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The Hidden Treasure in Europe's Garden Plants: Case Examples; *Berberis darwinni* and *Bergenia cordifolia*

Solomon Habtemariam*

Pharmacognosy Research Laboratories, Medway School of Science, University of Greenwich, Chatham-Maritime, Kent ME4 4TB, UK

Abstract

Numerous plants cultivated in European gardens have a history of traditional medicinal uses. Some are native to Europe, while others are introduced from other geographical regions. Systematic pharmacological and phytochemical studies on these plants could yield valuable lead compounds of pharmacological significance. In this short communication, two case examples using *Berberis darwinni* and *Bergenia cordifolia* are presented.

Keywords: European plants; Drug leads; *Berberis darwinni*; *Bergenia cordifolia*

Introduction

For centuries, plants have been used as sources of medicine by mankind. In many developing countries, plant medicines still serve as the primary means of healthcare for treating various illnesses, and current estimates indicate the share of plant-derived drugs in these regions to be about 80% [1]. It is needless to say that Europe and other western countries have recently seen the green medicine resurgence: the ever increasing list of herbal products on the shelves of local pharmacies and health food shops is testimony to people opting to use natural medicines. But how about the secrets within our European garden plants that we might have taken for granted? Some of them have a long history of medicinal uses substantiated by scientific evidence. It is not intended here to list herbal products that are on large scale production for their medicinal uses, but to give two selected examples from common European garden plants that highlight hidden treasures in our gardens.

Traditionally, the search of novel drugs from natural sources take one of the two routes: the ethnobotanical and random screening approach [2]. The ethnobotanical approach starts by documenting the traditional medicinal uses of plants and screen them for biological activities that closely match the indicated disease condition. There are numerous good examples one can use to validate this approach, including the discovery of anticancer drugs, podophyllotoxin derivatives, from studies on *Podophyllum species*. Artemisinin from *Artemisia annua* is another perfect example of the ethnobotanical approach of drug discovery studies. Getting the correct or all information from the ethnobotanical source and even understanding the information, as well as the time scale required for such studies however could be seen as the major challenge of this approach. For those institutions that could afford running hungry assays (e.g. big pharmaceutical industries), the random screening approach using a selected unique target area is an alternative drug discovery approach. This approach, from a well deserved example of the anticancer drug taxol identified from the bark of the Pacific yew tree, *Taxus brevifolia*, has its own success story. When one works in an academic institution like ours where funding is a major constraint, however, a combination of the ethnobotanical and random screening approach study seems very feasible. Hence, we select plants based on ethnobotanical information and use selected high-value targets for pharmacological screening. Whatever strategy is adopted, plants continued to be the source of novel, often structurally complex, chemical entities. Various authors further outlined that about 70% of novel chemicals identified during the last two decades are of natural products origin, of which over half are from plants [1].

Naturally, a drug discovery scientist looks a flora that has not yet been studied and probably those in the tropics and other exotic places with a rich history of traditional uses. There are lots of incentives in studying such plants as the continued deforestation, desertification and over exploitation of endemic plants could lead to their extinction prior to their secret treasures (chemical constituents) being documented. Hence, our research laboratories for over two decades have studied several endemic plants from North and South America, Africa, Asia and Australia. Through systematic pharmacological screening followed by bioassay-guided isolation studies, we have identified various bioactive compounds belonging to several chemical classes [3]. These studies also revealed numerous novel and known chemical entities that could be used for standardization, and/or modernization of traditional herbal medicines. During the course of our study, particularly during the 1990's, we also noticed that there actually exist a big gap in European medicinal plants, with due respect to their chemistry and pharmacology *versus* their claimed medicinal uses. Surprisingly, the chemistry and pharmacology of many European plants, including many acknowledged herbal medicines have not been fully documented. The reasons for these are:

1. There is a general perception that European medicinal plants are exhaustively studied, and there is little chance of getting a pharmacological hit. Most of the earlier studies on European medicinal plants, however, have limitations as the high value targets indentified in recent years were not accounted for. Similarly, our capability today in the isolation and identification of chemical compounds from natural sources is much better than some 50 years ago. Hence, compounds that were difficult to isolate/identify and exist in trace amounts can still be explored from common European plants.
2. It is quite difficult to get funding to document the chemistry and pharmacology of common European plants. European

*Corresponding author: Dr. Solomon Habtemariam, Pharmacognosy Research Laboratories, Medway School of Science, University of Greenwich, Chatham-Maritime, Kent ME4 4TB, UK, Tel: +44 208 331 8302; Fax: +44 208 331 9805; E-mail: s.habtemariam@gre.ac.uk

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pharmacognosists are, therefore, more involved in studying medicinal plants of exotic places than local plants.

In this brief perspective, the chemistry and pharmacology of two selected exemplary European common garden plants (Figure 1) studied in our laboratories during the last two years are presented.

Case Example 1–*Berberis darwinii*

First, let us see an example of botanical treasures discovered by one of the most outstanding British scientists of the 19th century. One might wonder who—perhaps the British chemist Michael Faraday among many other famous scientists of that era; but he was not really known for studying medicinal plants. How about Charles Darwin, whose theory of evolution has drastically shaped science and the human society, as we know it today? Darwin's legendary five-year voyage on H.M.S. Beagle is known to be the foundation for his famous book “*On the Origin of Species*” or the theory of evolution [4]. Besides his widely reported scientific observation in the Galapagos Islands, Darwin meticulously collected exotic plants and animals he encountered during his South American trip. One of the plants that he discovered in 1835, and later named in his honour, was Darwin's Barberry (*Berberis darwinii*). This native plant to southern Chile and Argentina is known to be introduced to Britain in 1849 by *William Lobb* [5]. Darwin's Barberry is now a popular garden and hedging shrub cultivating all over the world. The Royal Horticultural Society has also recently given it an Award of Garden Merit [6]. If one wonders why, this is a fast growing an evergreen plant with dark green shiny leaves and impressive orange flowers in spring that lead to purple-black berries in summer (Figure 1). The mature berries are known to have been eaten by native people in South America for centuries. Apparently, they are acidic and sour, but

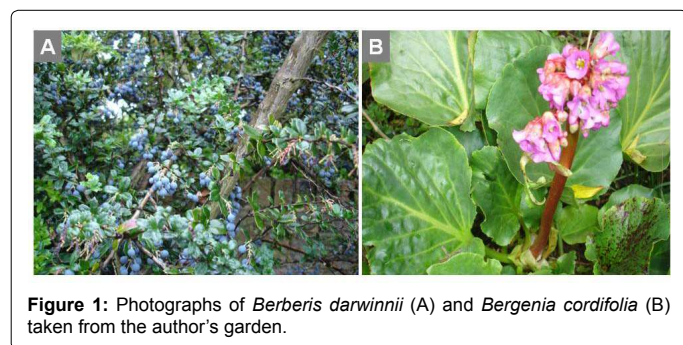


Figure 1: Photographs of *Berberis darwinii* (A) and *Bergenia cordifolia* (B) taken from the author's garden.



Figure 2: Stem wood (A) and stem bark (B) of *B. darwinii* appearing yellow due to their principal constituent, *Berberine*.

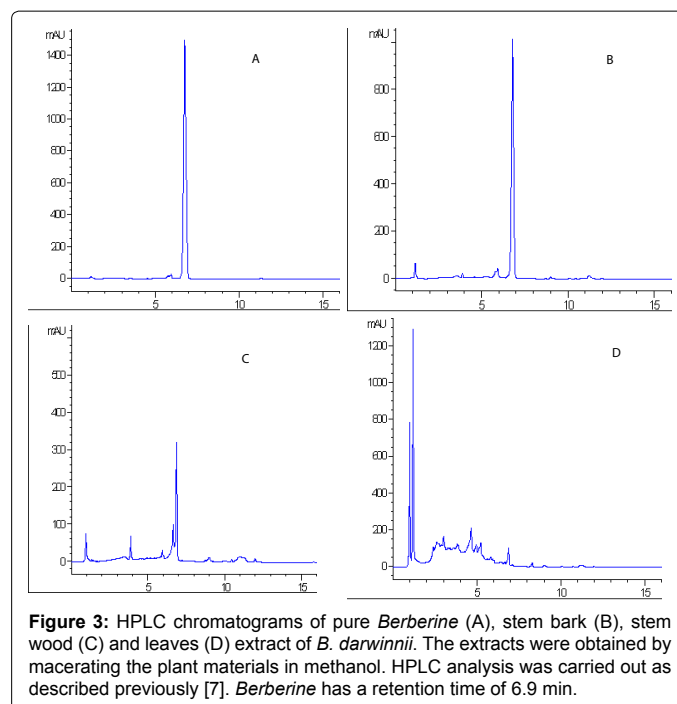


Figure 3: HPLC chromatograms of pure *Berberine* (A), stem bark (B), stem wood (C) and leaves (D) extract of *B. darwinii*. The extracts were obtained by macerating the plant materials in methanol. HPLC analysis was carried out as described previously [7]. *Berberine* has a retention time of 6.9 min.

birds in the Britain greedily feast on them.

If one has to cut the wood of Darwin's Barberry and remove the bark, the woody tissues and bark appear bright yellow in colour (Figure 2); this is due to a chemical called berberine. It is worth noting that plants containing berberine, such as Goldenseal (*Hydrastis canadensis*), and Chinese Goldthread (*Coptis chinensis*), are highly valued for their medicinal uses. But berberine in these plants is found together with other structurally related alkaloids, such as hydrastine, palmatine, and/or jatrorrhizine [7]. We have recently conducted studies on the chemistry and pharmacology of Darwin's Barberry [7]. As shown in Figure 3, HPLC chromatograms revealed the stem bark contained just one UV-visible component, berberine, not just from the alkaloid fraction, but the crude methanolic extract. This finding was remarkable given that plants normally contain a mixture of thousands of different chemicals in their tissues. One of the potential medicinal values of this plant and its chemical berberine that many laboratories looked at so far is for combating Alzheimer's disease (AD).

AD is principally associated with progressive neurodegenerative pathological changes in the forebrain cholinergic system, though other brain areas are also known to be affected. It has been well established that the loss of cholinergic system, and/or decreased levels of acetylcholine is associated with pathological accumulation of β -amyloid protein in the affected areas. One popular therapeutic strategy for AD is, therefore, through enhancing the cholinergic system via inhibition of the enzyme (acetylcholinesterase) that breaks down acetylcholine [8]. Agents that reduce the accumulation of β -amyloid or those preventing -amyloid mediated, and/or oxidative-stress associated neurotoxicity could also have beneficial effect in managing AD. Remarkably, Darwin's Barberry extract and its chemical (berberine) have potential to treat AD through the entire above mentioned multiple targets [7]. There is currently a flurry of scientific activities worldwide to synthesize drugs related to this natural product. It is hoped that a more active and easily obtainable anti-AD drug could be found based on this model of natural product. Given that *B. darwinii* offers a high yield and relatively pure

source of berberine, its potential as anti-AD therapy deserves further investigation.

Berberine has also shown to display numerous other pharmacological properties, including antimicrobial effects against pathogenic bacteria such as *Vibrio cholera*, *Shigella dysenteriae*, *Salmonella species* and various multidrug resistant bacterial strains [9-14]. Berberine is widely regarded as a potent anti-inflammatory agent [15-19] that could be explained in part by its action at the molecular level as an inhibitor of leucocytes adhesion to activated endothelial cells [20], cyclooxygenase-2 expression [21,22], NF- κ B activation [23], cytokines expression [24], etc. In conjunction with its anti-inflammatory and antioxidant effects, berberine has been shown to display anti-atherosclerosis property [25,26]. The lipid lowering effect of berberine has been reviewed by various authors [27-29], and such effect could partly explain its reputed cardio- and hepatoprotective effects [30,31]. In this connection, the potential of berberine in combating fatty liver diseases has been emphasised in recent years [32-34]. Once again, the protective role of berberine in mammalian tissues could be linked to its antioxidant and anti-inflammatory effects as the expressions of multipotent biomolecules, such as COX-2, proinflammatory cytokines, such as TNF- α and inducible nitric oxide synthase are all inhibited by berberine [35].

The other productive area of research on berberine and berberine-containing plants have been on their potential therapeutic potential for diabetes [36-38], and associated diseases such as diabetic neuropathy [39] and nephropathy [40,41]. Among the various possible mechanism of berberine's antidiabetic action are through inhibition of peroxisome proliferator-activated receptors expression [42,43] carbohydrate digestion [44], various signalling pathways [45], modulation of protein tyrosine phosphatase 1B activity [46], activation of glucose transport pathway of GLUT-1 [47], promoting the secretion of glucagon-like peptide secretion [48], increasing insulin receptor expression [49], control of lipid dysregulation [50] antioxidant mechanisms and aldose reductase inhibitory activity [51], and anti-inflammatory mechanisms [52].

Berberine and berberine-containing plants are also highly sought after for their potential anticancer effects. Numerous studies have highlighted that berberine not only directly induces apoptosis in cancer cells [53-55], but also sensitise them to other chemotherapeutic agents and radiation therapy [56,57]. Suppression of gene transcription [58], reactive oxygen species mechanisms [59], mitochondrial and caspase pathways [60], anti-calmodulin property [61] inhibition of key kinase enzymes [62], and many other multiple mechanisms [63] have been suggested as the possible mode of action for berberine-induced apoptosis in cancer cells. Inhibition of cancer metastasis through downregulation of activities and expression levels of key enzymes, such as heparanase [64] and matrix metalloproteinases 2 and 9 [65], are also among the various anticancer study reports on berberine.

In view of the numerous above mentioned exemplary pharmacological activities of berberine, the finding the common garden plant, *B. darwini*, as a good source of this therapeutically useful drug, is very significant.

Case Example 2–*Bergenia cordifolia*

To date, around 300 million people worldwide are known to suffer from diabetes. Hand in hand with diabetes, obesity has become the most serious public health problem worldwide, and its prevalence during the last few decades has dramatically increased with epidemic proportions

[66]. α -Glucosidase and pancreatic lipase enzymes inhibition are two established strategies for targeting diabetes and obesity respectively [67-69]. Other strategies that showed benefit in treating diabetes-related diseases are antioxidant therapeutics [70]. In our laboratories, several hundreds of plants identified from their traditional medicinal uses, and/or scientific reports are screened for digestive enzyme inhibitions and antioxidant effects. Plant extracts that offer multifunctional effects are given priority, and their active constituents subjected to isolation and structural elucidation. One of the promising plants identified in our laboratories was the most widely grown garden plant in Europe, *B. cordifolia*. Though the plant is known to predominantly contain arbutin and bergenin, no comprehensive phytochemical or pharmacological analysis has ever been reported on it.

In addition to potent antioxidant effect, we found that the rhizome extract of *B. cordifolia* was about 103-fold more active in inhibiting α -glucosidase than the standard antidiabetic drug, acarbose [71]. We further demonstrated that this enzyme inhibition by the extract was not a non-selective pharmacological effect as 111-times more potency in α -glucosidase inhibition was observed when compared to mitigation of acetylcholinesterase enzyme activity. By excluding the major constituents (arbutin and bergenin) that do not account both for the antioxidant and potential antidiabetic properties, the search for the minor constituents with the indicated biological activities lead to the identification of three compounds: catechin 3-*O*-gallate, catechin 3,5-di-*O*-gallate and 1,2,4,6-tetra-*O*-galloyl- β -D-glucopyranoside [71]. The latter two compounds were rare natural products isolated as potent natural antilipase [72] and antiviral agents [73], respectively. In addition to displaying the highest level of antioxidant effects, these two compounds further scored 78 and 159-fold respectively more potent α -glucosidase enzyme inhibition than acarbose [71]. Hence, the identified compounds and the plant have enormous therapeutic potential for treating diabetes, obesity and associated diseases.

It is also worth noting the pharmacological activities of the two most abundant *B. cordifolia* constituents; bergenin and arbutin. The most notable biological activity of arbutin is potent inhibition of tyrosinase enzyme that attributes to its use as a commercial skin lightening agent [74-76]. On the other hand, bergenin has numerous biological effects, including antiviral [77], antiulcer [78], antiarthritic [79], antidiabetic and anti-obesity [80], anti-inflammatory [81], immunomodulatory [82] and hepatoprotective [83-85] effects.

We have numerous other examples where European garden plants have been shown to display unique pharmacology and chemistry. These plants, as with other plants in exotic places, need to be looked at not only for validating their centuries-old medicinal uses, but also as a source of valuable medicines.

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