ANNALI DI BOTANICA
Ann. Bot. (Roma), 2024, 14: 127–156
annalidibotanica.uniroma1.it | E-ISSN 2239-3129 | ISSN 0365-0812

HISTORICAL USE OF MEDICINAL PLANTS AND FUTURE POTENTIAL: FROM PHYTOTHERAPY TO PHYTOCHEMICALS

Claro A.E.[1,2*], Palanza C.[3], Mazza M.[4], Muti Schuenemann G.E.U.[5], Rigoni M.[1], Pontecorvi A.[6], Janiri L.[4], Pitocco D.[2], Muti P.[1]

[1]*Department of Biomedical, Surgical and Dental Sciences, University of Milan, Milan, Italy*
[2]*Diabetes Care Unit, Department of Medical and Surgical Sciences, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Rome, Italy, Università Cattolica del Sacro Cuore, Rome, Italy*
[3]*Department of Environmental Biology, Sapienza University of Rome, Italy*
[4]*Unit of Psychiatry, Department of Neurosciences, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy*
[5]*Health Research Methods, Evidence and Impact Department, McMaster University, Ontario, Canada*
[6]*Division of Endocrinology, Department of Endocrine-Metabolic and Dermo-Rheumatology, Fondazione Policlinico Universitario Agostino Gemelli IRCCS, Università Cattolica del Sacro Cuore, Rome, Italy*
**Corresponding Author Email: angelo.claro@unimi.it*

(Received 15 Sept 2023; received in revised form 20 Feb 2024; accepted 30 Apr 2024)

Abstract – Since prehistoric times, humans have understood that plants possessed healing properties. The knowledge of herbal medicine has been accumulated for millennia by traditional healers and has been passed down from generation to generation. Phytotherapy was used as the main therapy until the 18th century. Even today, between 40% and 80% of pharmaceuticals are phytochemicals or of plant origin and many of these have significantly changed or are still changing medical therapy. Most people in the world are or have been treated with phytochemicals or drugs derived from phytochemicals. Examples include antineoplastic agents (vinblastine, vincristine, etoposide, teniposide, paclitaxel, irinotecan, topotecan), antibiotics and antivirals (cephalosporins and oseltamivir), antiparasitic drugs (quinine and artemisinin), Intensive Care Unit (ICU) drugs (morphine, neuromuscular blockers, ephedrine), cardiovascular drugs (digoxin, quinidine, atropine, reserpine), antidiabetics (metformin), and many others. Many of these agents are included in the WHO list of essential medicines. Plant-derived medicines have changed human history, contributing fundamentally to the survival and improvement of our species' life expectancy. Phytochemicals, derived from interactions between plants and the environment, are substances often created over millennia. If humans had not drawn on these substances for medical therapy, they probably would never have been able to produce substances so complex and effective in treating disease. Since knowledge of the healing properties of plants is present in traditional medicines, ancient manuscripts should be studied as potential sources of contemporary pharmacotherapy. Unfortunately, in recent years several trends have started to threaten biodiversity and consequently also phytochemical resources. From this perspective, the "One Health" approach is further justified and could also encourage the discovery of new revolutionary phytochemicals.

Keywords: phytochemicals, phytotherapy, antineoplastic agents, hypoglycemic agents, one health, medicine chinese traditional.

Introduction

Since the prehistoric times, humans have understood that plants, in addition to their nutritional properties, possessed healing abilities (Halberstein, 2005; Kaur et al., 2019). Knowledge of the healing properties of plants, sought in the bark, seeds, and fruiting bodies, has been accumulated over millennia by traditional healers through trial and error, and has been passed down from generation to generation (Khan, 2014; Petrovska, 2012). Indeed evidence, in the form of written documents, monuments and even original medicines, indicates that medicinal plants represent the oldest and most widespread form of healing in human history (Khan, 2014; Petrovska, 2012). Plant medicine has been the basis of medicine (Hassan, 2015) in fact it was used as the main therapy until the 18th century (Halberstein, 2005). Herbal medicine declined in the 19th century, and only in the late 20th century did a renewed interest in herbal medicine begin (Ijinu et al., 2022).

doi: 10.13133/2239-3129/18564

Phytomedicine and Phytochemicals

French physician Henri Leclerc coined the term **phytomedicine** in 1913. The term phytomedicine or **phytotherapy** denotes a medical practice, recognized by official science, involving the use of botanical raw materials such as fruiting bodies or flowers, roots, bark, seeds, and leaves for medicinal and therapeutic purposes (Falzon & Balabanova, 2017). The phytotherapeutic effects of plants can be traced to combinations of so-called secondary metabolites present in the plant (Falzon & Balabanova, 2017; Guerriero et al., 2018). Unlike primary metabolites, which are directly required for plant growth, secondary metabolites, also called **phytochemicals**, mediate plant-environment interactions (Al-Khayri et al., 2023; Erb & Kliebenstein, 2020). Phytochemicals act by protecting plants from pathogens such as germs, fungi, insects, animals, and other threats (Dar et al., 2017), thus enabling plants to adapt and survive in their environment (Erb & Kliebenstein, 2020; Kaur et al., 2019). For this reason, phytochemicals have evolved in as biologically active compounds capable of bringing about pharmacological or toxicological effects in humans and animals (Iyer et al., 2023). There are three main groups of secondary metabolites in plants, namely terpenes, phenols, and nitrogen compounds (Al-Khayri et al., 2023; Erb & Kliebenstein, 2020; Twaij & Hasan, 2022).

Today, between 40% and 80% of pharmaceutical products are derived from plants (Fitzgerald et al., 2019; WHO, 2023b) and many of the landmark drugs are phytochemicals (or derivatives of phytochemicals) discovered in plants or fungi and have decisively changed the history of medicine, including modern medicine (just to name a few: antineoplastic agents, antibiotics and antiviral drugs, antiparasitic drugs, Intensive Care Unit (ICU) drugs, cardiovascular drugs, antidiabetics etc.) (Awosika, Below, et al., 2024). Furthermore according to data from the World Health Organization (WHO), in developing countries 80% of the population uses phytotherapy as the first source of treatment (Alves & Rosa, 2005; Aziz et al., 2018; International Agency for Research on Cancer, 2002). Even in developed countries, the use of traditional herbal medicines is a rapidly growing phenomenon. To give some examples, in China 30-50% of total drug consumption is represented by traditional herbal preparations (Aziz et al., 2018). In Nigeria, Ghana, Zambia and Mali, herbal medicines are used in 60% of cases as the first intervention in children suffering from malaria (Aziz et al., 2018). In Saudi Arabia 80% of people use herbal medicine for medications (Ullah et al., 2020). China is currently the most advanced country in terms of the number of publications on the use of medicinal plants in medicine, although all countries in the world have their own traditions in the use of medicinal plants in medicine (Fitzgerald et al., 2019; Liu et al., 2016; Lu et al., 2022). Today, herbal medicines are marketed in very different ways around the world. In Germany, for example, they are subject to the same efficacy, safety and quality criteria as other pharmaceutical products and are sold as "phytomedicines". In the United States, on the contrary, most herbal products are marketed as food supplements and are therefore not subject to efficacy, safety and quality criteria (International Agency for Research on Caner, 2002).

History of Phytotherapy

It is impossible to trace a complete history of the use of plants in the treatment of human diseases since it is as old as humankind and has been practiced in virtually all cultures. In fact numerous sources attest, with ample evidence, that primitive people used phytotherapy (Halberstein, 2005; Kaur et al., 2019; Kong et al., 2003). In all countries and ethnic groups analyzed around the world, organized and systematized traditional herbal remedies have been described by anthropologists and ethnobotanists (Halberstein, 2005). In ancient times, in Chinese, Indian, Egyptian, Native American and European cultures, the use of plants for healing purposes was widespread (Kaur et al., 2019). Written evidence of the use of phytotherapy can be found in Sumerian clay tablets dating back to 5,000 BC, in the Old Testament, in Egyptian papyri, in the books of the Greek physicians Hippocrates and in the works of the Roman writers Pliny, Dioscorides, Galen, Theophrastus and others (Šantić et al., 2017). In numerous ancient cultures these preparations were used both as a cure for physical illnesses and as psychoactive substances (Merlin, 2003). This ancient knowledge through the Middle Ages, Renaissance and modern history has been passed down to the present day. In the 19th century there was a breakthrough, with the beginning of the extraction of phytochemicals from plants and the understanding of the action of individual molecules on the organism (Kaur et al., 2019).

Zoopharmacognosy

It would appear that humans learned to use plants to treat diseases both from direct experiences by gaining knowledge through trial and error (for example, humans who used plants in their diet began to discover that they could have side effects, be toxic, or sometimes improve certain symptoms (Šantić et al., 2017)) but also by observing how animals used plants for healing purposes (De la Fuente et al., 2022; Halberstein, 2005; Huffman, 1997). This second hypothesis

was described as early as 2000 BC in the Rigveda, one of the oldest Indian texts, which states that humans acquired knowledge about differentiating edible from poisonous plants by observing animals (Prasathkumar et al., 2021). Today, indeed, it is known that primates use some plants as treatments that act as anti-inflammatories, immunostimulants, analgesics, antimicrobials, antidiarrheals, digestive aids, and fertility regulators (Huffman, 1997). Furthermore, humans, gorillas, chimpanzees, and monkeys use the same plants to manage similar diseases and health problems (Halberstein, 2005). For example, the plant Vernonia amygdalina is used by chimpanzees to treat parasitic infections. The same plant is used by the human inhabitants of Tanzania to cure fever (Huffman, 1997). Not only primates, but also other animals, use fruits, leaves, bark, roots and flowers of plants for both curative and preventive purposes (Šantić et al., 2017). Precisely, to study the activity of sick animals that seek remedies in nature, a field of scientific study was created, **Zoopharmacognosy** (Shurkin, 2014). Even today, the observation of self-medication by animals can be a source of discovery of new drugs (Domínguez-Martín et al., 2020; Hardy, 2021). For example very recently, a Sumatran orangutan was described treating an open wound on its cheek with a poultice made from a medicinal plant (Vaidyanathan, 2024). This behavior was the first documented case of a wild animal treating a wound with a plant species known to contain biologically active substances and provides new information on the origins of human wound care, as well as providing research insights into the healing properties of the plant (Laumer et al., 2024). Below we illustrate how the use of plants for healing purposes has been practiced throughout history in some human cultures.

India

Traditional Indian medicine or Ayurveda (a Sanskrit word literally meaning "knowledge of life"), which dates to 6000 BC. approximately, contains, in the Atharvaveda text collection, among the oldest references to the medicinal use of plants in Asia (Ijinu et al., 2022; Khan, 2014; Prasathkumar et al., 2021; Šantić et al., 2017). Ayurveda is a theory of the functioning of the human body, developed by the ancient Rishis of India, which defines man as composed of 7 fundamental tissues that work in harmony, while disease occurs due to the imbalance of these components (Ijinu et al., 2022; Khan, 2014). Ayurveda aims to achieve the prevention and cure of diseases by coordinating the connection between body and mind with the help of a vegetarian diet, use of medicinal herbs, physical exercise and meditation (International Agency for Research on Cancer, 2002). The properties of medicinal plants described in the Vedic literatures, particularly in the Rig Veda and the Atharvaveda, constitute the first written documents available in the history of Indian medicine (Ijinu et al., 2022; Petrovska, 2012). Regarding Ayurveda, the Susrutha Samhita and the Charaka Samhita are the most accepted texts on surgical and internal medicine aspects respectively (Ijinu et al., 2022). Ayurvedic medicine continued to develop until the Mughal period in India and began its decline during the regime of the Europeans (Ijinu et al., 2022). The Sushruta Samhita, dating back to the 4th-6th century BC, describes the medicinal values of around 700 plant species (Kaur et al., 2019; Khan, 2014; Loukas et al., 2010; Prasathkumar et al., 2021).

China

One of the oldest treatment systems is Traditional Chinese Medicine (TCM) which is unique in terms of theories, treatments and therapies (Khan, 2014). Fu Xi (2953 BC) is considered the pioneer of TCM (Khan, 2014). Later, emperors Shen Nung and Hong Ti, developed the system more significantly (Khan, 2014). The writings of Shen Nung, in 2838 BC, are considered between the oldest written documents providing guidelines on the treatment and use of medicinal plants (Šantić et al., 2017). The book "Pen Ts'ao",on root and herb, written by Emperor Shen Nung (3000 BC), lists 365 medicinal plants and their uses, including ginseng, jimsonweed, camphor, cinnamon and ephedrine, many of which are still in use as medicinal plants (Kaur et al., 2019; Petrovska, 2012). An author who made important contributions to TCM is Wang Tao (702-772). In his work "Waitai Miyao" described approximately 6,000 herbal prescriptions (Kopp et al., 2003). Another great Chinese physician and naturalist, Li Shizen, wrote an even more inclusive pharmacopoeia, Ben Ca Gang Mu, which was published in 1596. This work contains 1894 herbal preparations and is still used as a reference and guide for research and education in China (Khan, 2014). TCM was a knowledge passed down from generation to generation until the 1950s when it was introduced into university teaching (Khan, 2014). Although TCM also uses substances of mineral and animal origin to produce its treatments, the main source of remedies in this ancient form of medicine relies on substances of plant origin (International Agency for Research on Cancer, 2002). TCM consists of the clinical practice of a diagnosis followed by the prescription of a complex and often individualized remedy. To date, this type of medical approach is still widespread in China with

more than half of the population regularly using traditional remedies, especially in rural areas. Traditional remedies account for about a fifth of the entire Chinese pharmaceutical market (International Agency for Research on Cancer, 2002; Xu et al., 2021).

Mesopotamian

In Nippur Mesopotamia, in present-day Iraq, clay tablets dating back to 5000 BC were found, which described the use of plants for medicinal preparations (Khan, 2014; Šantić et al., 2017). These tablets, which constitute between the oldest written testimony of the use of plants as medicines contain the description of 12 medicines prepared using over 250 plants including myrrh, bay, opium, cumin, henbane and mandrake (Hassan, 2015; Kaur et al., 2019; Khan, 2014; Petrovska, 2012; Šantić et al., 2017). These plants and their phytochemical derivatives are still used today worldwide for medicinal purposes (Hassan, 2015; Kaur et al., 2019; Khan, 2014; Petrovska, 2012; Šantić et al., 2017). Further evidence of the use of plants for healing purposes was also found in Mesopotamia on clay tablets with cuneiform characters dating back to subsequent periods ranging from 2600 BC. to 1800 BC. These documents describe the uses of oils derived from myrrh, cedar, licorice, poppy, and cypress (Dar et al., 2017; Hassan, 2015; Prasathkumar et al., 2021).

Egyptians

In the period between 3000 and 6000 years ago, the Egyptians developed an elaborate and effective pharmacological collection obtained from natural resources (Halberstein, 2005). The medical knowledge of this people is demonstrated by writings found in tombs and papyri dating back to the Old Kingdom of Egypt (Hassan, 2015). The Ebers papyrus, written around 1550 BC, is the most important of these testimonies and describes the use of over 850 plants for medicinal purposes by the Egyptians (Attorre & Bruno, 2022; Hassan, 2015; Khan, 2014; Prasathkumar et al., 2021; Šantić et al., 2017). The Egyptians used plants such as mandrake, garlic, juniper, cannabis, aloe, pomegranate, castor, senna, garlic, onion, fig, willow, coriander, juniper, centaury and preparations such as wine and beer for medical purposes (Halberstein, 2005; Kaur et al., 2019; Petrovska, 2012). For example, mandrake was used to relieve pain and garlic was used to try to treat heart and circulatory disorders (Halberstein, 2005; Kaur et al., 2019; Petrovska, 2012). Herbal preparations were administered enterally, applied topically and administered by fumigation and vapor inhalation (Halberstein, 2005). It would also appear that the ancient Egyptians were the first to develop the concept of posology that is, to describe the use of specific dosages to be used for each individual drug (Attorre & Bruno, 2022).

Bible

In the Bible, specifically in the Old Testament, written in 1200 BC, and in the Jewish sacred book Talmud numerous medicinal plants are described (Hassan, 2015; Petrovska, 2012; Šantić et al., 2017). An example of the use of plants for healing purposes cited in the Bible is "poultice" (poultice, also called cataplasm, is a soft and moist mass, often heated and medicated, which is spread on a cloth on the skin to treat a sore, inflamed or painful part of the body (Yadav et al., 2021); these types of preparations, improved, are still used today to accelerate the healing of wounds especially of secondary intention (Nagappa & Cheriyan, 2001; Samiee-Rad et al., 2022) prepared with figs that Isaiah applied to Hezekiah to heal a wound (Attorre & Bruno, 2022).

Ancient Greek

Among the populations of the Mediterranean basin, knowledge of phytomedicine deepened further, from 3000 to 1500 years ago, in ancient Greece (Halberstein, 2005). Homer around 800 BC in the poems Iliad and Odyssey, described 63 plant species of Minoan, Mycenaean, Assyrian and Egyptian pharmacotherapy. Some of these plants were given the names of mythological characters from the Homeric poems. For example, the Elecampane Inula helenium (Inula helenium of the family Asteraceae) is named in honor of Helen, who was at the center of the Trojan War (Petrovska, 2012). Hippocrates, lived from 460 to 337 BC. (is considered the father of modern medicine because he was the first to have hypothesized that diseases did not derive from supernatural influences, but from disturbances of the normal physiology of the human body and the first to have based clinical reasoning on observation and clinical signs) used many herbal remedies in his practice (Kaur et al., 2019; Yapijakis, 2009). He highlights almost 400 samples of medicinal substances of plant origin based on their action on the organism (Hassan, 2015; Khan, 2014): for example he used wormwood and centaury against fever; garlic against intestinal parasites; opium, henbane, nightshade

and mandrake as narcotics; fragrant hellebore and alfalfa as emetics; spring onion, celery, parsley, asparagus and garlic as diuretics and finally oak and pomegranate as astringents (Petrovska, 2012). Theophrastus lived between 371 B.C. and 287 BC. and is considered the father of botanical science for his great merits in the classification and description of plants and medicinal plants (Petrovska, 2012). He wrote the first systematic treatise on pharmaceutical botany, De historia plantarum (Solinas, 2009) and the book De Causis Plantarum (Petrovska, 2012). In these works, he drew up a classification of over 500 medicinal plants. He seems to have been the first to describe that humans can become accustomed to the toxic action of plants through gradually increasing doses (i.e. drug tolerance) (Petrovska, 2012).

America

The healers of the Aztec and Mayan cultures of Mexico and Central America developed a vast and effective pharmacopoeia with medicines made from animals, minerals and especially plants. They knew the use of at least 132 medicinal herbs to treat specific ailments ranging from nosebleeds to gout and epilepsy. Remedies obtained from a combination of different herbal products were used against respiratory and gastrointestinal infections and some preparations were prescribed to prevent some diseases (Halberstein, 2005) .

Romans

Celsus (25 BC – 50 AD), described around 250 medicinal plants in his book "De re medica" (Hassan, 2015). Greek military physician, Dioscorides, wrote De Materia Medica and is considered the most important writer of phytomedicine of antiquity. Is indeed regarded as the "father of **pharmacognosy**" (the science that deals with the natural drugs obtained from organisms such as most plants, microbes, and animals) (Khan, 2014; Orhan, 2014; Petrovska, 2012; Šantić et al., 2017; Upton, 2022). He lived between 60 and 78 AD, was a military physician in the army of the Roman Empire under Nero and studied medicinal plants wherever he traveled with the Roman army (Petrovska, 2012). He is known to have written about over 600 healing plants (Halberstein, 2005). Dioscorides' treatise De Materia Medica has been used as a reference for phytotherapy in Europe for more than a millennium and translated into several languages (Hassan, 2015). Dioscorides described 944 medicines of which 657 were of plant origin. In addition to the external appearance, he described the collection method, where to find them, also the name in other languages, how to prepare the medicine and its therapeutic effect. Among the plants described in his work we find mainly plants with a mild effect, but there is no shortage of references to plants with a greater pharmacological effect such as those containing alkaloids (scented hellebore, false hellebore, poppy, buttercup, jimsonweed, henbane, nightshade). He described, for example, different uses of chamomile, which was used as an antiphlogistic to treat wounds, stings, burns and ulcers, and to clean and rinse eyes, ears, nose and mouth. He was also responsible for the false belief, also inherited from the Arabs, that chamomile had abortifacient properties. In Dioscorides we also find the description of the use of willow (from which acetylsalicylic acid derives) as an antipyretic (Petrovska, 2012). A contemporary of Dioscorides was Pliny the Elder (23 AD-79), who traveled through Germany and Spain and in his book "Historia naturalis" described about 1000 medicinal plants. The writings of Dioscorides and Pliny the Elder contained all the knowledge of the time on phytomedicine (LacusCurtius, retrieved 2024). Galen (131 AD-200 AD) wrote and compiled "De succedanus", the first list of interchangeable drugs with similar or identical action (even if this list is not valid from today's pharmacological point of view) (Elufioye & Badal, 2017). Furthermore, Galen introduced into therapy some plants that his predecessors did not know such as Uvae ursi folium as uroantiseptic, still used today with this same indication and as a mild diuretic (Petrovska, 2012).

The Arabs

After the fall of the Roman Empire, Arab scholars translated the books of Greek and Roman authors and made great advances in science and medicine. They were the first to divide the work of the physician (diagnosis and treatment) from that of the pharmacist (drug extraction and formulation), further accelerating the development of these two fields (Khan, 2014). For example Jaber Bin Hayan extracted and isolated various chemical substances such as alcohols, nitric acids, sulfuric acids (Azaizeh et al., 2006). A famous Muslim scientist, Ali Ibn Rabban Al Tabri (782-855 AD) wrote a work, the Firdous Al Hikmat, which deals with various topics, one of which focuses on drugs and poisons (Khan, 2014). Abu Ali Al Hussan Ibn Sina – also known as Avicenna, 980-932 AD is considered the creator of the Greco-Arabic school of medicine. In his work Canon of Medicine, he condensed and summarized the experience of many centuries of Greek,

Indian and Central Asian medicine and the medicine of the Middle Ages, as well as pharmacology, pharmacy and pharmacotherapy (Buranova, 2015). He described many medicinal plants that are firmly rooted in the practice of traditional medicine in many countries and, some of them, even in modern medicine (Buranova, 2015). Abu Musa Jabir ben Hayyan wrote a comprehensive book on different plant poisons and antidotes: The Book on Poisons and Antidotes. This highlights how the Arabs, in addition to the therapeutic and curative characteristics, also described the toxic aspects of various plants (Khan, 2014). The Arabs, having numerous relations with India, introduced many new plants from that country into pharmacotherapy (Khan, 2014). The Arabs used aloe, nightshade, henbane, coffee, ginger, strichno, saffron, turmeric, pepper, cinnamon, rheuum, senna and so on. They were among the first to replace some strong-acting drugs, such as the purgatives Heleborus odorus and Euphorbium, mainly used until then, with milder-acting drugs, such as the mild laxative Sennae folium (Petrovska, 2012).

Middle Ages and Renaissance

In the Middle Ages, monasteries became the central place in Europe where therapeutic skills, the cultivation of medicinal plants and the preparation of medicines were concentrated (Attorre & Bruno, 2022; Petrovska, 2012; Šantić et al., 2017). Thus the so-called monastic medicine developed (Attorre & Bruno, 2022; Petrovska, 2012; Šantić et al., 2017). The phytotherapeutic treatments were mainly based on 16 medicinal plants (sage, anise, mint, Greek seeds, savory, tansy, etc.) which the medical monks commonly cultivated in the monasteries (Šantić et al., 2017). Charlemagne (742 AD-814) considered the founder of the renowned medical school of Salerno, in his "Capitularia" ordered which medicinal plants should be grown on state land. Charlemagne especially appreciated sage whose name in Latin means "to save, to cure". Even today, sage is an obligatory plant in Catholic monasteries (Petrovska, 2012). Among the Slavic populations in the 7th century AD, Rosmarinus officinalis, Ocimum basilicum, Iris germanica and Mentha viridis were used in cosmetics, Alium sativum as a remedy, Aconitum napellus as a poison in hunting and Veratrum album, Cucumis sativus, Urtica dioica, Achilea millefolium, Artemisia maritime, Lavandula officinalis, Sambuci against lice, fleas, moths, mosquitoes and spiders (Petrovska, 2012). As previously mentioned, throughout the Middle Ages European physicians consulted Arab works in which over 1000 medicinal plants were described, namely "De Re Medica" by John Mesue (850 AD), "Canon Medicinae" by Avicenna (980-1037) , and the "Liber Magnae Collectionis Simplicicum Alimentorum Et Medicamentorum" by Ibn Baitar (1197-1248) (Petrovska, 2012). The travels of Marco Polo (1254-1324), the discovery of America (1492), and the travels of Vasco De Gama in India (1498), led to the import of many medicinal plants into Europe (Šantić et al., 2017). Botanical gardens sprang up throughout Europe and attempts were made to cultivate domestic and imported medicinal plants from the old and new worlds. With the discovery of America, a large number of new medicinal plants enriched the materia medica: China, Ipecacuanha, Cacao, Ratanhia, Lobelia, Jalapa, Podophylum, Senega, Vanilla, Mate, tobacco, chili pepper, etc (Petrovska, 2012). Paracelsus (1493-1541) was a European physician and alchemist and great supporter of medicines chemically prepared from raw plants and mineral substances (Michaleas et al., 2021). However, he was firmly convinced that the collection of those substances had to be determined astrologically, highlighting how the sciences of the time had yet to emancipate themselves from magical beliefs. He supported the "Signatura doctrinae": that is, following this belief he asserted that god had directly designated through his "signature" the use of healing substances for certain diseases. According to this theory, the appearance, or precisely the "sign", with which each natural element of animal, vegetable or mineral origin presents itself, reveals by analogy its therapeutic function of the parts of the human body most similar to it (Petrovska, 2012).

Recent Modern History

In the 17th century, the use of the bark of the tree Cinchona succirubra under the name of countess powder, following the legend that the Countess of Chinchon was the first to use it, was introduced into European medicine to treat malaria. It immediately became one of the best herbal remedies ever (Achan et al., 2011). Quinine as an active pharmaceutical ingredient of the cinchona tree, however, was only isolated in 1820 (Hassan, 2015). In the 18th century, an important breakthrough was achieved with the taxonomic work of the revolutionary Swedish physician and naturalist Carolus Linnaeus, who classified botanical species in a standardized way. With his works Systema Naturae Genera Botanica, Critica Botanica and Philosophica Botanica he founded modern biological taxonomy, introducing the binomial denomination, and the identification of plants and their characteristics, also proceeding with the cataloging of all the species known at the time, i.e. over 5900 species of plants (Britannica, 2024; Reid, 2009).

His writings are so important that they are still consulted by botanists, herbalists, horticulturists and taxonomists today (Halberstein, 2005). An important discovery of the 18th century in the field of phytotherapy was the application of digitalis by the English doctor William Withering who used the plant (Digitalis purpurea) to treat edema associated with heart failure. Digitalis-derived digoxin is still in use today to treat chronic heart failure, particularly in association with atrial fibrillation.

The 19th century was a turning point because several phytochemicals were isolated as "pure" drugs extracted from plants (e.g. quinine, morphine and ephedrine) (Hassan, 2015) that marked the beginning of scientific pharmacological research (Petrovska, 2012). Subsequently, other pharmacological substances such as glycosides, tannins, saponosides, essential oils, vitamins and hormones were discovered and isolated. Towards the end of the nineteenth century and the beginning of the twentieth century, alkaloids and glycosides isolated in pure form increasingly replaced the medicinal plants from which they had been isolated. This occurred mainly because the isolated phytochemicals produced a greater effect than their phytotherapeutic counterparts (Petrovska, 2012).

Phytochemicals (and active ingredients derived from phytochemicals) successful in modern medicine

In humanity's long struggle against diseases, the human being has always sought remedies using what he had available, therefore also using plants. For this reason, throughout history, phytotherapy have been fundamental in helping humans in the fight against diseases. With the advent of modern pharmacology however, phytotherapy has lost part of the central role it had held in the past. Despite this, even in the 20th century plants contributed decisively to the development of new revolutionary drugs and are still important, if not fundamental, for the development of new drugs.

Between 1950s and 1990s, just to name a few examples, the following active ingredients derived from plants entered the market (Dar et al., 2017):

The vinca alkaloids, **Vincristine and Vinblastine**, both derived from Catharanthus roseus of the Apocynaceae family, also known as Madagascar Periwinkle. Vincristine is the drug of choice for the treatment of acute lymphoblastic leukemia and in a combination regimen it is used to Treat Hodgkin's Disease, Wilm's Tumor, Neuroblastoma, and Rhabomyosarcoma (Agrawal, 2007), while vinblastine has indications for the treatment of testicular carcinoma, Squamous cell carcinoma of head and neck, Hodgkin's lymphoma, Kaposi's sarcoma, histiocytic lymphoma, Mycosis fungoides and histiocytosis X (Agrawal, 2007).

Reserpina from Rauvolfia serpentina of the Apocynaceae family, is one of the first agents developed to treat hypertension in clinical practice (Cheung & Parmar M., 2023) and is still used as an antihypertensive in clinical practice. Introduced in the 1950s, not currently available in many countries, but still considered able to reduce blood pressure to the same level as frontline antihypertensives (James et al., 2014; Lemieux et al., 1956; Weir, 2020).

Artemisinin from the plant Artemisia Annua (Chinese name – Qinghao) of the Asteraceae family, is an antimalarial effective against all Plasmodium species and is particularly useful in cases of infections with chloroquine-resistant or multi-resistant parasites (WHO, 2015).

Teniposide and Etoposide both from the plants Podophyllum hexandrum and Podophyllum peltatum of Berberidaceae family. Teniposide is an antineoplastic agent used primarily for the treatment of childhood acute lymphoblastic leukemia, while Etoposide an antineoplastic agent used for the treatment of several types of cancer including testicular cancer, lung cancer, lymphoma, leukemia, neuroblastoma, and ovarian cancer, and hemophagocytic lymphohistiocytosis (Reyhanoglu & Tadi, 2024; Yoneda & Cross, 2010).

Irinotecan and **Toptecan** derivates of camptothecin, an alkaloid extracted from the Chinese plant Camptotheca acuminata belonging to the Nyssaceae family. Irinotecan is antineoplastic agent used for the treatment of metastatic carcinoma of the colon or rectum and pancreatic adenocarcinoma (Robert & Rivory, 1998) while Toptecan is antineoplastic agent used for the treatment of ovarian cancer, small cell lung cancer, or cervical cancer.

Paclitaxel, from Taxus brevifolia of the family Taxaceae, an antineoplastic agents that as indication for several cancers, including breast, ovarian, bladder, lung, prostate, melanoma, esophageal, Kaposi sarcoma, and various other solid tumors (Awosika, Farrar et al., 2024).

Today in the Western world, drugs are designed by chemists and biologists using computer models. The pharmaceutical industry mainly relies on screening libraries of inorganic compounds for the discovery of new drugs, as complexities exist in libraries based on natural products. However, this

approach has led to a decrease in the entry of new drugs into the market. Therefore, interdisciplinary approaches based also on natural products have become a necessity (Atanasov et al., 2015).

The wealth of possible therapeutic substances for humans present in plants is remarkable. It is estimated that approximately 70,000 plant species have the potential to treat various human diseases (Kuruppu et al., 2019). As demonstrated by history, plants and fungi are an abundant source of potential new drugs and often act as chemical models for the design of new drugs for the treatment of humanity's most serious ailments. We provide some instructive examples below:

Spindle Poisons Agents – Cancer is the second leading cause of death globally (WHO, 2022). Despite this, improvements in treatment have meant that cancer is now considered a chronic disease. In fact, cancer survivors represent one of the fastest growing subgroups of people entering health care systems. In this context, it should be emphasized that 60% of currently used anticancer agents come from natural sources, including plants (Efferth et al., 2007; Martino et al., 2018).Vinca alkaloids, for example, are the first discovered components, in the 1950s, of a new class of drugs called spindle poisons, which work by attacking the microtubule spindle that separates chromosomes during cell mitosis (Duffin, 2000; Hüsemann et al., 2020). They directly kill tumor cells and make them more susceptible to other chemotherapy treatments, which is why they are used in combination therapy. The class of spindle poisons also includes podophyllotoxins, derived from Podophyllum hexandrum and Podophyllum peltatum, and Paclitaxel, obtained from the Taxus brevifolia (Duffin, 2000; Hüsemann et al., 2020).

Vinblastine and vincristine – Vinca alkaloids (Vincristine and Vinblastine) were originally isolated in the 1950s by Canadian scientists Robert Noble and Charles Thomas Beer from the Madagascar periwinkle plant, Catharanthus roseus of the Apocynaceae family (Arora et al., 2024; Martino et al., 2018). Periwinkle is a small perennial with attractive white or pink flowers, is a popular ornamental plant in gardens and homes around the world and it is native to the island of Madagascar. In India, the Philippines and South Africa, the infusions obtained from the leaves of the plant have been used by the traditional healers to treat various diseases, especially diabetes. Vincristine currently has indications as chemotherapy for various types of cancer: leukemia, lymphoma, neuroblastoma and Wilms tumor. It is also used off-label to treat adult central nervous system (CNS) tumors, Ewing sarcoma, gestational trophoblastic tumors, multiple myeloma, ovarian cancer, primary central nervous system lymphoma, small cells and advanced thymoma (Awosika, Below, et al., 2024). Vinblastine is indicated to treat leukemia, Hodgkin's and non-Hodgkin's lymphoma, breast cancer, and testicular carcinoma (Arora et al., 2024). Vincristine and vinblastine belong to a class of drugs called spindle poisons that work by preventing cancer cells from dividing properly. These drugs act by interfering with the polymerization of microtubules, interrupting mitosis, and inhibiting cell division (Duffin, 2000; Hüsemann et al., 2020). They particularly act on rapidly dividing cells, such as cancer cells, which are highly dependent on the proper functioning of microtubules during cell division (Awosika, Below, et al., 2024). Normal cells, that have a lower division frequency, are relatively less affected by the action of these drugs, contributing to the reduction of some adverse effects. Despite being discovered in the 1950s, Vinca alkaloids still have a prominent place in combination chemotherapy. They are in fact among the first and most effective long-acting anti-tumor agents (Arora et al., 2024; Duffin, 2000; Hüsemann et al., 2020). The history of the discovery of Vinca alkaloids is closely linked to the history of the search for drugs to treat diabetes. In fact, the older brother of Robert Noble, one of the two scientists who described the anticancer activity of Vinca alkaloids, worked in the research group of J.J.R. Macleod, one of the discoverers of insulin, at the University of Toronto (Duffin, 2000). It was from Macleod that Robert Noble was introduced to endocrinological research, although he would have preferred to do cancer research. However, it was by studying the 'activity of a plant that in traditional medicines (Ayurveda and TCM) had been described as acting as an antidiabetic and antimalarial agent, the Madagascar periwinkle, that Noble discovered that this plant had potent anticancer activities (Martino et al., 2018). Researchers around the world at that time were in fact looking for oral hypoglycemic agents that would eliminate the needle injections required by insulin (Duffin, 2000). Noble's research group in 1949, in the Collip laboratory dedicated to research in endocrinology, was studying the hormonal properties of various plant extracts used in traditional medicines as antidiabetics. It was at that time that CD. Johnston sent him tea material from Jamaica, made from a West Indian shrub (Catharanthus roseus) that was supposed to help control diabetes (Noble et al., 1958). So he and his team began to study its activity as an antidiabetic in laboratory mice (Duffin, 2000). Although periwinkle extract was not very effective at reducing glycaemia in mice, the researchers noticed that the mice died of septicemia. They later realized that the extract was able to rapidly reduce the number of white blood cells, induce granulocytopenia and profoundly depressed bone marrow (Noble et al., 1958). Researchers who evaluated Madagascar periwinkle extracts hypothesized that they contained phytochemicals

useful against certain types of cancer, such as leukemia, which actually involves the proliferation of cancerous white blood cells called blasts (Duffin, 2000). Robert Noble's team then began working with Ely Lilly researchers to delve deeper into the plant's anti-tumor capabilities and a phytochemical study led to the separation and identification of vinblastine – the prototypical Vinca alkaloid – which had been shown to cause myelosuppression in xenografts mouse models of leukemia (Martino et al., 2018). In the 1960s, this remarkable discovery paved the way for a new therapeutic approach against cancer. In those years, vinca alkaloids were approved with indications for various types of cancer including leukemia (Lucas et al., 2010). Nearly 70 years later, vinca derivatives maintain an essential place in combination chemotherapy, making them among the first and longest-lasting effective anticancer agents. Five Vinca derivatives are in clinical use today: the natural vinblastine and vincristine, the semisynthetic derivatives vindesine, vinorelbine and vinfluine, a bis-fluorinated derivative for the second-line treatment of metastatic and advanced urothelial cancer (Martino et al., 2018). The chemical structures of vinca alkaloids are quite complex: they are part of the monoterpene indole alkaloid (MIA) family, a diverse family of complex plant secondary metabolites with many medicinal properties (Zhang et al., 2022). Until 2022 the global vinblastine supply chain was based on the low-throughput extraction and purification of vindoline and cataranthin precursors from the plant Catharanthus roseus (Ishikawa et al., 2009; Jeong & Lim, 2018). Therefore until 2022 access to these chemicals was only possible through extraction from the Madagascar periwinkle and approximately 500 kg of dried leaves were required to produce 1 g of vinblastine. Only in 2022 a group of researchers led by Jay Keasling managed to engineer a yeast for the production of MIA and vinca derivatives (the same group engineered Escherichia coli for the production of artemisinin which, like vinblastine, until 2003 was mainly derived directly from the plant), resulting in a notable step forward for the supply of these drugs (Martin et al., 2003; Zhang et al., 2022; Zhao et al., 2022).

Etoposide – Belongs to the class of topoisomerase II inhibitor drugs. This class of antineoplastic agents acts by blocking the ligation phase of the cell cycle, which generates single- and double-strand DNA breaks, leading to cell death by apoptosis (Swedan et al., 2023). Is a medication used in the management and treatment of various cancers such as Hodgkin's and non-Hodgkin's lymphoma, brain cancer, testicular cancer, prostate cancer, bladder cancer, stomach and lung cancer (Reyhanoglu & Tadi, 2024). Its pharmacodynamics outlines the action and contraindications of etoposide as a valuable agent in the management of the various cancers listed above and other cancer forms (Reyhanoglu & Tadi, 2024). Etoposide is derived from the podophyllotoxins of the plants Podophyllum peltatum (also known as American mandrake), Podophyllum Emodi of the Berberidaceae family, and other plants (Imbert, 1998). It is known that podophyllotoxins have been used as a treatment for more than a thousand years (Slevin, 1991). The mandrake, despite being a poisonous plant and having a foul odor, has a centuries-old history of use by Native Americans. The natives used an aqueous extract of the roots of the mandrake as an emetic, anthelmintic or laxative (Moerman, 1991). Furthermore, the plant was used against snake bites and as a means of suicide, but some Native tribes also used it to treat cancer (Imbert, 1998). The inhabitants of the Himalayas used the extracts of the Podophyllum Emodi, for uses similar to those of the Native American (Kelly & Hartwell, 1954). In England, during the early Middle Ages, the roots of wild chervil, which contain deoxypodophyllotoxin, were used to treat cancer (Cockayne et al., 1864). The use of the plant as an emetic, laxative and cholagogue (not as an anticancer) was later borrowed from the American pioneers (Imbert, 1998). In this way the use of the plant as an emetic laxative and cholagogue entered the American pharmacopoeia in 1820 and the English one in 1864. By 1850 the plant extract, podophyllin, was commercially available, supplanting the use of the plant itself. The structure of podophyllotoxin was first established in the 1930s (Imbert, 1998). In 1944 it was described as capable of curing venereal warts (Culp & Kaplan, 1944), a few years later its antimitotic abilities were described (Kern & Fanger, 1950), and it was subsequently demonstrated that it was capable of killing experimental cancers in animals (Imbert, 1998). In the 1970s, starting from podophyllin, Sandoz Pharmaceuticals synthesized a derivative, etoposide (Slevin, 1991). The drug is now included in the World Health Organization's list of essential medicines (a list that contains the drugs considered most effective and safe to meet the most important needs for the treatment of diseases (WHO, 2023a)) with worldwide sales expected to exceed $1 billion by 2029.

Artemisinin – It is currently the drug of first choice in combined therapy in the treatment of malaria, the most widespread parasitic disease in the world today, which causes 500 million cases and between 1.5 and 2.7 million deaths every year (Buck & Finnigan, 2024). It is effective against all Plasmodium species and is particularly useful in cases of infections with chloroquine-resistant or multi-resistant parasites (WHO, 2015). The drug is also effective in the treatment of toxoplasmosis, leishmaniasis and infections due to some species of Babesia. Artemisinin endoperoxide bridge is thought to be essential for antimalarial activity, as it causes free radical damage to the parasite's membrane systems, including: inhibition of the parasite's sarcoplasmic-

endoplasmic reticulum calcium ATPase, interference with mitochondrial electron transport, with parasite transport proteins, and disruption of parasite mitochondrial function (Meshnick, 1998). It also appears to have potential as an anticancer agent. Artemisinin was discovered in China by studying Artemisia Annua (Chinese name – Qinghao) of the Asteraceae family (Tu, 2011). In the book "52 prescriptions" found in a tomb of the Han Mawangdui dynasty dating back to 2000 years ago, the first evidence of medicines used to treat intermittent fevers (some of which were probably malarial) was found (Nosten et al., 2022). The text mentions the use of the medicinal herb Qinghao, a remedy later found in the manual of prescriptions for emergencies by Ge Hong in 341 AD (Nosten et al., 2022). Between the 1950s and 1980s, Chinese scientist Tu Youyou worked on Chinese herbal medicine at the Chinese Academy of Chinese Medical Sciences (formerly known as the Academy of TCM) (Tu, 2011). Malaria, caused by Plasmodium falciparum, has been a deadly disease for thousands of years. After the failure of international attempts to eradicate the disease in the 1950s, it began to spread again across much of the world due to the appearance of parasites resistant to existing antimalarial drugs, such as chloroquine (Tu, 2011). This has led to an urgent need for new antimalarial drugs. In 1967 Tu became head of Project 523, a Chinese national research project launched to find a cure for malaria. The scientist's institute consisted of both phytochemical and pharmacological researchers. The group began working on Chinese herbal materials by extracting and isolating components with possible antimalarial activities. In their work they studied more than 2,000 Chinese herbal preparations, among which they identified 640 that had possible antimalarial activities. The extracts were evaluated in a mouse model of malaria (Tu, 2011). The scientist's research group ultimately tested more than 240,000 compounds for use as antimalarials (Nature portfolio, 2024). The turning point occurred when the team found an extract of Artemisia Annua that showed a promising degree of inhibition against parasite growth. Their discovery, however, was not immediately reproducible in subsequent experiments and was in contradiction with what was reported in the literature. So Tu and colleagues carried out an in-depth review of the literature on qinghao, also researching ancient texts of TCM. And they found the solution to the problem in the text of Ge Hong's Emergency Prescription Manual (Fig. 1), in which the use of the plant's medicinal preparation was described as carried out cold. In fact they found that the heating involved in the conventional extraction stage of the preparation used to obtain the drug resulted in the destruction of its active components. (Nature portfolio, 2024; Tu, 2011). Then they used a low-temperature extraction method. On October 4, 1971, they obtained an extract 100% effective against parasitemia in mice infected with Plasmodium berghei and in monkeys infected with Plasmodium cynomolgi. According to the World Health Organization, since 2000 more than three million lives have been saved by using antimalarials containing artemisinin. Tu received the Nobel Prize for his work in 2015 (Nature portfolio, 2024; Tu, 2011).

Finally, some interesting facts about the discovery of artemisinin:

The effectiveness of artemisinin against malaria was discovered in the 1970s in China. The results of its effectiveness were presented to the WHO in the 1980s (Miller & Su, 2011). However, given Western countries' distrust of China and lack of cooperation from the Chinese government, artemisinin did not prove effective against malaria outside China until 2006, when it became the first-line drug in combination with other antimalarials (Maude et al., 2010). The discovery of artemisinin by Tu Youyou remained unknown both in China and the rest of the world until 2011, when Miller LH and Su X traced Tu Youyou as the originator of the discovery (Miller & Su, 2011). The discovery remained secret because it occurred during the years of the Cultural Revolution in China, as an initiative of the Chinese government to help the North Vietnamese in their war against the United States (Miller & Su, 2011). At the time, malaria caused by chloroquine-resistant Plasmodium falciparum was a great problem, and both the United States and China were searching for drugs that could defeat the disease. Thus the United States discovered mefloquine, a single-dose curative compound against chloroquine-resistant parasites (Trenholme et al., 1975). The North Vietnamese turned to the Chinese government for help. Therefore, in 1967 the secret national program called Project 523 was initiated in China (Miller & Su, 2011). This led, in the short term, to the discovery of three drugs against malaria in 1969 and, in the long term, to the discovery of artemisinin.

It should be mentioned that Linnaeus was aware of the use of quinine but also, less known and rather surprising, of artemisia annua in the treatment of malaria (Miller et al., 2023).

Cephalosporins – Are a class of β-lactam antibiotics derived from the fungus Cephalosporium acremonium. Discovered by Giuseppe Brotzu, an Italian physician and hygienist working in Cagliari around 1945. His studies and clinical interests were in the treatment of malaria and typhoid infections. By studying the presence of Salmonella Typhi in the sewers of the city of Cagliari and mapping the most contaminated areas, he observed that Cagliari

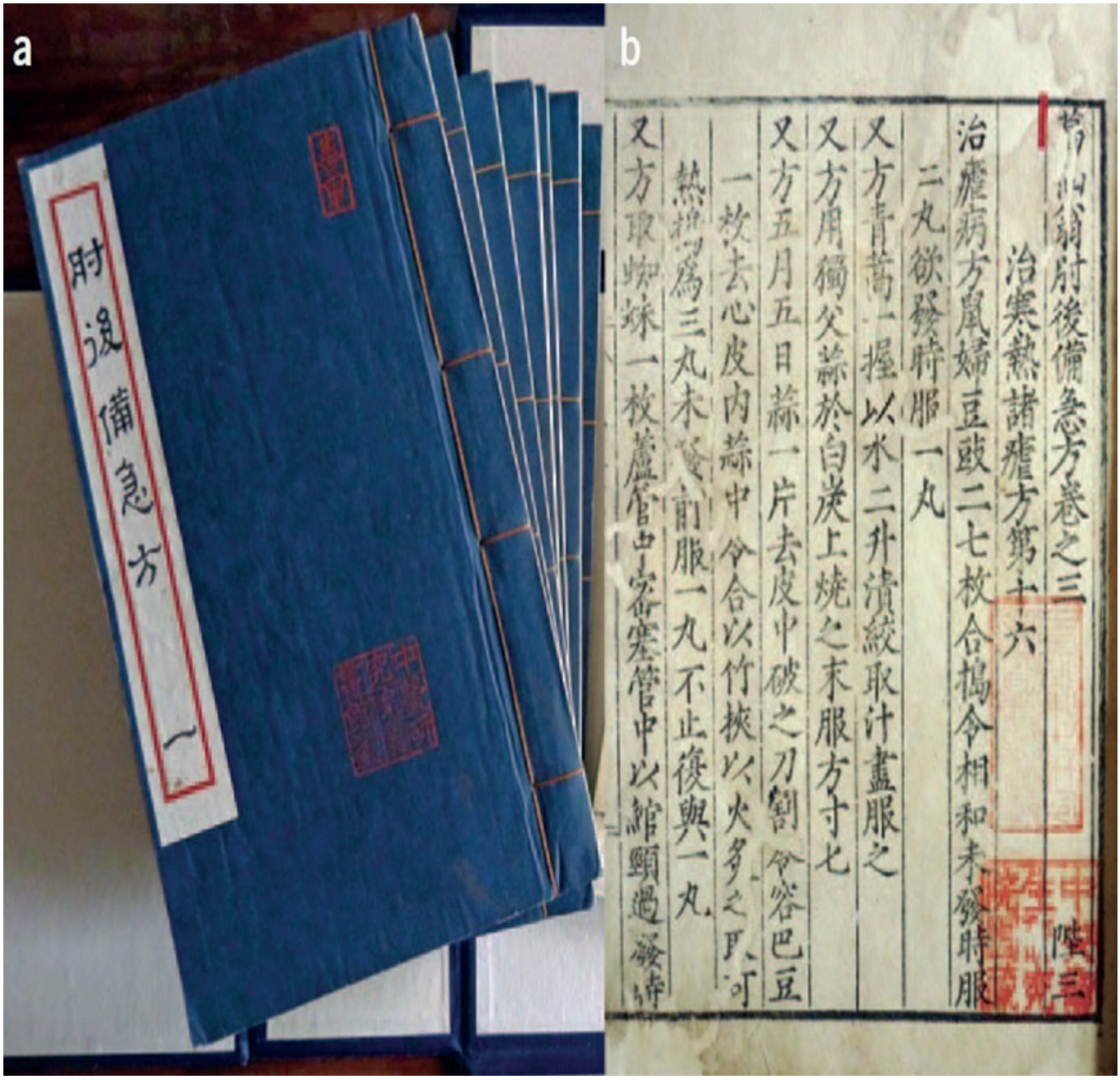

Figure 1. Ming dynasty version (1574 CE) of the handbook Emergency Prescription Manual by Ge Hong (Tu, 2011).

residents who bathed in the city sea, where sewage was discharged, didn't get typhoid fever (Bo, 2000). In order to understand this peculiarity, not assuming that sewage would be diluted once in the sea, he tried to understand where seawater's self-purifying capacity came from. In fact, Sardinians who bathed in the sea did not develop typhoid fever or skin disease except very rarely. By culturing a water sample taken from that sea area in July 1945, he first isolated Cephalosporium Acremonium (Brotzu, 1948). During his studies, he realized that the mycete produced a substance that could inhibit the growth of various pathogens in vitro. Brotzu named the substance mycetin (a beta-lactam inhibitor of bacterial wall synthesis like penicillins) and immediately began testing its validity on patients suffering from various types of staphylococcal infections, brucellosis, etc., achieving remarkable improvements and sometimes cures. He had discovered cephalosporins. The importance of this discovery is best understood in light of history: Fleming had discovered penicillin in 1928, but large-scale production of the drug had not begun until 1945. Despite

this, in 1945 the drug was still not available worldwide as World War II had just ended. Until 1945, moreover, infectious diseases, particularly pneumonia, tuberculosis, and gastroenteritis, were the leading causes of death in all age groups worldwide (Adedeji, 2016; Office for National Statistics, 2017; Sakai & Morimoto, 2022). Before 1945, in fact, there were no cures for infectious diseases. Brotzu had therefore made a revolutionary discovery and was aware of it. To better purify and identify the substance with antibiotic properties he discovered, he applied for funding from Italian institutions, but unfortunately the funding was denied. (Bo, 2000). At that time, a British medical officer, serving in the occupation forces in Sardinia, had asked to visit the Institute of Hygiene in Cagliari. Through him, Professor Brotzu sent a sample of the fungus to Sir Howard Florey of Oxford University, head of the Anglo-American Antibiotic Research Group. Thanks to Brotzu's work, after 18 years of research in 1962 Edward Abraham's research group isolated the Chealosporin C. This was the progenitor molecule of a new generation of antibiotics, namely cephalosporins. Cephalosporins are antibacterial agents that are still widely used, mainly because of their broad spectrum of activity and low toxicity, and are indicated against both Gram-positive and Gram-negative bacterial infections. They are classified into 5 generations, and some of the newer derivatives of this class are being evaluated in clinical trials. In addition, they are currently among the few antibiotics still effective in the treatment of MRSA (methicillin-resistant Staphylococcus aureus) (Bavaro et al., 2024; Bui et al., 2024). This class of antibiotics is still critically important in the treatment of infections, as antimicrobial resistance (AMR) poses a serious threat to global public health, even in developed countries. In fact, it is estimated that AMR is responsible for 1.27 million deaths worldwide and contributes to 4.95 million deaths.

Morphine – The opium poppy "Papaver somniferum" has played an important role in human history. It appears to have been cultivated as early as the Neolithic period, in 6000 BC. (Brook et al., 2017; Hassan, 2015; Šantić et al., 2017). In cuneiform tablets it was described as the "plant of happiness". In 1500 BC. opium is mentioned in the Ebers Papyrus along with other medicinal plants. In 1100-800 B.C. Arab physicians created many opium-containing drugs to treat mental problems, epilepsy, flu, and eye fatigue. The poppy entered Greek mythology and took the name of morphine in honor of Morpheus, the god of dreams. In 800 BC Homer describes Helen and Presephone in the Odyssey as using a wine drugged with opium to relieve pain and sadness. In 500 BC Hippocrates knew its excellent narcotic and analgesic action and used it against coughs and for some gynecological condition. During Hellenism the poppy had spread to India, Persia, China and other countries (Brook et al., 2017). In 300 BC. the Chinese surgeon Hua T'o used an anesthetic based on wine and opium. In the 1st century AD, at the time of Emperor Nero, the physician Andromachus used opium in a medical preparation which he called Theriaca andromaci and Dioscorides in De Materia Medica was the first to provide a written description of how to obtain opium from the poppy. In the Middle Ages, between the 5th and 14th centuries AD, opium was produced by apothecaries. In the 14th-17th centuries AD. Paracelsus produced the opium tincture called Laudanum. In the 17th century Thomas Sydenham created what became a staple in European medicine, his alcohol-based opium tincture called laudanum, mentioned in Shakespeare's Othello. Between the 18th and 19th centuries, the use of laudanum for medical or recreational purposes was common. Benjamin Franklin, Napoleon, and Egar Allan Poe, among other notable figures of the time, were opium users. From the beginning of the 19th century opium was widely used. Opium is obtained from the juice collected from the shells of poppy heads. From 1805 to 1950, a series of discoveries followed that led to further advances.. In 1805 Serturner isolated morphine, in 1819 Meissner classified morphine as the first compound of the alkaloid class, in 1847 Lauren determined the chemical formula of morphine. Robinson managed to determine the structural formula of morphine and won the Nobel Prize for Chemistry in 1947, while in 1952 Gates and Tschudi synthesized morphine for the first time in the laboratory (Brook et al., 2017). To date, although it is possible to artificially synthesize morphine, it is still manly obtained from the plant using techniques that have remained substantially unchanged in eight millennia. Morphine is an iconic example of a phytochemical that has stood the test of time and remains one of the most used medications for the control of severe pain. Even today, despite advances in chemical production capabilities, humans cannot compete with extraction from plants, which is much cheaper and more efficient than synthetic production. Regarding the pharmacodynamics of morphine, it determines most of its analgesic effects by binding to the mu-opioid receptor in the central nervous system (CNS) and peripheral nervous system (PNS). (Murphy et al., 2023). Morphine is currently included in the WHO list of essential drugs (WHO, 2023a) and is indicated in the treatment of moderate to severe pain resistant to other painkillers, particularly in cancer-associated pain, myocardial infarction, and postoperative pain. It is also indicated in acute pulmonary edema, general and local anesthesia, and epidural analgesia during childbirth (Murphy et al., 2023; Šantić et al., 2017).

Acetylsalicylic acid – At some point in life, most people have taken a pain or fever control medication derived from

willow bark, namely acetyl salicylic acid derived from salicyline. Salyciline is a glycoside contained in the willow bark of Salix alba and Salix fragilis, plants belonging to the Salicaceae family (Fig. 2). To date, acetylsalicylic acid is the most used drug in the world and among the oldest remedies still in use (Mann, 2000). Acetylsalicylic acid inhibit the activity of the enzyme called cyclooxygenase (COX) which leads to the formation of prostaglandins (PGs) that cause inflammation, swelling, pain and fever (Vane & Botting, 2003). This is another example of how nature and traditional knowledge have contributed to modern medicine. The first written evidence of the use of willow bark dates back to over 3,500 years ago, when it was used as an analgesic, anti-inflammatory and anti-rheumatic by the Sumerians and Egyptians (Montinari et al., 2019). The ancient Egyptians in the Ebers Papyrus describe the use of decoctions of myrtle and willow leaves, to be applied on the abdomen and back to relieve local inflammatory and painful conditions (Bryan, 1930).

Hippocrates, about 1000 years later, and subsequently Galen, were aware of the medicinal properties of Salicaceae plants. Willow bark was prescribed by Hippocrates to treat inflammatory pain and to relieve the pain of childbirth (Montinari et al., 2019). In De Materia Medica, Dioscorides describes willow decoctions for the treatment of gout, colic and earache. In Natural History, Pliny the Elder also reports the use of of preparations of these plants as antipyretic and analgesic remedies (Jeffreys, 2008). Populations from different parts of the world, who had no contact with each other, such as the indigenous populations of the Hottentots of South Africa or the American Indians used willow extracts to treat fever, arthrosis and headaches. The use of willow bark spread throughout the Western world from 216 AD, as military and commercial maritime contacts intensified. Thus, it then arrived in China and other eastern countries. Decoctions of plants containing salicylates were used to treat wounds, rheumatic pain, ulcers, headaches and dysmenorrhea during the Middle Ages, the Renaissance and up to the 18th century (Jeffreys, 2008). In the following centuries, starting from the 18th and 19th centuries, a series of notable advances occurred in the characterization of the active ingredient contained in willow bark. In 1758 Edward Stone of Chipping Norton, Oxfordshire, England, looking for a valid and economical remedy compared to expensive cinchona bark to cure "fever" (i.e. malaria), studied the healing properties of willow (Wood, 2015). He administered the aqueous extract of Salix alba bark to treat 50 febrile patients and discovered that the administration of these extracts had a marked antipyretic action. This study by Stone is now recognized as the first to demonstrate with scientific rigor the effectiveness of willow bark in the treatment of fever. The first extraction of the active component of willow

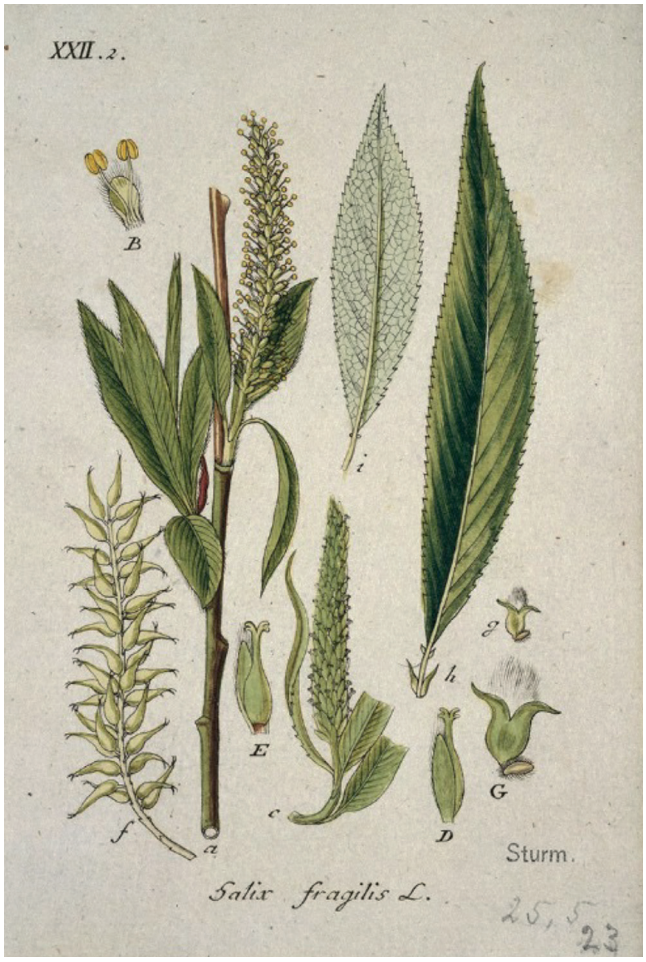

Figure 2. Illustration of Salix Fragilis, from the Museum's Botany Library Plate Collection.

bark appears to have been carried out in 1824 by two Italian pharmacists from Verona, Francesco Fontana (Fontana, 1824) and Bartolommeo Rigatelli (Rigatelli, 1824). Rigatelli called the drug "indigenous substitute for quinine sulphate" (Rigatelli, 1824) and "very bitter antipyretic saline solution" (Rigatelli, 1826) , while Fontana (Fontana, 1824) used the name salicin, the same term that a few years later would be adopted by others.

In 1828 the pharmacologist Joseph Buchner also isolated the active ingredient of willow "Salicin" while the following year Henri Leroux perfected the salicin extraction process allowing the extraction of a significant quantity of pure salicin (Montinari et al., 2019). Raffaele Pirìa, a 19th century Italian chemist, extracted salicylic acid from salicin and determined its molecular formula (Montinari et al., 2019). In 1852 the French chemist Charles Gerhardt synthesized acetylsalicylic acid, without realizing it, but in an impure and unstable form (Gerhardt, 1853). In 1855 Cesare Bertagnini, a student of Raffaele Piria, first described the ototoxicity that occurs

following high ingestions of the drug (Montinari et al., 2019). In 1859 Hermann Kolbe synthesized salicylic acid in the laboratory, and in the following years his students began producing it on an industrial scale at a price 10 times lower than that of willow bark (Sneader, 2005). In 1876 Franz Stricker and Thomas MacLagan published on the efficacy of sodium salicylate and salicin, extending their indications not only as an antipyretic but also as an antirheumatic and analgesic (Maclagan T., 1876; Montinari et al., 2019). In 1877 the effectiveness of sodium salicylate was described by Germain See in chronic rheumatism and gout (Sée G., 1877). In 1877 and 1878 Noemisio Bosisio and Giovanni Brugnoli described the effectiveness of salicylic acid also in the treatment of rheumatic fever (Montinari et al., 2019). In those years the pharmaceutical company Bayer set to work to produce a salicylate derivative that did not cause the negative effects of sodium salicylate, namely nausea, gastric irritation and tinnitus. This task was accomplished by Felix Hoffman, a chemist who synthesized acetylsalicylic acid on August 10, 1897 (Zündorf, 1997). In 1899 Bayer registered the new compound as "Aspirin", a name derived from acetyl and Spiraea ulmaria, the tree from which salicylic acid was extracted (Montinari et al., 2019). In 1948 and 1953 respectively Paul Gibson proposed salicylic acid in the treatment of coronary thrombosis (Gibson, 1949) and Lawrence Craven used aspirin in primary cardiovascular prevention (Craven, 1953). In 1971 Vane discovered the mechanism of action of aspirin for which he later received the Nobel Prize. In 1974, the first randomized trial on the use of aspirin in the secondary prevention of coronary thrombosis and myocardial infarction was conducted (Montinari et al., 2019). Between 1975 and 1988 it was discovered that aspirin: reduces the synthesis of thromboxane A2, inhibits cyclooxygenase, is effective in the secondary prevention of stroke, can be used in the prophylaxis of unstable angina and that early treatment with aspirin is effective in reducing mortality from myocardial infarction (Montinari et al., 2019). In addition to recent developments in secondary and primary cardiovascular prevention, regular aspirin use has been found to have another important benefit: decreasing the risk of developing cancer (National Cancer Institute, 2014). Finally, low-dose acetylsalicylic acid is now prescribed to pregnant women at high risk of developing preeclampsia to reduce their risk of developing it and also to prevent preterm delivery and intrauterine growth restriction (ACOG, 2018).

Curare (d-Tubocurarine) – Curare is obtained from various plants, including Chondrodendron tomentosum of the Menispermaceae family and Strychnos toxifera of the Loganiaceae family (Burr & Leung, 2014). d-Tubocurarine acts as a non-depolarizing competitive antagonist at nicotinic acetylcholine receptors on the motor end plate of the neuromuscular junction, causing the relaxation of skeletal muscle (Burr & Leung, 2014). For centuries, Curare has been used by indigenous South American tribes to hunt (Raghavendra, 2002; Šantić et al., 2017). Tales of the mysterious "flying death" were brought to the Old World by Spanish conquerors and thus began the characterization of the active ingredient and its evolution into today's synthetic drugs in Europe. A chronicler of the Spanish court, Peter Martyr d'Anghera, in his book De Orbe Novo first described arrows poisoned with Curare in 1516 (Sykes, 1993). The description he made was composed of a mixture of reality and fantasy and contributed significantly to starting the search for Curare. In 1594, in the book Discovery of the Large, Rich and Beautiful Empire of Guyan, Sir Walter Raleigh mentions the use of arrows poisoned with Curare, a name given to the poison by one of his lieutenants, during his visit to Venezuela (Birmingham, 1999; Crul, 1982; Rowbotham, 1948). Further exploration of South America, until the 18th century, was prevented by wars between the English, Spanish and Portuguese. Until the physician Edward Bancroft spent five years in South America and brought samples of raw Curare back to Europe. Sir Benjamin Brodie, thanks to the use of these samples, demonstrated by injecting curare into small animals that they could be kept alive thanks to artificial respiration with bellows (Brodie, 1968). Charles Waterton, an explorer, obtained several samples of curare in South America and later tested them on large animals in 1814. In particular, he demonstrated to an audience, which included Sir Benjamin Brodie among others, the effects of curare on three donkeys, showing that if the animals injected with curare were ventilated, they survived. Furthermore, he demonstrated that if curare was injected into a limb and allowed to act only on that limb through the action of a tourniquet, the animal survived (Raghavendra, 2002). This was an early indication that Curare act on the neuromuscular junction. Claude Bernard in 1846 with experiments on frogs definitively demonstrated that the Curare acted on the neuromuscular junction (Raghavendra, 2002). He demonstrated that the drug injected into a limb blocked muscle contraction, but that this could still be induced by external nervous stimulation.In the 1800s, a series of discoveries laid the foundation for the subsequent use of neuromuscular blocking drugs in anesthesia, which actually began after World War II. One of these events is linked to the chemical activity of alkaloids (Bynum, 1970). At the end of the 19th century, the role of acetylcholine, underlying neuromuscular transmission, was established in Great Britain by Sir Henry Dale and colleagues (Dale, 1934). Harold King isolated d-tubocurarine from a sample of Curare (National Library of Medicine, 1968). Richard Gill, an American living in Ecuador, became ill with multiple sclerosis, and his neurologist in the United States, Walter

Freeman, suggested that he might benefit from curare therapy. From Ecuador Gill brought back Curare in crude form and samples of the plants from which Curare was obtained (Humble, 1982). These samples were analyzed and recognized as plants of two families: Menispermaceae, which includes the genus Chondrodendron; and Loganiaceae, which includes the genus Strychnos. Oscar Wintersteiner and James Dutcher in 1942 were the first to isolate the alkaloid d-tubocurarine from samples of Chondrodendron tomentosum (Wintersteiner & Dutcher, 1943). A H Holladay standardized the commercial preparation of curare by naming the drug Intocostrin. A neuropsychiatrist AE Bennett, who used convulsive electroshock in the therapy of his patients due to the high incidence of vertebral fractures, was on the verge of abandoning this type of intervention when he decided to try to also include in the technique the use of curare (Raghavendra, 2002). In 1940, Bennett presented a film on the use of the curare at the 91st annual session of the American Medical Association at which Lewis Wright was among the attendees. Wright hypothesized that Curare could be useful in anesthesia and donated Intocostrin to EA Rovenstine of New York University so that he could experiment with the drug during surgical practice. Rovenstine gave it to one of his residents, EM Papper. Pepper tested it on two patients undergoing ether anesthesia who developed apnea and were then manually ventilated throughout the night (Betcher, 1977). At the time, indeed, endotracheal intubation was not commonly used. In the 1940s, a Montreal hospital anesthesiologist and cyclopropane enthusiast, Harold Randall Griffith, was specialized in endotracheal intubation to overcome occasional episodes of apnea induced by cyclopropane. He started to use curare. Together with his resident Enid Johnson in 1942 they administered curarization to a young patient undergoing appendectomy (Gillies & Wynands, 1986). Griffith is considered to be the one who introduced curarization into anesthesia (Kyle & Shampo, 1992). World War II interrupted work on curare derived drugs. Until John Halton, an anesthetist from Liverpool, had Intocostrin brought from the United States by an American soldier friend (Raghavendra, 2002). The experiences of Halton and Cecil Gray with the use of the cure on patients were successful and were reported by the two in 1946 (Gray & Halton, 1946). This laid the foundations of what became known as the Liverpool technique: a triad of narcosis, analgesia and muscle relaxation. This technique is still used today for all surgical procedures by all anesthetists. The study of Curare as a neuromuscular blocking drug has revolutionized the practice of anesthesia, surgery and medicine in general, allowing physicians to achieve results never seen before in terms of treatment. Before the discovery of neuromuscular blockers, anesthesia was induced and maintained using intravenous or inhaled agents, tracheal intubation was rare, and muscle relaxation, if necessary, was provided by deep inhalation anesthesia with the attendant risks of respiratory or cardiac depression (Raghavendra, 2002). With the introduction of neuromuscular blockers, anesthesia has undergone a conceptual change, being redefined as a triad of narcosis, analgesia and muscle relaxation. To produce each of these effects, specific drugs are used, of which neuromuscular blockers are one of the three essential drug categories. To date, tubocurarine is no longer used in anesthesia but has been replaced by a series of neuromuscular blockers (depolarizing such as succinylcholine and non-depolarizing such as rocuronium, vecuronium, atracurium, cisatracurium, mivacurium) (Cook & Simons, 2024; Raghavendra, 2002). Most of these are of synthetic origin and were created taking inspiration from Curare. The synthesis of neuromuscular blocking molecules has become necessary because some of the existing drugs, including tubocurarine, present a series of side effects and pharmacokinetics that do not adapt perfectly to all clinical scenarios. Neuromuscular blocking drugs belong to two groups, depolarizing and non-depolarizing (Cook & Simons, 2024). Depolarizers act on the neuromuscular junction by imitating the effect of acetylcholine, first causing muscle contractions (fasciculations) and then paralysis. Suxamethonium, a drug that belongs to this class, has the advantage of acting within 60 seconds. It induces muscle relaxation lasting less than 5 minutes. It does not respond to anticholinesterases such as neostigmine, but plasma cholinesterase causes the effect to wear off quickly. Among the side effects it induces are life-threatening hyperkalemia, malignant hyperpyrexia, increased intraocular pressure. A large number of deaths attributable to hyperkalemic cardiac arrest in children with undiagnosed muscular dystrophies have occurred following the use of suxamethonium (Raghavendra, 2002). There is now a clinical need for a safer drug that works just as quickly. As for non-depolarizing drugs, they are characterized by a slower onset of action (2-3 minutes) and are therefore unsuitable for rapid control of the airways. Neostigmine reverses their action and works through competitive blockade of the neuromuscular junction and does not cause initial muscle fasciculation. Given the side effects described so far, the search for the "ideal neuromuscular blocking drug" continues today (Prabhakar et al., 2016; Shah et al., 2021) (i.e. with short, non-cumulative and non-depolarizing neuromuscular action, with rapid onset and recovery, reversible with an appropriate antagonist and free of clinical side effects).

Quinine and (its stereoisomer) Quinidine – Cinchona succirubra of the Rubiaceae family contains two important alkaloids: quinine, which became famous as the first

antimalarial, and quinidine, still used today against cardiac arrhythmias (Petrovska, 2012). To further underline how deeply medicine and botany are intertwined, in 1735 Linnaeus graduated in medicine from the University of Harderwijk with a thesis on malaria (Linnaeus, 1735). In his thesis two treatments derived from plants effective against malaria are cited: cinchona bark and Artemisia Annua . It is speculated that he was aware of the use of the latter, probably because travelers such as Marco Polo had introduced knowledge of Chinese pharmacopoeia to Europe. (Aydin-Schmidt et al., 2010). Quinine is certainly one of the greatest discoveries of all time in the field of herbal medicine. While we don't know exactly who discovered the use of cinchona to treat malaria, there is no doubt that the drug was used by indigenous Andean people for medical purposes (Miller et al., 2023). It is also known that the Jesuits brought the knowledge of quinine to Europe in the 1600s to cure intermittent fever (as malaria was called at the time). In 1631, for example, the vice king of Peru fell ill with malaria in Lima and recovered thanks to the administration of cinchona bark powder by a Jesuit (Miller et al., 2023). In fact, it would seem that Andean healers used cinchona as a fever medicine in general (Crawford, 2016). This knowledge would have developed in the Loja region of Ecuador, where there was an important center of traditional medical knowledge. It should in fact be underlined that Plasmodium spp. (one of four protozoa of the genus Plasmodium that cause malaria) it is not native to South America but seems to have arrived in this region with the African slave trade to South America started by the Portuguese in the first decades of the 16th century who transferred malaria parasites to the New World. It is thought that local healers were therefore confronted, from that moment on, with at least more than a century of circulation of Plasmodium spp., experimented with the effects of cinchona bark in the area in which they practiced, and taught its use to Europeans, in particular to the Jesuits, whose presence in the region dates back to 1568 (Klaiber, 2004). Molecular studies confirm that malaria parasites began arriving in the Americas from Africa in the mid-16th century. (Rodrigues et al., 2018). Quinine bark was introduced to Spain in 1638 (Achan et al., 2011). Until 1820 the antimalarial drug was produced by drying cinchona bark, grinding it into a powder which was then dissolved in a liquid and drunk. Pierre Joseph Pelletier and Joseph Caventou isolated quinine from the bark in 1820 which later became the standard treatment against malaria (Achan et al., 2011). The phytochemical alkaloids of cinchona are different and in addition to quinine they include quinidine, quinine and cinchonidine, all effective against malaria. Quinidine is also one of the first antiarrhythmics discovered (Hellgren et al., 2014). However, after 1890 quinine became the predominantly used alkaloid to treat malaria (Achan et al., 2011). Until the 1920s, when more effective synthetic antimalarials became available, quinine remained the mainstay of malaria treatment. Chlorquine is the most important of these synthetic drugs and has been widely used especially since the 1940s (Hellgren et al., 2014). However, starting in the late 1950s, due to the intense use of chloroquine, chloroquine-resistant Plasmodium falciparum developed. This initially occurred in Southeast Asia and South America in the late 1950s, then spread to nearly all areas affected by falciparum malaria in the 1980s. As we described in the part about artemisinin, in this period other very effective drugs were developed against chloroquine-resistant malaria. Moreover, with the development of increasing resistance to chloroquine, quinine was rediscovered especially in the treatment of severe malaria (Hellgren et al., 2014) and still plays a significant role in the management of malaria today. Quinidine is a stereoisomer of quinine, so it can be derived from the bark of the cinchona tree or prepared from quinine (Jain & Sisodia, 2024). Quinidine, classified as a class IA antiarrhythmic, was first described in 1848 by Van Heymingen and named by Pasteur in 1853 and has a long history as an antiarrhythmic (Yang et al., 2009). It works by prolonging the effective refractory period and reducing automaticity in the heart, and has been used in the treatment of nearly all cardiac arrhythmias, particularly atrial fibrillation (AF), since the beginning of the 20th century (Vitali Serdoz et al., 2019). As an antimalarial, quinidine accumulates in the food vacuole of the parasite and forms a complex with heme, inhibiting the activity of heme polymerase leading to the accumulation of cytotoxic-free heme (Jain & Sisodia, 2024).Over the past two decades, primarily due to concerns about side effects, such as proarrhythmia, and the new availability of therapies such as new antiarrhythmic drugs and the availability of catheter ablation procedures, there has been a decline in quinidine prescriptions.. Despite this, quinidine still remains one of the oldest cardiac drugs available in the modern era of antiarrhythmic therapy (Vitali Serdoz et al., 2019). Quinidine is currently indicated for: the treatment of Plasmodium falciparum malaria in cases of severe and complicated malaria, both as an independent therapy and in association with exchange transfusion, as pharmacological conversion therapy of atrial fibrillation/flutter to sinus rhythm, in atrial fibrillation/flutter to reduce the frequency of relapses, for the suppression of ventricular arrhythmia and, finally, for the treatment of pseudobulbar syndrome in association with dextromethorphan. (Jain & Sisodia, 2024). The mechanism of action of quinine, instead, has not yet been fully elucidated. The drug could intercalate between DNA chains, blocking their activity, or it could interfere with oxygen uptake or carbohydrate metabolism. Quinine could also increase intracellular pH.

Metformin and Biguanides from Galega Officinalis – The fascinating history of metformin for the treatment of type 2 diabetes begins in medieval Europe (Zhao H. et al., 2021). Galega officinalis (also known as goat's rue, French lilac, Italian fitch, Spanish sainfoin, or professor's herb) of the Fabaceae family, from which metformin is derived, was already used by medieval herbalists to treat polyuria (excessive urination), a key symptom in patients with diabetes (so much so that the name of the disease, diabetes, which is derived from the Greek diabaínō, means excessive emission of urine) (Bailey & Day, 2004; Bailey & Day, 1989; Bailey & Turner, 1996). At that time, nothing was known about the causes of diabetes and the active ingredient of the plant was unknown (Pollak, 2010). However, Galega owes its name ("Galega" comes from the Greek and means "stimulating milk") to the fact that it was a plant with widely recognized galactagogue power in Europe in ancient times (an indication for which Galega is still prescribed today as a phytotherapy and is widely used internationally for this purpose) (Drugs and Lactation Database (LactMed®), 2006). Furthermore, around 1600-1700 Galega was also used and described to treat helminth infections, epilepsy, fever and plague (Bailey, 2017). In the mid-1800s, chemical analyzes were conducted on G. officinalis which demonstrated that the plant, particularly the immature pods, was rich in guanidine (metformin – dimethylbiguanide – is a derivative of guanidine) and related compounds (Bailey, 2017). Around the 1920s, guanidine was discovered to reduce blood glucose in animals. In particular, several mono-guanidine derivatives have proven effective for this purpose, in particular galegin (isoamylene guanidine) and diguanidines, such as syntylin (two guanidines separated by a methylene chain) (Bailey, 2017). However, around the 1930s, a toxicity of these substances was described which reduced their use and, at the same time, the newly discovered insulin became more widely available thus contributing to the reduction in the use of guanidine derivatives (Bailey, 2017). Metformin was synthesized in 1922 and was used in animal experiments to reduce glycaemia (Werner & Bell, 1922). Although metformin has been found to be much less toxic than mono- and diguanidines (Slotta & Tschesche, 1929) due to the high doses required to achieve modest hypoglycemic effects in nondiabetic animals, the true potential of this agent has been underestimated. Therefore, for the reasons described above, neither biguanides nor other guanidine-based agents were developed for the treatment of diabetes and were forgotten in the following decade. Subsequently, however, the usefulness of metformin in type 2 diabetes was rediscovered thanks to studies on antimalarial research (development of a guanidine-based antimalarial, proguanil – Paludrine which was modified into metformin); metformin in the 1940s, both in clinical studies and in clinical practice, proved useful in the treatment of influenza (at the time it was marketed under the name of flumamine), also demonstrating a hypoglycemic effect (Chen & Anderson, 1947; Curd et al., 1945; Garcia, 1950). The hypoglycemic properties of flumamine were then studied and explored in animal studies and clinical models by Jean Sterne, a French physician, who first reported the use of metformin to treat diabetes in 1957 (Sterne, 1959). Despite Stern's studies, metformin had received at that time limited attention because compared to other biguanides such as phenformin and buformin it was less potent in its oral hypoglycemic activity (McKendry et al., 1959; Ungar et al., 1957). However, the use of phenformin and buformin was discontinued in the late 1970s due to the high risk of lactic acidosis they caused (Bailey, 2017). The reputation and reliability of metformin, belonging to the biguanide class, was thus questioned even though there was evidence demonstrating considerable tolerability of metformin compared to other biguanides. Despite this, pharmacokinetic and pharmacodynamic studies conducted in Europe in the 1980s highlighted metformin's ability to counteract insulin resistance and address hyperglycemia in adulthood without causing weight gain or increased risk of hypoglycemia (Bailey, 2017; Pollak, 2010; Zhao H. et al., 2021). In the United States, the FDA, mindful of the negative experiences with other biguanides, did not look favorably on the use of metformin. Nonetheless, at the insistence of Dr. Gerard Daniel, the FDA initiated a thorough review of the literature and after some clinical trials metformin was considered available for clinical use in the United States starting in 1995 (DeFronzo & Goodman, 1995; Bailey et al., 2007). In 1998, new reasons for the adoption of metformin as initial therapy to manage hyperglycemia in type 2 diabetes were highlighted, i.e. the long-term cardiovascular benefits of metformin were described. Sixty years after its introduction in the treatment of diabetes, metformin (dimethylbiguanide derived from guanidine contained in galega officinalis) has become the first-line and most prescribed oral hypoglycemic drug in the world for the management of type 2 diabetes, with potential to further therapeutic applications (for example in cancer treatment) (Bailey, 2017; Pollak, 2010; Zhao H. et al., 2021). The mechanism of action of metformin is now known: it works by lowering blood glucose levels, decreasing glucose production in the liver, reducing intestinal glucose absorption, and improving insulin sensitivity (Corcoran & Jacobs, 2024). Today metformin is still the most prescribed anti-diabetic worldwide despite the revolutionary discovery of SGLT2 inhibitors and GLP1 receptor agonists (Drzewoski & Hanefeld, 2021) and is included in the World Health Organization's (WHO's) essential medicines list (WHO, 2023a) . Currently, as of 2022, $4,028 billion has been spent on metformin worldwide, a figure that is expected to reach $6,420 billion by 2030 (DBMR – Data Bridge Market Research, 2023).

Ephedrina – Ephedra sinica (called Ma huang in Chinese) or guarana of the family Ephedraceae, known and used for at least 5000 years millennia in TCM, is the plant from which ephedrine is derived (Statler et al., 2023; Torpy et al., 2003). Around 2,700 BC it was described in the famous work of the Chinese emperor Shen Nung, who cataloged 365 herbs based on their bitterness (Lee, 2011). Li Shih-Chen in his work Pents'ao Kang Mu, in the latter part of the 16th century, clearly described the plant. In TCM it was used as a circulatory stimulant, diaphoretic and antipyretic. It has also been used for over a millennium as a remedy for respiratory illnesses, which is why the stem has become an important ingredient in many cough preparations and the basis of many herbal medicines for managing respiratory disease outbreaks. It has also recently been used in China to manage the symptoms of Covid-19. (Li et al., 2022; Tian et al., 2022). A fundamental impulse in the discovery of the alkaloid ephedrine came from Japan, a country where the dried stems of the plant were exported from China at the end of the 16th century. In fact, about 300 years later, the pure alkaloid ephedrine was isolated and characterized for the first time by the Japanese scientist Nagayoshi Nagai (1844-1929) in 1885. It was then forgotten until it was rediscovered by Chen and Schmidt in the early 1920s (Lee, 2011). Ephedrine became a very popular and effective treatment for asthma, especially because, unlike adrenaline (until then the standard therapy), it could be administered orally. Ephedrine as a treatment for asthma reached its peak in the late 1950s, since then there has been a gradual and inevitable decline in its therapeutic use. In the 1990s and 2000s, ephedra and ephedrine were then used for weight loss, a use that had never been contemplated in traditional medicine (International Agency for Research on Cancer, 2002; Shaw, 1998). Finally, ephedrine has also become one of the street drugs as ephedrine represent a major source of methamphetamine production and is therefore currently banned in many countries. At the pharmacodynamic level, ephedrine acts by directly activating alpha- and beta-adrenergic receptors and stimulating the release of norepinephrine from nerve endings. The pharmacological actions of ephedrine are akin to those of catecholamines and include: bronchial smooth muscle relaxation, bladder smooth muscle relaxation, sphincter contraction and detrusor muscle relaxation, intestinal muscle relaxation, increased hepatic glycogenolysis, and oxygen consumption, relaxation of the uterine muscles , stimulation of the respiratory center, cyclopegia without loss of accommodation, cardiac stimulation and increased systolic and diastolic blood pressure. Due to these effects, ephedrine is indicated for the treatment of clinically significant hypotension during spinal anesthesia, as a bronchodilator and finally as a nasal decongestant (Statler et al., 2023). In most countries worldwide it is no longer indicated as a weight loss drug.

In conclusion, there are numerous other herbal drugs that are used or have been used effectively for clinical therapy. But because there are so many, it is impossible to mention them all, so below we will mention only a few in a short list:

Atropine – derived from various plants including Atropa belladonna of the Solanaceae family, is the first-line therapy (Class IIa) for symptomatic bradycardia in the absence of reversible causes, it is also used as a pretreatment in Rapid Sequence Intubation (RSI) (McLendon & Preuss, 2023).

Oseltamivir – derived from the Shikimic acid contained in the Illicium verum of the Schisandraceae family, is an antiviral medication used to manage acute, uncomplicated influenza A or B in adult and pediatric patients, including neonates older than 2 weeks and off label for the treatment avian influenza strains, including the highly pathogenic avian influenza A (H5N1) (Sur et al., 2024).

Digoxin – from Digitalis lanata of the Scrophulariaceae family (Šantić et al., 2017), a cardioactive glycoside used to manage and treat heart failure , certain types of arrhythmia and in inducing fetal demise prior to abortion (David & Shetty, 2023).

Galantamine – from Galanthus nivalis of the Amaryllidaceae family an acetylcholinesterase inhibitor used to manage Alzheimer disease by elevating acetylcholine levels in the brain, thereby improving cognitive function and memory (Kalola et al., 2024).

Bearberry leaf – from the plant Arctostaphylos uva-ursi is a species of the Ericaceae family introduced in therapy by Galen as an uroantiseptic and a mild diuretic, (Petrovska, 2012) is actually available as a treatment of uncomplicated cystitis in several European countries (Tóth et al., 2022).

Senna – from the plant Senna alexandrina belonging to the Fabaceae family introduced by the ancient Arabs as a laxative (Petrovska, 2012), it is still used today for this purpose and is part of the class of stimulant laxatives (Bashir & Sizar, 2024) **.**

Hypericum perforatum, commonly known as St John's wort, of the family Hypericaceae described by Paracelsus (Petrovska, 2012) acts as Serotonin and norepinephrine reuptake inhibitors (SNRI) i.e. as an atypical antidepressant and is prescribed for mild to moderate depression (Peterson & Nguyen, 2023).

Scopolamine – from the Hyoscyamus niger of the Solanaceae family Scopolamine used to treat postoperative nausea, vomiting and motion sickness. With off-label indication for the treatment of chemotherapy-induced nausea, asthma, depression, as a smoking cessation therapy, for excessive sweating and for the treatment of gastrointestinal spasms (Riad & Hithe, 2023).

Conclusion and future directions

Most people in the world are being treated or have been treated with phytochemicals or drugs derived from phytochemicals.

Furthermore, many of these are included in the WHO list of essential medicines (WHO, 2023a). Plant-based drugs have changed human history, providing a fundamental contribution to the survival and improvement of life expectancy of our species (Dar et al., 2017). Excellent examples are chemotherapy drugs (vinblastine, vincristine, etoposide, teniposide, paclitaxel, irinotecan, topotecan) antibiotics and antivirals (cephalosporins and oseltamivir), antiparasitic drugs (quinine and artemisinin), ICU drugs (morphine, neuromuscular blockers, ephedrine), cardiovascular drugs (digoxin, quinidine, atropine, reserpine) antidiabetics (metformin) derived from plants and fungi (Raghavendra, 2002).

Plants often contain more than one phytochemical useful for different diseases and indications. Examples include Galega officinalis (the phytotherapeutic is useful as a galactagogue, while metformin was subsequently synthesized from the guanidine contained in the plant (Bailey, 2017)), the Cinchona succirubra (from which quinine and quinidine are derived (Hellgren et al., 2014)) or the Catharanthus roseus (from which vinblastine and vincristine were extracted (Martino et al., 2018)). However, there are many other plants being studied to search for phytochemical substances useful for therapy. An example is Fibraurea tinctoria of the Menispermaceae family which has antidiabetic, antimicrobial, antiprotozoal, antitumor, lipid-lowering properties and which is already used in numerous traditional Asian medicines (Laumer et al., 2024).

Some lessons can be drawn from the history of the use of phytotherapeutics and phytochemicals:

- plants have developed secondary metabolites as phytochemicals over thousands of years, creating a very diverse number of compounds with numerous pharmacological activities over time (Dar et al., 2017; Khan, 2014). Often, in fact, numerous phytochemicals with different pharmacological activities are present in the same plant. It is therefore the task of scientists to identify useful compounds (see vincristine, etoposide, metformin to name just a few examples) and use them directly as phytochemicals or to create active derivatives as treatments. Furthermore, as happened with vincristine, vinblastine, morphine and artemisinin, plant phytochemicals, once discovered, are not always immediately replicable through laboratory synthesis. We must therefore continue to draw on this practical "knowledge" of defense and interaction with the environment developed by plants over thousands of years and passed down throughout the plant kingdom. The history of the use of plants in therapy demonstrates how current knowledge of pharmacotherapy is based on plant products. Perhaps it would have been impossible for humans to discover some essential drugs for medicine, independently of phytochemicals of plant origin.
- Ancient manuscripts on medicinal plants and also the Western and non-Western traditional medicines should not be looked upon with superiority and disillusionment (see, for example, the discovery of artemisinin as an antimalarial derived from TCM or that Linnaeus knew of the use of Artemisia Annua to treat malaria (Martin et al., 2003; Nature Portfolio, 2024; Zhang et al., 2022; Zhao L. et al., 2022). Rather they need to be studied with a critical eye as potential sources of contemporary pharmacotherapy, given the recent fundamental discoveries in the treatment of diseases derived from it. A prime example of ancient practices borrowed from traditional medicine (unrelated to the use of plants in medicine) that have allowed modern medicine to definitively eradicate devastating and deadly human diseases is the practice of variolation. In 1721, Lady Mary Wortley Montagu observed the popular Turkish practice of vaccination among Greek and Armenian women (the practice involved transferring material from smallpox sores to healthy people, causing milder forms of the disease) and successfully vaccinated her son against smallpox. This practice was also used in Persia, China, India and Africa. The development of the smallpox vaccine was inspired by this experience (WHO, 2023b). We must draw on the knowledge acquired since immemorial time that humans have discovered by researching the cure of diseases in the plant kingdom. Our ancestors identified the healing properties of plants through practical experience and passed them on to subsequent generations. In this way, knowledge was refined from generation to generation, transferring it from one generation to another who modernized old properties and discovered new ones, up to the present day (Petrovska, 2012). For this reason, ethnobotanical studies could help in the discovery of new drugs (Aziz et al., 2018). The properties of periwinkle in the treatment of cancer were known, for example, in TCM (Efferth et al., 2007; Wang et al., 2012). Therefore, knowing that this plant was already used in traditional medicine might have allowed its anticancer activities to be identified earlier.

Today it is estimated that more than 20,000 medicinal plants have been inventoried by the World Health Organization (WHO) and only a few have been analyzed to identify their phytochemical components. It can therefore be hypothesized that there are probably many plants with medicinal properties that are still waiting to be discovered (Domingo-Fernández et al., 2023; International Agency for Research on Caner, 2002). For these reasons about 250 pharmaceutical companies worldwide are currently involved in the study of medicinal plants in scientific laboratories (Pelkonen et al., 2014; Šantić et al., 2017). Pfizer, for example, owns a laboratory in the New York Botanical Garden to study the pharmacological potential of North American flora (NYBG, 2024).

Nowadays it is possible to accelerate drug discovery from plants by combining knowledge gained in automation, biotechnology and chemistry through machine learning, high-pressure liquid chromatography (HPLC), gas chromatography (GC) ,mass spectrometry (MS) and high-throughput mass spectrometry revealing the chemical structures of plant compounds, thus discovering potentially useful phytochemicals more quickly and easily (Kaur et al., 2019 (Nature Portfolio, 2024). Identifying the chemical structures of molecules produced by plants and fungi allows to radically accelerate the selection process for studying drug candidates. So, through virtual screening, coupling small molecule libraries of plant-derived bioactive components with protein structures that are more likely to bind to specific drug targets found in databases allows for notable progress as well as great time savings. These isolated substances can also be exploited as a starting point for the synthesis of new compounds effective in therapy. In addition, a revolutionary breakthrough is the use of artificial intelligence (AI) applied to the study of vast traditional medical knowledge. This technology makes possible the mapping of evidence, patterns and trends once elusive in traditional systems of care. Given the history of plant-based drugs useful to humans, since there are numerous medicinal plants in the world, most of which have not yet been thoroughly studied for their properties, and because it has been estimated that phytochemicals are often more effective drugs than those developed in the laboratory (Khan, 2014) it can be speculated that plants may still be a source of useful drugs in the treatment of disease (Kaur et al., 2019).

However, it should not be underestimated that the study of phytochemicals in plants can be frustrating and arduous. Tu Youyou gives an exemplary vision of it. When she received the Nobel Prize for Physiology and Medicine, she stated that the study of plants is challenging because it involves numerous difficulties ranging from the management of extraction and purification technologies to the variables at play in the study of different species, to the collection and use of the different parts of the plant (et al., 2015). Furthermore, given the great dependence on environmental factors, even cloned plants can produce roots, leaves and fruits of varying quantity and quality. This can contribute to hindering attempts to characterize the numerous botanical extracts such as those used for example in traditional medicines.

But molecules of plant origin still hold promise and can lead to exceptional discoveries. In fact, among other peculiarities, molecules of plant origin also have particular pharmacokinetic characteristics: some, for example, such as colchicine, an alkaloid used for the treatment of gout and extracted from plants of the Colchicum autumnale of the Colchicaceae family, have a short half-life which however corresponds to a local action in the liver (Nature Portfolio, 2024). Molecules of plant origin possess these characteristics which are difficult to obtain with synthetic drugs, which are often instead absorbed systemically.

In the end we suggest that, since there are numerous technical and taxonomic challenges in plant research, it would be useful to deepen taxonomic knowledge in this field by accelerating knowledge of taxonomy with machine learning and research on genomic, chemical, morphological and ecological traits. An example in this sense is the Commercial Innovation Unit of the Royal Botanical Gardens, Kew, London, one of the largest botanical collections in the world where research on plants aimed at pharmaceutical products is monitored and where a research group of 300 people currently operates focused on discovering potential plant-derived drugs (Nature Portfolio, 2024). A project has also been launched at Kew to improve the replication of studies on plants used in TCM, through more controlled global standards. To this end, the Good Practice in TCM Research Association was founded in 2012. This association involves 112 institutions and 24 countries, working to create better guidelines (Corporate Member/ Institutional Member Showcase | ASSOCIATION, 2024).

Furthermore, since today phytotherapeutic products are increasingly prescribed independently and in combination with synthetic drugs, it would be useful to develop a separate herbal pharmacopoeia and develop a rational phytotherapy, in which the effectiveness of the preparations is verified through clinical trials and which is based on the application of preparations whose effectiveness depends on the dose applied and the active components identified (Falzon & Balabanova, 2017; Fürst & Zündorf, 2015). This could also serve to further reduce the possibility of human poisoning by herbal drugs (Farzaei et al., 2020; Halberstein, 2005). This is even more important in developing countries, i.e. 75-80% of the world's population, which rely heavily on medicinal plant medicine, and which in recent decades have invested significantly in ethnobotanical research and the use of medicinal herbs (Prasathkumar et al., 2021).

Unfortunately, in recent years a series of trends have begun to threaten biodiversity and consequently also phytochemical resources. Fortunately, however, a countertrend is underway to preserve natural botanical resources through the implementation of ecological laws and social movements but also the creation of botanical gardens, arboretums, greenhouses, herbariums, tissue cultures, propagation laboratories and seed banks. The history of phytotherapy and phytochemicals further highlights and justifies the importance of the scientific perspective of "One Health," based on the recognition that human health, animal health and ecosystem health are inextricably linked. (Pitt & Gunn, 2024). The preservation of biodiversity, in fact, represents the opportunity to draw on one of the major sources of curative medicines for humans (Halberstein, 2005; Prasathkumar

et al., 2021). By following the "One Health" approach of preserving nature, in addition to impacting human health by reducing pollutants, reducing the emergence of multidrug-resistant pathogens, and positively affecting mental health, it could also foster the discovery of revolutionary new phytochemicals.

In conclusion, the study of medicinal plants and phytotherapy are among the ancient healing practices that have changed and continue to change human history. Examples of medical practices, similar in effectiveness and very old, are variolation (Ellenberger, 1970; WHO, Retrieved May 20, 2024), psychotherapy (Ellenberger, 1970), the interpretation of dreams (Kurland, 1972; Palagini & Rosenlicht, 2011; Scarpelli et al., 2022), and body-mind therapies (WHO, 2023b). Some of these approaches, viewed with suspicion and considered folkloric until recently, are being rediscovered in this historical period. Indeed, as our time is characterized by the burden of chronic diseases, which are currently the leading cause of death, these practices, which are proving to be revolutionary in the fight against chronic diseases (Claro et al., 2024) and at the same time in the implementation of the "One Health" approach, should be increasingly implemented. Finally, the WHO has also recognized the importance of the ancient medical practices and their effectiveness in current medical treatments (WHO, 2023b)

References

Achan J., Talisuna A.O., Erhart A., Yeka A., Tibenderana J.K., Baliraine F.N., Rosenthal P.J., D'Alessandro U., 2011. Quinine, an old anti-malarial drug in a modern world: Role in the treatment of malaria. Malaria Journal 10, 144. https://doi.org/10.1186/1475-2875-10-144

ACOG – American College of Obstetricians and Gynecologists, Committee Opinion No. 743, 2018. Low-dose aspirin use during pregnancy. Obstetrics & Gynecology 132, e44–52. https://www.acog.org/clinical/clinical-guidance/committee-opinion/articles/2018/07/low-dose-aspirin-use-during-pregnancy

Adedeji W.A., 2016. THE TREASURE CALLED ANTIBIOTICS. Annals of Ibadan Postgraduate Medicine 14(2), 56-57.

Agrawal K., 2007. Vincristine. In In S. J. Enna & D. B. Bylund (Eds.), xPharm: The Comprehensive Pharmacology Reference, 1-4. Retrieved June 4, 2024, from https://www.sciencedirect.com/science/article/abs/pii/B9780080552323628533

Al-Khayri J.M., Rashmi R., Toppo V., Chole P.B., Banadka A., Sudheer W.N., Nagella P., Shehata W.F., Al-Mssallem M.Q., Alessa F.M., Almaghasla M.I., Rezk A.A.-S., 2023. Plant Secondary Metabolites: The Weapons for Biotic Stress Management. Metabolites 13(6), Article 6. https://doi.org/10.3390/metabo13060716

Alves R.R., Rosa I.L., 2005. Why study the use of animal products in traditional medicines? Journal of Ethnobiology and Ethnomedicine 1, 5. https://doi.org/10.1186/1746-4269-1-5

Arora R.D., Chen R.J., Menezes R.G., 2024. Vinca Alkaloid Toxicity. In StatPearls. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK557842/

Atanasov A.G., Waltenberger B., Pferschy-Wenzig E.-M., Linder T., Wawrosch C., Uhrin P., Temml V., Wang L., Schwaiger S., Heiss E.H., Rollinger J.M., Schuster D., Breuss J.M., Bochkov V., Mihovilovic M.D., Kopp B., Bauer R., Dirsch V.M., Stuppner H., 2015. Discovery and resupply of pharmacologically active plant-derived natural products: A review. Biotechnology Advances 33(8), 1582-1614. https://doi.org/10.1016/j.biotechadv.2015.08.001

Attorre F., Bruno F. (Eds.), 2022. Roma e il suo Orto Botanico: Storia ed eventi-3 ediz. Sapienza Università Editrice. Retrieved May 28, 2024, from https://www.editricesapienza.it/book/8156

Awosika A.O., Below J., Das J.M., 2024. Vincristine. In StatPearls. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK537122/

Awosika A.O., Farrar M.C., Jacobs T.F., 2024. Paclitaxel. In StatPearls. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK536917/

Aydin-Schmidt B., Thorsell W., Wahlgren M., 2010. Carolus Linnaeus, the ash, worm-wood and other anti-malarial plants. Scandinavian Journal of Infectious Diseases 42(11-12), 941–942. https://doi.org/10.3109/00365548.2010.513065

Azaizeh H., Saad B., Khalil K., Said O., 2006. The State of the Art of Traditional Arab Herbal Medicine in the Eastern Region of the Mediterranean: A Review. Evidence-Based Complementary and Alternative Medicine 3(2), 229–235. https://doi.org/10.1093/ecam/nel034

Aziz M.A., Adnan M., Khan A.H., Shahat A.A., Al-Said M.S., Ullah R., 2018. Traditional uses of medicinal plants practiced by the indigenous communities at Mohmand Agency, FATA, Pakistan. Journal of Ethnobiology and Ethnomedicine 14(1), 2. https://doi.org/10.1186/s13002-017-0204-5

Bailey C.J., 2017. Metformin: Historical overview. Diabetologia 60(9), 1566-1576. https://doi.org/10.1007/s00125-017-4318-z

Bailey, C.J., Day, C., 1989. Traditional plant medicines as treatments for diabetes. Diabetes Care 12(8), 553-564. https://doi.org/10.2337/diacare.12.8.553

Bailey C.J., Day C., 2004. Metformin: Its botanical background. Practical Diabetes International 21(3), 115-117. https://doi.org/10.1002/pdi.606

Bailey C.J., Campbell I.W., Chan J.C.N., Davidson J.A., Howlett H.C.S., Ritz P. (Eds.), 2007. Metformin – The gold standard: a scientific handbook. Wiley. Retrieved June 14, 2024, from https://research.aston.ac.uk/en/publications/metformin-the-gold-standard-a-scientific-handbook

Bailey C.J., Turner R.C., 1996. Metformin. New England Journal of Medicine 334(9), 574-579. https://doi.org/10.1056/NEJM199602293340906

Bashir A., Sizar O., 2024. Laxatives. In StatPearls [Internet]. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK537246/

Bavaro D.F., Belati A., Bussini L., Cento V., Diella L., Gatti M., Saracino Annalisa, Pea F,. Viale P., Bartoletti, M., 2024. Safety and effectiveness of fifth generation cephalosporins for the treatment of methicillin-resistant staphylococcus aureus bloodstream infections: a Narrative Review Exploring past, present and future. Expert opinion on drug safety 23(1), 9-36. https://doi.org/10.1080/14740338.2023.2299377

Betcher A.M., 1977. The civilizing of curare: A history of its development and introduction into anesthesiology. Anesthesia and Analgesia 56(2), 305-319. https://doi.org/10.1213/00000539-197703000-00032

Birmingham A.T., 1999. Waterton and Wouralia. British Journal of Pharmacology 126(8), 1685-1690. https://doi.org/10.1038/sj.bjp.0702409

Bo G., 2000. Giuseppe Brotzu and the discovery of cephalosporins. Clinical Microbiology and Infection: The Official Publication of the European Society of Clinical Microbiology and Infectious Diseases 6 (Suppl 3), 6-9. https://doi.org/10.1111/j.1469-0691.2000.tb02032.x

Britannica, 2024 (May, 19). Carolus Linnaeus, Taxonomy, Binomial Nomenclature, Systematics. https://www.britannica.com/biography/Carolus-Linnaeus

Brodie, Sir B.C., 1968. Further experiments and observations on the action of poisons on the animal systems. International Anesthesiology Clinics, 6(2), 425-426.

Brook K., Bennett J., Desai S.P., 2017. The Chemical History of Morphine: An 8000-year Journey, from Resin to de-novo Synthesis. Journal of Anesthesia History 3(2), 50-55. https://doi.org/10.1016/j.janh.2017.02.001

Bryan C.P., 1930. Ancient Egyptian Medicine – The Papyrus Ebers. Retrieved June 10, 2024, from https://peachv.org/images/MuslimGeo/EgyptMedEbersBryan.pdf

Brotzu G., 1948. Ricerche su di un nuovo antibiotico. Lavori dell'Istituto d'Igiene di Cagliari, 1-11.

Buck E., Finnigan N.A., 2024. Malaria. In StatPearls. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK551711/

Bui T., Patel P., Preuss C.V., 2024. Cephalosporins. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing. https://pubmed.ncbi.nlm.nih.gov/31855361/

Buranova D.D., 2015. The value of Avicenna's heritage in development of modern integrative medicine in Uzbekistan. Integrative Medicine Research 4(4), 220-224. https://doi.org/10.1016/j.imr.2015.06.002

Burr S.A., Leung Y.L., 2014. Curare (d-Tubocurarine). In P. Wexler (Ed.), Encyclopedia of Toxicology (Third Edition), Academic Press (pp. 1088-1089). https://doi.org/10.1016/B978-0-12-386454-3.00482-6

Bynum W.F., 1970. Chemical structure and pharmacological action: A chapter in the history of 19th century molecular pharmacology. Bulletin of the History of Medicine 44(6), 518-538.

Chen K.K., Anderson R.C., 1947. The toxicity and general pharmacology of N1-p-chlorophenyl-N5-isopropyl biguanide. The Journal of Pharmacology and Experimental Therapeutics 91(2), 157-160.

Cheung M., Parmar M., 2023. Reserpine (Archived). In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan. https://pubmed.ncbi.nlm.nih.gov/32491699/

Claro A.E., Pitocco D, Muti P. Molecular aspects of mind–body interaction: Do mind–body therapies influence low-grade chronic inflammation and cardiovascular disease risk? Heart Mind 8(4), 353-355. DOI: 10.4103/hm.HM-D-24-00069. DOI: 10.4103/hm.HM-D-24-00069

Cockayne, T.O. (Ed.). (1865). Leechdoms, Wortcunning and Starcraft of Early England: being a collection of Documents, for the most part never before printed, Illustrating the History of Science in this Country before the Norman Conquest (Vol. 2). Longman. https://wellcomecollection.org/works/dq5gv7ch

Cook D., Simons D.J., 2024. Neuromuscular Blockade. In StatPearls. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK538301/

Corcoran C., Jacobs T.F., 2024. Metformin. In StatPearls. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK518983/

Corporate Member/ Institutional Member Showcase – ASSOCIATION, (2024). Good Practice in Traditional Chinese Medicine. https://www.gp-tcm.org/index.php/corporate-member-institutional-member-showcase/

Craven L.L., 1953. Experiences with aspirin (Acetylsalicylic acid) in the nonspecific prophylaxis of coronary thrombosis. Mississippi Valley Medical Journal (Quincy, Ill) 75(1), 38-44.

Crawford M.J., 2016. The Andean wonder drug: Cinchona bark and imperial science in the Spanish Atlantic, 1630-1800. University of Pittsburgh Press. Retrieved June 13, 2024, from https://upittpress.org/books/9780822944522/

Crul J.F., 1982. Relaxant drugs: From native drugs to the selective agents of today. Acta Anaesthesiologica Scandinavica 26(4), 409-415. https://doi.org/10.1111/j.1399-6576.1982.tb01790.x

Culp O.S., Kaplan I.W., 1944. Condylomata Acuminata: Two Hundred Cases Treated With Podophyllin. Annals of Surgery 120(2), 251-256.

Curd F.H.S., Davey D.G., Rose F.L., 1945. Studies on synthetic antimalarial drugs; some biguanide derivatives as new types of antimalarial substances with both therapeutic and causal prophylactic activity. Annals of Tropical Medicine and Parasitology 39, 208-216.

Dale H., 1934. CHEMICAL TRANSMISSION OF THE EFFECTS OF NERVE IMPULSES. British Medical Journal 1(3827), 835-841. https://doi.org/10.1136/bmj.1.3827.835

Dar R.A., Shahnawaz M., Qazi P.H., 2017. General overview of medicinal plants: A review. The Journal of Phytopharmacology 6(6), 349-351. https://doi.org/10.31254/phyto.2017.6608

David M.N.V., Shetty M., 2023. Digoxin. In StatPearls [Internet]. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK556025/

DBMR – Data Bridge Market Research, 2023. Global Metformin Market – Industry Trends and Forecast to 2030. Retrieved June 14, 2024, from https://www.databridgemarketresearch.com/reports/global-metformin-market

De la Fuente M.F., Souto A., Albuquerque U.P., Schiel N., 2022. Self-medication in nonhuman primates: A systematic evaluation of the possible function of the use of medicinal plants. American Journal of Primatology, 84(11), e23438. https://doi.org/10.1002/ajp.23438

DeFronzo R.A., Goodman A.M., 1995. Efficacy of metformin in patients with non-insulin-dependent diabetes mellitus. The Multicenter Metformin Study Group. The New England Journal of Medicine 333(9), 541-549. https://doi.org/10.1056/NEJM199508313330902

Domingo-Fernández D., Gadiya Y., Mubeen S., Healey D., Norman B.H., Colluru V., 2023. Exploring the known chemical space of the plant kingdom: Insights into taxonomic patterns, knowledge gaps, and bioactive regions. Journal of Cheminformatics 15(1), 107. https://doi.org/10.1186/s13321-023-00778-w

Domínguez-Martín E.M., Tavares J., Ríjo P., Díaz-Lanza A.M., 2020. Zoopharmacology: A Way to Discover New Cancer Treatments. Biomolecules 10(6), 817. https://doi.org/10.3390/biom10060817

Drugs and Lactation Database (LactMed®) [Internet]. Bethesda (MD): National Institute of Child Health and Human Development; 2006. Goat's Rue. [Updated 2021 Feb 15]. Available from: https://www.ncbi.nlm.nih.gov/books/NBK501817/

Drzewoski J., Hanefeld M., 2021. The Current and Potential Therapeutic Use of Metformin—The Good Old Drug. Pharmaceuticals 14(2), 122. https://doi.org/10.3390/ph14020122

Duffin J., 2000. Poisoning the spindle: Serendipity and discovery of the anti-tumor properties of the Vinca alkaloids. Canadian Bulletin of Medical History = Bulletin Canadien D'histoire De La Medecine 17(1-2), 155-192. https://doi.org/10.3138/cbmh.17.1.155

Efferth T., Li P.C.H., Konkimalla V.S.B., Kaina B., 2007. From traditional Chinese medicine to rational cancer therapy. Trends in Molecular Medicine 13(8), 353-361. https://doi.org/10.1016/j.molmed.2007.07.001

Ellenberger H.F., 1970. The discovery of the unconscious: The history and evolution of dynamic psychiatry (Vol. 1, pp. 280-281). New York: Basic books. Retrieved June 17, 2024. https://bac-lac.on.worldcat.org/oclc/299357348

Elufioye T.O., Badal S., 2017. Chapter 1—Background to Pharmacognosy. In S. Badal & R. Delgoda (Eds.), Pharmacognosy (pp. 3-13). Academic Press. https://doi.org/10.1016/B978-0-12-802104-0.00001-9

Erb M., Kliebenstein D.J., 2020. Plant Secondary Metabolites as Defenses, Regulators, and Primary Metabolites: The Blurred Functional Trichotomy1[OPEN]. Plant Physiology 184(1), 39-52. https://doi.org/10.1104/pp.20.00433

Falzon C.C., Balabanova A., 2017. Phytotherapy: An Introduction to Herbal Medicine. Primary Care 44(2), 217-

227. https://doi.org/10.1016/j.pop.2017.02.001

Farzaei M.H., Bayrami Z., Farzaei F., Aneva I., Das S.K., Patra J.K., Das G., Abdollahi M., 2020. Poisoning by Medical Plants. Archives of Iranian Medicine 23(2), 117-127.

Fitzgerald M., Heinrich M., Booker A., 2019. Medicinal Plant Analysis: A Historical and Regional Discussion of Emergent Complex Techniques. Frontiers in Pharmacology 10, 1480. https://doi.org/10.3389/fphar.2019.01480

Fontana F., 1824. Salicilina, principio medicamentoso del salice bianco (salix alba) o base vegetale salificabile. Giornale di farmacia-chimica e scienze accessorie o sia Raccolta delle scoperte, ritrovati e miglioramenti fatti in farmacia ed in chimica (1824 dic, Serie 1, Volume 1, Fascicolo 12). L'Emeroteca Digitale, Biblioteca Nazionale Braidense. Retrieved June 11, 2024, from http://emeroteca.braidense.it/eva/sfoglia_articolo.php?IDTestata=41&CodScheda=128&CodVolume=1372&CodFascicolo=3448&CodArticolo=106141

Fürst R., Zündorf I., 2015. Evidence-Based Phytotherapy in Europe: Where Do We Stand? Planta Medica 81(12-13), 962-967. https://doi.org/10.1055/s-0035-1545948

Garcia E.Y., 1950. Flumamine, a new synthetic analgesic and anti-flu drug. Journal of the Philippine Medical Association 26(7), 287-293.

Gerhardt C.H., 1853. Untersuchungen über die wasserfreien organischen Säuren. Justus Liebigs Annalen Der Chemie 87(2), 149-179. https://doi.org/10.1002/jlac.18530870206

Gibson P.C., 1949. Aspirin in the treatment of vascular diseases. Lancet (London, England) 2(6591), 1172-1174. https://doi.org/10.1016/s0140-6736(49)91829-2

Gillies D., Wynands J.E., 1986. Harold Randall Griffith. The pioneer of the use of muscle relaxants in anaesthesia. British Journal of Anaesthesia 58(9), 943-945. https://doi.org/10.1093/bja/58.9.943

Gray T.C., Halton J., 1946. A Milestone in Anæsthesia?: (D-Tubocurarine Chloride). Proceedings of the Royal Society of Medicine 39(7), 400-410.

Guerriero G., Berni R., Muñoz-Sanchez J.A., Apone F., Abdel-Salam E.M., Qahtan A.A., Alatar, A.A., Cantini C., Cai G., Hausman J.-F., Siddiqui K.S., Hernández-Sotomayor S.M.T., Faisal M., 2018. Production of Plant Secondary Metabolites: Examples, Tips and Suggestions for Biotechnologists. Genes 9(6), 309. https://doi.org/10.3390/genes9060309

Halberstein R.A., 2005. Medicinal plants: Historical and cross-cultural usage patterns. Annals of Epidemiology 15(9), 686-699. https://doi.org/10.1016/j.annepidem.2005.02.004

Hardy K., 2021. Paleomedicine and the Evolutionary Context of Medicinal Plant Use. Revista Brasileira De Farmacognosia 31(1), 1-15. https://doi.org/10.1007/s43450-020-00107-4

Hassan H.M.A., 2015. A Short History of the Use of Plants as Medicines from Ancient Times. Chimia 69(10), 622-623. https://doi.org/10.2533/chimia.2015.622

Hellgren U., Ericsson O., Gustafsson L.L., 2014. Handbook of Drugs for Tropical Parasitic Infections (2nd ed.). CRC Press. https://doi.org/10.1201/9781482272536

Huffman M.A., 1997. Current evidence for self-medication in primates: A multidisciplinary perspective. American Journal of Physical Anthropology 104(S25), 171-200. https://doi.org/10.1002/(SICI)1096-8644(1997)25+<171::AID-AJPA7>3.0.CO;2-7

Humble R.M., 1982. The Gill-Merrill expedition: Penultimate chapter in the curare story. Anesthesiology 57(6), 519-526. https://doi.org/10.1097/00000542-198212000-00014

Hüsemann L.C., Reese A., Radine C., Piekorz R.P., Budach W., Sohn D., Jänicke R.U., 2020. The microtubule targeting agents eribulin and paclitaxel activate similar signaling pathways and induce cell death predominantly in a caspase-independent manner. Cell Cycle 19(4), 464-478. https://doi.org/10.1080/15384101.2020.1716144

Ijinu T.P., George V., Pushpangadan P., 2022. History of Research on Medicinal Plants in India. In Máthé Á., Khan I.A. (Eds.), Medicinal and Aromatic Plants of India Vol. 1 (pp. 35-61). Springer International Publishing. https://doi.org/10.1007/978-3-030-98701-5_2

Imbert T.F., 1998. Discovery of podophyllotoxins. Biochimie 80(3), 207-222. https://doi.org/10.1016/s0300-9084(98)80004-7

International Agency for Research on Cancer, 2002. IARC MONOGRAPH VOLUME 82—History of Use of Traditional Herbal Medicines (Vol. 82). IARC. https://publications.iarc.fr/Book-And-Report-Series/Iarc-Monographs-On-The-Identification-Of-Carcinogenic-Hazards-To-Humans/Some-Traditional-Herbal-Medicines-Some-Mycotoxins-Naphthalene-And-Styrene-2002

Ishikawa H., Colby D.A., Seto S., Va P., Tam A., Kakei H., Rayl T.J., Hwang I., Boger D.L., 2009. Total synthesis of vinblastine, vincristine, related natural products, and key structural analogues. Journal of the American Chemical Society 131(13), 4904-4916. https://doi.org/10.1021/ja809842b

Iyer M., Pal K., Upadhye V., 2023. Chapter 17 – Phytochemicals and cancer. In Pati S., Sarkar T., Lahiri D. (Eds.), Recent

Frontiers of Phytochemicals (pp. 295-308). Elsevier. https://doi.org/10.1016/B978-0-443-19143-5.00007-4

Jain A., Sisodia J., 2024. Quinidine. In StatPearls. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK542193/

James P.A., Oparil S., Carter B.L., Cushman W.C., Dennison-Himmelfarb C., Handler J., Lackland D.T., LeFevre M.L., MacKenzie T.D., Ogedegbe O., Smith S.C. Jr, Svetkey L.P., Taler S.J., Townsend R.R., Wright J.T. Jr, Narva A.S., Ortiz E., 2014. 2014 Evidence-Based Guideline for the Management of High Blood Pressure in Adults: Report From the Panel Members Appointed to the Eighth Joint National Committee (JNC 8). JAMA 311(5), 507-520. https://doi.org/10.1001/jama.2013.284427

Jeffreys D., 2008. Aspirin: The Remarkable Story of a Wonder Drug. Bloomsbury Publishing.

Jeong W.T., Lim H.B., 2018. A UPLC-ESI-Q-TOF method for rapid and reliable identification and quantification of major indole alkaloids in *Catharanthus roseus*. Journal of Chromatography B, Analytical Technologies in the Biomedical and Life Sciences 1080, 27-36. https://doi.org/10.1016/j.jchromb.2018.02.018

Kalola U.K., Patel P., Nguyen H., 2024. Galantamine. In StatPearls [Internet]. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK574546/

Kaur N., Kumar V., Rishi P., Sehrawat N., Dilawari R., Kumar P., Aggarwal N. K., 2019. 6. Phytomedicine: History, scope and future prospects. In Industrial Biotechnology: Plant Systems, Resources and Products, de Gruyter, 105-120. de Gruyter. https://doi.org/10.1515/9783110563337-006

Kelly M., Hartwell J.L., 1954. The biological effects and the chemical composition of podophyllin: A review. Journal of the National Cancer Institute 14(4), 967-1010.

Kern A.B., Fanger H., 1950. Podophyllin in the treatment of cutaneous carcinoma. AMA Archives of Dermatology and Syphilology 62(4), 526-532. https://doi.org/10.1001/archderm.1950.01530170052006

Khan H., 2014. Medicinal Plants in Light of History: Recognized Therapeutic Modality. Journal of Evidence-Based Complementary & Alternative Medicine 19(3), 216-219. https://doi.org/10.1177/2156587214533346

Klaiber J., 2004. The Jesuits in Latin America: Legacy and Current Emphases. International Bulletin of Missionary Research, 28(2), 63-66. Retrieved June 13, 2024, from http://archive.org/details/jesuits-in-latin-america

Kong J.-M., Goh N.-K., Chia L.-S., Chia T.-F., 2003. Recent advances in traditional plant drugs and orchids. Acta Pharmacologica Sinica 24(1), 7–21.

Kopp J., Wang G.Y., Horch R.E., Pallua N., Ge S.D., 2003. Ancient traditional Chinese medicine in burn treatment: A historical review. Burns 29(5), 473-478. https://doi.org/10.1016/S0305-4179(03)00053-6

Kurland M.L., 1972. Oneiromancy: An historic review of dream interpretation. American Journal of Psychotherapy 26(3), 408-416. https://doi.org/10.1176/appi.psychotherapy.1972.26.3.408

Kuruppu A.I., Paranagama P., Goonasekara C.L., 2019. Medicinal plants commonly used against cancer in traditional medicine formulae in Sri Lanka. Saudi Pharmaceutical Journal: SPJ: The Official Publication of the Saudi Pharmaceutical Society 27(4), 565-573. https://doi.org/10.1016/j.jsps.2019.02.004

Kyle R.A., Shampo M.A., 1992. Harold R. Griffith—Introduction of muscle relaxants to anesthesia. Mayo Clinic Proceedings 67(3), 237. https://doi.org/10.1016/s0025-6196(12)60098-6

LacusCurtius. La Storia naturale di Plinio il Vecchio. (n.d.). Retrieved May 29, 2024, from https://penelope.uchicago.edu/Thayer/I/Roman/Texts/Pliny_the_Elder/home*.html

Laumer I.B., Rahman A., Rahmaeti T., Azhari U., Hermansyah, Atmoko S.S.U., Schuppli C., 2024. Active self-treatment of a facial wound with a biologically active plant by a male Sumatran orangutan. Scientific Reports 14(1), 8932. https://doi.org/10.1038/s41598-024-58988-7

Lee M.R., 2011. The history of Ephedra (ma-huang). The Journal of the Royal College of Physicians of Edinburgh 41(1), 78-84. https://doi.org/10.4997/JRCPE.2011.116

Lemieux G., Davignon A., Genest J., 1956. Treatment of Arterial Hypertension with Rescinnamine , A New Alkaloid Isolated from Rauwolfia Serpentina. Canadian Medical Association Journal 74(2), 144-145.

Li L., Wu Y., Wang J., Yan H., Lu J., Wang Y., Zhang B., Zhang J., Yang J., Wang X., Zhang M., Li Y., Miao L., Zhang H., 2022. Potential Treatment of COVID-19 with Traditional Chinese Medicine: What Herbs Can Help Win the Battle with SARS-CoV-2? Engineering (Beijing, China) 19, 139-152. https://doi.org/10.1016/j.eng.2021.08.020

Linnaeus C., 1735. Dissertatio medica inauguralis in qua exhibetur hypothesis nova De febrium intermittentium causa (Vol. 1), apud hæred. Joh. Rampen

Liu M.-Y., Ren Y.-P., Zhang L.-J., Ding J.Y., 2016. Pretreatment

with Ginseng Fruit Saponins Affects Serotonin Expression in an Experimental Comorbidity Model of Myocardial Infarction and Depression. Aging and Disease 7(6), 680-686. https://doi.org/10.14336/AD.2016.0729

Loukas M., Lanteri A., Ferrauiola J., Tubbs R.S., Maharaja G., Shoja M.M., Yadav A., Rao V.C., 2010. Anatomy in ancient India: A focus on the Susruta Samhita. Journal of Anatomy 217(6), 646-650. https://doi.org/10.1111/j.1469-7580.2010.01294.x

Lu L., Geng Q., Wang J., Bai C., Cheng G., Cui Y., Dong B., Fang J., Gao F., Huang R., Huang S., Li Y., Liu G., Liu Y., Lu Y., Ren Y., Mao J., Shi D., Su H., …& Liu M., 2022. Expert Consensus on Diagnosis and Treatment of Adult Mental Stress-Induced Hypertension in China (2022 Revision): Part B. Heart and Mind 6(3), 101. https://doi.org/10.4103/hm.hm_16_22

Lucas D.M., Still P.C., Pérez L.B., Grever M.R., Kinghorn A.D., 2010. Potential of Plant-Derived Natural Products in the Treatment of Leukemia and Lymphoma. Current Drug Targets 11(7), 812-822.

Mann J., 2000. Murder, Magic, and Medicine. Oxford University Press.

Martin V.J.J., Pitera D.J., Withers S.T., Newman J.D., Keasling J.D., 2003. Engineering a mevalonate pathway in Escherichia coli for production of terpenoids. Nature Biotechnology 21(7), 796-802. https://doi.org/10.1038/nbt833

Martino E., Casamassima G., Castiglione S., Cellupica E., Pantalone S., Papagni F., Rui M., Siciliano A.M., Collina S., 2018. Vinca alkaloids and analogues as anti-cancer agents: Looking back, peering ahead. Bioorganic & Medicinal Chemistry Letters 28(17), 2816-2826. https://doi.org/10.1016/j.bmcl.2018.06.044

Maclagan T., 1876. The treatment of acute rheumatism by salicin. The Lancet, 108(2774), 601-604. https://doi.org/10.1016/S0140-6736(02)49509-8

Maude R.J., Woodrow C.J., White L.J., 2010. Artemisinin Antimalarials: Preserving the "Magic Bullet." Drug Development Research 71(1), 12-19. https://doi.org/10.1002/ddr.20344

McKendry J.B., Kuwayti K., Rado P.P., 1959. Clinical experience with DBI (phenformin) in the management of diabetes. Canadian Medical Association Journal 80(10), 773-778.

McLendon K., Preuss C.V., 2023. Atropine. In StatPearls [Internet]. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK470551/

Merlin M.D., 2003. Archaeological Evidence for the Tradition of Psychoactive Plant Use in the Old World. Economic Botany 57(3), 295-323.

Meshnick S.R., 1998. Artemisinin antimalarials: Mechanisms of action and resistance. Medecine Tropicale: Revue Du Corps De Sante Colonial 58(3 Suppl), 13-17.

Michaleas S.N., Laios K., Tsoucalas G., Androutsos G., 2021. Theophrastus Bombastus Von Hohenheim (Paracelsus) (1493-1541): The eminent physician and pioneer of toxicology. Toxicology Reports 8, 411-414. https://doi.org/10.1016/j.toxrep.2021.02.012

Miller L.H., Rojas-Jaimes J., Low L.M., Corbellini G., 2023. What Historical Records Teach Us about the Discovery of Quinine. The American Journal of Tropical Medicine and Hygiene 108(1), 7-11. https://doi.org/10.4269/ajtmh.22-0404

Miller L.H., Su X., 2011. Artemisinin: Discovery from the Chinese herbal garden. Cell, 146(6), 855-858. https://doi.org/10.1016/j.cell.2011.08.024

Moerman D.E., 1991. The medicinal flora of native North America: An analysis. Journal of Ethnopharmacology 31(1), 1-42. https://doi.org/10.1016/0378-8741(91)90141-Y

Montinari M.R., Minelli S., De Caterina R., 2019. The first 3500 years of aspirin history from its roots – A concise summary. Vascular Pharmacology 113, 1-8. https://doi.org/10.1016/j.vph.2018.10.008

Murphy PB, Bechmann S, Barrett MJ. Morphine. 2023 May 22. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2024 Jan.

Nagappa A.N., Cheriyan B., 2001. Wound healing activity of the aqueous extract of Thespesia populnea fruit. Fitoterapia 72(5), 503-506. https://doi.org/10.1016/s0367-326x(01)00275-1

National Cancer Institute (NCI – nciglobal, ncienterprise), 2014. Can Taking Aspirin Help Prevent Cancer?. (2014, April 21). [cgvArticle]. https://www.cancer.gov/about-cancer/causes-prevention/research/aspirin-cancer-risk

National Library of Medicine, 1968. Curare alkaloids. I. Tubocurarine by Harold King. International Anesthesiology Clinics, 6(2), 518-530.

Nature Portfolio, 2024. Revitalizing the science of traditional medicinal plants. Springer Nature. Retrieved May 20, 2024, from https://www.nature.com/articles/d42473-021-00478-9

Noble R.L., Beer C.T., Cutts J.H., 1958. Role of chance observations in chemotherapy: Vinca rosea. Annals of the

New York Academy of Sciences 76(3), 882-894. https://doi.org/10.1111/j.1749-6632.1958.tb54906.x

Nosten F., Richard-Lenoble D., Danis M., 2022. A brief history of malaria. Presse Medicale (Paris, France: 1983) 51(3), 104130. https://doi.org/10.1016/j.lpm.2022.104130

NYBG, 2024. Plant Talk – Pfizer Plant Research Laboratory. Retrieved June 14, 2024, from https://www.nybg.org/blogs/plant-talk/tag/pfizer-plant-research-laboratory/

Office for National Statistics, 2017. Causes of death over 100 years. Retrieved June 7, 2024). https://www.ons.gov.uk/peoplepopulationandcommunity/birthsdeathsandmarriages/deaths/articles/causesofdeathover100years/2017-09-18

Orhan I.E., 2014. Pharmacognosy: Science of natural products in drug discovery. BioImpacts: BI 4(3), 109-110. https://doi.org/10.15171/bi.2014.001

Palagini L., Rosenlicht N., 2011. Sleep, dreaming, and mental health: A review of historical and neurobiological perspectives. Sleep Medicine Reviews 15(3), 179-186. https://doi.org/10.1016/j.smrv.2010.07.003

Pelkonen O., Xu Q., Fan T.-P., 2014. Why is Research on Herbal Medicinal Products Important and How Can We Improve Its Quality? Journal of Traditional and Complementary Medicine 4(1), 1-7. https://doi.org/10.4103/2225-4110.124323

Peterson B., Nguyen H., 2023. St. John's Wort. In StatPearls [Internet]. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK557465/

Petrovska B.B., 2012. Historical review of medicinal plants' usage. Pharmacognosy Reviews 6(11), 1-5. https://doi.org/10.4103/0973-7847.95849

Pitt S.J., Gunn A., 2024. The One Health Concept. British Journal of Biomedical Science 81, 12366. https://doi.org/10.3389/bjbs.2024.12366

Pollak M., 2010. Metformin and Other Biguanides in Oncology: Advancing the Research Agenda. Cancer Prevention Research (Philadelphia, Pa.) 3(9), 1060-1065. https://doi.org/10.1158/1940-6207.CAPR-10-0175

Prabhakar A., Kaye A.D., Wyche M.Q., Salinas O.J., Mancuso K., Urman R.D., 2016. Novel drug development for neuromuscular blockade. Journal of Anaesthesiology, Clinical Pharmacology 32(3), 376-378. https://doi.org/10.4103/0970-9185.188833

Prasathkumar M., Anisha S., Dhrisya C., Becky R., Sadhasivam S., 2021. Therapeutic and pharmacological efficacy of selective Indian medicinal plants – A review. Phytomedicine Plus 1(2), 100029. https://doi.org/10.1016/j.phyplu.2021.100029

Raghavendra T., (2002). Neuromuscular blocking drugs: Discovery and development. Journal of the Royal Society of Medicine 95(7), 363-367.

Reid G.M., 2009. Carolus Linnaeus (1707–1778): His life, philosophy and science and its relationship to modern biology and medicine. *Taxon 58*(1), 18-31. Retrieved June 17, 2024, from https://onlinelibrary.wiley.com/doi/abs/10.1002/tax.581005

Reyhanoglu G., Tadi P., 2024. Etoposide. In StatPearls. StatPearls Publishing. http://www.ncbi.nlm.nih.gov/books/NBK557864/

Riad M., Hithe C.C., 2023. Scopolamine. In StatPearls [Internet]. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK554397/

Rigatelli B., 1824. Sostituto indigeno del solfato di chinina, Biblioteca Italiana o sia Giornale di Letteratura. Scienze ed Arti, 33, 267-271.Robert J., Rivory L., 1998. Pharmacology of irinotecan. Drugs of Today (Barcelona, Spain: 1998) 34(9), 777-803. https://doi.org/10.1358/dot.1998.34.9.485276

Rigatelli B. 1826. Sale amarissimo antifebbrile (Atti dell'Accademia di agricoltura, commercio e arti di Verona). Giornale di farmacia-chimica e scienze accessorie o siano Annali Universali delle scoperte, ritrovati e miglioramenti fatti in farmacia ed in chimica (1826 set, Serie 1, Volume 4, Fascicolo 9). L'Emeroteca Digitale, Biblioteca Nazionale Braidense. Retrieved June 11, 2024, from http://emeroteca.braidense.it/eva/sfoglia_articolo.php?IDTestata=42&CodScheda=129&CodVolume=1376&CodFascicolo=3475&CodArticolo=106798

Robert J., Rivory L., 1998. Pharmacology of irinotecan. Drugs of Today (Barcelona, Spain) 34(9), 777- 803. doi: 10.1358/dot.1998.34.9.485276

Rodrigues P.T., Valdivia H.O., de Oliveira T.C., Alves J.M.P., Duarte A.M.R.C., Cerutti-Junior C., Buery J.C., Brito C.F.A., de Souza J.C., Hirano Z.M.B., Bueno M.G., Catão-Dias J.L., Malafronte R.S., Ladeia-Andrade S., Mita T., Santamaria A.M., Calzada J.E., Tantular I.S., Kawamoto F., … & Ferreira M.U., 2018. Human migration and the spread of malaria parasites to the New World. Scientific Reports 8(1), 1993. https://doi.org/10.1038/s41598-018-19554-0

Rowbotham S., 1948. CURARE: ITS HISTORY, NATURE AND CLINICAL USE By A. R. McINTYRE, PH.D., M.D. Chicago: University of Chicago Press. 1947. pp. 240, with 24 illustrations. Price $5 net. International Journal of Clinical Practice 2(1), 7-7. https://doi.org/10.1111/j.1742-1241.1948.tb02024.x

Sakai T., Morimoto Y., 2022. The History of Infectious Diseases and Medicine. Pathogens 11(10), 1147. https://doi.org/10.3390/pathogens11101147

Samiee-Rad F., Hosseini Sedighi S.F., Taherkhani A., Gheibi, N., 2022. Evaluation of Healing Effects of Poultice Containing 0.5% Fulvic Acid on Male White-Male Rats with Skin Ulcer. Journal of Cutaneous and Aesthetic Surgery 15(1), 40-47. https://doi.org/10.4103/JCAS.JCAS_215_20

Šantić Ž., Pravdić N., Bevanda M., Galić, K., 2017. The historical use of medicinal plants in traditional and scientific medicine. Psychiatria Danubina 29(Suppl 4), 787–792.

Scarpelli S., Alfonsi V., Gorgoni M., De Gennaro L., 2022. What about dreams? State of the art and open questions. Journal of Sleep Research 31(4), e13609. https://doi.org/10.1111/jsr.1360

Sée G., 1877. Traitement du rhumatisme de la goutte aiguë et chronique et de diverses affections du système nerveux par le salicylate de soude.Free Download, Borrow, and Streaming: Internet Archive. (n.d.). Retrieved June 11, 2024, from https://archive.org/details/BIUSante_43460/page/n7/mode/2up

Shah S.B., Chawla R., Pahade A., EL-Molla A., 2021. Neuromuscular blockers and their reversal: Have we finally found the on-off switches? Ain-Shams Journal of Anesthesiology 13(1), 15. https://doi.org/10.1186/s42077-021-00130-0

Shaw D. 1998. Risks or remedies? Safety aspects of herbal remedies in the UK. Journal of the Royal Society of Medicine 91(6), 294-296. https://doi.org/10.1177/014107689809100602

Shurkin J., 2014. News Feature: Animals that self-medicate. Proceedings of the National Academy of Sciences of the United States of America 111(49), 17339-17341. https://doi.org/10.1073/pnas.1419966111

Slevin M.L., 1991. The clinical pharmacology of etoposide. Cancer 67(S1), 319-329. https://doi.org/10.1002/1097-0142(19910101)67:1+<319::AID-CNCR2820671319>3.0.CO;2-D

Slotta K.H., Tschesche R., 1929. Über Biguanide, II.: Die blutzucker-senkende Wirkung der Biguanide. Berichte Der Deutschen Chemischen Gesellschaft (A and B Series) 62(6), 1398-1405. https://doi.org/10.1002/cber.19290620605

Sneader W., 2005. Drug Discovery. Wiley Online Books. (n.d.). Retrieved June 11, 2024, from https://onlinelibrary.wiley.com/doi/book/10.1002/0470015535

Solinas M.N., 2009. Materia medica e prodotti naturali nella Chimica Farmaceutica.

Statler A.K., Maani C.V., Kohli A., 2023. Ephedrine. In StatPearls [Internet]. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK547661/

Sterne J., 1959. Treatment of diabetes mellitus with N,N-dimethylguanylguanidine (LA. 6023, glucophage). Therapie 14, 625-630.

Sur M., Lopez M.J., Patel P., Baker M.B., 2024. Oseltamivir. In StatPearls [Internet]. StatPearls Publishing. https://www.ncbi.nlm.nih.gov/books/NBK539909/

Swedan H.K., Kassab A.E., Gedawy E.M., Elmeligie S.E., 2023. Topoisomerase II inhibitors design: Early studies and new perspectives. Bioorganic Chemistry 136, 106548. https://doi.org/10.1016/j.bioorg.2023.106548

Sykes K., 1993. Harold Griffith Memorial Lecture. The Griffith legacy. Canadian Journal of Anaesthesia = Journal Canadien D'anesthesie 40(4), 365-374. https://doi.org/10.1007/BF03009637

Tóth B., Jávorházy A., Nyirády P., Csupor-Löffler B., Birinyi P., Zhanel G., Naber K., Länger R., Vörhendi N., Gede N., Váncsa S., Hegyi P., Csupor D., 2022. Bearberry in the treatment of acute uncomplicated cystitis (BRUMI): protocol of a multicentre, randomised double-blind clinical trial. BMJ Open 12(6), e057982. doi: 10.1136/bmjopen-2021-057982

Tian N.-N., Yang X.-H., Zhu Y.-X., Zeng X.-S., Yuan J.-Y., Yang J.-L., Jia W.-W., Li C., 2022. [Mahuang (herbaceous stem of Ephedra spp.): Chemistry, pharmacodynamics, and pharmacokinetics]. Zhongguo Zhong Yao Za Zhi = Zhongguo Zhongyao Zazhi = China Journal of Chinese Materia Medica 47(13), 3409-3424. https://doi.org/10.19540/j.cnki.cjcmm.20220425.601

Torpy J.M., Lynm C., Glass R.M., 2003. Ephedra and Ephedrine. JAMA 289(12), 1590. https://doi.org/10.1001/jama.289.12.1590

Trenholme C.M., Williams R.L., Desjardins R.E., Frischer H., Carson P.E., Rieckmann K.H., Canfield C.J., 1975. Mefloquine (WR 142,490) in the treatment of human malaria. Science (New York, N.Y.) 190(4216), 792-794. https://doi.org/10.1126/science.1105787

Tu Y., 2011. The discovery of artemisinin (qinghaosu) and gifts from Chinese medicine. Nature Medicine 17(10), 1217-1220. https://doi.org/10.1038/nm.2471

Twaij B.M., Hasan M.N., 2022. Bioactive Secondary Metabolites from Plant Sources: Types, Synthesis, and Their Therapeutic Uses. International Journal of Plant Biology 13(1), Article 1. https://doi.org/10.3390/ijpb13010003

Ullah R., Alqahtani A.S., Noman O.M.A., Alqahtani A.M., Ibenmoussa S., Bourhia M., 2020. A review on ethno-medicinal plants used in traditional medicine in the Kingdom of Saudi Arabia. Saudi Journal of Biological Sciences 27(10), 2706-2718. https://doi.org/10.1016/j.sjbs.2020.06.020

Ungar G., Freedman L., Shapiro S.L., 1957. Pharmacological studies of a new oral hypoglycemic drug. Proceedings of the Society for Experimental Biology and Medicine. Society for Experimental Biology and Medicine (New York, N.Y.) 95(1), 190-192. https://doi.org/10.3181/00379727-95-23163

Upton R., 2022. Chapter 5 – Traditional herbal medicine, pharmacognosy, and pharmacopoeial standards: A discussion at the crossroads in the age of COVID. In P. K. Mukherjee (Ed.), Evidence-Based Validation of Herbal Medicine (Second Edition) (pp. 109-148). Elsevier. https://doi.org/10.1016/B978-0-323-85542-6.00003-2

Vaidyanathan G., 2024. 'Orangutan, heal thyself': First wild animal seen using medicinal plant. Nature 629(8013), 737. https://doi.org/10.1038/d41586-024-01289-w

Vane J.R., Botting R.M., 2003. The mechanism of action of aspirin. Thrombosis Research 110(5-6), 255-258. https://doi.org/10.1016/s0049-3848(03)00379-7

Vitali Serdoz L., Rittger H., Furlanello F., Bastian D., 2019. Quinidine-A legacy within the modern era of antiarrhythmic therapy. Pharmacological Research 144, 257-263. https://doi.org/10.1016/j.phrs.2019.04.028

Wang S., Wu X., Tan M., Gong J., Tan W., Bian B., Chen M., Wang Y., 2012. Fighting fire with fire: Poisonous Chinese herbal medicine for cancer therapy. Journal of Ethnopharmacology 140(1), 33-45. https://doi.org/10.1016/j.jep.2011.12.041

Weir M.R., 2020. Reserpine: A New Consideration of an Old Drug for Refractory Hypertension. American Journal of Hypertension 33(8), 708-710. https://doi.org/10.1093/ajh/hpaa069

Werner E.A., Bell J., 1922. CCXIV.—The preparation of methylguanidine, and of ββ-dimethylguanidine by the interaction of dicyanodiamide, and methylammonium and dimethylammonium chlorides respectively. Journal of the Chemical Society, Transactions 121, 1790-1794. https://doi.org/10.1039/CT9222101790

WHO (World Health Organization), History of smallpox vaccination. Retrieved May 20, 2024, from https://www.who.int/news-room/spotlight/history-of-vaccination/history-of-smallpox-vaccination

WHO (World Health Organization), 2015. Guidelines for the treatment of malaria. World Health Organization, Geneva. http://www.ncbi.nlm.nih.gov/books/NBK294440/

WHO (World Health Organization), 2022. Cancer. Retrieved June 12, 2024, from https://www.who.int/news-room/fact-sheets/detail/cancer

WHO (World Health Organization), 2023a. Model List of Essential Medicines – 23rd list. Retrieved June 10, 2024, from https://www.who.int/publications-detail-redirect/WHO-MHP-HPS-EML-2023.02

WHO (World Health Organization), 2023b. Traditional medicine has a long history of contributing to conventional medicine and continues to hold promise. World Health Organization [Internet].[cited 25 Feb 2024]. Available: https://www. who. int/news-room/feature-stories/detail/traditional-medicine-has-a-long-history-of-contributing-to-conventional-medicine-and-continues-to-hold-promise.

Wintersteiner O., Dutcher J.D., 1943. Curare Alkaloids From Chondodendron Tomentosum. Science (New York, N.Y.), 97(2525), 467-470. https://doi.org/10.1126/science.97.2525.467

Wood J.N., 2015. From plant extract to molecular panacea: a commentary on Stone (1763) 'An account of the success of the bark of the willow in the cure of the agues.' Philosophical Transactions of the Royal Society B: Biological Sciences, 370(1666), 20140317. https://doi.org/10.1098/rstb.2014.0317

Xu L., Hu J., Liu L., Zhan S., Wang S., 2021. Trends and Patterns in Traditional Chinese Medicine Use Among Chinese Population in Late Adulthood: An Eight-Year Repeated Panel Survey. The American Journal of Chinese Medicine, 49(2), 269-283. https://doi.org/10.1142/S0192415X21500142

Yadav S., Mishra A.P., Kumar S., Negi A., Asha, Maurya V. K., 2021. Chapter 8 – Herbal wound healing agents. In Egbuna C., Mishra A.P., Goyal M.R. (Eds.), Preparation of Phytopharmaceuticals for the Management of Disorders (pp. 169-184). Academic Press. https://doi.org/10.1016/B978-0-12-820284-5.00007-1

Yang F., Hanon S., Lam P., Schweitzer P., 2009. Quinidine revisited. The American Journal of Medicine, 122(4), 317-321. https://doi.org/10.1016/j.amjmed.2008.11.019

Yapijakis C., (2009). Hippocrates of Kos, the Father of Clinical Medicine, and Asclepiades of Bithynia, the Father of Molecular Medicine. In Vivo, 23(4), 507-514.

Yoneda K.Y., Cross C.E., 2010. 8.24 – The Pulmonary Toxicity of Anticancer Agents. In McQueen C.A. (Ed.), Comprehensive Toxicology (Second Edition) (pp. 477-510). Elsevier. https://doi.org/10.1016/B978-0-08-046884-6.00924-6

Tu Youyou, Institute of Chinese Materia Medica, China Academy of Chinese Medical Sciences, Beijing, China, 2015. Artemisinin—A Gift from Traditional Chinese Medicine to the World.pdf. (n.d.). China Academy of Chinese Medical Sciences, Beijing, China. Nobel Lecture [serial online]. Retrieved June 17, 2024, from https://www.nobelprize.org/uploads/2018/06/tu-lecture.pdf

Zhang J., Hansen L.G., Gudich O., Viehrig K., Lassen L.M.M., Schrübbers L., Adhikari K.B., Rubaszka P., Carrasquer-Alvarez E., Chen L., D'Ambrosio V., Lehka B., Haidar A. K., Nallapareddy S., Giannakou K., Laloux M., Arsovska D., Jørgensen M.A.K., Chan L.J.G., Kristensen M., Christensen H.B., Sudarsan S., Stander E.A., Baidoo E., … Keasling J.D., 2022. A microbial supply chain for production of the anti-cancer drug vinblastine. Nature 609(7926), 341-347. https://doi.org/10.1038/s41586-022-05157-3

Zhao H., Swanson K.D., Zheng B., 2021. Therapeutic Repurposing of Biguanides in Cancer. Trends in Cancer 7(8), 714-730. https://doi.org/10.1016/j.trecan.2021.03.001

Zhao L., Zhu Y., Jia H., Han Y., Zheng X., Wang M., Feng W., 2022. From Plant to Yeast—Advances in Biosynthesis of Artemisinin. Molecules 27(20), 6888. https://doi.org/10.3390/molecules27206888

Zündorf U., 1997. Aspirin, 100 Years: The Future Has Just Begun. Bayer AG, Consumer Care Business Group.