# MEDICINAL PLANTS AND PHYTOMEDICINES

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**Keywords**: Medicinal plants, Biodiversity, Phytomedicines, Secondary metabolites, Therapeutic potential

## Contents



## Summary

Phytomedicines are mixtures of plant metabolites that exhibit some therapeutic properties. It is well-known that mixtures of plant metabolites are generally obtained by

extraction with water or ethanol. However, simple infusions such as teas are also used today. Phytomedicines require good quality plant material and rigorous production methods to obtain extracts with therapeutic efficacy and safety. Modern biological screening methods and the mechanisms of action, as well as the importance of synergy, are described. Twelve phytomedicines commonly used worldwide are summarized in terms of applications, efficacy and safety. Finally, the study case of new phytomedicine development is described as an example of the biodiversity potential in supplying novel medicinally important compounds.

## 1. Introduction

The use of plants for therapeutic purposes is one of the oldest practices of humankind. The Egyptians recorded the analgesic use of opium, as well as the use of fungi with antibiotic properties. Other civilizations, such as India and China, also left records on the use of medicinal plants, with a collection of 700 species, and still play an important role in traditional medicine. Today, according to the World Health Organization (WHO), approximately 80% of the world's population uses plants to treat basic illnesses, mostly in the form of extracts or their active ingredients. The marketing of these phytomedicines has expanded considerably throughout the world, particularly in the European countries, such as Germany, France, Italy, the UK, and Spain, and more recently, the United States. Brazil has an important role in this field, as it has the largest biodiversity in the world, with more than 35,000 catalogued species, of a total of between 350,000 and 550,000 plant species identified worldwide. Thus, expertise in the areas related to the development of phytomedicines, including organic chemistry, pre-clinical pharmacology, clinical pharmacology and pharmaceutical sciences, has increased in recent years. Phytomedicines are products that contain plant metabolites as their pharmacologically active compounds.

Phytomedicines is defined as the use of a crude drug (dried herb), an essential oil, an extract or fraction of it for medicinal properties and quite often complex mixtures of compounds that generally occur in low (variable) concentrations. The most commonly used phytomedicines are plant extracts obtained through the use of solvents, by maceration or percolation of the dried plants. The extracts can be used as liquid preparations or in powdered form. The solvents most commonly used for extraction are water and alcohol. In some cases, fractions are used, which contain more concentrated levels of the active principles, and are generally obtained by partition with solvents of increasing polarity. However, due the increasingly popularity and expanding global market for phytotherapeutics, the safety of plant products has become a major public health concern. A lack of regulation and distribution channels (Internet sales) may result in poor quality products and consequently, adverse reactions. The most common causes of adulteration are products with undeclared potent pharmaceutical substances, substitution or misidentification with toxic plant species, incorrect doses, and interactions with conventional medicines.

The availability and quality of the raw materials are frequently problematic because the active principles are often unknown, and standardization and stability, though feasible, are not easy. Compared with modern medicine, herbal medicines cost less, are more often used to treat chronic diseases, and appear to have less frequent undesirable side effects. Thus, modern techniques have received attention in recent years, and the number of publications produced annually in this field has increased considerably. The most notable technique in this field is the hyphened analytical technique, which has enabled a reliable fingerprint to be obtained. This has led to a growing class and a promising market, as it generates revenue of $ 21.7 billion a year.

## 2. Quality Control of Phytomedicines

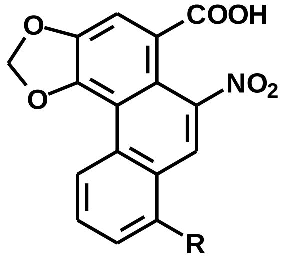
### 2.1. Quality and Efficacy of Plant Material

The use of plants with medicinal purposes involves the action of multiple compounds generally in a very low concentration. Thus, its safety is known and accepted, but not its effectiveness. A disadvantage of phytotherapy is that in most cases, there is a lack of clearly-defined, complete information on the composition of the extracts. Furthermore, phytomedicines require a thorough, in-depth assessment of their pharmacological qualities, which can now be done through the use of new biological technologies. Consequently, the development of fast and effective analytical methods for fingerprinting plant extracts is of high interest. In this context, several studies have shown that ESI-MS and LC-MS methods are particularly effective for characterizing plant extracts.

Synergy between compounds is a basic principle of medicinal plants, which will be discussed in this chapter. However, efforts are especially dedicated to studying single molecules, rather than identifying synergies among different compounds. From a scientific perspective, the extracts of medicinal plants as a whole constitute the “active principles”. Thus, the measurement of one or more components as markers is necessary. Also, in the case of extracts in which an active constituent has been determined, there is generally a group of substances that are active. It is therefore necessary to obtain a “fingerprint” of the extract in which all the possible constituents can be characterized and/or identified. This is now possible through various modern technological methods. Phytotherapy requires plant material with a standardized composition; however, natural material growing in the wild does not always have the same quality, due to different affecting factors such as climate, soil, genetic constitution, etc. Therefore, it is more efficient to cultivate the plants, in order to reduce variations in the constituents and to ensure controlled content of the pharmaceutically relevant constituents.

To improve the accuracy and consistency of control of phytomedicine preparations, regulatory authorities worldwide are requesting research into new analytical methods, for more rigorous standardization of phytomedicines. Significant differences have been observed in chamomile extracts by NMR-based metabolomics, which combine high-resolution $^{1}$H-NMR spectroscopy with chemometric analysis, showing that the origin, purity and preparation methods contributed to these differences.

Over the last ten years, numerous cases of intoxication, leading in most cases to end-stage renal failure, have been reported after consumption of weight loss diets containing Chinese herbal preparations. These intoxications were associated with species of the *Aristolochia* genus, such as *A. fangchi*, known to contain very nephrotoxic and carcinogenic metabolites called aristolochic acids (Figure 1). Several dietary supplements, teas, and phytomedicines used in weight loss diets were analyzed. The presence of aristolochic acid I was confirmed by HPLC/UV-DAD/MS analysis. These products were immediately recalled from the Swiss market.




**(1) R=H; aristolochic acid I**
**(2) R=OMe; aristolochic acid II**

Figure 1. Aristolochic acids

Pesticides, which are mainly applied to crops to protect the plants, have been found in medicinal plants, as well as in infusions, decoctions, tinctures and essential oils. Zuin *et al.* (2000), reviewed this important aspect of medicinal plants in a review article spanning more than thirty years. Other studies indicate the incidence of toxigenic fungi and their mycotoxins in 152 Argentinean medicinal and aromatic dried plants belonging to 56 species, which are used as raw material for phytomedicines.

## 2.2. Production Methods

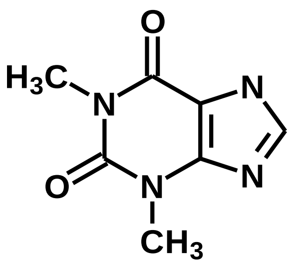
The nature of the solvents and the extraction and drying methods affects the composition of the extracts. For liquid phytomedicines, water and alcohol are the principal solvents. Polar compounds are soluble in water, and non-polar lipophilic compounds are soluble in alcohol. However, when identical solvents are used, the extraction methods can yield extracts with different pharmacological actions. Studies have indicated, in the case of essential oils, that water steam distillation in acidic medium can be more advantageous than the traditional method if the volatile terpene derivatives present in the plants are in the form of glycosides or dimeric lactones. (*i.e.* oregano, wormwood oils, siderites). Comparing the composition of essential oils obtained by water steam distillation and supercritical fluid extraction (SFE), it was found that SFE fractions are richer in ester constituents because the possibility of hydrolysis is reduced and the oils are more valuable than the classic oils. However, when the transformation processes are important (chamomile) the distillation should be the appropriate method.

A Korean researcher has patented a method for the quantitative standardization of medicinal herbs by i) preparing the sample of medicinal herbs and measuring the weight of the sample; ii) roasting the sample by controlling the intensity of a fire; and iii) classifying the sample into three types: a low, medium and strong flame. However some authors have indicated problems in the standardization of flavonoids in crude drugs and extracts from medicinal plants, and in the application of HPLC, HPTLCdensitometry and spectrophotometry in standardization. This fact demanded new and more efficient methods of analysis for controlling the quality of the extracts.

## 3. Medicinal Teas Today

Tea is the second most commonly consumed liquid on earth, after water. It has been drunk socially and regularly since 3000 BC. Its medicinal effects date back almost 5000 years. Tea is an infusion obtained from dried leaves of different plants, or roots, herbs, spices, fruits or flavors in hot water. Scientific research around the world has provided clear evidence of the health benefits associated with drinking herbal tea. Today there are teas that prevent cholesterol, high blood pressure, fatigue, diabetes, excess weight, and detoxification, among others. A related compound found in tea is theophylline (Figure 2), a licensed medicine for the treatment of respiratory diseases such as asthma. Tea infusions can be prepared from individual plants or from plant mixtures. A basic distinction is made between:

- Non-medicinal teas that are consumed for pleasure, such as black tea, flavored teas, etc.
- Medicinal teas




**(3)**

Figure 2. Theophylline

The indications for the use of medicinal teas are psychosomatic disorders, colds, urinary problems, constipation and diarrhea, and gastrointestinal disorders, among others.

There are no controlled clinical studies on the efficacy of medicinal teas. Their medicinal values are based largely on empirical evidence. The placebo effect must contribute to their efficacy. Several studies describe the findings of these ethnomedicines research efforts throughout the world over time.

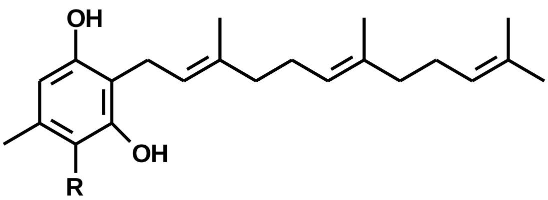
## 4. Modern Phytotherapy

Studies have indicated that in order to investigate an extract, which is a complex system, a reductionist method should be applied to determine each active compound separately, but according to previous discussion above. Such research must be carried out with caution, as it will never quite explain the efficacy of the entire extract. The statement that "the whole is more than the sum of all the individual parts" is applicable to phytopharmaceuticals. After analyzing the progress introduced by the modern analytical method and *in vitro* and *in vivo* pharmacological assays with models of biological molecular test, the phytotherapy was significantly improved.

### 4.1. New scientific screening

There have been significant increases in news and important methods for biological screening. Assays on Alzheimer's disease have focused on agents that counteract the loss of cholinergic activities. The Ellmann microplate assay and silica gel thin-layer chromatography were used to screen extracts from plants as possible new sources of AchE inhibitors. Activity in the NF-kB and the HET-CAM-test used to investigate the anti-inflammatory potential and potential inmunomodulating activity was investigated, evaluating the influence of extracts of medicinal plants of Mexico in various *in vitro* assays using murine and human lymphoid cells.

Peruvian medicinal plants were analyzed with respect to their antibacterial activity using a versatile microplate bioassay for rapid and sensitive determination of the organic compounds. Grifolin and grifolic acid (Figure 3), which are *S. aureus* and *S. epidermidis* growth inhibitors, were determined as the main active principles. A recently developed method studied the correlation between the chemical composition and bioactivity of herbal medicine, and identified the active components from the complex mixture. The advantage of this method compared with bioassay-guided isolation was demonstrated by its application on a typical herbal drug.




**(4) R=H; Grifolin**
**(5) R=COOH; Grifolic acid**

Figure 3. Grifolin and grifolic acid

### 4.2. Mechanism of Action

Drug resistance has been a major obstacle in cancer chemotherapy. Active principles from plants used in traditional Chinese medicine may act by different molecular targets from those of clinically used antitumor drugs, making them attractive candidates for new therapeutics. 531 natural products were tested for correlation with the microarray-based mRNA expression of six genes involved in nucleotide excision repair. The results showed no evidence associated with the expression of these genes, suggesting that mRNA expression is not related to resistance of the cell lines of these substances. In addition, other genes were identified, but none of these appear to be involved in DNA repair.

Studies have been carried out using the electrophoretic mobility assay (EMSA) as a suitable technique for the identification of plant extracts that alter the binding between transcription factors and the specific DNA elements. These studies demonstrate that low concentrations of extracts from *Hemisdesmus indicus*, *Polyalthia longifolia*, *Moringa olifera* and *Lagerstroemia speciosa* inhibit the interactions between nuclear factors and target DNA elements, mimicking sequences recognized by the nuclear factor kappa B (NF-kB). Extracts of *Paederia foetida*, *Cassia sophera* and *Ocimunm sanctum* were unable to inhibit NF-kB/DNA interactions. Extracts that inhibit both NF-kB binding activity and tumor cell growth might be a source for antitumor compounds, while those that inhibit NF-kB/DNA interactions with lower effects on cell grow could be of interest in inflammatory diseases.

### 4.3. Synergy

The term synergism means that the effect of two or more substances causes better biological activity than pure substances administered in a single dose. In this context, this effect occurs by different chemical and biological means. The phytotherapeutics that are available on the market in different forms (extract or fraction) generally exhibit synergism that has an important effect in improving the therapeutic potency. However, a contrary effect can sometimes be observed, leading to a decrease in biological activity, called antagonism.

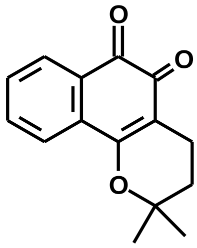
Although only a few clinical studies have confirmed the existence of synergism, pre-clinical studies have been extensively described, and large amounts of experimental evidence can be found in the literature.

To better illustrate the phenomenon of synergism, three recent examples are detailed:

1- *Tabebuia avellanedae* bark extract and β-lapachone (Figure 4) were combined to investigate the hematopoietic response of tumor-bearing mice. Administration of extract (30-500 mg/kg) and β-lapachone (1-5mg/kg) in distinct combinations caused a dose-dependent reversion of these effects. The best combination was that of 120 mg/kg extract and 1 mg/kg β-lapachone, which prolonged the life span of tumor-bearing mice, both producing the same rate of extension in the duration of survival. Toxic effects were evidenced by the higher doses of β-lapachone in normal and tumor-bearing mice. The studies by TLC and HPLC suggested that the antitumor action of extract and β-lapachone also act synergistically with other factors, such as specific cytokines.

2- A recent review showed that distinct plant extracts have caused synergistic effects against human pathogenic microorganisms. Although the traditional antibiotics have exhibited effective therapeutic action in the treatment of infectious diseases caused by fungi or bacteria, resistance to these drugs has re-emerged of old diseases. The use of combined drugs or plant extracts with drugs has been used as a strategy for decreasing this resistance, like the described use of β-lactams associated with β-lactamase inhibitors. Synergy has been confirmed between some components extracted from plants, such as flavonoids and essential oils, and synthetic antibiotics used to inhibit bacterial, fungal and mycobacterial infections. The potency and/or mechanisms of action of some types of combination are very different from that of drugs used pure, demonstrating the existence of synergism in these cases.

3- A more recent paper describes the antiplasmodial potential of thirteen plant species (and combination of plants to determine a possible synergism) used in traditional folk medicine in Kenya, for the treatment of malaria. 25% of the tested plants were highly active, and 46% exhibited moderate activity against the malaria parasite. Both synergism and antagonism were demonstrated for combination of some studied extracts. *Uvaria acuminata* and *Premna chrysoclada* presented the highest synergy, while the interaction between *Grewia plagiophylla* and *Combretum illairii* caused a pronounced antagonistic effect.



**(6)**

Figure 4. β-lapachone

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Web sites: Several web sites were used for some plants included in this chapter, such as PubMed (http://www.ncbi.nlm.nih.gov/pubmed), Google (www.google.com); Scielo (www.scielo.org); Science direct (www.sciencedirect.com)

## Biographical Sketches

**Rosendo Augusto Yunes:** Graduate (1962), Ph.D. (1965) in organic chemistry from the Universidad Nacional del Litoral (Santa-Fe, Argentina). He was a visiting professor at the Institute of Chemistry, University of São Paulo (Brazil, 1971) and the Department of Chemistry, Indiana University - Bloomington (USA, 1974-1975). He was Chairman of the Department of Chemistry of the Universidad Nacional del Litoral (Argentina). He worked for 22 years as teacher and researcher at the Federal University of Santa Catarina (Brazil). He is currently Senior Researcher for the CNPq (National Council for Scientific and Technological Development) and a volunteer teacher at the University of Vale do Itajaí (UNIVALI), Brazil. He has experience in the area of physical organic chemistry and phytochemistry. He is a reviewer for several scientific journals, and has authored over 350 published papers and five book chapters, and has edited two books. He has been awarded many prizes during his career, including the Scopus Award 2009 (Capes – Elsevier) and Ph.D *Honoris causa* awarded by UNIVALI.

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