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Plant Biodiversity as Sustainable Source of New Drug Candidates and Phytotherapeutics

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Abstract

Plant kingdom has a great biodiversity in terms of species number. Among them, medicinal plants have always possessed a major importance in terms of exploring new drug candidates as well as phytotherapeutics since ancient civilizations. Many plants have still remained from Chinese traditional medicine, Ayurvedic medicine, Unani medicine, Kampo medicine, etc. in our day to be used for human health. In this sense, protection and sustainability of plant species are of great importance, while almost 80% of world population relies on traditional or folk medicine. On the other hands, intellectual rights are also vital for local people as well as inventors. However, it is still reality that plants are attractive targets for drug discovery and research as many clinically used drugs (quinine, aspirin, tubocurarine, taxol, artemisinin etc.) had been isolated from plants initially. Not only plants, but also other organisms such as microorganisms, macro-fungi, insects, animal venoms as well as marine organisms are used for this purpose. Turkey has a very rich flora consisting of approximately 12.000 plant taxa, which is due to various climatic conditions throughout the country. It is the richest flora considering whole Europe continent. In our extensive search and screening through Turkish flora as well as other countries, we have so far identified many promising natural compounds with significant bioactivities, particularly enzyme inhibitors by in vitro and in silico approaches. In this review, importance of plant diversity in drug research will be underlined through examples from known molecules along with our own studies.

Key words: Plants, Herbal Medicines, Natural Sources and Drug Research

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1. Introduction

Use of plants has been known for human being since ancient times as food, cure as well as other ethnobotanical purposes. They have also been directly-used in clinic as drug active ingredients or acted as hit or lead molecules for synthetic drugs. Therefore, ethnomedicinal, phytochemical and pharmacological properties of plants have been always attractive to scientists in drug discovery and development. Examples of plant-derived medicines could be mentioned as tubocurarine, quinine, physostigmine, taxol, galanthamine, artemisinine, etc. In this sense, global plant biodiversity is quite important to be used as biosources. However, since the beginning of 20th century; some factors such as difficulties to collect some plant species, extinction risk on many plant species, endemic plants as well as changing political conditions in many countries (embargo, war, etc.) limited use of plants as drug material for some time. Despite of these factors, plants have always been considered as the important sources in drug discovery and cosmetic industry up to date.

On the other hand, approximately 1/8 of all plant species in the world has been reported to be under the risk of extinction [1]. But we still medicinal plants for sure because number of molecules entering in the drug market is on decrease, whereas cost of drug discovery and development is on increase. It is also obvious that traditional knowledge is very important since 80% of the world population still relies on traditional medicine, where many communities in various parts of the World has no access to modern pharmaceuticals. In fact, according to NAPRALERT database; 15% of all plant species have been investigated for their phytochemistry up to date, while only 5% of the plants have been screened for their biological activities [2]. Besides, the research has proven that uses of plants with traditional knowledge are 5 times more effective in finding new drug molecules [3].

2. Some Well-known Examples of Plant-Derived Medicines

Without any doubt, plants have been source of many clinical drugs. One of the important examples could be said as tubocurarine, which was a curare alkaloid obtained from the bark of the South American plant *Chondodendron tomentosum* Ruiz and Pavon (Menispermaceae) as active ingredient of tube-curare [4, 5]. Tubocurarine was reported as the first muscle relaxant [6, 7]. Later on, acetylsalicylic acid (aspirin) isolated from the willow bark (*Salix alba* L.) has been a legendary drug, which is still the most commonly used drug worldwide [8, 9]. Its chemical synthesis dates back to 1897 by Felix Hoffman, a chemist worked at Bayer, whereas the willow bark was used as medicine since the times of Sumerians and Egyptians. Aspirin has antipyretic and anti-inflammatory effects, where its antiplatelet activity was also discovered after 70 years by the pharmacologist John Vane [10]. Quinine is another old instance of plant-derived medicines with antimalarial effect, which was isolated from *Cinchona* sp. bark, mainly *Cinchona ledgeriana* (Howard) Bern. Moens ex Trimen (Rubiaceae). It was introduced to Europe in 17th century from South America [11] and cultivation of the plant to supply quinine was long time managed by Dutch cinchona-quinine enterprise, which was a strong alliance [12, 13]. Nevertheless, the use of quinine has declined due to its marked toxicity, whereas it is still prescribed in resource-limited locations in severe malaria [14].

Considering more recent plant-derived drugs, paclitaxel (Taxol®) is an antitumor molecule of diterpenoid-derivative isolated from Western yew or Pasific yew tree (*Taxus brevifolia* Nutt., Taxaceae) in 1972 and approval for clinical use was granted in 1993 [15]. It is the first microtubule stabilizing agent described in the literature and particularly effective against breast, lung, ovarian cancers as well as Kaposi's sarcoma, which also causes neutropenia and peripheral neuropathies [16]. Currently, support continues to basic research in order to investigate how paclitaxel works in different cell types and how it can be used to treat other types of cancer. On the other hand, galanthamine is a recent anti-Alzheimer drug of herbal origin firstly isolated from the bulbs of *Galanthus woronowii* Losinsk (Amaryllidaceae). It acts as a long-acting, selective, competitive, and reversible inhibitor of acetylcholinesterase, which was characterized in the early 1950s in Bulgaria and released into the clinic in the year of 2000 [17-19]. Galanthamine can easily pass blood-brain barrier and possesses less adverse effects than the other clinically available drugs for Alzheimer's disease (AD) [20]. Artemisinine, a natural compound having a sesqiterpene lactone skeleton isolated from *Artemisia annua* L. (Compositae), is a potent and rapid antimalarial drug of natural origin, which was recommended as the first-choice treatment for malaria by World Health Organization (WHO) in 2006 [21]. It was firstly tested in the 1970s in China. From artemisinin, a number of its analogus/derivatives (arteether, artemether, artemiside, artemisinin, artemisone, artesunate, and dihydroartemisinin) have been semi-synthesized [22-24]. In fact, Youyou Tu, the Chinese scientist, was granted with Nobel Prize in 2015 for her discovery on artemisinin [25]. Besides, the anti-cancer properties of artemisinin and their derivatives have been emerged since the late 1990s [26, 27].

3. Our Ongoing Studies on Plant-Derived Molecules as Hit Compounds with Enzyme Inhibitory Activity

Turkey, a country bridging between Asia and Europe and known as "Asia minor", enjoys a coastline of over 8300 km, the country of has over 10,000 plant species with over 30% endemism rate [28, 29]. Turkey, having one of the richest floras and a center of genetic diversity all over the world, is the only country covered almost entirely by 3 of the world's 34 biodiversity hotspots, *i.e.* Euro-Siberian, Irano-Anatolian, and Mediterranean, hosts around 10,000 plant species & 80,000 animal species, possesses a rich cultural history and an archeological record extending to the Paleolithic era, a rich heritage of traditional knowledge of biocultural diversity, and a variety of climates, ecosystems, and habitats within a relatively limited area (35–42°N and 25–45°E) [30]. It also takes advantage of location between the temperate and subtropical regions at the convergence of three continents.

As a result, Turkey is blessed with a generous biodiversity, as aforementioned, which is enjoyable a lot by natural product chemists and Pharmacognosists. In this sense, our group has been working on exploring new hit molecules from plants with various inhibitory activities against a number of enzymes such as cholinesterases, tyrosinase, elastase, collagenase, lipoxygenase, xanthine oxidase, hydroxymethylglutaryl coenzyme-Q10, phosphodiesterase-I, etc. Among them, we have so far identified many coumarin derivatives of plant origin as hit compounds with potent and selective butyrylcholinesterase (BChE) inhibition, which is related to pathogenesis of AD [31]. The first coumarins with strong cholinesterase inhibition that we reported were imperatorin, xanthotoxin, and bergapten isolated from the fruits of *Angelica officinalis* L. (Apiaceae) growing in Poland [32]. Molecular docking studies confirmed potent interactions between BChE and the tested furanocoumarins. Pteryxin (IC_{50}= 12.96 ± 0.70 g/ml) is a dihydropyranocoumarin derivative that we isolated from *Mutellina purpurea* with selective BChE inhibitory potential [33] (Figure 1). Molecular docking experiments revealed different possible binding modes for pteryxin with both polar and hydrophobic interactions inside the binding pocket of BChE. Relevantly, in our most recent papers, we described potent and selective BChE-inhibiting effect of natural and semisynthetic *O*-alkylcoumarin derivatives [34] as well as several furanocoumarins [35].

In addition to natural coumarins, we have also reported many phenolic compounds with enzyme inhibitory effect. Among them cholinesterase-inhibiting compounds such as flavonoids [36-38] and terpenes (tanshinones) etc. [39, 40], phenolics (rosmarinic acid) etc. [39], alkaloids (*N*-acetyltryptophan) [41]; carbonic anyhydrase and urease-inhibiting plant-derived compounds [42], tyrosinase-inhibiting compounds such as cinnamic acid derivatives [43] as well as several phosphodiesterase-1 (PDE-1)-inhibiting natural products [44] (Figure 1).

4. Threatens to Plant Biodiversity in Turkey

Many plant species, communities, and their ecological interactions, including the many relationships between plant species and human communities and cultures, are in danger of extinction, threatened by such human-induced factors as climate change, habitat loss, over-exploitation, alien invasive species, pollution, clearing for agriculture, urbanization, and collection from the wild. For example; approximately 300 plant species, *e.g. Trifolium parchycalyx* (yonca), *Lathyrus undulatus* (Istanbul nazendesi), *Centaurea iconiensis* (Konya gasagi, tülüşah), *Thermopsis turcica* (Eber sarısı, piyam), *Sonchus erzincanicus* (Erzincan süt otu), *Silene sangaria* (Karadeniz salkımı), etc. are endangered in Turkey [45,46]. In addition, many geophyte species are endangered in Turkey, where total number of geophytes in our country is about 600 species [47]. Another plant species under risk of extinction in Turkey is orchids due to illegal and unconcious collection of orchid tubers. Actually, Turkey is very rich in orchid species with about 200 species, 30 of which are endemic, whereas 120 million orchids, which are collected to sacrifice for making a special ice cream as well as a traditional hot drink called “salep” are collected annually in Turkey by local people [48-50]. For instance; although collection prohibited since 1974 by the Turkish Ministry of Forestry and Agriculture, we have unfortunately only 200 left from *Ophrys lycia* Renz & Taubenheim (Orchidaceae) growing only in Turkey. Relevantly, another plant genus that needs to be mentioned in this regard is *Fritillaria*. Turkey is the richest country in terms of *Fritillaria* species in the world with total number of 43 species [51, 52]. In particular, *F. imperialis* (ters lale) and *F. persica* (Adıyaman lalesi) are the most popular ones as ornamental flowers, where one bulb costs around 5 to15 Euro in Europe. Therefore, these two species are known as the most smuggled ones from Turkey.

5. Conclusion

Up to date, we have screened over 100 plant-derived compounds having a noteworthy inhibitory activity towards different enzymes which are target for many diseases threatening human health. Targeting these compounds, we preceded them to in silico experiments in order to figure out the interactions at molecular level. All this research point out to the fact that medicinal and aromatic plants are always fruitful sources for drug research as aforementioned.

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