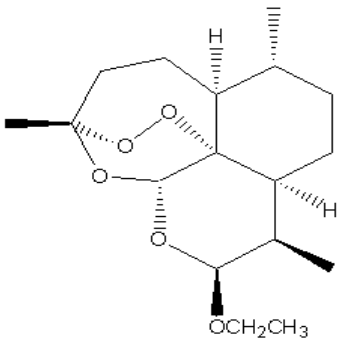
Phorbol



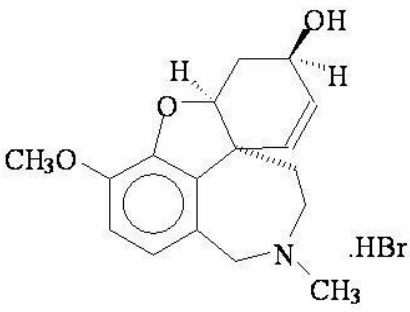
12, 13-diesters of phorbol

4. Recent successes of plants

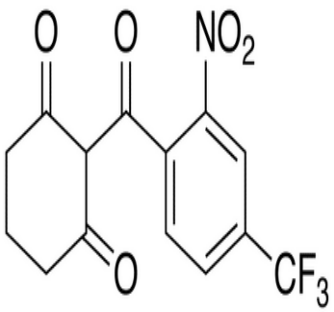
There was phenomenal increase in research about medicinal plants efficacy and safety.[23] Between 2000 & 2005, over 5 new drugs on the market from plants appeared (11) e.g. Arteether (potent anti-malarial drug derived from artemisinin, a sesquiterpene lactone isolated from *Artemisia annua* L. (Asteraceae),[24] Galantamine hydrobromide (used for the treatment of Alzheimer's disease, first isolated from *Galanthus woronowii Losinsk.* (Amaryllidaceae)[25] Nitisinone, Tiotropium bromide and Apomorphine hydrochloride (used for treatment of chronic obstructive pulmonary disease is based on ipratropium, a derivative of atropine that has been isolated from *Atropa belladonna* L. (Solanaceae).[26]



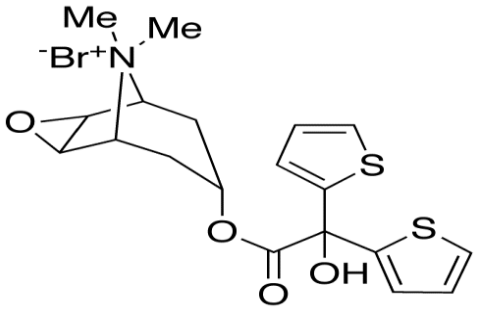
Artemisinin



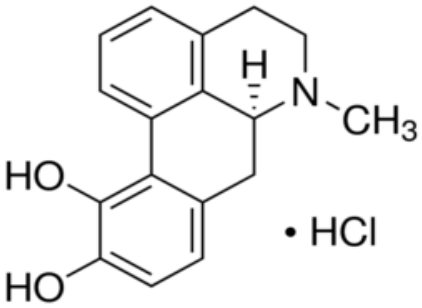
Galantamine hydrobromide



Nitisinone



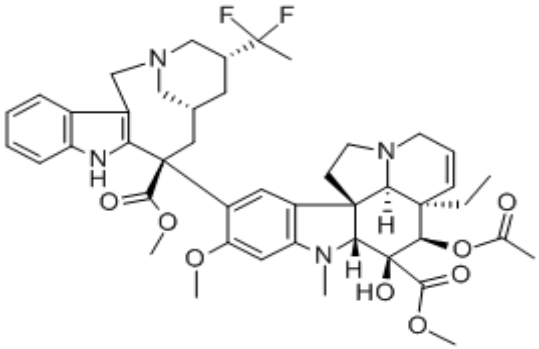
Tiotropium bromide



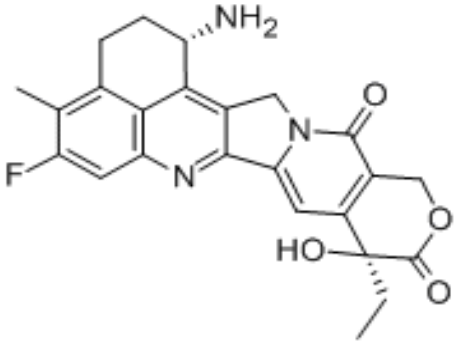
Apomorphine hydrochloride

From 2005 to 2007, thirteen natural products related drugs (most of them coming from plants of cultural importance) were approved and over a 100 new products are in clinical development, particularly as anticancer and anti-infective agents.[27]

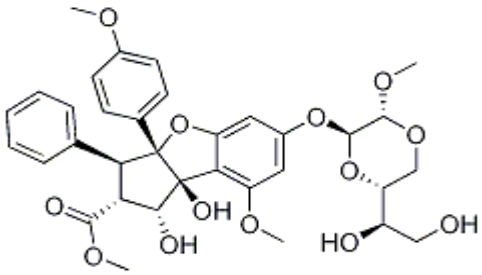
Several promising plant-derived compounds are in clinical trials through the auspices of the U.S. National Cancer Institute as potential cancer chemopreventive agents e.g. Vinflunine (modification of vinblastine from *Catharanthus roseus* (L.) (Apocynaceae),[28] Exatecan (an analog of camptothecin *from Camptotheca acuminata* (Nyssaceae)[29] pervilleine A (isolated from the roots *of Erythroxylum pervillei* (Erythroxylaceae)), silvestrol (isolated from the fruits of *Aglaia foveolata*. (Meliaceae)[29] Ingenol 3-*O*-angelate (obtained from *Euphorbia peplus* (Euphorbiaceae)[30] and 8-Triptolide (diterpene triepoxide, was isolated from *Tripterygium wilfordii* (Celastraceae).[31]



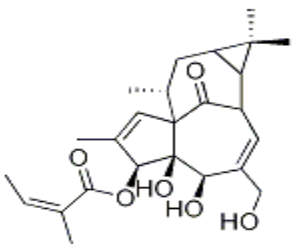
Vinflunine



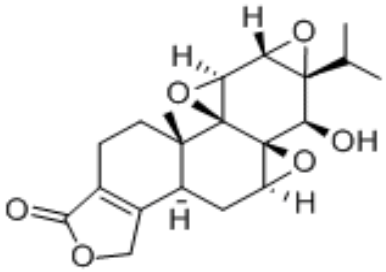
Exatecan



Silvestrol



Ingenol 3-*O*-angelate



Triptolide

Large pharmaceutical companies, such as CIBA, Galaxo, Boehringer and Syntex now have specific departments dedicated to the study of new drugs from natural sources.[27]

5. Future role of plants in medicine

The development of automated high-throughput techniques with advances in data handling systems and robotics, high-throughput screening assay methods have been developed with computational filtering methods to identify and remove potentially problematic compounds that can give false-positive results, all that allowed the rapid screening of plant extracts; thus, the biological assay is no longer the rate-limiting step in the drug-discovery process.[32]

In addition the structure(s) of compounds in wells of these plates that show(s) activity can be determined by NMR and MS, and known compounds can be ruled out quickly based on their NMR spectroscopic and MS information. In instances where the active compound has a new structure, further isolation can be carried out from the plant material, provided there are enough samples. Alternatively, the compound can be synthesized for further bioassay, and combinatorial chemistry can be used to design new analogs based on the parent molecules.[32]

Compounds that are uneconomical to synthesize and only available in a small quantities from plants such as *Catharanthus* alkaloids, diosgenin from *Dioscorea* and the *Panax ginseng* ginsenosides, the use of plant cell cultures is an alternative production method.[32]

The use of single herb as a drug (senna products as laxative and St john's wort for moderate depression) or using herbal formulations containing mixture of several herbs (synergistic effect of many compounds in these herbs extracts was observed) after standardization and adjustment of the doses were expected to increase in the future because Many scientists account for that by many herbs show remarkable activity while their isolates show less or no activity.[33]

6. CONCLUSION

1. Plants have provided humans with many of their essential needs, including life-saving agents for centuries.
2. As only 6% of the available higher plant species have been screened biologically, drug discovery from plants should remain an essential component in the search for new medicines, particularly with the development of highly sensitive and versatile analytical methods.
3. We are without delay need a huge national multidisciplinary project for drug discovery from natural sources.
4. Plants play important role in medicine but need good cooperative human efforts to discover and benefit from their treasures.

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