The medicinal use of plants is age-old, and might be related to the discovery of the beneficial properties of certain food plants, a process documented in the veterinarian literature not only in primates, but also in animals more evolutionally distant from Man.\(^1\) While zoopharmacy, that is the medicinal use of plants by animals, might have predated the birth of human medicine and have inspired it,\(^1\) there are several indications that the distinction between food plants and medicinal plants was rather blurred in the past. Thus, food plants (legumes), and not medicinal plants were used in the first recorded description (Book of Daniel of the Bible) of what we would now consider a clinical trial.\(^2\) Remarkably, food plants (\textit{Citrus} fruits) were also used, almost 2000 years later, by the naval surgeon James Lindt in his classic study on the prevention of scurvy, the first modern clinical trial in the history of medicine.\(^2\) The Lind comparative study of several preventive treatments for scurvy (\textit{Citrus} fruits, legumes, vinegar, acids) is considered the starting date for modern medicine, just like the experiments of the young German pharmacist Sertürner, who in 1818 obtained a white powder from opium, marked the beginning of modern pharmaceutical research.\(^3\) Sertürner baptized the product morphine in honor of Morpheus, the Greek God of sleep, since this compound could reproduce, in a magnified form, the analgesic and sedative properties of opium. The impact of this discovery was enormous and far-reaching. The old alchemic theories on the quintessential of things seemed to materialize: from a crude product it was possible to obtain one constituent that recapitulated its biological properties. This condensate (quintessence in the para-alchemical lingo of the early pharmacy) was named active principle, \textit{Wirkstoff} in German, the scientific \textit{Ingua franca} of that time. The example by Sertürner was contagious, and, by the end of the 19th century, the active principles of most medicinal plants with a marked bioactivity (heroic medicinal plants) had already been isolated. Because of their powerful action and low therapeutic margin, these medicinal plants (poppy, foxglove, belladonna) are not directly used in medicine any more, and have been replaced by their purified active ingredients (morphine, papaverine, lanatosides, atropine), by semi-synthetic derivatives, or by fully synthetic analogs prepared in chemical laboratories. These heroic plants are nowadays only used as a starting material for the isolation of their pure active principles, and are substantially outside the realm of phytotherapy, whose field use is largely limited to chronic conditions characterized by complex etiology. Nowadays, it would be foolish or even criminal to use plants like foxglove or belladonna rather than their purified active ingredients dosed with precision and formulated to optimize activity.

Most medicinal plants are, however, not heroic. Their study is much more complex,
and had to wait the technological and biomedical progresses of the past decades to move from anecdotic empirism to rational investigation. Thus, most medicinal plants are not characterized by the presence of a single active ingredient, with a single molecular target and a single mechanism of action. Furthermore, the active ingredients are sometimes present in the plant as precursors, activated during digestion by intestinal enzymes, or by the intestinal bacteria.

Chamomile, a medicinal plant universally known, will guide us in this tour of modern phytotherapy and its subtleties. Chamomile (Matricaria chamomilla L.) shows anti-inflammatory activity qualitatively similar, but less potent, than non-steroidal anti-inflammatory drugs (NSADIs). Only recently, however, it was possible to identify its active ingredients and molecular targets. Chamomile extracts show only modest anti-inflammatory activity in vitro assays, but they are much more potent in vivo. The textbooks of phototherapy list an intimidating series of potential active ingredients for chamomile: flavonoids, polyacetylenic spiroethers, α-bisabolol, chamazulene, coumarins, polyphenolics and the essential oil are all mentioned as active constituents of the plant, puzzling readers. If, however, we scour the literature, we discover that all these ingredients are poorly absorbed, extensively degraded during storing, require high temperatures for their formation, or are contained also in other plants for which the anti-inflammatory actions of chamomile have never been claimed. It is therefore easy to dismiss chamomile as medical archeology. Actually, the situation is more complex (and exciting for researchers). Chamomile tastes bitter because of the presence of the terpene lactone matricin. Matricin substantially lacks biological activity beyond its sensory properties, but in the acidic stomach environment it is turned into chamazulene carboxylic acid, a structural analogue of the well-known NSAID ibuprofen. This compound has a more marked COX-2 affinity than ibuprofen, and any lingering stomach-damaging activity mediated by the residual COX-1 affinity is buffered by the soothing activity of another constituent, α-bisabolol, on gastric mucosa. Given the overall low intake of matricin from a standard dosage of chamomile, it is difficult to translate these observation into a clinical activity, but the anti-inflammatory activity of chamazulene carboxylic acid could be magnified by the presence of several flavonoids. Chamomile is rich of apigenin glycosides, from which the parent flavonoid is generated by removal of the sugar decoration in the small intestine. Apigenin is a potent spasmylic agent, at least potent as papaverine fom opium, and can interfere with the transcription of the genes coding for COXs and other inflammatory enzymes and factors. Add also that chamomile is taken as a warm infusion, and that the trigeminal stimulation of the thermo-sensors of the oral cavity has an intrinsic mild anti-inflammatory action, and we arrive at a complex scenario where activity is generated in a way that substantially transcends the concept of active principle.

The principle that ‘a rose is a rose is a rose’ does not apply to chamomile, since there are several types of chamomile, containing different compounds and therefore endowed with different grades of activity. The flowerheads of chamomile have two types of flowers, the white and ligular peripheral ones, and the central yellowish ones (Figure 2). The two types of flowers contain different compounds. The white peripheral ones contain most of the flavonoids, while most matricin is contained in the central yellowish ones. Incidentally, we could note that Nature is complicated, since flavonoids were named in this way because many of them are yellowish, but glycosidation, as occurs in chamomile flavonoids, is detrimental for color. To benefit from the activity of the plant, you need both types of flowers, but most of the chamomile of the commerce contains only the central flowers, since the peripheral ones are easily lost during drying. And this is only the beginning of the complications!

The next one is the ‘expiring date’. Everything that is natural degrades, since natural products are, by principle, all biodegradable (the alternative would be that they would sequester all carbon on earth!). They have been around for enough time to induce their microbial degradation. Matricin is an unstable compound, and its concentration in chamomile decreases with time. Nothing is immortal in Nature, and another of its law is that nothing is exactly equal, with variability being a sort of ‘insurance’ for survival. Not all chamomile samples contain the same phytochemical profile. In particular, some of them are completely devoid of matricin, others of bisabolol, and the composition of the essential oil is also highly variable. The distribution of these chemical races is essentially geographical, with most South-American samples being devoid of matricin, and most European ones containing this...
compound. If Nature secures variability, humans can cause confusion, as exemplified by the adulteration issues. Certain plants look like chamomile, and are cheaper and easier to grow than chamomile, raising the issue of adulterated chamomile samples. Most of the times the adulteration is harmless, but sometimes can lead to toxicity. For instance, *Anthemis cotula* L. looks very much like chamomile, and is easy to grow. However, it lacks the properties of chamomile, and contains high concentrations of anthecolulin, a powerful allergen. It is now believed that the allergic reactions reported for chamomile are actually related to the presence of this adulterant, and not a property of the real herb.

Considerations like those we have described for chamomile apply to many medicinal plants, whose medicinal profile is therefore complex. In general, the rational basis for the use of phytotherapy is synergy, namely the presence of active constituents with complementary activity that can mutually reinforce each other. It is what is known in pharmacology as the "entourage effect". Medicinal plants contain a cocktail of constituents that interact in terms of both pharmacokinetomic and pharmacodynamic, and whose biological profile substantially transcend that of any of its single constituent. This cocktail has been named "phytocomplex", a vague definition that, nevertheless, made its way into the research literature, and that needs discussion. A phytocomplex is like a secondary color. If we were looking for the essence of green with an analytical and reductionistical strategy, we will never end up in anything. "Greeness" does not exist, but is, rather, the result of the overlapping of two primary colors, yellow and blue. In the same way, in most cases the activity of medicinal plants cannot be traced back to a simple and unique active principle, a "quintessential" constituent. The complexity of composition of many medicinal natural products is impressive. Escin, a topical anti-inflammatory agent from chestnut fruits, is a mixture of at least 50 closely related saponins, and we are discussing only a "single" constituent of the plant! Also bilberry has a complex composition, with a bouquet of 15 distinct anthocyanosides, while the roots of ginseng contain at least 60 distinct triterpene saponins known as ginsenosides. Medicinal plants are a complex matrix, and trying to apply them simple criteria of molecular validation, is somewhat like trying to open the digital lock of a door with a key. On the other hand, it is also important not to confuse medicinal plants into a limbo of improvable generalities, or evaluate them only on the basis of vague properties whose only strength is the impossibility to prove them. Tonic effect, depurative properties, draining and purifying claims are popular in folk medicine, but are substantially alien to modern medicine. The translation of folk medicine indications into therapeutical uses is generally not straightforward, and gingko (*Gingko biloba* L.) is an example. The leaves of gingko contain a complex mixture of flavonoids and terpenoids, to which various properties related to memory and brain circulation have been associated. These properties underlie the use of gingko for the prevention of senile dementia and Alzheimer’s disease, but are scarcely documented in the medicinal use of gingko in traditional Asian medicine. It is, nevertheless, still unclear how gingko work, if it works for everyone, or if its activity can indeed be related to the molecular targets so far identified for its constituents. The leaves of gingko are not used for the preparation of herbal teas, but only as a source of standardized extracts. There are two reasons for this. The first one is that the concentration of the active ingredients are too low in the leaves, and the second one is that the leaves contain a series of potently allergenic compounds, the ginkgolic acids, whose contents cannot be higher than 5 mg/kg in ginkgo extracts.

In some cases, skepticism on the clinical properties of a medicinal plant is related to the lack of understating on the molecular mechanism(s) underlying activity, a reasoning that would remove from our medicinal portfolio important drugs, like metformin or antidepressants, whose molecular targets are still unclear. They work, and were approved for this reason, and not for the subtleties of the many mechanisms that have been proposed for their activity. No one would refuse a tasty meal only because he does not understand digestion! On the other hand, the mechanisms underlying the activity of medicinal plants can be different from those identified for synthetic compounds used for the treatment of a specific disease. This is the case of St. John’s worth (*Hypericum perforatum* L.), and ant depressant plant. The potency of St. John’s worth extracts is comparable, at least for minor depression, to that of synthetic anti-depressants, but none of its constituents show a clear activity towards the various molecular targets of antidepressants (MAO, biogenic amine transporters). The mechanism of action of St. John’s worth was clarified only recently, identifying the phosphoglucuronol derivative hyperforin as a critical constituent. Hyperforin binds to a novel anti-depressant target, the ion channel TRPC6, a so far overlooked anti-depressant target. In a drug-discovery context, hyperforin qualifies as a first-in-the-class agent, showing that sometimes the failure to identify specific targets for the action of medicinal plants is due to our limited knowledge in the mechanism of many diseases. In this context, the case of Veregen...
is exemplificative.\textsuperscript{15} Veregen is a mixture of green tea polyphenolics (kaunicatechin) approved by FDA for the topical treatment of genital and perianal condiloma acuminata in the almost complete lack of knowledge on its mechanism of action.\textsuperscript{15} Veregen works, is not toxic, and there are few alternative options for the management of this disease.

Sometimes, complex extracts are better tolerated than single active ingredients, as \textit{Cannabis} demonstrates. \textit{Cannabis} and its psychotropic principle tetrahydrocannabinol (THC) are useful for the management of weight loss (cachexia) associated to the terminal stages of cancer and HIV infection, and of vomit associated to cancer chemotherapy.\textsuperscript{16} Both THC (produced semi-synthetically from cannabidiol, CBD) and its totally synthetic analogue dronabinol are used in many countries, US included, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions. However, due to their psychotropic and anxiogenic effects, medicinal marijuana is preferred by patients, for these conditions.

In general, three elements can be identified in a phytocomplex, namely the pharmacodynamic-, the pharmacokinetic- and the modulatory components. The pharmacodynamic component is represented by constituents that act on specific targets of relevance for a disease, while the pharmacodynamic element is represented by compounds that can affect, both positively and negatively, the absorption of the pharmacodynamic fraction. For instance, tannins are well known to delay, and in many cases decrease as well, the absorption of other phytochemicals and especially alkaloids, while piperine from black pepper has the capacity to promote the absorption of phytochemicals, rationalizing its universal inclusion in the Indian medicinal formulations.\textsuperscript{18} The modulatory component affects the stability of the compounds endowed with pharmacodynamic and the pharmacokinetic properties, and can minimize their toxicity. This is an important issue, especially in the context of liver toxicity. Many medicinal plants contain compounds potentially poisonous for the liver, but that can, however, be “neutralized” by the presence of thiol derivatives in the plant, or by that of compounds capable to activate the cellular response to oxidants and electrophilic compounds. For instance, comfrey (\textit{Symphytum officinale L.}) contains hepatotoxic pyrrolizidine alkaloids, but their activity is neutralized, so as to say, by the high concentration of cystine derivatives present in the plant.\textsuperscript{19}

Nowadays phytotherapy rarely uses medicinal plants, largely replaced by standardized extracts. As exemplified by gingko, this replacement makes it possible to use plants having low concentration of active ingredients, or containing toxic compounds that can be removed by purification.\textsuperscript{20} Furthermore, extracts are easier to standardized than whole plants, and are also easier to store, securing efficacy and stability. Standardization is also essential to identify dosages and safety of a product. Plant extracts are somewhat similar to multi-component preparations, and their standardization is therefore more difficult than that of monomolecular drugs. Standardization can refer to a single constituent (e.g. hypericin or hyperforin for St. John’s wort) but most often makes reference to a structurally homogenous class of constituents, like ginsenosides for ginseng or anthocyanines for bilberry. In some cases, more than one class of compounds is quantified, as in gingko, whose extracts are standardized in flavonoids (24%) and terpene lactones (6%).\textsuperscript{21} Many extracts and compounds used in phytotherapy come from food plants, as exemplified by curcumin, silymarin, and grape seeds. Since the absorption of natural products can be very different between a food matrix and a pharmaceutical matrix (capsules, soft gels), various promoters of absorption are used, promoting absorption with a pharmacological (piperine)- or formulative strategy. Within the formulation strategies, lecithin formulations have become increasingly popular in the healthfood arena.\textsuperscript{22} Lecithin is a dietary phospholipid endowed with “soap-like” properties on compounds that do not dissolve well into water. Lecithin formulations have been developed for many herbal ingredients, including curcumin,\textsuperscript{20} silibin, grape seeds proanthocyanidins, and boswellic acids, validating in terms of improved absorption and efficacy this important strategy.\textsuperscript{23}

In the light of these considerations, it is clear that the contrast between phototherapy and pharmacology is not that between modernity and obsolescence, but that between the technology of Nature and that of Man, or, better, between combinations of active ingredients, like a plant extract can be considered, and monomolecular drugs. Just like modern medicines, also medicinal plants and the extracts prepared from them act because they contain specific compounds capable of modulating in a beneficial way certain biological structures (enzymes, transcription factors, receptors, nucleic acids) whose malfunctioning underlie the development of a disease. Phytotherapy relies undoubtedly on tradition and the use of plants in folk medicine, but there is ample potential for innovating in the light of this tradition.

Despite the poverty of the pharmaceutical pipeline, three new drugs of plant origin were approved by FDA in 2012.\textsuperscript{2} One of them (Croplemeler) is a complex polyphenolic extract from an Amazonian species (\textit{Croton lechleri}).\textsuperscript{22} Most plant diversity lies, indeed, in the tropics, and is still substantially untapped from a medicinal standpoint. Five centuries ago, the search for tropical spices fostered the Age of Exploration, and the study of tropical medicinal plants has, undoubtedly, the potential to help medicine to better navigate the perilous seas of human diseases and to discover access to new continents of medicines.


