Understanding Medicinal Plants: their Chemistry and Therapeutic Action

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Abstract

This paper attempts to study **Medicinal plants** ; defined as the plants that possess **therapeutic** properties or exert beneficial **pharmacological effect** on the human or animal body The ancient tradition of taking parts of a plant or preparing plant extracts for treating certain discomforts and maladies has long been lacking a scientific rationale to support its preparation and still widespread use in several parts of the world. A mechanistic hypothesis is generated when a metabolite is known to be present in a given plant, that plant is known to be used to treat a certain disease, that disease is known to be linked to the function of a given protein, and that protein is finally known or predicted to interact with the original metabolite. The construction of plant–protein networks from mutually connected metabolites and diseases facilitated the identification of plausible mechanisms of action for plants being used to treat analgesia, hypercholesterolemia, diarrhea, catarrh, and cough. Pharmacopoeial methods focus on authentication and quality of herbal materials; however, metabolomics allow us to go a step beyond authentication and look in more detail at a broad range of secondary metabolites.

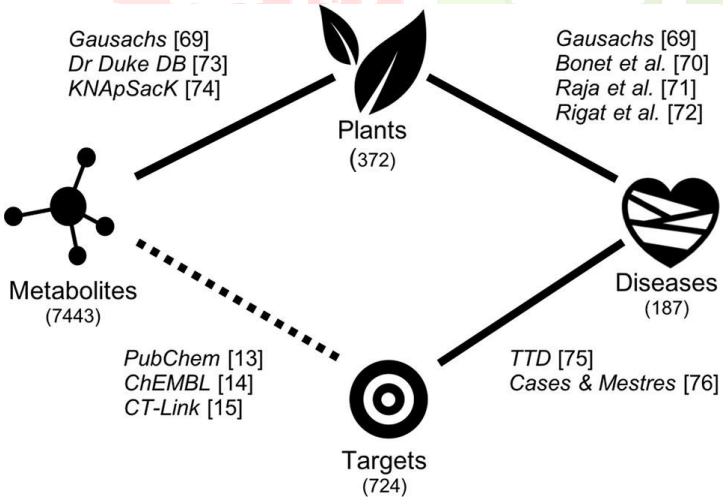
By coupling analytical data to multivariate software, this allows us to develop statistical models to firstly differentiate between species but also to get a better idea of a typical metabolite composition for a particular species. The advantage of this is that it can help to inform any laboratory test or clinical intervention. There has been great emphasis on making sure that any experiment or intervention uses plant material that is authenticated, with a herbarium specimen deposited. This is where metabolomics can provide essential information—by collecting a wide range of samples from different geographical locations, altitudes, growing conditions, it allows us to map their metabolite differences and highlight how diverse or how similar metabolite composition is. When an experiment is performed, we have the choice to use a specimen that may be typical, i.e., contains an average composition or we can look at compositions that are atypical, containing greater amounts of specific metabolites or even different metabolites. Moreover, if a particular experiment produces positive results and we want to reproduce the data, a metabolomic model allows us to choose species that have a similar composition. Additional concrete examples using both experimentally known and computationally predicted, and subsequently experimentally confirmed, metabolite–protein interactions to close the connection circle between metabolites, plants, diseases, and proteins offered further proof of concept for the validity and scope of the approach to generate mode of action hypotheses for some of the therapeutic uses of remedial herbs.

Key words: **Medicinal plants** , therapeutic, metabolite composition, remedial herbs, plant material

Introduction

Plant leaves, roots, barks, and extracts have been used since the dawn of human history to treat various discomforts and maladies. The healing properties of remedial herbs were most likely identified through a long and serendipitous learning process that once acquired was carefully passed through generations. Still today, traditional medicines represent a well-established therapeutic alternative to synthetic drugs in vast parts of the world (Tao et al., 2012). However, there is still a profound lack of understanding about the specific chemical ingredient(s) and the exact mechanism(s) of action by which medicinal plants exert their therapeutic effect.

In recent years, global efforts to generate, collect, store, and make publicly available data connecting plants with their endogenous metabolites (phytoconstituents), interacting proteins, and disease indications have set the ground to develop novel systems approaches to unveiling the mode of action of remedial herbs (Liu et al., 2012; Lagunin et al., 2012; Chen et al., 2012). This is schematically illustrated in Figure 1. A number of publicly available well annotated databases on medicinal plants in use in different regions of the planet exist already (Chen, 2011; James et al., 2012; Ntie-Kang et al., 2012; Tota et al., 2012; Pathania et al., 2012; Mohanraj et al., 2012). Once data connecting the different aspects of ethnopharmacological relevance are known, the circle is closed and mechanistic hypotheses emerge naturally. The problem arises when gaps of data exist and the circles cannot be closed. In this respect, most current ethnomedicinal studies still focus on which parts of the plant are used to treat common ailments (Chassagne et al., 2012). Initiatives to identify and isolate some of the chemical structures present in those parts of therapeutic interest are expensive and inefficient. This notwithstanding, at least 50,000 endogenous plant metabolites have been already identified (Hounsome et al., 2008).



However, in vitro affinity data between plant metabolites and human proteins are scarce to find in public repositories (Bolton et al., 2008; Gaulton et al., 2012). Therefore, more efforts are needed in this direction to close the gap between therapeutic use and mode of action in remedial herbs (represented as a dotted line in Figure 1). One option is to process large libraries of isolated small molecules from plants through in vitro high-throughput screening assays to identify affinities for therapeutically relevant proteins. This is a highly tedious

and expensive endeavor if one wants to be comprehensive. Alternatively, modern state-of-the-art computational methods to predict the affinity of small molecules across thousands of proteins can be used to prioritize any further in vitro testing of selected small molecules on particular proteins (Vidal et al., 2011; Garcia-Serna et al., 2012). Applications on predicting the targets of natural medicines are increasingly being reported (Keum et al., 2012; Fang et al., 2012; Sawada et al., 2012; Yi et al., 2012).

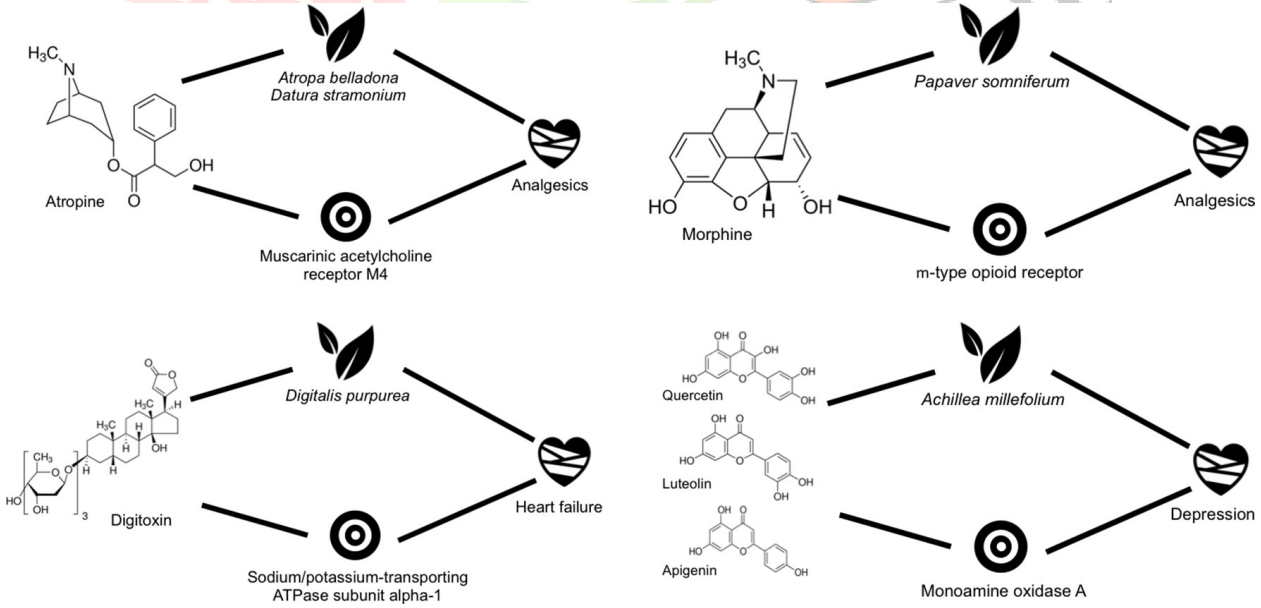
The last step involves connecting those confirmed interacting proteins with the actual disease for which the plant is prescribed. This task is now facilitated by the recent construction of databases connecting human genes with diseases (Piñero et al., 2012). The aim of this work is to collect and integrate all pieces of data and processes that allow for automatically generating mechanistic hypotheses for the known therapeutic uses of plants.

Objective:

This paper intends to explore and analyze wide array of biological and **pharmacological** properties. Also **Therapeutic** Approaches and Treatment Modalities of some **plants** or products isolated from them

Retrospective Validation

Among the molecules involved in the mechanistic hypotheses generated with known metabolite–protein interactions, we identified some well-known single active principles, such as atropine, morphine, and digitoxin, as well as a mixture of active principles, such as the one composed of quercetin, luteolin, and apigenin



Among the 372 medicinal plants present in our integrated database, Sambucus nigra (black elder) is the plant associated with the highest number of therapeutic uses (31). It is recommended for bronchitis, migraine, diarrhea, nausea, hyperuricemia, and influenza, to name just a few. Genus Sambucus belongs to the Caprifoliaceae family

of flowering plants, whose leaves, flowers, and berries are traditionally used worldwide for a wide variety of medicinal applications (Dulf et al., 2012; Mahmoudi et al., 2012). Following Sambucus nigra in the list of plants with widest therapeutic use are Allium sativum (24), Rosmarinus officinalis (22), Mentha spicata (21), Urtica dioica (21), Salvia officinalis (21), and Thymus vulgaris (21), all of them found easily in many parts of the world and used as food and/or spice.

Atropine is found mainly in Atropa belladonna and Datura stramonium (Kurzbaum et al., 2001; Caksen et al., 2003), both used commonly for their analgesic action (Duttaroy et al., 2002; Overington et al., 2006). This molecule is known to be active against the muscarinic acetylcholine receptor M4, a therapeutic target associated with some analgesics. Therefore, we have all links described in Figure 1 confirmed and thus forming a mechanistic hypothesis for the analgesic action of these plants (Soni et al., 2012; Owais et al., 2012).

Another widely recognized molecule for its analgesic activity is morphine. It is found in Papaver somniferum (opium poppy), and it was the first active alkaloid extracted from this plant (Jurna, 2003). Opium has been used in traditional medicinal as sedative and analgesic (Calixto et al., 2001). According to all links established in our database, morphine would be directly identified as a candidate to contribute to the analgesic action of opium through its interaction with μ-type opioid receptor (Choi et al., 2006; Yamada et al., 2006), a receptor well known for its association with analgesia (Inturrisi, 2002).

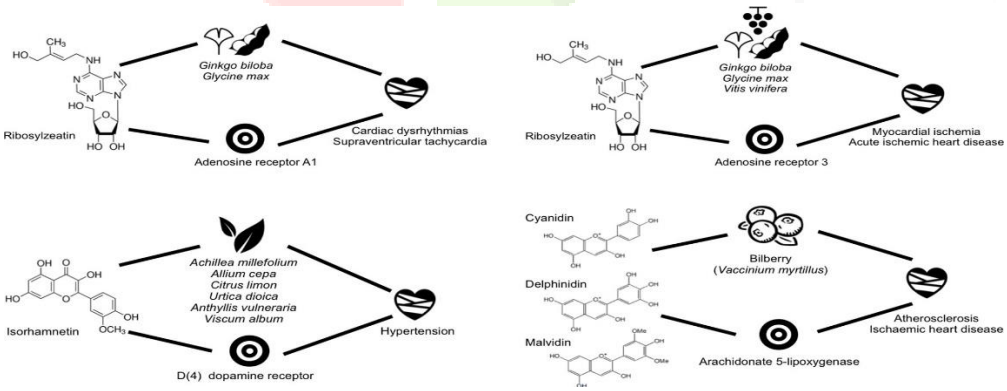
Digitoxin is a glycoside with known activity against the sodium/potassium-transporting ATPase subunit α-1, a protein associated with heart failure (Müller-Ehmsen et al., 2002; Hauck et al., 2009). Digitoxin is found in Digitalis purpurea (Chen et al., 2001), a plant used in traditional medicine for treating precisely this particular disease. Digitoxin has not only been proven to interact with the sodium/potassium-transporting ATPase subunit α-1, but it has also been shown to be indeed effective in heart failure (Belz et al., 2001).

An example in which three compounds, namely, quercetin, luteolin, and apigenin, all confirmed endogenous metabolites of Achillea millefolium (yarrow), a plant used traditionally for treating depression, are known to have biologically relevant affinities for monoamine oxidase A (Lemmens-Gruber et al., 2006; Han et al., 2007; Benetis et al., 2008; Bandaruk et al., 2012), which, in turn, is one of the target proteins for depression (Thase et al., 1995).

A more systematic analysis of all the mechanistic hypotheses that could be derived directly from known data and associations revealed that, among all disease categories, the circulatory, respiratory, and musculoskeletal systems collectively represented over 47% of all mechanistic hypotheses generated. The plant–protein networks derived for some specific diseases within these categories are shown

If we focus on cardiovascular diseases, a total of 171 plants were found to be associated with 46 different therapeutic uses. For illustrative purposes, the network of plants linked to cardiovascular diseases is shown in Figure 2. Among those, Ginkgo biloba is the plant with the most cardiovascular uses (with 14), followed by Camellia sinensis (with 8) and Allium cepa, Crataegus monogyna, Olea europea, Urtica doica, and Vitis vinifera (with 7). Among diseases, hypertension, hypercholesterolemia, hyperglycemia, and haemorrhoids are clearly the cardiovascular aspects being most addressed by remedial herbs.

Ginkgo biloba and Camellia sinensis are indigenous plants from Asia (Cybulska-Heinrich et al., 2012; Moore et al., 2009). The extracts of the leaves and nuts from Ginkgo biloba have been used for hundreds of years to treat a wide variety of disorders, such as asthma, vertigo, tinnitus, as well as general circulatory problems (Cybulska-Heinrich et al., 2012). Camellia sinensis is a plant from which green tea can be produced. This beverage has a long traditional use as social drink but also as medicine in the treatment and prevention of disorders, dysfunctions, or diseases in humans and other animals (Batista et al., 2009; Moore et al., 2009). Aesculus hippocastanum (horse chestnut) is native to the countries of the Balkan Peninsula, but it is cultivated worldwide for its beauty. Historically, seed extracts from this plant have been used as a treatment for many ailments (Anonymous, 2009). Crataegus monogyna (hawthorn) is known as a traditional medicinal plant in many countries, growing in shrub communities and decidious thin forests (Öztürk and Tunçel, 2011). Vitis vinifera (grapevine) is an indigenous plant from southern and Western Asia, but it is cultivated today in all temperature regions of the world (Nassiri-Asl and Hosseinzadeh, 2009).



Finally, Allium cepa (onion) is one of the most important vegetables worldwide and is extensively cultivated. It is an herbaceous bulbous plant that has a long tradition of being beneficial against inflammation, general cardiovascular diseases, and cancer (Slimestad et al., 2007). Regarding knowledge on the chemical composition of plants, Camellia sinensis (green tea) is the plant with the highest number of chemical structures identified (710), followed by Zea mays (677) and Panax ginseng (601). Other chemically well characterized plants are

Citrus sinensis (orange tree), Apium graveolens (celery), and Daucus carota (carrot), with 589, 533, and 507 known molecules, respectively. In contrast, many plants in the database have only one or very few endogenous metabolites identified, such as Rhamnus alaternus (Mediterranean blackthorn), Lonicera etrusca (honeysuckle), or Hernaria glabra (herniaria).

A detailed analysis of all the links between plants, metabolites, targets, and diseases in our integrated database (Figure 1) identified a total of 31,808 mechanistic hypotheses. At this stage, a mechanistic hypothesis is generated if a given plant known to have some therapeutic use contains at least one endogenous metabolite that is either known or predicted to interact with a human protein associated with its original therapeutic use. It ought to be stressed here that the concentration of any plant metabolite in a herbal preparation is very low and that, by any means, the results presented below imply that the metabolite assigned to the mechanistic hypothesis is the sole responsible of the therapeutic action of the plant but it will somehow contribute it. In this respect, a total of 893 mechanistic hypotheses for its different therapeutic uses could be generated for Glycine max (soybean). Among the plants with the highest number of mechanistic hypotheses generated, we found Ginkgo biloba (793), Camellia sinensis (781), Citrus limon (578), and Vitis vinifera (563). Out of the total number of 31,808 mechanistic hypotheses generated, 14,308 involved known interactions between endogenous metabolites and protein targets, whereas the remaining 17,500 hypotheses emerged from predicted interactions. Ribosylzeatin is an endogenous metabolite present in Ginkgo biloba (gingko), Glycine max (soybean), and Vitis vinifera (grapevine). This small molecule was predicted to have low micromolar affinity for the adenosine A1 and A3 receptors and in vitro testing performed subsequently confirmed 57% and 65% binding, respectively, at 10mM concentration. Accordingly, a mechanistic hypothesis could be derived suggesting that the interaction of ribosylzeatin with the adenosine A1 and A3 receptors may be contributing to the beneficial effects of those plants in the treatment of a number of cardiovascular diseases where these receptors are known to play a role, namely, cardiac dysrhythmias, supraventricular tachycardia, acute ischaemic heart disease, and mycocardial ischemia (Kiesman et al., 2009; Fishman et al., 2012). In this respect, soybean is known as an important source of proteins in diet, widely used as herbal medicine for the treatment of several cardiovascular diseases. Also, the cardioprotector properties of grapevine have been exploited in folk medicine since ancient times. In particular, the therapeutic action of grapevine against ventricular tachycardia was recently demonstrated in rats (Zhao et al., 2010). However, in this study, the authors used a proanthocyanidin grape seed extract. On the basis of the hypothesis generated here, we would suggest that ribosylzeatin is one of the active ingredients in grapevine participating in this therapeutic effect in synergy with other proanthocyanidins.

Isorhamnetin is a phytochemical present in multiple plants used for the treatment of hypertension. A low micromolar affinity between isorhamnetin and the dopamine D4 receptor was predicted. Upon in vitro testing, the experimental value obtained was only 28% binding. Despite this rather low affinity value, we could suggest that this compound may well be contributing to some extent to the effect on hypertension of the plants in which

it is present. In fact, a similar chemical present in most of those plants listed and suggested to be partly responsible for their therapeutic action on hypertension is quercetin, reported to have also a low experimental affinity value of 5 μM against the same dopamine D4 receptor.

Finally, very much along the same lines reported above for the hypotheses generated from known metabolite–protein interactions, we were also keen on having a prospective mixture example. Accordingly, we predicted activity of cyanidin, delphinidin, and malvidin, all present in Vaccinium myrtillus (bilberry), on the arachidonate 5-lipoxygenase (ALOX5). In vitro testing of its mixture confirmed a 41% inhibition. This result provides a mechanistic hypothesis for the therapeutic use of bilberry for atherosclerosis and ischemic heart disease. It has been already suggested that quercetin is partially responsible for the therapeutic action of this plant due to its affinity for the ALOX5. We could add now delphinidin, cyanidin, and malvidin to the list of potential chemical effectors of this plant. Indeed, bilberry fruit contains high concentration of several anthocyanidins (Cassinese et al., 2007; Chu et al., 2011). In fact, other anthocyanidins present in bilberry, such as peonidin and petunidin, were also predicted to be active against this protein. So all these compounds may actually contribute synergistically to the therapeutic effect attributed to bilberry for the treatment of atherosclerosis and ischemic heart disease.

Conclusion

The analysis of medicinal plants has had a long history, and especially with regard to assessing a plant's quality. The first techniques were organoleptic using the physical senses of taste, smell, and appearance. Then gradually these led on to more advanced instrumental techniques. Though different countries have their own traditional medicines China currently leads the way in terms of the number of publications focused on medicinal plant analysis and number of inclusions in their Pharmacopoeia. The monographs contained within these publications give directions on the type of analysis that should be performed, and for manufacturers, this typically means that they need access to more and more advanced instrumentation. We have seen developments in many areas of analytical analysis and particularly the development of chromatographic and spectroscopic methods and the hyphenation of these techniques. An effort to integrate data linking metabolites, plants, diseases, and proteins has been shown to be useful to generate mechanistic hypotheses for some of the therapeutic uses of remedial herbs. In this respect, the use of predicted interactions largely increases our ability to generate mechanistic hypotheses for plants for which known data is scarce. This notwithstanding, one ought to admit that many computationally derived hypotheses may either be false positives or not truly contribute to the therapeutic effect exhibited by the medicinal plant. Unfortunately, it is impossible to pursue experimental confirmation of all hypotheses generated and offer general statistics of this limitation. Nonetheless, the examples presented offer clear potential for the use of this type of systems approaches to contribute to finding a scientific rationale for traditional medicines. There is much more to learn about nature and its use for therapeutic purposes, and more research in this direction is certainly necessary.

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