ACTA MICROBIOLOGICA BULGARICA Volume 34 / 4 (2018)

Review

From Hildegard von Bingen to Evidence-Based Phytotherapy: Insight into Herbal Remedies for Infectious Diseases

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Abstract

Plants represent the oldest source of pharmacotherapy used by mankind. The medical use of plants strongly evolved over time, being integrated in cultural, philosophical, astrological or mystical systems. Several studies have shown correlations between modern herbal use and the claims provided by ancient European authors like the medieval abbess Hildegard von Bingen or the notorious English herbalist Nicholas Culpeper or by traditional systems (Arabic, Indian, Chinese). About 80% of the population living in the developing countries uses nowadays herbal medicine for treatment. In the developed countries, the current "bio" trend of replacing synthetic drugs with phytotherapy has led to a constant rise of the sales figures of herbal medicines. So far, only a few controlled clinical trials of antibacterial herbal medicines have been published, most of them being methodologically weak. Opening new horizons for the exploration of natural healing sources should be done from the perspectives of safety and efficacy. There is an obvious need for standardization of materials, methods and measures for preparation, preservation and administration of herbal drugs. It is time for the fundamental principles and approaches of the traditional systems to acquire a solid scientific validation. The development of evidence-based phytotherapy will be of much help in the process of evolving from an ideological overestimation of the power of nature to a scientifically proved option for the treatment of many disorders, including infectious diseases.

Keywords: herbal remedies, evidence-based phytotherapy, reverse pharmacology.

Резюме

Растенията са най-старият източник на фармакотерапия, използван от човечеството. Тяхното използване в медицината се е развило с течение на времето и е интегрирано в културни, философски, астрологически или мистични системи. Редица проучвания показват корелация между съвременната употреба на билки и твърденията на древните европейски автори като напр. средновековната игуменка Хилдегард фон Бинген и известния английски билкар Никола Кълпепер или традиционните системи (арабски, индийски, китайски). Около 80% от населението, живеещо в развиващите се страни, днес използва билките за лечение. Настоящата "био" тенденция на замяна на синтетични лекарства с фитотерапия доведе до постоянно покачване на продажбите на билкови лекарства. Досега са публикувани само няколко контролирани клинични изпитвания на антибактериални билкови лекарства, повечето от които са методологически слаби. Откриването на нови хоризонти за изследване на природните лечебни източници трябва да се извършва от гледна точка на безопасността и ефикасността. Очевидна е необходимостта от стандартизация на материалите, методите и мерките за подготовка, съхранение и администриране на билкови лекарства. Време е фундаменталните принципи и подходи на традиционните системи да придобият солидна научна валидация. Развитието на фитотерапия, основана на доказателства, ще бъде от голяма полза в процеса на преминаване от идеологическо надценяване на силата на природата до научно доказана възможност за лечение на много заболявания, включително инфекциозни.

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Ever since the birth of humankind, the history of human evolution has been continuously linked to the acquisition of knowledge regarding plants and their potential use as food, spices or medicine. In parallel with the advancements of conventional medicine, traditional medicine has been practiced all over the world, the medicinal plants being its backbone. In some societies traditional healing is regarded as the foundation of the healthcare system, while in others it just serves as a complement to it. About 80% of the population from the developing countries relies on traditional medicine, according to WHO estimates (Mukherjee and Wahile, 2006). The same organization describes traditional medicine as "the sum total of the knowledge, skills, and practices based on the theories, beliefs, and experiences indigenous to different cultures, whether explicable or not, used in the maintenance of health as well as in the prevention, diagnosis, improvement or treatment of physical and mental illness" (WHO, 2000). In most of the cases, the empirical basis of the traditional healing systems can be extrapolated in robust theoretical knowledge. The traditional healers were (and still are) trusted members of the communities, capable of analyzing religious and cultural elements in the frame of the societies they lived in, and thus provide a holistic approach (Oumeish, 1998).

Phytotherapy is a concept that has developed over the centuries. Regarded by most as empiric, it has always been an evidence-based knowledge, proofs of its effectiveness being in close connection with the evolution of human beliefs and knowledge. Each period of evolution of humankind had its own landmarks and evaluation criteria: keen observation of the healing effects of different components of plants, correlations between the efficiency of plants and the astrological influences to which they were subjected, discovery of the chemical compounds involved in the pharmacological action.

Archeological evidence of the use of medicinal plants can be traced back to the Paleolithic. At the Iraqi Shanidar burial sites plants with therapeutic potential have been found. There is still a debate whether the choice of these plants has been intentional or incidental, but strong suspicions plead for the first (Lietava, 1992). Ötzi the Iceman's body, aged about 5000 years, was discovered in the Alps, body frozen, with grains of einkorn and barley, seeds of flax and poppy and kernels of the blackthorn tree around him (Heiss and Oeggl, 2008).

The Sumerian clay tablets contain lists of medicinal plants used in Mesopotamia (myrrh and opium among them). The Ancient Egyptian Ebers Papyrus (around 1500 BC, during the reign of Amenhotep I) contains information on over 850 plant medicines, including garlic, juniper, cannabis, castor bean, aloe, and mandrake. Besides, ancient Egyptian tombs have been discovered, with wall paintings or jars containing traces of herbs. Studies have shown that the ancient Egyptian healers did not limit their activity to the use of local, indigenous plants, but also to imported ones, mainly from Lebanon (Sutherland, 2006).

Sanskrit writings such as the *Rig Veda* and *Atharva Veda* are some of the earliest available documents detailing the medical knowledge that formed the basis of the Ayurveda system. Ayurveda (literally "science of life") is one of the world's oldest whole-body healing system. Health was thought of as a prerequisite for the improvement of the human being (Mukherjee *et al.*, 2017). In this system herbs have been seen as spiritual essence. The 6th century BC foundational text of Ayurveda, *Sushruta Samhita,* describes about 700 medicinal plants (Mukherjee and Wahile, 2006). The adepts of Ayurvedic medicine acknowledged the existence of three biological forces, or doshas: vata, pitta, kapha, which they linked to the five Hindu elements (earth, water, fire, air and ether or space). Plant collection relied on land and drug selection, cultivating method and collection time, all of these being highlighted by the influences of the stars, planets, moon and sun. This botanical and philosophical system had a considerable influence on the medical thinking of neighbouring cultures in ancient times, as proven by the translations of the Ayurvedic writings in several languages, like Greek, Persian, Arabic, Chinese and Tibetan (Jaiswal *et al.*, 2016). The British colonization of India in the 19th century brought influences from Western medicine, but also extended Ayurvedic knowledge by publications in English, Sanskrit and vernacular languages (Mukherjee *et al.*, 2017). There have also been attempts to interpret Ayurvedic writings in the light of the European medical theories (Gangadharan, 1982).

Chinese herbal medicine can claim a tradition of about 5000 years. Archaeological sites of Bronze Age China dating from the Shang Dynasty were rich in seeds likely used for herbalism. The main figure of this tradition is the divine farmer Shennong, a mythological emperor. Legend says he was reputed for tasting hundreds of herbs per day and selecting those that were suitable as remedies. *The Herbal Classic of Shennong* (*Shennong Ben Cao Jing*) published around 500 AD, but with more an-

cient roots, lists a series of 365 medicinal plants with healing virtues, among them plants that later on revolutionized medicine, like ephedra, hemp, and chaulmoogra. Throughout history, several *Ben Cao* (Chinese traditional medical texts) have left us records of Chinese knowledge of medicinal plants (Jaiswal *et al.*, 2016). Constructed around the yin-yang principle, Chinese philosophy of cure also relies on the primordial qi theory (Sun *et al.*, 2013). Qi is a Chinese concept that defines the vital force or energy that can be compared with the Aristotelian Western concept of vitalism.

Ayurveda and Traditional Chinese Medicine are considered two of the most ancient systems of medicine, sharing several botanical formulations used for either similar or different therapeutic applications, as well as a similar philosophical approach concerning the human body as part of the universe.

Ancient Greeks and Romans largely contributed to the spread of knowledge concerning the herbs with healing properties. In the 4th century BC, Theophrastus was the artisan of the first systematization of the botanical world in his *Historia Plantarum.* Much later, in the 3rd century BC, Diocles of Carystus, and in the 1st century BC, Krateuas, gathered information on plants, considerably overlapping with the Egyptian herbals. The pattern for the later Western medicine was due mostly to Hippocrates with his *De herbis et curis* and to Galen with *Terapeutica* and *De simplicium medicamentorum facultatibus libris XI.* The writings of Hippocrates also provided the early basis used by Dioscorides in order to achieve his unparalleled work, *De Materia Medica,* a compendium of more than 600 plants which has long been, well into the 17th century, the authoritative reference of herbalism and still remains the core of the Western pharmacopoeia (de Vos, 2010; Alamgir, 2017).

In Europe, Hippocrates's theory of humors was highly accepted: illness was caused by an imbalance of the four humors: blood, phlegm, black bile and yellow bile. He recommended specific diets to help in the "cleansing of the putrefied juices". This Hippocratic highly individualistic system of medicine retained its popularity mainly due to the writings of Galen. Paracelsus, who besides being a physician, was an alchemist very prone to symbolic and esoteric thinking, proposed the doctrine of signatures, a holistic concept that pretended to be able to predict the therapeutic virtues of plants based on their attributes (shape, color, smell or taste). The main idea of this doctrine was rooted in folk medicine, but Paracelsus systematized it in conceptual opposition to the humoral pathology of Galen. It was through the works of Jacob Böhme, of Sir Thomas Browne or of the botanist William Coles that this doctrine was spread, and it emphasized the correspondence between macrocosm and microcosm. Today, the importance of this theory in traditional European herbal medicine is declining, though still present in the principles of homeopathy.

Arabic traditional medicine was much developed by Islamic scholars who expanded earlier knowledge and amplified its theoretical principles into a comprehensive system (AlRawi *et al.*, 2017). It was interconnected with philosophy and influenced by magic and religious beliefs, as well as by numerical and astrological symbolism (Oumeish, 1998). Arab-Islamic medicine influenced Western medical circles, especially in the Mediterranean region, at such an extent that it became a foundation stone of herbal medicine in Europe (Saad and Said, 2011). The Persian physician Avicenna, known as the most influential medical writer in the Middle Ages, was the author of the *Canon of Medicine*, which presents a clear and well organized summary of all the medical knowledge of the time, including a long list of drugs. Sir William Osler considered the Canon as "the most famous medical textbook ever written; a medical bible (sic!) for a longer time than any other work" (Mahdizadeh *et al*., 2015).

In the Middle Ages, while folk medicine was practiced in the small communities, either by wise persons from inside the community, or by wandering herbalists, while remedies were often prescribed along with spells and enchantments, a fact that frequently brought accusations of witchcraft, an important source of medical knowledge came from the Benedictine monasteries, where efforts were focused on copying, translating and compiling ancient manuscripts. Meantime, there was a tradition of "healing gardens" that provided the raw materials for treatment of common diseases, as well as a place for soul balancing. The most prolific representative of these monasteries was the 12th century abbess Hildegard von Bingen, nowadays considered a leading light of medieval learning. This multifaceted abbess - physician, philosopher, naturalist, composer, poet, author and linguist - left us a series of works, mainly in Latin (the visionary language of initiated people), related to the natural world and to herbal remedies. Two of Hildegard von Bingen's medical writings - *Physica* and *Causae et Curae* - detailed health problems to which she offered various treatments (more than 400 claims of health benefits from 175 different plants). A scientific study

using modern statistical approaches suggests that Hildegard's herbal remedies were far more correct than what could be explained by mere chance (Uehleke *et al.*, 2012).

Starting with the 15th century, humanity experienced "the great age of herbals", with most of the written productions available in English or other national languages rather than Latin and Greek. The first herbal to be published in English was the anonymous *Grete Herball* of 1526, followed by Gerard's *Herball* (a pirated translation of a book by the Belgian herbalist Dodoens, faultily matched with illustrations from a German botanical work) and that of Nicholas Culpeper. Culpeper's blend of traditional medicine with astrology, magic, and folklore was mocked by the physicians of his day, yet his book - like Gerard's and other herbals - enjoyed phenomenal popularity. Besides, Culpeper, in his quest for gaining popularity and for fighting against the medical establishment of his time, started making medical knowledge more accessible to healers, by first writing his own texts in English and by translating in English books written in Latin. He was among the adepts of the theory of signatures.

Contemporary to Culpeper, the most prominent herbalist figure from the Romanian territories was Ion Căianu (Kajoni Janos, Ioannes Caioni, 1629-1687) a Transylvanian Franciscan monk, who wrote an *Herbarium Terrae Transylvaniae*, annex to the *Hortus Sanitatis Venetis* (1511). His healing garden is still to be found in his native village.

The age of exploration and the Columbian exchange introduced new medicinal plants to Europe, together with written documents indicating their potential use. The Badianus Manuscript is considered America's Earliest Medical Book. This illustrated Aztec herbal was brought to Europe by the Spanish conquerors, who were very impressed by the medical skills of the Indians. Genuinely Aztec, the manuscript was not influenced by European knowledge. It was written by an Indian physician in Aztec, then translated into Latin, in 1552. When no Latin equivalents were available for most plant names, the original Aztec names were kept, along with color illustrations helpful in identifying the plants (Walcott Emmart, 1940).

From Hildegard von Bingen to Culpeper, botany was very much thought to be under the influence of astrology. Plants and humans were governed by planets. Planets exerted their effect on plants and their medicinal properties. A strong relationship has been described between planetary movements and biological activities. Astrology helped building a holistic approach. The use of medicinal astrological principles was helpful by the time, by selecting the appropriate herb for the precise ailment. The developing tradition of Astrology and alchemy (esoterism) brought up the theory that each plant had its own, unique embodiment of planetary forces.

The use of herbal remedies in the Antiquity, Middle Ages, Renaissance or 19th century was performed according to observation or experience. Tradition was rooted in practice. The remedies worked for generation after generation despite social and cultural changes in medical theory. "The how and the why" was less important than the fact that they worked. Largely accepted until the beginning of the 20th century, medicinal plants have been confronted in the past century with what was called "The great U turn": a gradual decrease in their use during the Second World War and three decades after, a re-evaluation of the use of herbs in medicine in the 70s and the 80s, followed by the recognition of their therapeutic virtues and their slow re-integration and, finally, acceptance, their re-emergence being thought of as an attractive option (Fig. 1). This U-turn can be explained by the modern "evidence-based" philosophy of medicine that made its way in clinical practice. A shift took place, from the magical/shamanic or energetic approaches, to the functional dynamic and chemical ones.

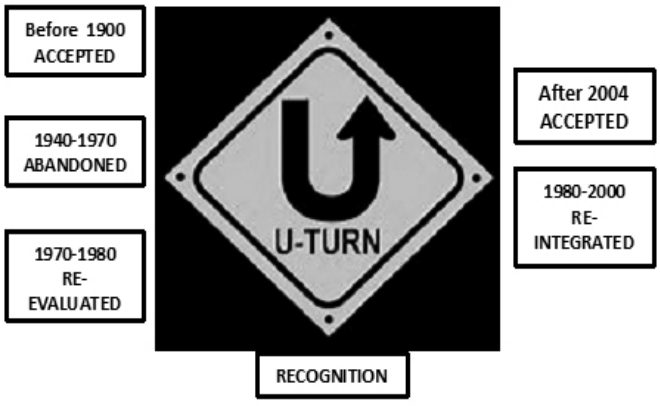

Fig. 1. The great U-turn of medicinal herbs

Modern evidence-based phytotherapy is a very complex field which deals with the exploration of the pharmacological properties of medicinal plants through very thorough research projects, including gathering of worldwide data in reviews and monographs as well as clinical studies. In order to obtain reliable, reproducible, standardized evidence-based information, phytocompounds have to

be identified and their metabolites analyzed. Studies should focus on the several types of activities exhibited by these metabolites.

Ancient texts, European or Ayurvedic, describing thousands of single or poly-herbal formulations which have been in therapeutic use for a long time are of course precious sources of information for modern pharmacology. Yet, pharmaco-epidemiological evidence must be generated to support both their efficacy and safety. In time, nomenclature, cultivation conditions and ways of processing of plants have changed, so re-evaluation is necessary (Brand, 2014).

Drug discovery and development need not always be confined to new molecular entities. Reverse pharmacology, a novel, promising approach to herbal drug development, can fast-track drug development by selecting herbs that are already used in traditional healing systems and also offer a smart strategy for the development of rational synergistic botanical formulations. Rationally designed, carefully standardized, these drugs can be further evaluated using both exploratory clinical studies and experimental studies in order to offer explanations for the mechanisms that lead to their clinical activity (Patwardhan and Mashelkar, 2009).

In terms of safety, the toxicity of phytocompounds has to be very carefully assessed. Prolonged and apparently safe use of herbs has often been considered as evident, which has led to the neglect of safety assessment. As evidence of the toxicity of some herbal products has accumulated over time, it is important to develop this research field. There is an obvious need for standardization of materials, methods and measures for preparation, preservation, presentation and administration of herbal drugs.

Nowadays, conventional medicine can no longer ignore herbal medicine, even if the modern solid knowledge about it is still scarce if not, in some cases, non-existent. In the developed countries, the current "bio" trend of replacing synthetic drugs with phytotherapy has led to a constant rise of the sales figures of herbal medicines. There is also a growing interest in the use of herbal medicines as multi-component agents to modulate the immune system. Research has to be pursued, with regard to potential for healing, rather than profit (de Vos, 2010).

In the light of this new evidence-based concept, clinical up-to-date studies are compulsory, in order to assess the efficacy or the safety of herbal remedies (Rees, 2001). So far, only a few controlled clinical trials of antibacterial herbal medicines have been published, most of them being methodologically weak. It is nevertheless time for the fundamental principles and approaches of the traditional systems to acquire a solid scientific validation, based on the standards of modern pharmacology and bioethics. The development of evidence-based phytotherapy will be of much help in the process of evolving from an ideological overestimation of the power of nature to a scientifically proved option for the treatment of many disorders, including infectious diseases.

Tables 1 and 2 show ancient-modern concordance with respect to plant effectiveness in the healing of several conditions. Table 1 emphasizes "lucky strikes": ancient herbs described along history for specific ailments with modern evidence-based pharmacological action. In Table 2 herbs are presented under their planetary ruler, as described in the time of Hildegard for Bingen or of Culpeper. Modern studies have almost forgotten the astrological influence on plants, focusing mainly on the phytocompounds and their mechanisms of action. Nevertheless, ruled or not by planets, the biological action of the plants seems to be consistent in time.

Laboratory and clinical evaluation of herbs and their active principles are on their way. So far, the research results have been very heterogeneous, due to lack of regulations in this field. New approaches are needed.

The first decade of this millennium was surprisingly poor in trials, and when these trials were performed they showed obvious signs of weakness and lacked randomization. The second decade of this century has been much more fruitful in achievements in the field, with clinical studies of the efficacy of several plant extracts. Table 3 states just a few examples, selected from literature, of promising results regarding the use of bioactive herbal compounds in the treatment of problematic infectious diseases, mainly due to drug-resistant bacteria. The aim of all these studies is to contribute to the process of combating microbial resistance, by switching from phytocompounds to phytodrugs.

To conclude, traditional medical thinking worldwide was the starting point for modern pharmacology. Herbs and medical recipes recorded in the past are worth being carefully studied, and research into the bioactive compounds of the most prominent herbal substances of the different pharmacopoeias conducted. A cross-cultural ethnopharmacological database, if achieved, could link

Table 1. Examples of ancient – modern concordance in the use of herbals for alleviating / treating symptoms of infectious diseases

Plant/Herb	Ebers Papyrus, cca. 1550 BC (Sutherland, 2016)	Nicholas Culpeper (1653) (Culpeper, 1995)	Evidence-based medicine (21st century literature reference)
Aloe (*Aloe vera*)	Burns, ulcers, skin diseases, allergies	Hot in the 2nd degree, and dry in the 3rd; heals wounds, closes up old ulcers, good against inflammation, hurts, cures sore mouths, sore gums, sore throat	Gupta and Malhotra, 2012
Bayberry (*Myriaceae*)	Diarrhea, hemorrhoids, ulcers	Takes away the marks of the skin and flesh; good for pains in the bowel from wind and cold griefs of the stomach	Silva *et al.*, 2015.
Carraway, fennel, cumin (*Carum carvi*)	Soothed digestion, breath freshener	Emenagogue, carminative, diuretic (hot 3rd degree, dry 1st degree)	Sachan *et al.*, 2016.
Dill (*Anethum graveolens*)	Laxative and diuretic properties	Warms or dissolves humors and imposthumes, stays the belly and stomach from casting	Altameme *et al.*, 2017.
Fenugreek (*Trigonella foenum-graecum L.*)	Respiratory disorders; stomach cleansing, calming of liver and pancreas	Heat and dry in the 1st degree, helps suppure.	Thomas, 2006.
Frankincense (*Boswellia***)**	Infections of throat, larynx; stops bleeding and vomiting	Heats and binds, fills up old ulcers and flesh, stops bleeding	Al-Yasiry and Kiczorowska, 2016.
Liquorice (*Glycyrrhiza glabra*)	Mild laxative, expels phlegm, and alleviates chest and breathing problems	Soothes respiration (hot & moist 1st degree)	Wang *et al*., 2015.
Onion (*Allium cepa)*	Prevents colds and addresses problems of the heart	Helps an inveterate cough and expectorates the tough phlegm	Teshika *et al*., 2018.
Parsley (*Petroselinum crispum*)	Diuretic	Good for cuts; diuretic, carminative, opens obstruc-tions (hot and dry 2nd degree)	Agyare *et al.*, 2017.
Thyme (*Thymus*)	Pain reliever	Purges the body of phlegm; eases pain	Dauqan and Abdullah, 2017.

Table 2. Medieval herbs, by planetary ruler, used for treating fever, skin, intestinal or respiratory disorders, for which modern pharmacological studies revealed concordant anti-bacterial, anti-inflammatory and anti-oxidant effects

Planetary ruler	Plant	Clinical destination	Modern evidence-based references
Mars	Garlic (*Allium sativum*)	Abscesses, skin disorders with pus	Kyung, 2012
	Barberry (*Berberis*)	Dysentery	Joshi *et al.*, 2011
	Monk's rhubarb (*Rhumex alpinus*)	Diarrhoea, dysentery	Ozturk and Ozturk, 2007
Jupiter	Cinquefoil (*Potentilla*)	Abscesses, skin disorders with pus; diarrhoea	Tomczyk and Latte, 2009
	Water agrimony (*Bidens tripartite*)	Abscesses, skin disorders with pus	Al-Snafi, 2015
	Dandelion (*Taraxacum*)	Abscesses, skin disorders with pus	Qian *et al*., 2014
	Sage (*Salvia officinalis*)	Abscesses, skin disorders with pus	Ghorbani and Esmaeilizadeh, 2017
	Gilliflower (*Dianthus caryophyllus*)	Fever	Al-Snafi, 2017
Saturn	Oats (*Avena sativa*)	Abscesses, skin disorders with pus	Perrelli *et al.*, 2018
	Fleawort (*Plantago*)	Abscesses, skin disorders with pus	Adom *et al.*, 2017
	Flaxseed (*Linum usitatissimum*)	Diarrhoea	Palla *et al.*, 2015
	Hemp (*Cannabis sativa*)	Diarrhoea	Hasenoehrl *et al.*, 2017
Moon	Chickweed (*Stellaria media*)	Abscesses, skin disorders with pus	Bae *et al.*, 2018
Mercury	Dill (*Anethum graveolens)*	Abscesses, skin disorders with pus; diarrhoea	Altameme *et al.*, 2017
	Scabious (*Scabiosa arenaria*)	Abscesses, skin disorders with pus	Besbes Hlila *et al.*, 2016
	Clover (*Trifolium*)	Abscesses, skin disorders with pus	Renda *et al.*, 2013
	Liquorice (*Glycyrrhiza glabra*)	Upper respiratory tract infections	Kuang *et al.*, 2018
Venus	Winter cherry (*Withania somnifera*)	Abscesses, skin disorders with pus	Dar *et al.*, 2016
	Mallow (*Malva*)	Abscesses, skin disorders with pus	Gurbuz *et al.*, 2018
	Sorrel (*Rumex acetosa*)	Abscesses, skin disorders with pus	Orbán-Gyapai *et al.*, 2017
	Sanicle **(***Sanicula europaea*)	Respiratory disorders	Karagöz *et al.*,1999
	Violet (*Viola*)	Fever	Khan *et al*., 2017
	Plantain (*Plantago major*)	Diarrhoea	Neamsuvan and Ruangrit, 2017
Sun	Mistletoe (*Viscum album*)	Abscesses, skin disorders with pus	Nazaruk and Orlikowski, 2015
	Tormentil (*Potentilla erecta*)	Diarrhea and dysentery	Triantafillidis *et al.*, 2016
	Marigold (*Tagetes*)	Fever	Salehi *et al.*, 2018

past to present and facilitate an up-to-date analysis using modern technologies and modern approaches. Exploration of worldwide herbal medicines with modern scientific validation might illustrate a "from tradition to trend" approach. Herbal medicine is one of the facets of unconventional alternative integrative medicine. Its philosophical, cultural and historical aspects make it pretty much part of the art of healing. And, after all, in a very pragmatic century, connecting once again with plants and planets might possibly help us better understand the ways of the world.

Table 3. Selection of clinical studies testing the efficacy of herbs in severe infectious diseases

Herb	Traditional use	Reference	Clinical study description / reference	Outcome
Rhizoma Anemarrhenae (Shen nong)	Nourishes the yin and checks virtual fire; acts on the kidney meridian.	http://www.shen-nong.com	Zhang, 2013 Chinese clinical study was performed on patients with recurrent UTIs with pandrug resistant strains refractory to Western medicine treatment.	The study results were considered excellent, in terms of significant symptomatic relief, lower recurrence rate, and lack of side-effects when compared with antibiotic treatment. Further research will have to select the precise metabolites responsible for these actions and study them thoroughly.
Cortex Phellodendri Chinensis (Huáng bǎi)	Clears heat and dries dampness, drains fire and resolves toxins	Flaws, 1999		
Angelica sinensis (Dong Quai)	Tonifies the qi, releases the exterior wind cold	https://theory.yinyanghouse.com		
Rehmannia glutinosa Libosch (Sheng Di huang)	Nourishes the yin, cools the blood	https://theory.yinyanghouse.com		
Wolfiporia cocos (China root, fu ling)	Drains dampness	https://theory.yinyanghouse.com		
Salvia miltiorrhiza (red sage, dan shen)	Invigorates Blood	https://theory.yinyanghouse.com		
Rheum rhabarbarum (Rhubarb, Dàhuáng)	Drains downward	https://theory.yinyanghouse.com		
Polygonum aviculare L. (knotgrass, bian xu),	Influences the bladder, by clearing damp-heat and promoting urination.	http://www.shen-nong.com		
Dianthus superbus (qu mai)	Influences the bladder, by clearing damp-heat and promoting urination.	http://www.shen-nong.com		
Talcum (sacred lotus, hua shi)	Promotes urination and drains heat from the bladder	http://www.shen-nong.com		

Commiphora molmol (myrrh, oleo-gum resins)	Heating, soporific, agglutinative, desiccative and astringent properties. Helps with chronic cough, pain of the side and chest. Used for healing wounds, including bone wounds, facial eruptions and afflictions of the ear.	(de Vos, 2010).	Abdallah *et al.*, 2009	Several phytocompounds showed good *in vitro* activity against methicillin-resistant *Staphylococcus aureus* (MRSA) strains.
Boswellia papyrifera (frankincense, oleo-gum resins)	Febrifuge, treats leprosy. Its resin is ten times more potent than that of related species.	Fitchl and Admasu, 1994. Tucker, 1986	Abdallah *et al*., 2009	
Tabernaemontana alternifolia (stem-bark)	Used to treat skin diseases.	Duraipandiyan *et al.,* 2006	Marathe *et al.*, 2013	
Piper betle (betel) leaves	Cool leaf, relieves hot illnesses, heals wounds	Ahuja and Ahuja, 2011	Valle Jr. *et al.*, 2015	
Flos lonicerae (Jin yin hua),	Clears heat and relieves toxicity	http://www.shen-nong.com	Cai *et al.*, 2017 Testing for the effectiveness of Chinese herbal medicines combined with antibiotics in treating infections due to extensively drug-resistant strains (XDR) of *Pseudomonas aeruginosa*, *Acinetobacter baumannii*, *Klebsiella pneumoniae* or *Escherichia coli*.	Herbal medicines combined with antibiotics achieved more desirable effectiveness in treating infections due to extensively drug-resistant bacteria (XDR) compared with antibiotic monotherapy. The outcome was more desirable in improving the temperature, WBC count and neutrophil level.
Radix Angelicae Sinensis (Dang gui),	Tonifies blood	http://www.shen-nong.com		
Radix Astragali seu Hedysari (Huang qi),	Tonifies qi	http://www.shen-nong.com		
Radix Paeoniae Rubra (Chi shao),	Invigorates blood	http://www.shen-nong.com		
Radix Rehmanniae Recens (Sheng di huang)	Cools the blood	http://www.shen-nong.com		
Fructus Gardeniae (Zhi zi)	Drains fire	http://www.shen-nong.com		
Azorella compacta,	Used to treat colds and pains, asthma or bronchitis	Wickens, 1995	Gupta *et al*., 2017 Testing of *in vitro* activity against *M. tuberculosis* multi drug-resistant (MDR) strains	Phytomolecules acting synergistically with standard anti-TB drugs may enhance the bactericidal action of current anti-TB drugs at a lower concentration.
Citrullus colocynthis,	Used to treat asthma and bronchitis.	Hussain *et al.*, 2014		
Curcuma longa,	Used for treating cough (including whooping cough),	Gupta SC, 2017, Lelli *et al*., 2017		
Justicia adhatoda, (Malabar nut)	Used to treat dry cough, hoarseness and laryngeal pain, paroxysmal cough, severe dyspnea, bronchial catarrh.	Patil, 2005		
Larrea tridentate (creosote bush)	Used to treat common cold and fever	Navarro *et al.*, 1996		

References

Abdallah, E. M., A. S. Khalid, N. Ibrahim (2009). Antibacterial activity of oleo-gum resins of *Commiphora molmol* and *Boswellia papyrifera* against methicillin resistant *Staphylococcus aureus* (MRSA). *Sci. Res. Essay.* **4**: 351-356.

Adom, M. B., M. Taher, M. F. Mutalabisin, M. S. Amri, M. B. Abdul Kudos, M. W. A. Wan Sulaiman, P. Sengupta, D. Susanti (2017). Chemical constituents and medical benefits of *Plantago* major. *Biomed. Pharmacother.* **96**: 348-360.

Agyare, C., T. A. Agana,Y. D. Boakye, J. A. Apenteng (2017). *Petroselinum crispum*: a Review. In Kuete R (ed.), Medicinal Spices and Vegetables from Africa, 1st ed., 2017, Elsevier, pp. 527-547.

Ahuja, S. C., U. Ahuja (2011). Betel leaf and betel nut in lndia: history and uses. *Asian Agri-History* **15**: 13-35.

Alamgir, A. N. M. (2017). Therapeutic Use of Medicinal Plants and Their Extracts: Volume 1, Pharmacognosy, Springer International Publishing, pp. 38-40.

AlRawi, S. N., A. Khidir, M. S. Elnashar, H. A. Abdelrahim, A. K. Killawi, M. M. Hammoud, M. D. Fetters (2017). Traditional Arabic & Islamic medicine: validation and empirical assessment of a conceptual model in Qatar, *BMC Complement. Altern. Med.* **17**: 157.

Al-Snafi, A. E. (2015). Chemical constituents and pharmacological importance of *Bidens tripartitus* - a review. *J. Pharm. Sci. Res.* **5**: 257-263.

Al-Snafi, A. E. (2017). Chemical contents and medical importance of *Dianthus caryophyllus* - A review. *IOSR J. Pharm.* **7**: 61-71.

Altameme, H. J., I. H. Hameed, L. Fadhil (2017). *Anethum graveolens:* physicochemical properties, medicinal uses, antimicrobial effects, antioxidant effect, anti-inflammatory and analgesic effects: A Review. *Intl. J. Pharm. Qual. Ass.* **8**: 88-91.

Al-Yasiri, A. R., B. Kiczorowska (2016). Frankincense-therapeutic properties. *Postepy. Hig. Med. Dosw.* **70**: 380-391.

Bae, S. J., J. W. Choi, B. J. Park, J. Lee, E. K. Jo, Y. H. Lee, S. B. Kim, J. M. Yuk (2018). Protective effects of a traditional herbal extract from *Stellaria dichotoma* var. *lanceolata* against *Mycobacterium abscessus* infections. *PLoS One* **13**: e0207696.

Besbes Hlila, M., H. Mosbah, K. Majouli, A. Ben Nejma, H. Ben Jannet, M. Mastouri, M. Aouni, B. Selmi (2016). Antimicrobial activity of *Scabiosa arenaria* Forssk. Extracts and pure compounds using bioguided fractionation. *Chem. Biodivers.* **13**: 1262-1272.

Brand, E. (2014). Changes in herbal medicines from ancient times to the present. *Acupuncture Today* **15**, Article ID: 32908.

Cai, Y., Q. Zhang, Y. Fu, L. Li, N. Zhao, A. Lu, Q. Liu, M. Jiang (2017). Effectiveness of Chinese herbal medicine combined with Antibiotics for extensively drug-resistant *Enterobacteria* and Nonfermentative bacteria infection: Real-life experience in a retrospective cohort. *Biomed. Res. Int*. Article ID 2897045.

Culpeper's Complete Herbal. A list of natural remedies for ancient ills. Wordsworth Editions Ltd., 1995.

Darp, P. A., L. R. Singh, M. A. Kamal, T. A. Dar (2016). Unique medicinal properties of *Withania somnifera*: phytochemical constituents and protein component. *Curr. Pharm. Des.* **22**: 535-540.

Dauqan, E. M. A., A. Abdullah (2017). Medicinal and functional values of thyme (*Thymus vulgaris* L.) herb. *J. Appl. Biol. Biotechnol.* **5**: 017-022.

de Vos, P. (2010). European materia medica in historical texts: longevity of a tradition and implications for future use. *J. Ethnopharmacol.* **132**: 28-47.

Duraipandiyan, V., M. Ayyanar, S. Ignacimuthu (2006). Antimicrobial activity of some ethnomedicinal plants used by Paliyar tribe from Tamil Nadu, India. *BMC Complement. Altern. Med.* **6**: 35.

Fitchl, R., A. Admasu (1994). Honeybee Flora of Ethiopia. Margraf Verlag, Weikersheim, Germany, 510 p.

Flaws, B. (1999). 260 Essential Chinese Medicine, 1st Ed., Blue Poppy Press.

Gangadharan, N. (1982). The State of Ayurveda in the eighteenth and nineteenth centuries. *Indian J. Hist. Sci.* **17**: 154-163.

Ghorbani, A., M. Esmaeilizadeh (2017). Pharmacological properties of *Salvia officinalis* and its components. *J. Tradit. Complement. Med.* **7**: 433-440.

Gupta, S. C., A. B. Kunnumakkara, B. B. Aggarwal (2017). Curcumin, the Holistic Avant-Garde. In: Innovative Approaches in Drug Discovery. Ethnopharmacology, Systems Biology and Holistic Targeting, Patwardhan B. and Chaguturu R. (eds.) pp. 343-349.

Gupta, V. K., M. M. Kumar, D. Bisht, A. Kaushik (2017). Plants in our combating strategies against *Mycobacterium tuberculosis*: progress made and obstacles met. *Pharm. Biol.* **55**: 1536-1544.

Gupta, V. K., S. Malhotra (2012). Pharmacological attribute of *Aloe vera*: Revalidation through experimental and clinical studies. *Ayu* **33**: 193-196.

Gurbuz, I., B. Ozcelik, T. Gunbatan, E. K. Akkol, M. Sahinoz, G. Akaydin (2018). Antibacterial, antifungal and enzyme inhibitory effects of selected plants from Turkey. *Pak. J. Pharm. Sci*. **31**: 2471-2476.

Hasenoehrl, C., M. Storr, R. Schicho (2017). Cannabinoids for treating inflammatory bowel diseases: where are we and where do we go? *Expert Rev. Gastroenterol. Hepatol.* **11**: 329-337.

Heiss, A. G., K. Oeggl (2008). The plant macro-remains from the Iceman site (Tisenjoch, Italian-Austrian border, eastern Alps): new results on the glacier mummy's environment. *Veget. Hist. Archaeobot.* **18**: 23-35.

http://www.shen-nong.com/eng/herbal

https://theory.yinyanghouse.com/ - Chinese Herbs and Herbal Formulas

Hussain, A. I., H. A. Rathore, M. Z. A. Sattar, S. A. S. Chatha, S. D. Sarker, A. H. Gilani (2014). *Citrullus colocynthis* (L.) Schrad (bitter apple fruit): A review of its phytochemistry, pharmacology, traditional uses and nutritional potential. *J. Ethnopharmacol.* **155**: 54-66.

Jaiswal, Y., Z. Liang, Z. Zhao (2016). Botanical drugs in Ayurveda and traditional Chinese medicine. *J. Ethnopharmacol.* **194**: 245-259.

Joshi, P. V., A. A. Shirkhedkar, K. Prakash, V. L. Maheshwari (2011). Antidiarrheal activity, chemical and toxicity profile of *Berberis aristata. Pharm. Biol.* **49**: 94-100.

Karagöz, A., N. Arda, N. Gören, K, Nagata, A. Kuru (1999). Antiviral activity of *Sanicula europaea* L. extracts on multiplication of human parainfluenza virus type 2. *Phy-*

tother. Res. **13**: 436-438.
Khan, M. S., A. Hamid, M. Akram, S. B. Mustafa, A. Sami, S. M. A. Shah, K. Usmanghani (2017). Antipyretic potential of herbal coded formulation (Pyrexol). *Pak. J. Pharm. Sci.* **30**: 195-198.
Kuang, Y., L. Bin, J. Fan, X. Qiao, M. Ye (2018). Antitussive and expectorant activities of licorice and its major compounds. *Bioorg. Med. Chem.* **26**: 278-284.
Kyung, K. H. (2012). Antimicrobial properties of allium species. *Curr. Opin. Biotechnol.* **23**: 142-147.
Lelli, D., A. Sahebkar, T. P. Johnston, C. Pedone (2017). Curcumin use in pulmonary diseases: State of the art and future perspectives. *Pharmacol. Res.* **115**: 133-148.
Lietava, J. (1992). Medicinal plants in a Middle Paleolithic grave Shanidar IIV? *J. Ethnopharmacol.* **35**: 263-266.
Mahdizadeh, S., M. K. Ghadiri, A. Gorji (2015). Avicenna's canon of medicine: a review of analgesics and anti-inflammatory substances. *Avicenna J. Phytomed.* **5**: 182-202.
Marathe, N. P., M. H. Rasane, H. Kumar, A. A. Patwardhan, Y. S. Shouche, S. S. Diwanay (2013). *In vitro* antibacterial activity of *Tabernaemontana alternifolia* (Roxb) stem bark aqueous extracts against clinical isolates of methicillin resistant *Staphylococcus aureus. Ann. Clin. Microbiol. Antimicrob.* **12**: 26.
Mukherjee, P. K., A. Wahile (2006). Integrated approaches towards drug development from Ayurveda and other Indian system of medicines. *J. Ethnopharmacol.* **103**: 25-35.
Mukherjee, P. K., R. K. Harwansh, S. Bahadur, S. Banerjee, A. Kar, J. Chanda, S. Biswas, S. M. Ahmmed, C. K. Katiyar (2017). Development of Ayurveda - tradition to trend. *J. Ethnopharmacol.* **197**: 10-24.
Navarro, V., M. L.Villarreal, G. Rojas, X. Lozoya (1996). Antimicrobial evaluation of some plants used in Mexican traditional medicine for the treatment of infectious diseases. *J. Ethnopharmacol.* **53**: 143-147.
Nazaruk, J., P. Orlikowski (2015). Phytochemical profile and therapeutic potential of *Viscum album* L. *Nat. Prod. Res.* **30**: 373-385.
Neamsuvan, O., T. Ruangrit (2017). A survey of herbal weeds that are used to treat gastrointestinal disorders from southern Thailand: Krabi and Songkhla provinces. *J. Ethnopharmacol.* **196**: 84-93.
Orbán-Gyapai, O., E. Liktor-Busa, N. Kúsz, D. Stefkó, E. Urbán, J. Hohmann, A. Vasas (2017). Antibacterial screening of *Rumex* species native to the Carpathian Basin and bioactivity-guided isolation of compounds from *Rumex aquaticus*. *Fitoterapia* **118**: 101-106.
Oumeish, O. Y. (1998). The philosophical, cultural, and historical aspects of complementary, alternative, unconventional, and integrative medicine in the old world. *Arch. Dermatol.* **134**: 1373-1386.
Ozturk, S., A. Ozturk (2007). Antibacterial Activity of Aqueous and Methanol Extracts of *Rumexalpinus* and *Rumexcaucasicus*. *Pharm. Biol.* **45**: 83-87.
Palla, A. H, N. A. Khan, S. Bashir, N. Ur-Rehman, J. Iqbal, A. H. Gilani (2015). Pharmacological basis for the medicinal use of *Linum usitatissimum* (Flaxseed) in infectious and non-infectious diarrhea. *J. Ethnopharmacol.* **160**: 61-68.
Patil, J. D. (2005). Textbook of Applied Materia Medica, B. Jain Publishers, Delhi, India.
Patwardhan, B., R. A. Mashelkar (2009). Traditional medicine-inspired approaches to drug discovery: can Ayurveda show the way forward? *Drug Discov. Today* **14**: 804-811.
Perrelli, A., L. Goitre, A. M. Salzano, A. Moglia, A. Scaloni, S. F. Retta (2018). Biological activities, health benefits, and therapeutic properties of Avenanthramides: from skin protection to prevention and treatment of cerebrovascular diseases. *Oxid. Med. Cell. Longev.* Article ID 6015351.
Qian, L., Y. Zhou, Z. Teng, C. L. Du, C. Tian (2014). Preparation and antibacterial activity of oligosaccharides derived from dandelion. *Intl. J. Biol. Macromol.* **64**: 392-394.
Rees, L. (2001). Integrated medicine. *BMJ* **322**: 119-120.
Renda, G., F. N. Yalçın, E. Nemutlu, E. K. Akkol, I. Süntar, H. Keleş, H. Ina, I. Çalış, T. Ersöz (2013). Comparative assessment of dermal wound healing potentials of various *Trifolium* L. extracts and determination of their isoflavone contents as potential active ingredients. *J. Ethnopharmacol.* **148**: 423-432.
Saad, B., O. Said (2011). Greco-Arab and Islamic Herbal Medicine: Traditional System, Ethics, Safety, Efficacy, and Regulatory Issues, Wiley.
Sachan, A. K. R., D. R. Das, M. Kumar (2016). *Carum carvi* - an important medicinal plant. *J. Chem. Pharm. Res.* **8**: 529-533.
Salehi, B., M. Valussi, M. F. Bezerra Morais-Braga, J. N. Pereira Carneiro, A. L. A. B. Leal, H. D. Melo Coutinho, S. Vitalini, D. Kręgiel, H. Antolak, M. Sharifi-Rad, N. C. Cirone Silva, Z. Yousaf, M. Martorell, M. Iriti, S. Carradori, J. Sharifi-Rad (2018). *Tagetes* spp. essential oils and other extracts: chemical characterization and biological activity. *Molecules* **23**: E2847.
Silva, B. J. C., A. M. L. Seca, M. do Carmo Barreto, D. C. G. A. Pinto (2015). Recent breaktroughs in the antioxidant and anti-inflammatory effects of *Morella* and *Myrica* species. *Int. J. Mol. Sci.* **16**: 17160-17180.
Sun, D.-Z., S.-D. Li, Y. Liu, Y. Zhang, R. Mei, M.-H. Yang (2013). Differences in the origin of philosophy between Chinese medicine and western medicine: exploration of the holistic advantages of Chinese medicine. *Chin. J. Integr. Med.* **19**: 706-711.
Sutherland, A. (2016). The Ebers Papyrus - Most Famous Plant Medicine "Encyclopedia" Of Ancient Egypt, on http://www.ancientpages.com/2016/02/03/
Teshika, J. D., A. M. Zakariyyah, T. Zaynab, G. Zengin, K. R. Rengasamy, S. K. Pandian, M. M. Fawzi (2018). Traditional and modern uses of onion bulb (*Allium cepa* L.): A systematic review. *Crit. Rev. Food Sci. Nutr.* **58**: 1-75.
Thomas, J. E. (2006). Identification of *Trigonella foenum graecum* antimicrobial activity. *Can. J. Plant Sci*. **86**: 727-732.
Tomczyk M., K. P. Latté (2009). *Potentilla* - A review of its phytochemical and pharmacological profile, *J. Ethnopharmacol.* **122**: 184-204.
Triantafillidis, J. K., A. Triantafyllidi, C. Vagianos, A. Papalois (2016). Favorable results from the use of herbal and plant products in inflammatory bowel disease: evidence from experimental animal studies. *Ann. Gastroenterol.* **29**: 268-281.
Tucker, A. (1986). Frankincense and myrrh. *Econ. Bot.* **40**: 425-433.
Uehleke, B., W. Hopfenmueller, R. Stange, R. Saller (2012). Are the correct herbal claims by Hildegard von Bingen only lucky strikes? A new statistical approach. *Forsch. Komplementmed.* **19**: 187-190.

Valle Jr., D. L., J. I. Andrade, J. J. M. Puzon, E. C. Cabrera, W. L. Rivera (2105). Antibacterial activities of ethanol extracts of Philippine medicinal plants against multidrug-resistant bacteria. *Asian Pacific J. Trop. Biomed.* **5**: 532-540.

Walcott Emmart, E. (1940). The Badianus Manuscript (Codex Barberini Latin 241): An Aztec Herbal of 1552, Johns Hopkins University Press, Baltimore.

Wang, L., R. Yang, B. Yuan, Y. Liu, C. Liu (2015). The antiviral and antimicrobial activities of licorice, a widely-used Chinese herb. *Acta Pharm. Sin. B* **5**: 310-315.

WHO/EDM/TRM/2000.1. General Guidelines for Methodologies on Research and Evaluation of Traditional Medicine. World Health Organization, Geneva, 2000.

Wickens, G. E. (1995). Llareta (*Azorella compacta*, *Umbelliferae*); A review. *Econ. Bot.* **49**: 207-212.

Zhang, N., L. Huang, S. Liu, Y. Wang, Y. Luo, X. Jin, J. G.. Ke, J. Chen, X. Yuan, Z. Chen (2013). Traditional Chinese medicine: an alternative treatment option for refractory recurrent urinary tract infections. *Clin. Infect. Dis.* **56**: 1355.