Therapeutic Medicinal Plants

From Lab to the Market

Editors
Marta Cristina Teixeira Duarte
Mahendra Rai

CRC Press
Taylor & Francis Group
A SCIENCE PUBLISHERS BOOK

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CRC Press
Taylor & Francis Group
Boca Raton London New York

CRC Press is an imprint of the
Taylor & Francis Group, an **informa** business
A SCIENCE PUBLISHERS BOOK

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CRC Press
Taylor & Francis Group
6000 Broken Sound Parkway NW, Suite 300
Boca Raton, FL 33487-2742

Version Date: 20151020

International Standard Book Number-13: 978-1-4822-5404-4 (eBook - PDF)

Foreword

Traditional or ethno-medicine represents a series of empirical practices included in the knowledge of a social group, frequently transmitted orally from one generation to another, with the intention of solving health problems. It is often strongly connected to religious beliefs and practices of the respective culture. The knowledge of medicinal or herbal plants is an important component of traditional medicine. Traditional medicine is used globally and has rapidly growing economic importance. In developing countries, traditional medicine is often the only accessible and affordable treatment available. In many Asian countries traditional medicine is widely used, even though western medicine is often readily available. In our time of constantly expanding pharmacological research it is easy to forget that medicinal plants still continue to play a leading role in primary health care for 80% of the world's population living in developing countries. Natural products and medicinal products derived from them also constitute an essential element in the system of health care for the remaining 20% of the world population.

In Japan, 60–70% of allopathic doctors prescribe traditional medicines for their patients. In the US the number of visits to providers of Complementary Alternative Medicine (CAM) now exceeds by far the number of visits to all primary care physicians. The expense for the use of Traditional and Complementary Alternative Medicine is exponentially growing in many parts of the world. Traditional knowledge has proven to be an important source for therapeutic drugs.

The global inventory of plant diversity consists currently of about 350,000 species, and most current estimates expect about 420,000 plant species to exist. This tremendous diversity accounts for a wide range of phytochemicals, and a high variation of compound composition even within one single species, depending on growth conditions (soil, climate, nutrient status, etc.), and harvest practices and timing, not even taking intraspecific variation into account. While traditional plant use and medicine preparation normally take these details into account, they are often seen as of marginal importance in the herbal trade. In the United States, botanical supplements are supposed to be labeled, with the requirement to include the correct scientific name. However, in practice this does not prevent accidental or deliberate adulterations, or can contain heavy-metal contaminations. The most problematic occurrence in herbal medicine trade is, however, linked to the purchase and use, either in medication or research, of botanicals that are either accidentally or purposefully wrongly identified, or are simply collected under a vernacular name without any subsequent taxonomic treatment, and often without having any vouchered material that could later be used for the verification of plant identity. A much more frequent occurrence is, however, the often deliberate adulteration of botanicals with more common and cheaper species, which, although generally not toxic, might completely lack efficacy. Bulk herbs are readily available unprocessed, which allows for the retention of material for a botanical voucher. In contrast, raw botanicals are also often provided in ground or powdered form, which makes morphological identification very difficult or virtually impossible. In addition, little research has been done on the efficacy of traditionally made medicinal preparations, because most efforts have focused on the elucidation of lead compounds and subsequent clinical trials, with little regard to the correct harvesting or cultivation, and botanical identification of the source material. One example of the problems of plant collections and markets was illustrated by recent studies in the markets of La Paz, Bolivia, that focused on plants used for the treatment of urinary infections. One of the most frequently mentioned herbs was 'cola de caballo', horsetail, which normally signifies species of *Equisetum*. However, every single vendor in La Paz instead sold it as a species of *Ephedra*. Not only does *Ephedra* not have any properties related to treating urinary infections or inflammations, but also its main compounds can lead to serious side effects. Without the collection of botanical vouchers, this serious

health risk would not have been discovered. This clearly illustrates the great need of more studies that in fact follow therapeutic medicinal plants from the source to the laboratory.

The present volume is indeed a very worthy effort to outline and address these issues on a global scale. M.C. Texeira and M. Rai have done great job in bringing a broad field of accomplished contributors together, who in 19 chapters, illuminate all aspects of medicinal plant use from local collectors and markets to clinical trials in modern drug development.

Dominguez et al. provide an up to date view on traditional medicine in Mexico, and its translation into a source for the medicines of tomorrow, while Noun Jihad et al. address the possibilities and limitations of such an approach by using Lebanon as case study. In their contribution on Cuba, Escalona et al. highlight the great efforts of this country to create an independent, high-class medicinal system that offers patients the best of both traditional therapies and their applications in an allopathic setting. The chapter by Bussmann and Sharon follows a similar trajectory in illustrating the long way from traditional plant collectors to using medicinal plant extracts in bioassays.

A second set of contributions provides direct insights in applied research. Muñoz-Acevedo et al. review species from Latin American that could be promising for the cosmetics industry, while Ilhan et al. look at new remedies for hyperlipidemia, and Rojas and Buitrago as well as Teixeira Duarte and Teixeira Duarte address the possibilities of finding new antibacterial agents derived from essential oils. This approach culminates in a plethora of chapters focusing on individual species and the long way from traditional use to lead compounds in drug discovery: Vinet et al. (*Vitis vinifera* polyphenols), Al-Nahain et al. (*Centella asiatica*), Ríos and Andújar (*Crocus sativus*), Santana et al. (*Euphorbia hirta* and *E. hyssopifolia*), Patil and Lade (*Tribulus terrestris*), Rai et al. (*Vitex negundo*) and Ortega Hernández-Agero (*Melissa officinalis*).

In a last group of contribution the focus lies on the problems of production, quality control, toxicity and efficacy testing of herbal medicines. Melillo de Magalhães addresses the challenges in plant cultivation as first step to provide standardized source material for drug development, while Araujo focuses on the issue of toxicity in traditionally used medicinal plants. Rodrigues et al. take up the discussion on how to actually improve the properties and quality of plant extracts, and Mootoosamy and Mahomoodally finally review the current status of clinical trials of medicinal herbs, and highlight chances and challenges of future development.

It is to hope that 'Therapeutic Medicinal Plants: From lab to the market' will be widely read, and will become a standard reference for researchers in the whole chain of traditional medicines, from documentation of traditional medicinal practices, to plant harvest, production and markets, extraction, clinical studies and finally the elaboration of standardized herbal medicines for a global environment.

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Preface

Medicinal plants are known as a natural resource for the cure of different diseases since the dawn of civilization. They have been used in the prevention, diagnosis and elimination of diseases, and solely based on practical experience of thousands of years.

There are various reports of medicinal/ethnomedicinal plants by researchers all over the world. Unfortunately, the research being carried out in laboratories are still restricted to the 'four walls' of the laboratories. There is a greater need to initiate and transform these researches in fruitful formulations leading to the development of newer products for the cure of diseases with special reference to new and emerging diseases like AIDS, cancer, hepatitis and also for coping with multidrug resistance problems.

In 21st century, there is a greater need to validate the available knowledge of medicinal plants. World Health Organization (WHO) emphasized on use of herbal medicines after its validation. The next steps are formulation and finally the development of medicinal products.

The purpose behind editing a new book, is to gather recent developments in medicinal plant research for different diseases, formulation of products and market strategy.

The book would be immensely useful for botanists, medicos, ayurvedic experts, traditional healers, pharmacologists and common people who are interested in curative properties of medicinal plants.

MKR wishes to thank Dr. D.P. Rathod, and Dr. Shubhangi Ingole for their help in editing this work.

Marta Cristina Teixeira Duarte
Mahendra Rai

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Mexican Traditional Medicine: Traditions of Yesterday and Phytomedicines of Tomorrow

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Introduction

The arrival of the Spaniards radically modified the native medicine practices of the Aztecs and the use of medicinal plants. Diverse colonial documents, such as those of Martín de la Cruz, Juan Badiano, Bernardino de Sahagún and Francisco Hernandez, provide examples of the use of medicinal plants from the viewpoint of the Aztecs in works such as *Libellus de Medicinalibus Indorum Herbis* (Little Book of the Medicinal Herbs of the Indians). Additional works describe the actions of Mexican medicinal plants and suggest their usefulness, such as *Historia de las cosas dela Nueva España* (General History of the Things of the New Spain) by Fray Bernardino de Sahagún (Viesca 1992, Viesca 1996).

Libellus de Medicinalibus is a manuscript completed in Mexico in 1552 which refers to native medicinal plants, the curative effects of which were indicated in Latin texts. This medicinal '*herbarium*' was written with the intention of showing the King of Spain the rich variety of medicinal plants that grew in the New World. An elderly Indian physician and a native of Tlatelolco, Martín de la Cruz, described the use of each of plant and provided drawings of them, and Juan Badiano (a young Indian) translated the material from Nahuatl into Latin. This book was housed in the archives of the Vatican Library in Rome and was rediscovered in the 20th century by U.S. historians, who confused it with a pre-Hispanic Aztec codex and renamed it the *Cruz-Badiano Codex* or the *Badiano Codex* (Garibay 1964, De la Cruz 1964). This codex is currently found at the National Museum of Anthropology in Mexico City.

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In modern times, formal medical research of the codex and other texts began during the Porfirian era, in the last two decades of the 19th century. A major progression in formal medical research occurred in 1888, when the National Medical Institute in Mexico was created by the order of President Porfirio Díaz. The objective of the Institute was to conduct studies of the Mexican medicinal flora with the goal of incorporating medicinal plants into therapeutics at the national level. By 1915, the herbarium possessed 14,000 classified species and approximately 1,000 chemical compounds that were obtained from plants (García 1981). However, the modern era of interest in the chemistry of natural products surged in Mexico from 1940–1960 during the boom of steroidal sapogenins from inedible Mexican yams, which were used as a source of progesterone (Gereffi 1978). Indeed, this became the cornerstone of the Syntex Company that was founded in Mexico. Syntex initiated a true worldwide revolution in the organic synthesis of steroidal hormones; it was the first to achieve the synthesis of progesterone and cortisone. Additionally, the Syntex Company provided the basis for the first contraceptive, which was derived from the chemical and ethnobotanical studies of Russell Earl Marker concerning the chemical diosgenin that was obtained from the 'cabeza de negro' (black head) plant (*Dioscorea mexicana*) and later from the 'barbasco' (*Dioscorea composita*) plant. The barbasco plant is an endemic species of Mexico (Soto 2005). In 1975, the Mexican Institute for the Study of Medicinal Plants (IMEPLAM) was created. This institute was founded for the multidisciplinary study of the plants most widely used in Mexico to treat common illnesses. The Institute included historians, agronomical engineers, botanists, physicians, physiologists, chemists, and pharmacists that were under the direction of Dr. Xavier Lozoya. During the existence of IMEPLAM (1975–1980), numerous publications were produced, thus establishing the Institute as an icon in the research of medicinal plants in Latin America and reactivating this type of research (Lozoya 1976). At the same time, the Institute initiated the formation of the Medicinal Herbolarium, currently known as the Medicinal Herbolarium of the Mexican Institute of Social Security (IMSS), which is located at the Twenty-First Century National Medical Center in Mexico City. Its legacy comprises >120,000 specimens (Zolla 1980, Montes and Montes 2005). In 1980, the IMEPLAM became part of the IMSS Medical Research System.

The IMEPLAM embodied the tendencies of the 1960s with respect to the increased research interest in natural plant drugs, including: a) the *Indian Rauwolfia* drugs and their derivatives, which were demonstrated to successfully treat various mental disorders and other diseases; and b) the plant-derived drugs that induce psychotic symptoms akin to symptoms of mental illnesses. Indeed, interest in such psychosis-inducing drugs, which were traditionally used by healers and medicine men of 'primitive' cultures, resulted in an extensive search for substances possessing hallucinogenic properties (Viesca et al. 2000).

At the end of the 20th century, a second stage of studies on medicinal plants and their therapeutic potential ushered in a new era of phytopharmaceuticals. Currently, new mechanism actions are being proposed to explain the pharmacological effects of these plant extracts on several activities and functions.

In recent years, there has been a rapid increase in global technological and economic potential that has resulted in an increased ability to overcome problems related to poverty and poor health. However, many developing countries have an impaired health status due to the resurgence of infectious diseases and an increasing burden of noncommunicable diseases.

There are numerous methods to improve results in the healthcare sector including prevention, healing with an existing treatment, and research into better methods of prevention, diagnosis or treatment. Research results obtained for the prevention, diagnosis and treatment of diseases are reported to apply the gained knowledge in solving health problems. Generally, research results are disclosed in articles published in biomedical journals and/or theses.

However, commercially sponsored research results for drug, diagnostic and treatment techniques must be intellectually protected to obtain a health registry for proper marketing. One or more patents are used for the intellectual protection of research results. A patent has two important functions: protection, which allows the patent owner to exclude others from commercially exploiting the invention for a period of 20 years; and disclosure, because the patent provides information that can stimulate technological innovation.

In Mexico, the Mexican Institute of Industrial Property grants government patents. This type of intellectual protection is regulated by the Industrial Property Act and its rules. There have been no objections to granting phytomedicine patents; however, the invention must meet three basic criteria for patentability: novelty, inventive step, and industrial application.

The novelty criterion specifies that the invention is not derived from technical knowledge available to the public worldwide prior to the first filing date of the relevant patent application. The inventive criterion specifies that the invention would not have been obvious to a person skilled within the applicable field of technology. The industrial application criterion specifies that the invention must be capable of being used for industrial or business purposes.

In Mexico, there are few phytomedicine patents. As shown (Table 1.1), the first patent application in this area was in 2005 and to date there have been a total of 27 patent applications. It should be noted that 12 applications belong to the Mexican Social Security Institute. Medical applications of these patent applications include substances that have anti-inflammatory, anti-microbial, anti-neoplastic, and anti-hypertensive activity.

After scientists have identified specifically targeted new entities for disease diagnosis, treatment or pharmaceutical purposes, preclinical studies are undertaken comprising *in vitro* studies, animal testing and pharmacodynamic responses.

Table 1.1. Mexican patent applications of phytomedicines.

Phytomedicines	**Medical application**	**Patent**
Agave marmorata	Treating chronic degenerative diseases	MX2012010587
Tournefortia densiflora	Treating microbial infections in skin	MX2012007255
Buddleia cordata	Treating the discomforts generated by any type of gastritis	MX2012006934
Salvia elegans	Treating the comorbidity of high blood pressure disorders with anxiety	MX2012006426
Ageratina pichinchensis	Treating chronic venous ulcers	MX2012002783
Sechium chinantlense & Sechium compositum	Preventing and/or treating neoplasms	MX2012002675
Cydonia oblonga	Anti-inflammatory	MX2012002190
Bougainvillea xbuttiana	Anti-inflammatory	MX2011013522
Matricaria recutita & Calendula officinalis	Promoting the integrity of the corneal epithelium	MX2011013407
Stevia rebaudiana	Treating ocular diseases	MX2011013620
Taxus globosa	Treating anxiety	MX2011010853
Capsicum annum	Treating gastrointestinal problems	MX2011009963
Loselia mexicana	Treating anxiety	MX2011009446
Hibiscus sabdariffa	Anti-hypertensive	MX2011006660
Ageratina pichinchensis	Treating wound healing, and tinea	MX2011005607 MX2007013011
Petiveria alliacea	Treating of rheumatic diseases	MX2011003459
Amphipterygium adstringens	Treating skin lesions	MX2010013512
Heteropterys brachiata	Treating anxiety	MX2010007355
Cladocolea loniceroides	Treating breast cancer	MX2010006779
Psittacanthus calyculatus	Anti-hypertensive	MX2010004628
Galphimia glauca	Treating anxiety	MX2009007792
Fluorensia cernua	Anti-microbial agent against periodontopathogenic bacteria	MX2009007244
Psidium sartorianum	Anti-parasitic	MX2009004174
Allium spp.	Treating diabetic foot	MX2007016417
Echinacea angustifolia	Treating gingivitis	MX2005013173
Psidium guajava	Treating gastrointestinal problems	MX2005002081

It is necessary to have the proper authorization to market phytomedicines. In Mexico, the Federal Commission against Health Risk (COFEPRIS, for its acronym in Spanish) is responsible for granting the medical authorization for proper marketing. The COFEPRIS approval process begins when a manufacturer requests permission, by submitting an investigational new drug application, to begin human testing. The application must provide high quality preclinical data to justify the testing of the drug in humans.

The next stage is clinical trials, which use human subjects. Clinical trials include biopharmaceutical, pharmacokinetic, pharmacodynamic, efficacy, safety and studies designed to demonstrate the proposed therapeutic application. After application approval, the innovating company is allowed to distribute and market the drug.

However, despite the existence of phytomedicine patent applications, there have not been any clinical trials conducted that led to marketing authorization. There are various clinical trials of Mexican phytomedicines (Table 1.2). However, these clinical trials were not registered with the COFEPRIS.

For example, a double-blinded randomized clinical trial was conducted in 197 women with primary dysmenorrhea. Four intervention groups were defined: two extract doses of *Psidium guajava* (3 and 6 mg/day), ibuprofen (1200 mg/day) and placebo (3 mg/day). Participants were individually followed up for four months. The main outcome variable was abdominal pain intensity measured according to a visual analogue scale. The standardized phytomedicine reduced menstrual pain significantly compared with conventional treatment and placebo (Doubova et al. 2007). Currently, the patent for this phytomedicine has been granted and the Mexican Social Security Institute (IMSS) has granted an operating license to the company, Genomma Lab®. This phytomedicine is marketed under the name QG5®.

Table 1.2. Mexican clinical trials of phytomedicines.

Phytomedicines	**Clinical trial**	**Reference**
Solanum chrysotrichum	Safety and effectiveness for the treatment of *Tinea pedis*	Herrera-Arellano et al. 2003
Hibiscus sabdariffa	Anti-hypertensive effectiveness and tolerability	Herrera-Arellano et al. 2004
Galphimia glauca	Efficacy and tolerability on generalized anxiety disorder	Herrera-Arellano 2007
Ageratina pichinchensis	Effectiveness and tolerability on patients with mild to moderate onychomycosis	Romero-Cerecero et al. 2008

Data on patent applications and registration of herbal medicines demonstrate that Mexico lacks an adequate structure for phytomedicine development. This weakness is not due to Mexican scientific research, because research on natural products in Mexico has flourished since 1960 and has resulted in extensive literature concerning secondary metabolites in Mexican plants (Huerta-Reyes and Aguilar-Rojas 2009) including anti-cancer (Alonso-Castro et al. 2011) not given in reference section and anti-diabetic agents (Mata et al. 2013).

Despite the high scientific, technical level and experience of Mexican researchers, the low numbers of phytomedicine patent applications may be attributed to several factors, such as: scientific evaluation criteria, which are mainly based on recognition by the scientific community from publication within indexed periodicals; lack of information about the patent database (both free access and private); and low knowledge about patentability requirements, particularly the novelty criterion. Similarly, a strong policy of disclosure in the drug registration system is required because regulatory constraints lead to high costs for companies and there is a lack of information about the key steps required for medical authorization. Finally, a policy allowing cohesion between university-business-government to foster phytomedicine research, health registration and extensive marketing is necessary.

Herbalists Drugs (Phytomedicines)

Serenoa repens (W. Bartram) Small (Arecaeae) (001P2001, Tegrata; 044P2003, prostasan; oleomed p, 042P2003), a shrub-like species native to Mexico, the southeastern USA and West Indies, is used for the treatment of prostatic hyperplasia (Capasso et al. 2003). This plant contains fatty acids and their glycerides

(oleic, caprylic, myristic, etc.), sterols (e.g., β–sitosterol, campesterol, and cycloartenol) and sitosterol derivatives (Capasso et al. 2003). The therapeutic effects of this plant have been associated with the down-regulation of inflammation-related genes and the activation of the nuclear factor-kappa B pathway in prostate tissue (Silvestri et al. 2013). A clinical study indicated that this preparation improved physical symptoms caused by prostatic hypertrophy (Coulson et al. 2013).

Hypericum perforatum L. (Hypericaceae) (005P2001, Conexit; 024P2003, Motivare), a plant native to Europe, is used for the treatment of wounds, eczema, burns, trauma, rheumatism, neuralgia, gastroenteritis, ulcers, hysteria, bedwetting and depression (Ghasemi-Pirbalouti et al. 2014). The chemical constituents reported in this plant are α and β pinene, hypericin and hyperforin (Crupi et al. 2013). It has been proposed that the pharmacological effects of this plant are involved in the regulation of genes that control hypothalamic-pituitary-adrenal axis function and partially influence stress-induced effects on neuroplasticity and neurogenesis (Crupi et al. 2013). A review indicated that *Hypericum perforatum* significantly decreased depression when compared with placebo in 25 trials involving a total of 2129 patients (van der Watt et al. 2008).

Valeriana officinalis L. (Caprifoliaceae) (006P2001, Tegrarina; 011P2001, Insocaps; 020P2003, Lerisor; 010P2005, Ansisom), native to Europe and Asia and commonly known as valerian, has been used for the treatment of dysmenorrhea, anxiety, insomnia, seizures and migraine. Felgentreff et al. (2012) reported the presence of valerenic acid and acetoxy valerenic acid in this plant. Fernández-San-Martín et al. (2010) demonstrated that valerian extract increased subjective sleep quality compared with a placebo. However, other reports indicate that valerian decreases fatigue in patients, but its efficacy to improve sleep needs to be clarified (Barton et al. 2011). Furthermore, patients with generalized anxiety disorder who received valerian during a four-week period had a significant improvement in the Hamilton Rating Scale for Anxiety, but not in total anxiety scores (Andreatini et al. 2002). However, *Valeriana officinalis* is reported to induce hepatotoxicity (Cohen and Del Toro 2008, Vassiliadis et al. 2009).

Piper methysticum G. Forst (Piperaceae), commonly known as kava, is distributed throughout the South Pacific and is used for the treatment of anxiety and stress. Traditionally, kava extracts are prepared from masticated rhizome roots that are combined with coconut milk or water (La Porte et al. 2011). The major active constituents responsible for the pharmacological effects of kava are known as kavalactones or kavapyrones (Bilia et al. 2002). The anxiolytic activity of kava is controversial. There are reports that kava induces moderate anxiolytic effects (Sarris et al. 2012), whereas other reports indicate that kava lacks an anxiolytic effect (Sarris et al. 2009, Sarris et al. 2012). Nevertheless, prolonged treatment with kava has been demonstrated to induce hepatotoxicity (Teschke 2011).

Valeriana officinalis L. (Caprifoliaceae) and *Melissa officinalis* L. (Lamiaceae) (008P2001, Pokan; 003P2005, Isoren). *Melissa officinalis* L. (Lamiaceae), a perennial herb commonly known as lemon balm, is native to South Central Europe and the Mediterranean region. Its potentially active components include monoterpenoids and sesquiterpenes including geranial, neral, 6-methyl-5-hepten-2-one, citronellal, geranyl-acetate, b-caryophyllene and b-caryophyllene-oxide, and 1, 8 cineole (Tittel et al. 1982). Clinical trials have demonstrated that *Melissa officinalis* exerts an anxiolytic-like modulation of mood (Kennedy et al. 2002, Kennedy et al. 2004). The combination of *Melissa officinalis* and *Valeriana officinalis* reduced the levels of sleep disorders in menopausal women compared with a placebo (Taavoni et al. 2013).

Gingko biloba L. (Gingkoaceae) (009P2001, Tegramen; 001P2003, Nemoril, 003P2003, Kolob; 022P2004, Maxibiloba; Oleomed cer 014P2004; 013P2004, G-Kroll; 006P2004, Fylgoba) is used for failing memory, age-related dementias and poor cerebral and ocular blood flow. However, this species is under threat of extinction (IUCN 2012).

Tanacetum parthenium (L.) Sch. Bip., and *Matricaria chamomilla* L. (Asteraceae) (010P2001, Plusan). *Tanacetum parthenium* is an aromatic herb, commonly known as feverfew, native to the Balkan Peninsula. *Tanacetum parthenium* has been used as a folk remedy for fever, rheumatoid arthritis and migraines.

Parthenolide, its active compound, exerts anti-inflammatory activities in a dose-dependent manner by inhibition of thromboxane B2 and leukotriene B4. This compound also inhibits the release of pro-inflammatory mediators such as nitric oxide and TNF-α in macrophages (Sumner et al. 1992). In clinical trials, feverfew relieved symptoms associated with migraine (Ernst and Pittler 2000). The adverse effects associated with this plant are nervousness, tension headache, constipation, diarrhea and others (Ernst and Pittler 2000). Nevertheless, it was reported that feverfew did not affect the frequency of chromosomal aberrations in lymphocytes (Anderson et al. 1988). *Matricaria chamomilla* is native to Europe and Asia. This plant has been used for the treatment of flatulence, colic, hysteria and fever (Singh et al. 2011). Chamomile extract contains coumarins, herniarin and umbelliferone, and the phenolic compounds, herniarin and umbelliferone (coumarin), chlorogenic acid and caffeic acid (phenylpropanoids), apigenin, apigenin-7-O-glucoside, luteolin and luteolin-7-O-glucoside (flavones), quercetin and rutin (flavonols), and naringenin (flavanone) (Singh et al. 2011). In clinical trials, *Matricaria chamomilla* produces moderate anxiolytic effects (Amsterdam et al. 2009, Amsterdam et al. 2012).

Hedera helix L. (Araliaceae) (012P2001, Panot-s) leaf extract has been clinically studied as a cough treatment (Holzinger and Chenot 2011, Schmidt et al. 2012a).

Eucalyptus globulus Labill (Myrtaceae) (103P2001, Broncorub) in combination with menthol and turpentine. The chemical components reported in Eucalyptus globulus are 8-cineole, α-pinene, d-limonene and linalool acetate (Kumar et al. 2012). The essential oil from *Eucalyptus globulus* has minimum inhibitory concentrations (MIC) of 1.25 µL/mL against *Haemophilus influenzae*, *Haemophilus parainfluenzae* and *Stenotrophomonas maltophilia*. *Eucalyptus globulus* has also demonstrated anti-inflammatory activity *in vitro* in J774A.1 macrophages by decreasing nitric oxide production (Vigo et al. 2004).

Panax ginseng C.A. Mey (Araliaceae), *Gingko biloba* L. (Gingkoaceae), vitamins and minerals (015P2001, Biometrix; 018P2001, Centrum; 009P2003, Onesource; 019P2003, Pharseng; 030P2003, M Force; 011P2004, Wilvit; 002P2006, Pharmaton). *Panax ginseng*, commonly known as ginseng, is native to Asia. Ginseng is one of the most popular and best-selling herbal medicines worldwide.

The main chemical constituents of ginseng are glycosides, also called ginsenosides or ginseng saponin. Each ginsenoside has a common hydrophobic four ring steroid-like structure with attached carbohydrate moieties (Nah 2014). Multiple clinical studies have been performed to characterize ginseng's therapeutic properties including improving physical performance (Kulaputana et al. 2007), diabetes (Kim et al. 2011), hypertension (Rhee et al. 2011) and other diseases.

Passiflora incarnata L. (Passifloraceae), *Salix alba* L. (Salicaceae), *Valeriana officinalis* L. (Caprifoliaceae) and *Crataegus monogyna* Jacq. (016P2001, Passiflorine RN). *Passiflora edulis*, used to treat nervous anxiety and insomnia, contains the c-glycosyl flavonoids orientin, isoorientin, vitexin, isovitexin and vicenin 2 (Li et al. 2011a). *Passiflora edulis* demonstrated anxiolytic and sedative effects in mice (Li et al. 2011a). *Crataegus monogyna,* native to Europe, Northwest Africa and western Asia, is used to treat cardiac insufficiency. *Crataegus monogyna* demonstrated antioxidant effects *in vitro* and its chemical components are quinic acid, catechin, gallic acid, epigallocatechin gallate (Simirgiotis 2013). *Salix alba*, native to Europe and Asia, is used as an analgesic and anti-inflammatory agent, its primary component is salicylic acid. *Salix alba* and salicylic acid decreased the pro-inflammatory mediators TNF-α, IL-1β and IL-6 in THP1 macrophages. In addition, salicylic acid exerted antioxidant effects (Drummond et al. 2013).

Glycine max L. (Fabaceae), vitamin D and calcium carbonate (019P2001, Caltrate 600 + S; 015P2004, Prevefem; 002P2005, Prevefemcomplex; 007P2005, Advancebonde; 001P2006, Caflovan). *Glycine max*, native to Asia, is used to treat menopausal disorders such as bone loss (Potter et al. 1998). Its major and active component is the phytoestrogen, genistein. In a six month study, 90 mg/day of soy isoflavones protected postmenopausal women against lumbar spine bone loss (Potter et al. 1998). Supplementation with 120 mg/day soy isoflavone in healthy postmenopausal women over two years protected against general body bone loss, but did not specifically protect against lumbar spine, femoral neck, or total hip bone loss (Wong et al. 2009). The synergistic effect of vitamins, calcium and phytoestrogens remain to be elucidated.

Panax quinquefolium L. (Araliaceae) (004P2003, gingold American). This plant, native to United States and Canada, is considered 'vulnerable' according to its conservation status (IUCN 2012). Its active components are called ginsenosides of which there are two types: protopanaxadiol ginsenosides and protopanaxatriol ginsenosides. A protein fraction of American ginseng has demonstrated anti-fatigue and anti-oxidant effects in mice (Qi et al. 2014). In addition, *Panax quinquefolium* had cardioprotective effects *in vitro* and *in vivo* (Xu et al. 2013), anti-hyperglycemic effects (Sen et al. 2012) and anti-psychotic activity (Chatterjee et al. 2012).

Peumus boldus Molina (Monimiaceae) (006P2003, GESTISOR). This plant, native to South America, is used for the treatment of digestive and liver diseases (Falé et al. 2012). Its main active components are procyanidin B2, reticuline, norglaucin, quercitrin, kaempferitrin, boldine and others (Falé et al. 2012). *Peumus boldus* inhibits acetylcholinesterase activity and has antiproliferative effects against cancer cells. Furthermore, this extract is not modified during gastrointestinal digestion (Falé et al. 2012). However, there have been reports of neurotoxic effects, attributed to the presence of the alkaloid, boldine (Mejía-Dolores et al. 2014).

Arctium lappa L. (Asteraceae) (007P2003, aresor), commonly known as burdock, has been widely consumed as a vegetable in East Asia for centuries. *Arctium lappa* is used as a diuretic, depurative, digestive stimulant and anti-inflammatory (de Almeida et al. 2013). The chemical compounds isolated from this plant include arctigenin, arctiin, tannin, beta-eudesmol, caffeic acid, chlorogenic acid, lappaol, and diarctigenin (Chan et al. 2011). *Arctium lappa* has demonstrated potent antioxidant effects *in vitro* and *in vivo* (Liu et al. 2014) and intestinal anti-inflammatory effects in an acute experimental colitis model (de Almeida et al. 2013). In addition, this plant significantly improves metabolism in the dermal extracellular matrix and leads to visible wrinkle reduction *in vivo* (Knott et al. 2008).

Melissa officinalis L. (Lamiaceae), *Rosmarinus officinalis* L. (Lamiaceae), *Salvia officinalis* L. (Lamiaceae), *Tilia platyphyllos* Scop (Malvaceae) and *Thymus vulgaris* L. (Lamiaceae) (010P2003, Tisal-Sor 2). *Melissa officinalis*, *Rosmarinus officinalis*, *Salvia officinalis* and *Thymus vulgaris* inhibit acetylcholinesterase activity and have antioxidant properties. These plants have high contents of rosmarinic acid (>19 mg/g extract) (Vladimir-Knežević et al. 2014). *Thymus vulgaris*, native to Europe, is used as broncholytic and spasmolytic agent (Engelbertz et al. 2012). The chemical constituents of this plant are luteolin, apigenin, thymonin, 8-methoxycirsilineol and cirsilineol (Engelbertz et al. 2012). *Thymus vulgaris* has spasmolytic activity (Engelbertz et al. 2012) and antimicrobial effects against multidrug resistant pathogens (Sienkiewicz et al. 2012). *Tilia platyphyllos*, native to Europe, is used as a diuretic, anti-neuralgic and sedative (Yayalacı et al. 2014). The main constituents found in this plant are uercetin glycosides (rutin, quercitrin, and isoquercitrin), kaempferol glycosides and phenolic acids (caffeic, p-coumaric, and chlorogenic acids) (Yayalacı et al. 2014). However, there have been no conclusive pharmacological reports using this plant.

Ribes nigrum L. (*Grossulariaceae*), *Passiflora incarnata* L. (Passifloraceae), *Equisetum arvense* L. (Equisetaceae), *Fumaria officinalis* L. (Papaveraceae), *Viola tricolor* L. (Violaceae) and *Hyssopus officinalis* L. (Lamiaceae) (011P2003, Ribe-sor 23). *Ribes nigrum* is a woody shrub native to Europe and commonly known as blackcurrant. Its major chemical components are delphinidin-3-O-glucoside, delphinidin-3-O-rutinoside, cyanidin-3-O-glucoside, and cyanidin-3-O-rutinoside (Kapasakalidis et al. 2006). This plant is used for the treatment of arthritis, spasmodic cough, diarrhea, as a diuretic and sore throat treatment. *Ribes nigrum* has anti-influenza activity *in vitro* and *in vivo* without toxic effects or an induction of viral resistance (Ehrhardt et al. 2013). *Passiflora incarnata* is commonly used in clinical practice for the treatment of anxiety and sleep disorders (Miroddi et al. 2013). The chemical components of this plant are the flavonoids, vitexin, isovitexin, orientin, isoorientin, apigenin, kaempferol, vicenin, lucenin and saponarin and the indole alkaloids, harman, harmin, harmalin, harmol, and harmalol (Miroddi et al. 2013). The results from various clinical trials support its ethnomedical use by demonstrating potential effects for the treatment of generalized anxiety disorder, pre-surgery anxiety, insomnia, attention-deficit hyperactivity disorder, opiate withdrawal symptoms, and control of menopausal symptoms (Miroddi et al. 2013). *Equisetum arvense*, which is used as an anti-hemorrhagic agent, contains the chemicals apigenin

5-O-glucoside and kaempferol 3-O-glycoside (Mimica-Dukic et al. 2008). *Equisetum arvense* produced a diuretic effect comparable with hydrochlorothiazide (25 mg) with no alterations in liver or kidney function (Carneiro et al. 2014).

Desmodium adscendens D.C. (*012P2003, Ribe-sor 23*), native to Africa and South America, is used to treat asthma and other diseases associated with smooth muscle contraction (N'gouemo et al. 1996). The chemical characterization of this plant revealed the presence of vitexin and isovitexin, and soyasaponins such as soyasaponin I (Magielse et al. 2013). This plant has analgesic and anti-spasmodic activities (Addy and Dzandu 1986, N'gouemo et al. 1996). *Desmodium adscendens* demonstrated hepatoprotective effects, with similar potency to sylimarin, in rats with D-galactosamin induced acute liver damage (Magielse et al. 2013).

Olea europea L. (Oleaceae) (013P2003, Oleomed-pa) is used to treat respiratory infections.

Eleutherococcus senticosus (Rupr. & Maxim.) Maxim (014P2003, Men´s gin). This plant is a shrub native to northeastern Asia. This plant's chemical composition includes caffeic acid, isofraxidin, sesamin, sitosterol, β sitosterol and others (Davydov and Krikorian 2000). *Eleutherococcus senticosus* is used to promote physiological homeostasis (Davydov and Krikorian 2000). This plant increases sexual performance by inhibiting nitric oxide via the inhibition of cyclic GMP signal transduction (Goldstein et al. 1998).

Sambucus nigra L. (Adoxaceae), *Tilia platyphyllos* Scop (Malvaceae), *Echinacea angustifolia* D.C. (Asteraceae), *Plantago lanceolata* L. (Plantaginaceae), *Origanum vulgare* L. (016P2003, sambusor 29). *Sambucus nigra*, native to Africa, Europe and Asia, is used to treat constipation, increase diuresis, as a diaphoretic in upper respiratory tract infections, alleviation of low back and/or neuropathic pain, headache and toothache (Vlachojannis et al. 2010). The *Sambucus nigra* chemical components include hyperoside, isoquercitrin, rutoside, sambucin (cyanidin-3-O-rhamnoglucoside), sambucyanin (cyanidin-3-O-xyloglucoside) and others (Vlachojannis et al. 2010). Consuming large amounts of *Sambucus nigra* may cause adverse effects such as nausea and emesis. This plant has demonstrated anti-oxidant, anti-microbial and anti-proliferative effects against cancer cells *in vitro* and *in vivo* (Vlachojannis et al. 2010). However, controlled clinical trials have not been performed with this plant. *Plantago lanceolata*, native to America, Europe and Asia, is used in traditional medicine for the treatment of bronchitis, asthma and other respiratory diseases (Vigo et al. 2005). The chemical compounds isolated from this plant are luteolin, acteoside, plantamajoside, catalpol peracetate, catalpol, isoacteoside, lavandulifolioside and aucubin (Fleer and Verspohl 2007). *Plantago lanceolata* inhibited NO production and iNOS mRNA expression in LPS/IFN gamma stimulated J774A.1 murine macrophages (Vigo et al. 2005) and exerted antispasmodic activity on isolated guinea-pig ileum and tracheas (Fleer and Verspohl 2007).

Salix alba L. (Salicaceae), *Tilia platyphyllos* Scop (Malvaceae), *Melissa officinalis* L. (Lamiaceae), *Chamaemelum nobile* (L.) All. (Asteraceae) and *Citrus aurantium* L. (017P2003 Jake sor 22). *Chamaemelum nobile,* native to southern Europe, is used to treat dyspepsia, nausea, rheumatic pain, eczema, wounds, hemorrhoids and neuralgia (Zhao et al. 2014). The compounds isolated from this plant are derivatives of octulosonic acid (Zhao et al. 2014). *Chamaemelum nobile* and its chemical components have demonstrated *in vitro* anti-oxidant and anti-inflammatory effects (Zhao et al. 2014).

Grindelia hirsutula Hook. & Arn (Asteraceae) (synonym Grindelia robusta Nutt) (018P2003, Grine sor). *Grindelia hirsutula*, native to North America*,* is used as an anti-tussive and anti-asthmatic agent (La et al. 2010). This plant is primarily composed of the chemicals diosmetin-7-O-glucuronide-3'-O-pentoside+apigenin-7-O-glucuronide-4'-O-pentoside, apigenin-7-O-glucuronide+diosmetin-7-O-glucuronide and others (Ferreres et al. 2014). *Grindelia hirsutula* exhibited antioxidant and protective effects against oxidative stress (Ferreres et al. 2014), in addition to anti-inflammatory activities *in vitro* (La et al. 2010).

Ruscus aculeatus L. (Asparagaceae) (021P2003, Nikzon), native to Europe and Asia, has been used to relieve constipation, water retention and improve circulation (Aguilar-Peralta et al. 2007). The compounds teroidal saponins ruscogenin and neoruscogenin have been isolated from this plant (Mimaki et al. 1999).

Ruscus aculeatus has demonstrated anti-inflammatory and astringent properties (MacKay 2001). In clinical trials, *Ruscus aculeatus* decreased symptoms such as heavy lower legs, sensation of tension, and tingling sensations, in chronic venous insufficiency patients (Vanscheidt et al. 2002, Aguilar-Peralta et al. 2007).

Humulus lupulus L. (Cannabaceae) (022P2003, Asepxia). This plant, native to Europe, western Asia and North America, is used for the treatment of anxiety (Yamaguchi et al. 2009). The active compounds of this plant are humulones, lupulones, isohumulones and xanthohumol (Yamaguchi et al. 2009). *Humulus lupulus* and its active compounds have anti-microbial activities against the pathogens, *Propionibacterium acnes*, *Staphylococcus epidermidis*, *Staphylococcus aureus*, *Kocuria rhizophila* and *Staphylococcus pyogenes*, which produce acne. This plant also has anti-oxidant effects (Yamaguchi et al. 2009).

Aesculus hippocastanum L. (Sapindaceae), *Vitis vinifera* L. (Vitaceae), *Centella asiatica* (L.) Urban (Apiaceae) (023P2003, Goicotabs). These three plant species are used for the treatment of inflammatory diseases and varicose veins. *Aesculus hippocastanum* is native to southeastern Europe. Its main active compounds are aescin, quercetin and kaempferol (Bombardelli and Morazzoni 1996). *Aesculus hippocastanum* is used to decrease blue skin discoloration, edema, leg heaviness and pain in patients with venous insufficiency (Suter et al. 2006). *Vitis vinifera*, commonly known as grape vine, is native to Europe and Asia. This plant decreases heaviness and itching in patients with venous insufficiency (Costantini et al. 1999). The main compounds of *Vitis vinifera* are resveratrol and ε-viniferin. *Centella asiatica*, commonly known as centella, is native to Asia. Its active constituents are asiaticosides, madecassoside and madasiatic acid (Gohil et al. 2010). *Centella asiatica* effectively treats hypertensive microangiopathy and venous insufficiency by improving microcirculatory parameters (Veerendra Kumar et al. 2002).

Glycyrrhiza glabra L. (Fabaceae) (025P2003, Ulebex). This plant is an herbaceous perennial native to southern Europe. *Glycyrrhiza glabra* is widely used as a flavoring agent in candies, tobacco products, drug tablets, and soft drinks. Glycyrrhizin (glycyrrhizic acid), a triterpene saponin, is the primary water soluble constituent of *Glycyrrhiza glabra* and the main source of its sweet taste (Jiang et al. 2013). However, this plant species has been reported to induce nephrotoxicity (Allard et al. 2013).

Cassia senna L. (Fabaceae) (027P2003, Purifiq; 004P2005, Purifiq) is used as a laxative.

Garcinia cambogia (L.) N. Robson (Clusiaceae), *Cyamopsis tetragonoloba* L. (Fabaceae) and *Cassia angustifolia* Mill (Fabaceae) (031P2003, metaboltonics). The primary compound present in *Garcinia cambogia* is hydroxycitric acid, which inhibits the biosynthesis of lipids, promoting a hypotriglyceridemic effect independently of changes in leptin and insulin serum levels (Vasques et al. in press). *Cyamopsis tetragonoloba* helps to maintain nearly normal levels of anti-oxidant enzymes in the gastric and intestinal mucosa during ethanol-induced oxidative stress (Pande and Srinivasan 2013).

Prunus africana (Hook F) Kalkman (Rosaceae) (033P2003, PYG 500). This plant, native to sub-Saharan Africa, is used to improve self-rated symptoms, nocturia and post-void residual urine volume (Russo et al. 2013). Nevertheless *Prunus africana* and *Garcinia cambogia* are considered 'vulnerable' according to their conservation status (IUCN 2012).

Camellia sinensis L. Kuntze (Theaceae) (034P2003, ulcaps). This plant is native to Asia and its major flavonoids are catechins including (−)-epicatechin (EC), (−)-epicatechin-3-gallate (ECG), (−)-(EGC) and (−)-epigallo-catechin-3-gallate (EGCG), (+)-catechin (C), (+)-gallocatechin (GC), (+)-catechin gallate (CG), and (+)-gallocatechin gallate (GCG) (Bhardwaj and Khanna 2013). *Camellia sinensis* exerts anti-oxidant, anti-inflammatory, anti-platelet, anti-thrombotic effects and maintains vascular tone (Bhardwaj and Khanna 2013).

Amorphophallus konjac K. Koch (Araceae) (035P2003, Natural fit). This plant is used in tropical and subtropical Asia as a food source and as a traditional Chinese medicine. *Amorphophallus konjac* has demonstrated anti-obesity, anti-inflammatory, anti-hyperglycemic and hypercholesterolemia effects, in addition to laxative and prebiotic activities (Chua et al. 2010).

Artemisia vulgaris L. (Asteraceae) *Calendula officinalis* L. (Asteraceae), *Salvia officinalis* L. (Lamiaceae), *Cupressus sempervirens* L. (Cupressaceae), *Achillea millefolium* L. (Asteraceae), *Thymus vulgaris* L. (Lamiaceae) (046P2003, aurisor 15). *Artemisia vulgaris* is used to treat menstrual conditions such as amenorrhea, dysmenorrhea and oligomenorrhea, pregnancy disorders, and severe pain during labor and leucorrhea. It is also used as an emmenagogue, uterine sedative and postpartum tonic (de Boer and Cotingting 2014). The flavonoids, eriodictyol and apigenin, isolated from *Artemisia vulgaris* may have estrogen-like effects. The presence of these estrogen-like compounds may account for the folkloric use of *Artemisia vulgaris* for the treatment of menstrual disorders (Lee et al. 1998). *Calendula officinalis* has been traditionally used for the treatment of inflammation of internal organs, gastrointestinal ulcers and dysmenorrhea (Arora et al. 2013). The chemical constituents isolated from this plant are calendulaglycoside A, calenduladiol, rutin, kaempferol, heliantriol C, astragalin and others (Arora et al. 2013). Preparations of *C. officinalis* are generally applied as infusions, tinctures and ointments as a wound healing remedy for inflammation of the skin, mucous membranes, for poorly healing wounds, bruises, boils and rashes (Arora et al. 2013). *Achillea millefolium*, native to Europe and Asia, is prescribed for hemorrhoids, headaches and bleeding disorders (Akram 2013). The chemical constituents of *Achillea millefolium* are camphor, eucalyptol, β-pinene, α-terpineol, artemetin, dihydrodehydrodiconiferyl alcohol 9-O-β-D-glucopyranoside, apigenin and others (Akram 2013). This plant has exhibited estrogenic activity, as well as anti-hypertensive and anti-microbial effects (Akram 2013).

Psidium guajava Linn (Family: Myrtaceae), *Xalxócotl,*or guava (Register No. 003P2007, QG5) is an important food crop and a medicinal plant used in traditional and folk medicine worldwide, particularly in tropical and subtropical countries. *Psidium guajava* is native to Mexico and extends throughout South America, Europe, Africa and Asia (Gutierrez et al. 2008, Juárez et al. 2013).

Psidium guajava has long been used as a therapeutic agent for the treatment of numerous conditions such as arthritis*,* wounds, ulcers, toothaches, coughs, sore throats, inflamed gums, cancer, malaria, gastroenteritis, vomiting, diarrhea, dysentery, hypertension, obesity and type II diabetes mellitus. It also protects the kidney against diabetic nephropathy progression (Lutterodt 1992, Morales et al. 1994, Jaiarj et al. 1999, Karawya et al. 1999, Abdelrahim et al. 2002, Begum et al. 2004, Sunagawa et al. 2004, Ojewole 2006, SEA 2006, Chen et al. 2009, Lin and Yin 2012) via its anti-inflammatory and analgesic properties as well as its anti-oxidative, hypoglycemic, anti-glycative and anti-pathogenic microorganism effects (Rattanachaikunsopon and Phumkhachorn 2007, Ojewole et al. 2008, Shen et al. 2008, Soman et al. 2010, Livingston et al. 2012).

Phytochemical studies have demonstrated that the leaf, stem-bark and roots of *Psidium guajava* contain numerous tannins, polyphenolic compounds, flavonoids, ellagic acid, pentacyclic triterpenoids, meroterpenoids and triterpenes, guiajaverin, quercetin, reynoutrin, hyperoside and other chemical compounds (Begum et al. 2004, Ojewole 2006, Shu et al. 2010, Shu et al. 2012, Shao et al. 2012, Zhu et al. 2013).

Flavonol glycosides from *Psidium guajava* exert therapeutic effects against type II diabetes mellitus by inhibiting dipeptidyl peptidase activity (Eidenberger et al. 2013) and adipogenesis via the down-regulation of PPARγ and C/EBP alpha expression (Yang et al. 2012). While quercetin has anti-oxidant properties, quercetin-3-*O*-*β*-D-arabinopyranoside and quercetin-3-*O*-*α*-L-arabinofuranoside possess anti-bacterial and anti-fungal activities (Metwally et al. 2010). Hyperoside exhibits anti-inflammatory, anti-cancer and anti-oxidant activities (Liu et al. 2012). Reynoutrin inhibits a-glucosidase activity (Schmidt et al. 2012a, Schmidt et al. 2012b), Finally, 2,4,6-trihydroxy-3,5-dimethylbenzophenone 4-*O*-(6''-*O*-galloyl)-*β*-D-glucopyranoside has been demonstrated to significantly inhibit histamine release (Matsuzaki et al. 2010). *Psidium guajava* leaf extract significantly inhibited lipopolysaccharide (LPS)-induced production of nitric oxide and prostaglandin E_2 in a dose-dependent manner, suppressed the expression and activity of inducible nitric oxide synthase and cyclooxygenase-2 partially through the down-regulation of ERK1/2 activation in RAW264.7 macrophages. It also exhibits significant anti-inflammatory activity (Jang et al. 2014). Using a streptozotocin (STZ)-induced diabetes mellitus model, acute oral administrations of *Psidium guajava* extract reduced glycemia in normoglycemic and STZ-treated diabetic rats. In hypertensive Dahl salt-sensitive rats, acute intravenous administrations of the *Psidium guajava* extract reduced systemic arterial blood pressure and heart rates. Although the exact mechanisms of action of the *Psidium guajava* extract

still remain a topic of speculation, it is possible that the *Psidium guajava* extract causes hypotension in Dahl salt-sensitive rats via cholinergic mechanisms, because its cardiodepressant effects are resistant to atropine pretreatment (Ojewole 2005).

It is known that prostaglandin endoperoxide H synthase (PGHS) is a key enzyme for the synthesis of prostaglandins (PGs), which play important roles in inflammation and carcinogenesis. *Psidium guajava* leaf extract inhibits the cyclooxygenase reaction of recombinant human PGHS-1 and PGHS-2, as well as the PG hydroperoxidase activity of PGHS-1. Quercetin, one of the major components of *Psidium guajava*, inhibits the cyclooxygenase activity of both isoforms and also partially inhibits PG hydroperoxidase activity. These activities explain the anti-inflammatory, analgesic and anti-proliferative properties of *Psidium guajava* extract (Kawakami et al. 2009). In addition, methanolic and ethanolic extracts of *Psidium guajava* have inhibitory activities against gram-positive bacteria (*Staphylococcus aureus* and *Bacillus cereus*). Therefore, it may be a good candidate for a natural antimicrobial agent (Biswas et al. 2013). All these biochemical properties of *Psidium guajava* lend pharmacological credence to the ethnomedical and folkloric uses of the plant previously described.

Psyllium husks, Plantaginis ovatae, Plantago ovata, ispaghula (Register number 001P2007, METAMUCIL). Psyllium is a natural polysaccharide that is derived from biodegradable and biocompatible polymers.

The polysaccharides extracted from the husk of *Plantago ovata* contain a high proportion of polysaccharides such as cellulose and hemicellulose and 20–30% mucilage (a highly branched acidic arabinoxylan comprised of a xylan backbone chain with xylose andarabinose forming the side chains), as well as oil, proteins and steroids (Kennedy et al. 1979, Vanaclocha and Cañigueral 2003). Psyllium has historically been used as a dietary supplement to regulate bowel movements, as a laxative and a fecal bulking agent. Although the bulking effect mechanism of psyllium is still unclear, one possible mechanism of how dietary fibers increase stool weight is through the physical presence of indigestible fiber in the colon. The fiber's water holding capacity, stimulation of microbial growth and production of gas may increase stool volume and cause colonic propulsion. Other potential mechanisms include stimulation of colonic motility, by the mechanical action of the fiber on the colon, and by an increase in certain colokinetic end products of fiber fermentation (Prynne and Southgate 1979, Vanaclocha and Cañigueral 2003).

It has been proposed that daily dietary fiber intake helps prevent many nutritional disorders, i.e., gut related problems, cardiovascular diseases, certain types of cancer, obesity and type II diabetes (Verma and Banerjee 2010). In type II diabetes, plant fibers, particularly water-soluble fibers such as psyllium, can moderate postprandial glucose and insulin concentrations in non-insulin dependent diabetics if administered with meals (Pastors et al. 1991, Brigenti et al. 1995). In 1998, the U.S. Food and Drug Administration authorized the use of health claims on food labels and food labeling detailing the association between soluble fiber from psyllium seed husks and a reduced risk of coronary heart disease by lowering cholesterol levels (Romero et al. 2002).

Although Rosendaal et al. demonstrated in 2004 that psyllium administration had no effect on cholesterol-lowering or lipid parameters, in 2008, Uehleke et al. demonstrated that psyllium husk preparations may be therapeutic in patients with mild to moderately elevated cholesterol levels. They studied 54 patients who had significantly decreased total cholesterol and low density lipoprotein (LDL)-cholesterol after three weeks of treatment. Additionally, gastrointestinal symptoms were rated lower at the end of the study compared with the beginning of the study. However, triglycerides and high density lipoprotein (HDL) were unchanged.

Plantago psyllium (Register No. 001P2008, ALEXCIBRAN). Although true psyllium comes from the plant *Plantago psyllium*, the husk and seed of *Plantago ovata* (family Plantaginaceae) is commonly referred to as *psyllium*. The genus Plantago includes approximately 200 species (Rahn 1996), some with medicinal value. Species of Plantago are small herbs, mostly growing as weeds.

Psyllium husk is obtained by milling the seed of *Plantago ovata* to remove the hulls. In some studies, the seed has been used instead of the husk and is also commercially available. Psyllium husk contains hemicellulose (xylan backbone linked with arabinose, rhamnose, and galacturonic acid units), while the seed consists of soluble (35%) and insoluble (65%) polysaccharides (cellulose, hemicellulose, and lignin).

While its center of diversity is believed to be in central Asia, some species are now widely dispersed, with maximum concentrations in temperate regions. Psyllium is widely used as a fiber supplement for the treatment of constipation and has been used as an indigenous Ayurvedic and Unani medicine for a wide range of bowel problems including chronic constipation, amoebic dysentery and diarrhea. In addition to being used as a laxative, psyllium is also used in ice creams, chocolates, cosmetics and printing and finishing. It is also used to lower blood cholesterol levels (Dhar et al. 2005, Dhar et al. 2011). Dietary fibers from psyllium are used extensively as pharmacological supplements, food ingredients, in processed food to aid weight control, for glucose regulation in diabetic patients and to reduce serum lipid levels in hyperlipidemics (Singh 2007). Constipation is a health problem that negatively affects quality of life and increases colon cancer risk (Watanabe et al. 2004). Therefore, increased dietary fiber intake has been recommended to treat constipation (Marlett et al. 2002). It should be noted that soluble fiber absorbs water and becomes a gelatinous, viscous substance that is fermented by bacteria in the digestive tract, while insoluble fiber has a bulking action (Anderson et al. 2009). Psyllium is classified as a mucilaginous fiber due to its powerful ability to form a gel in water. Psyllium is effective in approximately 20% of constipation patients dependent on the cause of constipation, while it is effective in 37% of patients with rectocele, internal prolapse, anismus, and rectal hyposensitivity (Voderholzer et al. 1997). Psyllium also decreases by 50% the occurrence of incontinent stools in individuals with fecal incontinence due to liquid stools or diarrhea (Bliss et al. 2001). Anaerobic fermentation of the soluble non-starch polysaccharides in psyllium seeds result in the production of the short-chain fatty acids, acetate, propionate, and butyrate in the intestine (Mortensen and Nordgaard-Andersen 1993). Butyric acid exhibits antineoplastic activity against colorectal cancer (Nordgaard et al. 1996), is the preferred oxidative substrate for colonocytes, and may be helpful for the treatment of ulcerative colitis (Fernandez-Banares et al. 1999). Psyllium also reduces bleeding and congested hemorrhoidal cushions in hemorrhoid patients (Webster et al. 1978). Psyllium reduces cholesterol levels through a mechanism that is not fully understood. In animal studies, psyllium increases more than twice cholesterol 7 alpha-hydroxylase or cytochrome 7A (CYP7A) activity, the rate-limiting enzyme in bile acid synthesis, compared with cellulose or oat bran, but less than cholestyramine (Matheson et al. 1995). Moreover, in animals fed a high-fat diet, psyllium increased the activity of cholesterol 7 alpha-hydroxylase and HMG-CoA reductase (Vergara-Jimenez et al. 1998) and reduced Apo B secretion and LDL catabolic rates. In humans, psyllium lowered LDL cholesterol (via stimulation of bile acid synthesis by stimulating cholesterol 7 alphahydroxylase), decreased cholesterol absorption and increased the fractional turnover of chenodeoxycholic and cholic acids (Everson et al. 1992). In addition, psyllium reduces the postprandial rise of glucose (Anderson et al. 1999) and regulates appetite, as psyllium appears to reduce fat intake (Turnbull and Thomas 1995). Recently, psyllium consumption has contributed to a 30% decline in the coronary artery disease death rate (Petchetti et al. 2007).

However, psyllium must be used with caution, as several cases detailing individual allergic and anaphylactic reactions to psyllium have been published (James et al. 1991, Freeman 1994).

Soybean [*Glycine max* (L.) Merrill] is a major crop worldwide and is a source of protein, oil, sugars and minerals. Soybean seed oil composition and content are important for agronomic, nutritional and industrial applications and new energy uses (Clemente and Cahoon 2009). Soybean is a major source of high quality protein and oil, whose quality is often determined by seed nutritional and anti-nutritional parameters. The free fatty acid and triglyceride content ranges from 31–71 mg 100 $g^{(-1)}$ oil and 90.1–93.9 g 100 $g^{(-1)}$ oil, respectively. The anti-nutritional components include: mg $g^{(-1)}$, TIA (41.5–85.0), phytate (2.3–5.6), total phenols (1.0–1.5), flavonols (0.20–0.34) and ortho-dihydroxy phenols (0.10–0.21) (Sharma et al. 2014). The oil content in soybean seeds ranges from 13 to 22% in various soybean cultivars. The oleic acid content of seed oil varies between 21.4 (ATAEM7) and 26.6% (Türksoy). The proportion of linoleic acid in soybean oil ranges from 49.0 (Türksoy) to 53.5% (ATAEM7), while palmitic acid varies between 9.2 (Adasoy) and 11.2% (Noya). The major tocopherols are ¥-tocopherol, α-tocopherol and δ-tocopherol (Matthaus and Ozcan 2014). Soybean oil contains high levels of polyunsaturated fatty acids (PUFA) (60.8%), with a PUFA: saturated fat ratio of 4.0. Soybean contains 54% C18:2n-6 and 7.2% C18:3n-3 with a C18:2n-6:C18:3n-3 ratio of 7:1. Recent dietary guidelines suggest decreasing consumption of total and saturated fat and cholesterol, an objective that can be achieved by substituting soybean for animal fats. Such changes have consistently resulted in decreased total and low-density-lipoprotein cholesterol, which is thought to decrease the risk of cardiovascular disease (Meydani et al. 1991).

Use of vegetable oils such soybean increases C18:2n-6, decreases C20:4n-6, and slightly elevates C20:5n-3 and C22:6n-3 in platelets, which partly inhibit platelet thromboxane generation and *ex vivo* aggregation. Whether chronic use of this oil effectively blocks thrombosis at sites of vascular injury, inhibits pathologic platelet vascular interactions associated with atherosclerosis or reduces the incidence of acute vascular occlusion in coronary or cerebral circulation is uncertain (Meydani et al. 1991). Linoleic acid is required for normal immune response and Essential Fatty Acid (EFA) deficiency impairs B and T cell-mediated responses. Therefore, soybeans can provide adequate linoleic acid for the maintenance of the immune response. However, excess linoleic acid supports tumor growth in animals, an effect that has not been verified by data from diverse human studies concerning the risk, incidence, or progression of breast and colon cancers (Meydani et al. 1991). Nevertheless, soybean oil may protect against breast and prostate cancer and also may exert a beneficial influence when used in combination with other oils (Li et al. 2014).

Soybean oligosaccharides (SBOS) are able to reduce oxidative stress and alleviate insulin resistance in pregnant women with gestational diabetes mellitus, which indicates that SBOS may play an important role to control gestational diabetes mellitus complications (Fei et al. 2014).

Soybean oil and olive oil (Register No. 002P2008, SMOFLIPID). Olive oil is obtained from olives (*Olea europaea*; family Oleaceae). Olive is a traditional tree crop in the Mediterranean Basin. There are many different olive varieties, each one with different applications such as human consumption, domestic cooking or catering, animal feed, cosmetic, pharmaceutical and industrial uses, fuel for traditional oil lamps or other engineering applications. Olive oil was common in ancient Greek and Roman cuisine and is now used worldwide, predominantly in Mediterranean countries, particularly Portugal, Spain, Italy and Greece. Spain produces more than 40% of the world's production of olive oil, Italy more than 20%, Greece approximately 12%, Syria 6% and Portugal 5%. Australia also produces a substantial amount of olive oil.

Olive oil is primarily composed of the mixed triglyceride esters of oleic acid and palmitic acid and of other saturated and unsaturated fatty acids such as linoleic acid. Olive oil also has traces of squalene and sterols. Olive oil is a source of at least 30 phenolic compounds such as esters of tyrosol and hydroxytyrosol (oleocanthal and oleuropein) aldehydic secoiridoids, flavonoids and lignans as acetoxypinoresinol and pinoresinol (Tuck and Hayball 2002, Tripoli et al. 2005). It is well known that the Mediterranean people, great consumers of olive oil, are generally less affected with atheromatosis than the Anglo-Saxon people (Brozek et al. 1957). Moreover, when the diet is supplemented with olive oil, the plasma lipid profile is favorably altered and the susceptibility of LDL cholesterol to lipid peroxidation may be decreased in hypercholesterolemic subjects (Chan et al. 2007). Clinical studies have provided evidence that consumption of olive oil may lower the risk of heart disease by decreasing risk factors such as blood cholesterol levels and LDL cholesterol oxidation (Bagigo 2013). Olive oil may also influence inflammatory, thrombotic, hypertensive and vasodilatory mechanisms (Keys et al. 1986, Covas 2007, Mayo Clinic 2007), most likely due to the content of oleic acid, vitamin E and oleuropein, a chemical that may affect the oxidation of LDL particles (Coni et al. 2000).

Oleocanthal derived from olive oil is a non-selective inhibitor of cyclooxygenase (COX), similar to classical NSAIDs, e.g., ibuprofen. It has been suggested that long-term consumption of small quantities of oleocanthal may be partially responsible for the low incidence of heart disease associated with the Mediterranean diet (Lucas et al. 2011). Furthermore, hydroxytyrosol (2-(3,4-Di-hydroxyphenyl)-ethanol or DHPE) is a phenolic component of extra-virgin olive oil, which inhibits platelet aggregation and eicosanoid (thromboxane B2) formation *in vitro* (Petroni et al. 1995). These effects may further decrease the incidence of heart disease. Preliminary studies indicate that olive oil may be a chemopreventive agent for peptic ulcers or gastric cancer (Romero et al. 2007) because it reduces oxidative damage to DNA and RNA, which are carcinogenic factors (Machowetz et al. 2007). Moreover, consumption of olive oil may prevent the onset of Alzheimer's disease, possibly through a mechanism related to oleocanthal, by inhibiting the fibrillization of tau proteins (Monti et al. 2011).

Matricaria recutita [L.] Rauschert, Asteraceae (Register No. 002P2009, KAMILEN OCEAN) *Chamomilla recutita* L., *Matricaria chamomilla, Chamomille* is a well-known medicinal plant species widely used in herbal remedies in ancient Egypt, Greece, and Rome (Issac 1989). It is also used in folk and traditional medicine, where it is known by an array of names such as Baboonig, Babuna, Babuna camornile, Babunj, German chamomile, Hungarian chamomile, Roman chamomile, English chamomile, Camomilla, Flos

chamomile, single chamomile, sweet false chamomile, pinheads, and scented mayweed (Leung and Foster 1996, Franke 2005). Chamomile is an annual plant with thin spindle-shaped roots that only flatly penetrate the soil. The branched stem is erect, heavily ramified and grows to a height of 10–80 cm. The long and narrow leaves are bi- to tri-pinnate. The flower heads are placed separately, pedunculate and heterogamous with a diameter of 10–30 mm. The golden yellow tubular florets have five teeth that are 1.5–2.5 mm long and always end in a glandulous tube. The 11–27 white plant flowers are 6–11 mm long, 3.5 mm wide and arranged concentrically. The receptacle is 6–8 mm wide, flat in the beginning and conical later, hollow and without paleae. The fruit is a yellowish brown achene. Although this plant is native to southern and eastern Europe, Germany, Hungary, France, Russia, Yugoslavia and Brazil (Ivens 1979), it is currently cultivated worldwide and can be found in India, North Africa, Asia, North and South America, Australia and New Zealand (Singh et al. 2011).

The chamomile drug is included in the pharmacopoeia of many countries (Pamukov and Achtardziev 1986), including Mexico, and is an ingredient in several traditional, Unani, and homeopathic medicinal preparations due to its multi-therapeutic, cosmetic, and nutritional value (Lawrence 1987, Das et al. 1998, Kumar et al. 2001, Mann and Staba 2002, Singh et al. 2011). A large group of therapeutically active compounds such as sesquiterpenes, flavonoids, coumarins, and polyacetylenes have been identified in chamomile. The coumarins are represented in *M. chamomilla* by herniarin, umbelliferone, and other minor ones (Redaelli et al. 1981, Kotov et al. 1991). The glucoside precursors of herniarin, (Z)- and (E)-2-β-d-glucopyranosyloxy-4-methoxycinnamic acid (GMCA), have also been described in chamomile (Ohe et al. 1995). Eleven bioactive phenolic compounds (Gupta et al. 2010) such as herniarin and umbelliferone (coumarin), chlorogenic acid and caffeic acid (phenylpropanoids), apigenin, apigenin-7-O-glucoside, luteolin and luteolin-7-O-glucoside (flavones), quercetin and rutin (flavonols) and naringenin (flavanone) are also found in chamomile extract. More than 120 chemical constituents have been identified in chamomile flowers as secondary metabolites (Pino et al. 2002, Pirzad et al. 2006) including 28 terpenoids, 36 flavonoids (Kunde and Isaac 1980) and 52 additional compounds with potential pharmacologic activity (Mann and Staba 2002).

The primary pharmaceutically active components of chamomile flower oil are chamazulene and bisabolols. The α-bisabolol and cyclic ethers are anti-microbial (Isaac 1980, Manday et al. 1999), whereas chamazulene and α-bisabolol are antiseptic (Duke 1985). Chamazulene is a degradation product spontaneously formed during steam distillation from the sesquiterpene lactone, matricine, several bisabolol-type sesquiterpenes ((−)-α-bisabolol, bisabolol oxides), flavonoids and two en-in-dicycloethers. In addition to its flowers, chamomile roots and shoots are also rich in essential oils. Chamomile also contains sesquiterpene hydrocarbons and alcohols such as (E)-β-farnesene and spathulenol, respectively (Repcak et al. 1980, Reichling et al. 1984, Kumar et al. 2001, Schilcher et al. 2005). Additionally, chamomile was determined to have the most effective anti-leishmanial activity (Shnitzler et al. 1996).

In folk and traditional medicine, chamomile is used mainly as an anti-inflammatory, antiseptic, anti-spasmodic and mild sudorific (Mericli 1990). Chamomile is also used for disturbances of the stomach associated with pain or colic, sluggish digestion, diarrhea, nausea, flatulence, intermittent fever, inflammation of the urinary tract, painful menstruation and hysteria. In powder form, chamomile may be applied to wounds, skin eruptions and infections such as shingles and boils, hemorrhoids and inflammation of the mouth, throat, and eyes (Fluck 1988). During the last century it was demonstrated that a component of chamomile, umbelliferone, is fungistatic (Duke 1985). Additionally, using microbioassay *in vitro* studies, it was determined that chamomile flower essential oil may be a potential candidate to design effective anti-fungal formulations suitable for the treatment of medically important dermatophytosis, opportunistic saprophytes and other fungal infections (Jamalian et al. 2012). The anti-inflammatory effect of chamomile infusions at the gastric level was tested on phorbol 12-myristate 13-acetate-stimulated AGS cells and human neutrophil elastase. Chamomile infusion inhibited neutrophil elastase and gastric metalloproteinase-9 activity and secretion by inhibiting NF-kB driven transcription. This effect was due to flavonoid-7-glycosides, one of the major constituents of chamomile flowers (Bulgari et al. 2012).

In addition to its beneficial effects *in vitro*, recent chamomile extract studies in rats demonstrated potent anti-diarrheal and anti-oxidant properties, confirming their use in traditional medicine (Sebai et al. 2014). Similarly, the anti-hyperalgesic effects of bisabolol-oxide-rich matricaria oil has been examined in a rat

inflammation model induced by carrageenan using a modified 'paw-pressure' test, while its anti-edematous effects have been examined in a rat inflammation model induced by carrageenan, dextran and histamine using plethysmometry. In both experiments, bisabolol-oxide-rich matricaria oil was effective against the pain and edema present in different inflammatory conditions, which supports matricaria's traditional use as anti-inflammatory and analgesic (Tomić et al. 2014). Moreover, a randomized double blind clinical trial was performed in 90 students comparing the effects of chamomile extract and mefenamic acid on the intensity of premenstrual syndrome symptoms. Chamomile was determined to be more effective than mefenamic acid for relieving the intensity of premenstrual syndrome and its associated symptomatic psychological pain (Sharifi et al. 2014).

Platelet-rich plasma obtained from healthy donors was treated with polyphenolic-polysaccharide conjugates from chamomile, and this treatment resulted in a dose-dependent decrease of platelet aggregation induced by agonists such as ADP, collagen and arachidonic acid. Moreover, chamomile also reduced platelet aggregation in platelet-rich plasma obtained from patients with cardiovascular disorders. Therefore, compounds obtained from chamomile could lead to the development of a new anti-platelet agent that may be an alternative to currently used anti-platelet drugs for preventing cardiovascular diseases (Bijak et al. 2013). Chamomile flower extract also potently prevented fatty liver disease without the adverse side effects of classical peroxisome proliferator-activated receptor (PPAR) agonists. PPARs are a family of nuclear receptors that play a central role in cellular differentiation, glucose and lipid homeostasis, and can suppress inflammatory processes. Pharmacologic modulation of PPARs is a common strategy to treat insulin resistance and dyslipidemia (Berger and Moller 2002). Three different subtypes of PPAR exist: PPARα, PPARβ/δ and PPARγ. PPARα, predominantly expressed in the liver, controls fatty acid oxidation and lipoprotein metabolism and is also involved in gluconeogenesis and ketone body biosynthesis. PPARβ/δ is ubiquitously expressed and has a central role in fatty acid oxidation and adaptive thermogenesis. PPARγ plays a key role in adipose tissue differentiation and maintenance by regulating energy storage and balance. PPARγ is highly expressed in adipocytes but also controls differentiation and metabolic processes in the liver, macrophages, bone cells and skeletal muscle. Because PPARγ is involved in glucose metabolism by regulating insulin sensitivity (Lehrke and Lazar 2005) and chamomile flower extracts can activate PPARγ, chamomile flower extracts have therapeutic effects in type 2 diabetes and dyslipidemia in insulin-resistant, high-fat diet-fed mice (Weidner et al. 2013). It has been reported that chamomile may also have clinically meaningful anti-depressant activities in addition to its anxiolytic activity (Amsterdam et al. 2012).

Moreover, *Chamomilla* is a promising nephroprotective compound, reducing cisplatin nephrotoxicity, most likely through its anti-oxidant activities and by inhibiting gamma glutamyl transferase activity (Salama 2012). In experiments that tested chamomile in human blood platelets, mouse fibroblast cultures L929 and human lung cells A549, there were no observed cytotoxic effects (Bijak et al. 2013). However, chamomile pollen present in teas for eye washing can induce allergic conjunctivitis (Subiza et al. 1990).

Hedera helix L., English ivy, Common ivy (Register No. 001P2013, FLUIR) is a well-known native and ornamental plant in Europe. It is an evergreen, dioecious, woody liana renowned for its ability to adhere to vertical surfaces and is one of the 15 species of the genus *Hedera*, Araliaceae family. The adventitious roots of *Hedera helix* are responsible for the production of an adhesive compound composed of polysaccharides and spherical nanoparticles (Xia et al. 2011, Lenaghan and Zhang 2012) with optical absorption, light scattering properties. These nanoparticles' increased safety over commonly used metal oxide nanoparticles make them attractive candidates for sunscreen protection agents or fillers (Li et al. 2010, Ligin et al. 2010, Xia et al. 2010). Although in folkloric medicine it is used to cure benign warts, the dry extract of *Hedera helix* is currently known to act as an anti-inflammatory (Suleyman et al. 2003, Gepdiremen et al. 2005), anti-bacterial, mucolytic and spasmolytic agent with a bronchodilatatory effect on cell cultures (Trute et al. 1997, Sieben et al. 2009). Most of these effects are attributable to *Hedera helix*'s triterpene saponin content (Bedir et al. 2000, Trute et al. 1997). Because pharmaceutical manufacturers have demonstrated the efficacy of *Hedera helix* for the treatment of cough symptoms during acute and chronic bronchitis, among non-antibiotic cough remedies, herbal preparations containing extracts from *Hedera helix* leaves are popular in many European countries (Guo et al. 2006, Coca and Nink 2008, Glaeske et al. 2008). In 2007, more than 80% of herbal expectorants prescribed in Germany comprised *Hedera helix*

extract, amounting to nearly two million prescriptions nationwide (Coca and Nink 2008). The effect of dry extracts on the respiratory function of children with chronic bronchial asthma has been confirmed (Hofmann et al. 2003). Additionally, a post-marketing study in 9657 patients (5181 children) with bronchitis (acute or chronic bronchial inflammatory disease) where dried *Hedera helix* leaf extract was given over seven days resulted in the improvement or healing of symptoms in 95% of patients with an adverse event incidence of 2.1% (Fazio et al. 2009). However, Holzinger and Chenot (2011) maintain that evidence of the effectiveness of *Hedera helix* leaf extract for the treatment of acute upper respiratory tract infections in randomized controlled trials, nonrandomized controlled clinical trials and observational studies has not been convincing. For example, the therapeutic effect of orally administered *Hedera helix* on lung histopathology in a murine model of chronic asthma was not superior to dexamethasone treatment (Hocaoglu et al. 2012).

It has been proposed that the potent anti-inflammatory property of *Hedera* extract is similar to the effect of diclofenac. However, experimental animals could not tolerate peritoneal injections of more than 75 µl of ethanol *Hedera* extract. Therefore, additional animal studies need to be performed in this area (Rai 2013). Although *Hedera helix* is a potent herb for the treatment of arthritis in animals, the exact component possessing anti-inflammatory, analgesic and anti-arthritic properties needs to be isolated and tested. This could result in the use of *Hedera helix* as a cost-effective and potent herbal medicine for the treatment of inflammation and arthritis (Rai 2013).

Additionally, the antiviral activity of hederasaponin B, derived from *Hedera helix*, against EV71, which causes hand, foot and mouth disease, was evaluated in vero cells. Hederasaponin B demonstrated significant antiviral activity against the EV71 subgenotypes C3 and C4a by inhibiting viral VP2 protein expression, most likely due to the inhibition of viral capsid protein synthesis. Therefore, *Hedera helix* extract may be a novel drug candidate with broad-spectrum antiviral activity against various subgenotypes of EV71 (Song et al. 2014). Moreover, *Hedera helix* extract has been reported to have anti-oxidant properties (Gülçin et al. 2004) anti-allergic effects (Jones et al. 2009) and antitumor activities (Elias et al. 1990). The ripe fruits of *Hedera helix* crude extracts have a potential anthelmintic benefit (Eguale et al. 2007).

Astragalus membranaceus (*astragalus*) (Register No. 003RH2005, Commercial name, Astranaceus). *Astragalus* has historically been used in Chinese medicine, but is only now receiving attention in the U.S. and Europe. *Astragalus* is a perennial plant, approximately 16–36 inches tall, that is native to the northern and eastern parts of China, as well as Mongolia and Korea. It has hairy stems with leaves made up of 12–18 pairs of leaflets. The root is the medicinal part of the plant and is usually harvested from four-year-old plants. The Chinese name of the herb, huang qi, means 'yellow leader', and the herb was given this name because its root is yellow and is one of the most important herbs in Chinese medicine. It is often combined with other herbs to strengthen the body against disease. *Astragalus* is an adaptogen, meaning it helps protect the body against various stresses including physical, mental, or emotional stress. *Astragalu*s may protect the body from diseases such as cancer and diabetes. It contains anti-oxidants, which protect cells against damage, and is also used to protect and support the immune system, preventing colds and upper respiratory tract infections, lowering blood pressure, treating diabetes, and protecting the liver. *Astragalus* has anti-bacterial and anti-inflammatory properties. It is occasionally used on the skin for wound care. In addition, studies have demonstrated that *Astragalus* has antiviral properties and stimulates the immune system, suggesting that it may prevent colds (Sinclair 1998).

*Astragalu*s contains the plant pigments: formononetin, astraisoflavan, astrapterocarpan, 2'-3'-dihydroxy-7,4'-dimethooxyisoflavone, and isoliquiritigenin. Other major constituents include D-ß-asparagine, calycosin, cycloastragenol, astragalosides IVII, choline, betaine, kumatakenin, sucrose, glucuronic acid, ß-sitosterol 1, and soyasaponin I. Astragalan, a polysaccharide fraction with a molecular weight between 20,000 and 25,000, has been extracted and researched in China for its ability to enhance the *in vitro* secretion of tumor necrosis factor (Zhao and Kong 1993).

Astragalus has also been used in immunotherapy. The use of recombinant interleukin-2 (rIL-2) in immunotherapy is limited by the toxicity associated with higher doses. *Astragalus* was administered with 100 u/ml of rIL-2 versus 1,000 u/ml of rIL-2 alone in an *in vitro* study in murine renal carcinoma cells. The astragalus rIL-2 group had a tumor cell lysis rate of 88 versus 86% in the group with 1000 u/ml rIL-2

alone. This suggests a 10-fold potentiation in the *in vitro* antitumor activity of rIL-2 generated lymphokine-activated killer (LAK) cells (Wang et al. 1992). In the United States, researchers have examined astragalus as a possible treatment for patients whose immune systems have been compromised by chemotherapy or radiation. In these studies, astragalus supplements appear to help people recover faster and live longer. Research using astragalus in patients with AIDS has produced mixed results. Recent research in China suggests that because *Astragalus* is an anti-oxidant, it may benefit patients with severe forms of heart disease; relieving symptoms, lowering cholesterol levels, and improving heart function. At low-to-moderate doses, astragalus has few side effects. However, it does interact with a number of other herbs and prescription medications. Astragalus may also be a mild diuretic, meaning it helps rid the body of excess fluid. It has also demonstrated *in vitro* anti-bacterial activity against *Shigella dysenteriae, Streptococcus hemolyticus, Diplococcus pneumoniae*, and *Staphylococcus aureus.* The saponins contained in *Astragalus* had a positive effect on the function of the heart by inhibiting lipid peroxide formation in the myocardium and decreasing blood coagulation (Purmova et al. 1998, Cheng et al. 2011).

Capsicum annuum (*chile, Mex*) (Register No. 004RH2005, commercial name Green Marvel). In Mexico pepper fruits are important ingredients in a balanced diet; peppers are a vital source of compounds that offer health benefits and enrich the anti-oxidant pool of food products including vitamins C and E, provitamin A, carotenoids and phenolic compounds. Pepper belongs to the genus *Capsicum*, which is comprised of more than 200 varieties, with *Capsicum annuum, Capsicum baccatum, Capsicum chinense, Capsicum frutescens*, and *Capsicum pubescens* being the main five species (Zimmer et al. 2012). Peppers are consumed worldwide and their importance has gradually increased to place them among the most consumed spice crops in the world (Bown 2012). They are usually consumed as food and used as additives in the food industry. They also have a significant role in traditional medicine. In fact, in Indian, Native American, and Chinese traditional medicine, *Capsicum* species have been used for the treatment of arthritis, rheumatism, stomach aches, skin rashes, dog/snake bites, and flesh wounds. These therapeutic applications are related to the capsaicinoid, phenolic compounds, and carotenoid content of peppers (Zimmer et al. 2012). Carotenoids are the pigments responsible for the yellow, orange, and red color of many types of peppers; however, they are more than mere pigments and also play an important role as anti-oxidants. In their capacity as anti-oxidants, carotenoids protect cells and tissues from harmful Radical Oxygen Species (ROS), acting as scavengers of singlet molecular oxygen, peroxyl radicals, and Reactive Nitrogen Species (RNS) (Stahl and Siess 2003, Hernández-Ortega et al. 2013).

Capsicum annuum L. is reported to be an excellent source of polyphenols, particularly flavonoids such as quercetin and luteolin (Koo and Mohamed 2001). The principal pungent ingredient present in red peppers (*Capsicum annuum* L.) is the phenolic substance named capsaicin (8-methyl-N-vanillyl-trans-6-nonenamide). This compound has attracted considerable attention over the past two decades because of its chemoprotective properties against certain diseases. The presence of high concentrations of chlorophylls and carotenoids in a single food matrix, as occur in peppers at IRS, may be important because they can exert different protective effects and can protect from the same disease via different mechanisms. The consumption of carotenoids and chlorophylls has been associated with protective effects against atherosclerosis, some forms of cancer, osteoporosis, cataracts, neurodegenerative diseases, mutagenesis, and oxidative stress (Elliott 2005, Ferruzzi and Blakeslee 2007). The protective effects of carotenoids are mediated by their oxidant, anti-oxidant, redox sensitive cell signaling, induction of gene expression, and provitamin A properties (Elliott 2005). The contribution of chlorophylls to the anti-oxidant activity of fresh and processed Capsicum gene has been clearly demonstrated (Alvarez-Parrilla et al. 2011). Fox et al. (2005) observed that fruits of Robusta bell peppers at IRS presented a higher (29%) anti-oxidant activity than fruits at other ripening stages.

Capsicum annuum also exhibited significant peripheral analgesic activity at 5, 20, and 80 mg/kg and induced central analgesia at 80 mg/kg as well as indomethacin (7 mg/kg). Interestingly, guajillo pepper (dry pepper) carotenoid extract had a more prolonged effect than indomethacin, increasing the latency of response time even after five hours post treatment. The results suggest that the carotenoids in dried guajillo peppers have significant analgesic and anti-inflammatory benefits and may be useful for pain and

inflammation relief (Hernández-Ortega et al. 2012). Due to abundant phytochemicals and their culinary use, red peppers have become an important source of chemopreventive agents in the Orient. Agricultural wastes of plant origin have attracted considerable attention as potential sources of bioactive phytochemicals that can be used for various purposes in the pharmaceutical, cosmetic and food industries.

Malva parviflora L. (Malvaceae) (Register No. 005RH2005, Commercial name AZUL). *Malva parviflora* L. Ahala, Malba, country mallow, Malva de castilla, Malva of cheeses; State of Mexico: du-Jan (Mazahua); Oaxaca: baldag malv (*zapoteco*), belongs to the family Malvaceae that includes trees, shrubs and herbs and is widely distributed throughout Africa. Plants from this family are noted for their economic, horticultural and medicinal importance. Traditional healers and herbalists in Lesotho use dried powder or an infusion made from the leaves and roots of *Malva parviflora* to clean wounds and sores. A hot poultice made from leaves is also used to treat wounds and swelling and is incorporated into a lotion to treat bruised and broken limbs (Shale et al. 1999). An ethnobotanical survey observed that the leaves and stems of this plant, with or without the addition of heated brown sugar, is applied as a hot poultice to wounds and boils by the Xhosa people of South Africa. Shale et al. (1999) also reported the use of its lotion to treat bruises and broken limbs and the dried powder or infusion of the leaves and roots to clean wounds and sores by herbalists in Lesotho. The methanol extract of *Malva parviflora* also possessed appreciable activity against Gram-negative and Gram-positive bacteria, as well as anti-inflammatory activity against COX-1 (Shale 1999). In 1999, it was possible to isolate a new compound present in *Malva parviflora*, 5α-estigmast-9 (11)-en-3-one; however, their secondary metabolites have been under-researched, because over the last 55 years, research has been directed towards the metabolism of the primary (protein). Some studies have demonstrated the free radical scavenging activity of the methanolic extract of Malva. In a study by Afolayan et al. (2008), the plant demonstrated the ability to quench radicals, inhibiting 94.3% of radical cations. The plant possesses higher flavonoid content compared with phenolics and proanthocyanidins and a positive linear correlation was established between the polyphenols and free radical scavenging activity. Additionally, the hexane extract of *M. parviflora* leaves can efficiently inhibit insulin resistance, lipid abnormalities and oxidative stress, indicating that its therapeutic properties may be due to the interaction plant components soluble in the hexane extract with any of the multiple targets involved in diabetes pathogenesis (Pérez-Gutierrez 2012).

Eucalyptus (commercial name AGRIFEN). Labillardiere, common names Eucalipto (Méx, Ecu., Perú y Ven); Ocalito; Eucalipto macho (Bol.); Blue gum, Eucalipto bouton, Gommier bleu (USA), belongs to the family Malvaceae and is native to Australia. The genus *Eucalyptus* includes approximately 600 species. *Eucalyptus globulus* is most widely cultivated in subtropical and Mediterranean regions. Essential oils from *Eucalyptus* species are used in folk medicine and also widely used in modern cosmetics, food, and pharmaceutical industries (Gray and Flatt 1998).

The medicinal use of this plant is indicated for respiratory disorders, primarily coughs. For this purpose, a decoction of the leaves is ingested before bedtime, in addition to inhaling the stems. For severe coughs, it is prepared with camellia flowers or purple bougainvillea (*Bougainvillea* sp.) and mullein (*Gnaphalium attenuatum*) or cinnamon (*Cinnamomum zeylanicum*). This remedy is also used in other lung conditions and is consumed warm when necessary. The essential oils exert antibiotic activity against *Staphylococcus aureus, Pseudomonas aureginosa* and other *Pseudomonas* species, *Escherichia coli, Bacillus subtilis, Proteus mirabilis, P. morganii, P. rettgeri, Salmonella typhi, S. Wien, Haemophilus influenzae, Mycobacterium tuberculosis, Klebsiella* species, *Streptococcus*, *Enterobacter* and the fungus, *Candida albicans*. These compounds also exhibit antiviral activity against the influenza A2 virus, smallpox, and herpes type 2. The ethanol extract of the branches is active against *Plasmodium falsiparum* FMN-13, and slightly active against other types of *Plasmodium falsiparum*. The ether extract of the leaves has anthelmintic activity against *Stronggyloides stercoralis* and *antianquilostoma*, specifically, *A. duodenale* and *Ancylostoma caninum*. The molluscicidal action exerted by the extract has also been demonstrated (Hammer et al. 1999, Cimanga et al. 2002).

Other effects have been demonstrated experimentally including the hypoglycemic action of the aqueous extract of the leaves when administered in the diet of mice with streptozotocin-induced hyperglycemia and administered by gastric intubation and subcutaneously to hyperglycemic mice induced by alloxan.

Leaves and essential oil expectorant were administered to rats as a diuretic. In rabbits and cats, it was administered orally in doses of 150 and 100 mg/kg. The anthelmintic activity of *Eucalyptus globulus* leaf, flower and fruit extracts *in vitro* against *Fasciola hepatica* were lethal to parasites at concentrations of 2.5 mg plant/ml and 5.0 mg plant/ml. The leaves contain essential oils: monoterpenes camphene, Cineol, para-cymene; euglobal IB, IC and II A, alpha and beta-phellandrene, geraniol and acetate, iso-fenchone, limonene, myrcene, alpha and beta-pinene, trans-pineocarvol, terpineol, alpha-isomer and its acetate, valeraldehyde, aromandreno sesquiterpenes, allo-aromandreno, caryophyllene, euglobal III, IV A and IV B, globulol, epiglobulol, ledol and viridiflorol. *Eucalyptus* leaves contain: crisin flavonoids eucaliptín, hyperoside, galloyl procianidín B-2, B-2 prodelfinidín galloyl, prodelfinidín B-5 and its digaloil, quercetin, isoquercetin, rutin, and 8-desmethyl sewderoxilín sideroxilín. The essential oil of the fruit contains the monoterpenes 1-8 cineol, linalool oxide, beta-pinene, piperitone, last-4-ol, alpha, beta and gamma-terpinene and its alpha-isomer, gamma-cadinene, eremofileno, and alpha-gurguneno globulol. Cineol, an essential oil, has significant antibiotic activity against bacteria, fungi and viruses and is an expectorant. Additionally, phytochemical analysis of *Eucalyptus* revealed that it has an anti-cariogenic substance, alpha-farnesene, which is a sesquiterpene. The hexanoic and ethyl acetate extracts of *E. globulus* plant leaves have inhibitory potential against *Lactobacillus acidophilus* and a panel of cariogenic bacteria (Kalpesh et al. 2013). The alcoholic extract of *Eucalyptus globulus* administered orally to diabetic rats for 21 days at 0.05, 0.10, 0.20 and 0.40 g/kg significantly decreased serum glucose levels. Further, it increased serum insulin levels in a dose-dependent manner, suggesting it has anti-diabetic activity.

Crataegus sp. (Register No. 007RH2005, commercial name Strauds drops, native name Tejocote (Mex.)), is the *Crataegus* genus (Rosaceae) and comprises approximately 280 species and is found in northern temperate regions of East Asia, Europe, and eastern North America. The common name for the *Crataegus* species is hawthorn and is known as Tejocote in Mexico. Texocotl (Nahuatl), 'stone sour'; Chiapas: kanal chishte, chamomile, manzanita, bighorn haws; Federal District: texocotl (Nahuatl); State of Mexico: npeni (Otomi); Michoacán: karhasi (purhépecha). *Crataegus* sp. contains a number of chemical compounds: acids, triterpene acids, organic acids, sterols and trace amounts of cardioactive amines. Several biological activities for this genus have been reported, such as antispasmodic, diuretic, and digestive activities, among others. These reports are from Europe using numerous preparations and in combination with other herbal extracts. In addition, the *Crataegus* sp. has been used in Mexican traditional medicine, as well as in other countries, for the treatment of asthma (Digital Library, UNAM). Recently, the leaves of *C. mexicana* were reported to have a tracheal relaxant effect in a bioassay-guided study employing guinea-pig isolated tracheal rings as an experimental model. Assays by HPLC-MS reveal that at least 14 compounds may exist in the hexane extract. In addition, the results suggest that the relaxant effect of the effective fraction was partially related to the activity of β-adrenergic receptors and not K+ ATP channels. This study provides preliminary scientific support for the popular practice employing *Crataegus mexicana* for the treatment of respiratory diseases (Arrieta et al. 2010).

A 30% syrup derived from the fruit has pulmonary effects, which is useful for the treatment of airway diseases when the dominant symptoms are cough, bronchial congestion and lung inflammation. The leaves have a diuretic effect and promote healthy renal stimulation; traditionally a patient ingests two or three cups a day of a 10% infusion before meals when there is noticeable irritation in the urinary tract or kidney pain. The root has upnentel diuretic and only leaves have an effect, and it is useful for the treatment of inflammation of the kidneys and bladder (nephritis, pyelitis, pielinefritis, cystitis), particularly when there is anasarca (fluid retention in the tissues especially leg), or localized or general edema (infiltration skin tissue). It is also an advantageous treatment for kidney dysfunction and cardiac or vascular deficiency, having a similar effect as digitalis, caffeine or kola nut without their adverse effects. Therefore, it is effective as a cardiac tonic and sedative and for slight nervous hypotension (Long et al. 2006). It has also been demonstrated to reduce the amount of glucose in the urine and blood and may be useful in diabetes, resulting in the control of diabetes in some patients.

Cedronella mexicana,Cassia senna (Register No. 015RH2001, NATROSOLVE). *Cedronella mexicana,* currently named *Agastache mexicana* (H.B:K.) Lint & Epling, is used to alleviate anxiety or abdominal pain in folk medicine (the medical equivalent of sedatives and antispasmodics). In Mexico, it is commonly

called 'toronjil'. Due to large demand for this plant, it is cultivated in various regions such as Mexico City and the states of Hidalgo, Mexico, Morelos, Puebla and Veracruz. The blooming season is August and the seeds ripen in September. *A. mexicana* is used to treat the cultural disease known as 'empacho' (indigestion), 'mal de ojo' (evil eye) and for 'spiritual cleansings' (Argueta et al. 1994). As a medicinal remedy, all of the aerial parts and only the flowers of *A. mexicana* are usually prepared, fresh or dried, in boiling water as an infusion or decoction or as a maceration in ethanol which are used to treat anxiety, insomnia, cardiovascular disorders (Linares et al. 1988, Argueta et al. 1994), rheumatism, stomach pain, and gastrointestinal affections (Hernández 1942, Linares et al. 1988, Argueta et al. 1994, Linares et al. 1995). Inflorescences are preferred to alleviate pain and aerial parts produce a sedative effect (Madaleno 2007). *A. mexicana* extracts have recently been studied for pharmacological activity such as anxiogenic (Molina-Hernández et al. 2000), vasoactive and anti-oxidant effects (Ibarra-Alvarado et al. 2010). Its medicinal properties on nociception have been tested by systemic administration in different experimental models of nociception to identify what types of nociception may be alleviated by using this plant. These studies have provided experimental support for its use in traditional medicine in the treatment of abdominal, inflammatory and gouty arthritis pain (González-Ramírez et al. 2012). This vegetal species is often combined with *Cassia senna*. There are over 400 known species of Cassia. The leaves and seedpods (fruit) have laxative activity, due to the presence of anthraquinone compounds. Anthranoid laxatives are a group of substances generally described as herbal laxatives because of their natural origin (Laitinen et al. 2007). Sennosides, the most well-known members of the anthranoid family, are obtained from senna plant dried leaflets and pods. Anthranoid laxatives are commonly used in clinical practice as self-medication for chronic constipation. Although the short-term use of these laxatives is generally safe, results from *in vitro* and animal studies suggest that they are potentially tumorigenic (National Toxicology Program 2012). However, translation of animal studies to humans is problematic, as these results were obtained in an experimental setting with relatively high and lengthy exposures for the lifespan of the animals (van Gorkom et al. 1999). Currently available evidence does not support a genotoxic risk for patients who consume senna-based laxatives (Morales et al. 2009). However, several human studies have suggested possible carcinogenic effects after long-term administration (van Gorkom et al. 1999). Therefore, these substances should be used with caution and should not be chronically applied.

Damiana (Register No. 005RH2001, DAMIN). *Turnera aphrodisiaca* Ward (synonym *Turnera diffusa* Willd. family Turneraceae) is commonly known as '*Damiana*'. It is a small shrub with an aromatic leaf found on dry, sunny, rocky hillsides in South Texas, southern California, Mexico, and Central America. The leaf has been used as an aphrodisiac and to boost sexual potency by the native peoples of Mexico including the Mayan Indians. The two species used in herbal medicine, both which are referred to as damiana, are *Turnera aphrodisiaca* and *T. diffusa*. *Turnera diffusa* is registered alone (Register No. 017RH001, DEBORDER) and combined with *Tecoma stans* and *Medicago sativa* (Register No. 014RH2001, AZOTH). Historically, damiana has been used to relieve anxiety, nervousness, and mild depression, particularly when these symptoms have a sexual component. The herb is used as a general tonic to improve wellness and has also been used traditionally to improve digestion and to treat constipation. It is also used as a diuretic, cough treatment, and in large doses is thought to have a mild laxative effect. Studies of preparations of *T. aphrodisiaca* as tinctures have provided evidence of significant anxiolytic activity. These tinctures have similar classes of phytoconstituents such as flavonoids, alkaloids or steroids, which may be responsible for the activity of damiana (Kumar and Sharma 2005). In addition, it is reported that *T. diffusa* significantly reduced the post-ejaculatory interval, supporting an aphrodisiac effect, and may be effective against sexual dysfunction (Estrada-Reyes et al. 2009).

Echinacea angustifolia alone (Register No. 006RH2001, EQUINOL) and combined with *Marrubium vulgaris* and *Glycyrrhiza glabra* (Register No. 007RH2001, K-NUT). *E. angustifolia* plant preparations (family Asteraceae) are widely used in Europe and North America for common colds and the flu. Most consumers and physicians are not aware that products available under the term *Echinacea* differ appreciably in their composition. This variability is mainly due to the use of variable plant material, extraction methods and the addition of other components (Karsch-Völk et al. 2014). Despite its worldwide acceptance, only limited data are available on its prophylactic efficacy. Prophylactic treatment with *Echinacea* for over four

months appeared to be beneficial, suggesting that *Echinacea* has an advantageous safety profile; there was not a greater incidence of adverse effects observed with *Echinacea* use compared with placebo treatment. Overall, the risk/benefit results from this clinical study suggested that long-term treatment with *E. purpurea* over four months can be recommended (Jawad et al. 2012). This study is reinforced by a study examining an early intervention with a standardized *Echinacea* formulation that resulted in reduced symptom severity in subjects with naturally acquired upper respiratory tract infections (Goel et al. 2004). Evidence from preclinical studies supports some of the traditional and modern uses for *Echinacea*, particularly its reputed immunostimulatory (or immunomodulatory) properties (Barnes et al. 2005).

Ganoderma lucidum (Lingzhi or Reishi, Register No. 001RH2001). These mushrooms are being developed as nutraceuticals to obtain the essence of mushrooms and ease consumption. Scientific validation of traditional knowledge has confirmed the benefit of consuming mushrooms, fresh or processed, on human health (Sabaratnam et al. 2013). The effectiveness of *Ganoderma lucidum*, commercially named 'Reishi mushroom' or 'Medicine of kings', has been extensively studied and resulted in data from laboratory and clinical studies for a variety of diseases and conditions. *Ganoderma lucidum* is known as a bitter mushroom and has remarkable health benefits. The active constituents present in mushrooms include polysaccharides, dietary fibers, oligosaccharides, triterpenoids, peptides, proteins, alcohols, phenols, mineral elements (such as zinc, copper, iodine, selenium, and iron), vitamins, and amino acids. The bioactive components in the *G. lucidum* mushroom have numerous health properties for the treatment of diseases such as hepatopathy, chronic hepatitis, nephritis, hypertension, hyperlipemia, arthritis, neurasthenia, insomnia, bronchitis, asthma, gastric ulcers, atherosclerosis, leukopenia, diabetes, anorexia, and cancer. Despite the voluminous literature available, *G. lucidum* is used mostly as an immune enhancer and a health supplement, not therapeutically (Batra et al. 2013).

Ginkgo biloba (Register No. 004RH2001, TALIESIN). *Ginkgo biloba* is a dioecious tree that has been historically used in traditional Chinese medicine. Although the seeds are most commonly employed in traditional Chinese medicine, recently standardized leaf extracts have been widely sold as a phytomedicine in Europe and a dietary supplement in the United States and Mexico. The primary active constituents of the leaves include flavonoid glycosides and unique diterpenes known as ginkgolides; the latter are potent inhibitors of platelet activating factors (Smith et al. 1996). Ginkgo is recommended for inflammation and asthma treatment (Mahmoud et al. 2000). Clinical studies have demonstrated that ginkgo extracts exhibit therapeutic activity in a variety of central nervous system disorders including Alzheimer's disease (Maclennan et al. 2002), failing memory (Sakatani et al. 2014), age-related dementias (Ahlemeyer and Krieglstein 2003), poor cerebral and ocular blood flow, and congestive symptoms of premenstrual syndrome (Ozgoli et al. 2009). Due in part to its potent anti-oxidant properties and ability to enhance peripheral and cerebral circulation, ginkgo's primary application lies in the treatment of cerebrovascular dysfunctions and peripheral vascular disorders (McKenna et al. 2001).

Heterotheca inuloides (Register No. 009RH2001, SPLENDID). *Heterotheca inuloides* Cass. (Asteraceae) grows abundantly in the cooler, temperate regions of Mexico. The flowers of this plant are widely used in Mexican traditional medicine. Internally, they are used for the treatment of inflammatory diseases, fever and other disorders; externally, to treat contusions and wounds. Products containing Mexican arnica can be ointments and lotions for external or topical application and teas, tablets, or homeopathic tinctures for internal application. Components of *H. inuloides*, such as sesquiterpenoids, have been identified as anti-microbial agents (Kubo et al. 1994). The aqueous extract obtained from *H. inuloides* flowers has been assessed for analgesic and anti-inflammatory activity in several experimental models (Gené et al. 1998), in which several chemical constituents have also been tested (Delgado et al. 2001).

Jacobina spicigera 'Muicle' (Register No. 018RH2001, RIKLY). *Jacobina spicigera* Schlecht., also named *Justicia spicigera* Schlecht. (Acanthaceae), is a plant used as an immunostimulant and for the empirical treatment of cervical cancer in Mexican traditional medicine. There is evidence that one of the active constituents is kaempheritrin, which exerts immunostimulatory effects mediated by splenocytes, macrophages, human peripheral blood mononuclear and NK cells (Del Carmen et al. 2013) and cytotoxic,

anti-tumoral effects against HeLa cells (Alonso-Castro et al. 2013). It is also considered a significant plant because of the effect it may have in patients with hematopoietic disorders. However, experiments in different hematopoietic cells, human leukaemic cell lines, umbilical cord blood cells, and mouse bone marrow cells indicated that *Justicia spicigera* infusions do not produce any hematopoietic activity. However, it does induce apoptosis by inhibiting bcl-2 and is linked to cell proliferation, demonstrating cytotoxic activity (Cáceres et al. 2001).

Matricaria recutita combined with *Salvia officinalis* (Register No. 016RH2001, CARDON) and with *Lycopersicum esculentum* Mill and *Citrus aurantiifolia* (Register No. 001RH2010, EXHER). *Matricaria recutita* L. (Asteraceae) commonly known as chamomile is one of the most widely used and well-documented medicinal plants in the world. It is included in the pharmacopoeia of 26 countries (Salamon 1992a). The use of chamomile as a medicinal plant dates back to ancient Greece and Rome. The name 'chamomile' comes from two Greek words meaning 'ground apple' for its apple-like smell. The ancient Egyptians considered the herb a sacred gift from the sun god and used it to alleviate fever and sun stroke. In the sixth century, it was used to treat insomnia, back pain, neuralgia, rheumatism, skin conditions, indigestion, flatulence, headaches and gout. In Europe, it is considered a 'cure all', and in Germany, it is referred to as 'alles zutraut', meaning capable of anything (Berry 1995). Chamomile is widely used throughout the world. Its primary uses are as a sedative, anxiolytic and anti-spasmodic and as a treatment for mild skin irritation and inflammation. Chamomile's main active constituents are chamazulene, apigenin and bisabolol. Despite its widespread use as a home remedy, relatively few trials have evaluated chamomile's many purported benefits. Randomized controlled studies have produced conflicting results for the treatment of dermatologic and mucosal irritations including eczema and mucositis. Animal trials suggest efficacy as a sedative, anxiolytic and anti-spasmodic, but clinical studies in humans are still required (Salamon 1992b). An alcoholic extract of chamomile inhibited acetylcholine- and histamine-induced spasms. Essential oil of chamomile was comparable to papaverine in reducing isolated guinea pig ileum spasms. Apigenin and bisabolol have dose-dependent spasmolytic effects on isolated guinea pig ileum (Achterrath-Tuckermann et al. 1980). Extracts of chamomile flowers have an inhibitory effect on gastric acid secretion (Tamasdan et al. 1981). The anti-inflammatory effects of chamomile are well documented in animals. Bisabolol reduced inflammation, fever and adjuvant arthritis in animal studies. Bisabolol was also an anti-pyretic in yeast-induced fever in rats. Apigenin has demonstrated anti-inflammatory properties in animal studies. It demonstrated potent anti-inflammatory activity in carrageenan-induced rat paw edema and delayed type hypersensitivity in mice (Jakovlev et al. 1979, Ammon et al. 1996). Chamomile extracts significantly reduced locomotor activity in rats (Avallone et al. 1996). Chamomile has also been widely used for the treatment of digestive system disorders. A chamomile extract has demonstrated potent anti-diarrheal and anti-oxidant properties in rats, confirming their use in traditional medicine (Sebai et al. 2014). *Salvia officinalis* has been used in herbal medicine for many centuries. It has been suggested to, on the basis of traditional medicine, modulate mood and improve cognitive performance in humans. Therefore, *Salvia officinalis* may provide a novel natural treatment for Alzheimer's disease (Akhondzadeh et al. 2003, Russo et al. 2013). In the form of an infusion, the principal and most valued application, it is used as a wash to cure diseases of the mouth and as a gargle for inflamed sore throats, being excellent for the relaxation of the throat and tonsils and for ulcerated throats. Activity against inflammatory processes has been demonstrated after stimulation by chemical agents such as acetic-acid, formalin, glutamate, capsaicin and cinnamaldehyde (Rodrigues et al. 2012). This has been reinforced by observing that *Salvia officinalis* tinctures significantly reduced total leukocyte, monocyte percentages and activated circulating phagocytes (Oniga et al. 2007). Tomato (*Lycopersicum esculentum* or *Solanum lycopersicum* L.) is an important fruit crop in the Americas, southern Europe, Middle East and India with increasing production in China, Japan, and Southeast Asia. It is amenable to producing pharmaceuticals, particularly for oral delivery, for many of the same reasons that make it a popular vegetable. Its fruit is nontoxic and is palatable uncooked. It is easily processed and the plants can be propagated by seed or clonally from tip or shoot cuttings. Tomato plants have high fruit yields, there is a reasonable biomass and protein content and they are easily grown under containment (Van Eck et al. 2006). In preclinical studies, it has been demonstrated that guanosine from *S. lycopersicum* possesses anti-platelet (secretion, spreading, adhesion and aggregation) activity

in vitro and inhibits the platelet inflammatory mediator of atherosclerosis (sCD40L) (Fuentes et al. 2013). The anti-oxidant effects of tomatoes have also been examined and there was an association with dietary intake and a lowered risk of cancer, neurodegenerative, and cardiovascular diseases (Li et al. 2011b, Dubois et al. 2013, Aydin et al. 2013).

Mentha piperita, Tila platyphyllos and *Crataegus oxyacantha* (Register No. 012RH2001, BIOCALM). *Mentha piperita* 'Peppermint' has a wide variety of health and medicinal uses. It is used to help treat the common cold, calm inflammation and soothe digestive problems. The ancient Egyptians, one of the most medically advanced ancient cultures, cultivated and used peppermint leaves for indigestion. The ancient Romans and Greeks also used peppermint to soothe their stomachs. The plant was used by Europeans in the 18th century, especially western Europe. Peppermint oil has the most uses and data, the oil is considered relevant to leaf extract formulations as well. Topical preparations of peppermint oil have been used to calm pruritus and relieve irritation and inflammation (Herro and Jacob 2010). Many of peppermint's health and medicinal uses have been verified by scientific trials. Its anti-nociceptive and anti-inflammatory activity has been tested in several experimental models (Atta and Alkofahi 1998). *Crataegus* spp. 'hawthorn' (a genus comprising approximately 300 species) has been utilized by many cultures for a variety of therapeutic purposes for many centuries. Cardiovascular disease has become one of the most significant causes of premature death and recent research into the therapeutic benefits of hawthorn preparations has focused primarily on its cardiovascular effects (Tassell et al. 2010).

Tilia mexicana, Olea europaea, and *Casimiroa edulis* (Register No. 013RH2001, ESPIGOL). *Tilia americana* var. *mexicana* (Tiliaceae) is distributed in 14 states of Mexico, from the northern states of Chihuahua and Coahuila to the southern states of Guerrero and Oaxaca. Although this plant has a relatively large geographical distribution, the populations of this species are confined to lower mountainous forests, which cover less than 1% of Mexican territory (Flores et al. 1971). Tilia is a tree used in traditional medicine primarily as a non-narcotic sedative for sleep disorders or anxiety. Flower infusions (teas) of this species have generally been regarded as non-toxic; diluted teas are commonly given to overanxious children as a mild sedative. The inflorescence of Tilia are sold year-around in popular town markets located in several regions of Mexico (Pérez-Ortega et al. 2008). It has been observed that during the flowering months (April–June), there is an increase in the marketing of inflorescences of this species, because it is believed that the medicinal effect is greater when the infusion is produced during this period (Pavón and Rico-Gray 2000). Moreover, Tilia inflorescences are sold in markets where it is stored for almost a year; these samples may be adulterated by mixing with other species such as *Ternstroemia pringlee* (Theaceae), which is also known as Tilia. Tilia inflorescences acquired from local markets or freshly collected in different states of Mexico induce similar sedative and anti-anxiety effects in experimental models, supporting its use in folk medicine (Aguirre-Hernández et al. 2007a, 2007b). The presence of flavonoids such as quercetin and kaempferol derivatives (Herrera-Ruiz et al. 2008, Aguirre-Hernández et al. 2007a, 2010) and beta-sitosterol are thought to be responsible for this activity (Aguirre-Hernández et al. 2007b).

Conclusions

Although Mexican traditional medicine is one of the most diverse and complete medicine around the world, there are no Mexican phytomedicine production facilities. Trying to understand this situation is hard because the use of medicinal plants by the Aztec Indians in México had been described in different colonial documents since 1552. Such documents provide examples of the use, actions, and usefulness of different medicinal plants. Moreover, the formal medicine research in this area was started in 1888 when the National Medical Institute in Mexico was created by the order of President Porfirio Díaz. By 1915, the Institute's herbarium possessed 14,000 classified species and approximately 1,000 chemical compounds obtained from plants. In 1975, the Mexican Institute for the Study of Medicinal Plants (IMEPLAM) was founded with the aim to study the most widely utilized plants in Mexico to treat common illnesses. This Medicinal Herbarium is now known as the Medicinal Herbarium of the Mexican Institute of Social Security (IMSS) which has a legacy of more than 120,000 specimens. The Institute was considered an icon in

medicinal plant research in Latin America during the late 90s, and at the end of the 20th century. Actually, mechanisms of action, activity, and pharmacological effects of several medicinal plant extracts are under study, but commercially sponsored research results for drug, diagnostic, and treatment techniques must be intellectually protected to obtain a health registry, and the patents for proper marketing. Unfortunately, in Mexico, there are few phytomedicine patents registered by the Mexican Institute of Industrial Property. Moreover, the first patent application in this area was in 2005, and to date there have been just 27 patent applications including plants such as Agave marmorata, Tournefortia densiflora, Buddleia cordata, Salvia elegans, Ageratina pichinchensis, Sechium chinantlense & Sechium compositum, Cydonia oblonga, Bougainvillea xbuttiana, Matricaria recutita & Calendula officinalis, Stevia rebaudiana, Taxus globosa, Capsicum annuum, Loselia mexicana, Hibiscus sabdariffa, Galphimia glauca, and Psidium guajava.

Once the patent is obtained, it is necessary to have the proper authorization to market phytomedicines and the Federal Commission against Health Risk (COFEPRIS, for its acronym in Spanish) who grants the medical authorization for proper marketing in Mexico, if and when the application provides high quality preclinical data to justify the testing of the drug in humans. Because of the beneficial effects of medicinal plants, a large and growing global interest has emerged, both in developed and developing countries. However, it is important to consider that the fact that something which is natural does not necessarily make it safe or effective. Many pharmacological studies have validated their ethnomedicinal use. Nevertheless, clinical and toxicological studies should be conducted with medicinal plants in order to guarantee their safety and effectiveness. The isolation and identification of their active compounds is also highly desirable. Another consideration of importance is to perform pharmacokinetic studies with active compounds from medicinal plants. Taking this into consideration, the integration of phytomedicine in the health system should be developed with scientific evidence of effective therapeutic properties. Clinical trials should then be conducted in humans to test and validate biopharmaceutical, pharmacokinetic, pharmacodynamic, efficacy, safety, and therapeutic applications.

If the application is approved, the innovating company is allowed to distribute and market the drug. As of now, there have not been any clinical trials conducted in Mexico that have led to marketing authorization of a drug. This could be due to the rigidity of scientific evaluation criteria, lack of information about the patent database, low knowledge about patentability requirements, or a lack of information about the key steps required for medical authorization. In addition, updating pharmacopeias of Mexico with new information about the use of medicinal plants is necessary.

Quality control for efficacy and safety of herbal products is of great importance. The assurance of the safety of an herbal drug requires monitoring of the quality of the finished product as well as the quality of the consumer information on the herbal remedy. All of these points require appropriate attention and correction for producing phytomedicines. Another relevant point that needs attention is the creation of a policy that allows cohesion between university-business-government agencies to foster phytomedicine research, health registration, and extensive marketing.

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