Chapter 1
The Evolution of Modern Medicine: Garden to Pill Box

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1.1 Introduction

To first explore how natural substances have been used to treat humans, one can look to Colombia and Peru over 8,000 years ago. Historical evidence suggests that these ancient foraging societies chewed on the leaves of the cocoa tree to keep warm, to battle altitude sickness, and to provide a quick source of instant energy (Mortimer 1974). As history progressed, the cocoa leaf became an integral panacea medicine for nearly all illnesses and diseases in Andean Incan society. This is the first documented example of the utilization of biologically-active, plant-derived substances—referred to as phytochemicals—to treat human ailments. Over the last few millennia, thousands of other herbal substances have been used by various cultures to combat a myriad of sicknesses. Human society has consistently been able to harness the power of phytochemicals, even though at times the exact mechanisms of action were not well understood. In the contemporary age, naturally derived medicine has allowed society to tackle diseases in numerous areas of healthcare. Although there are too many such drugs to discuss in this chapter, a few medications in select healthcare categories will be highlighted.

From an economic standpoint, the medicinal plant industry has been equally productive. Global imports and exports (2000–2008) of medicinal plants were worth USD $1.59 and $1.14 billion/year, respectively, with a >40% growth rate per annum (Rajeshwara Rao and Rajput 2010). As is evident in this statistic, the medicinal plant industry is growing at an ever-increasing rate. However, it is important to note that out of the 3000 medicinal plants traded internationally, only 900 are

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under cultivation, and the vast majority of exported biomass is harvested from the wild (Rajeshwara Rao and Rajput 2010). Hence, this implies that more than two-thirds of the medicinal plants currently exported have yet to be cultivated commercially, signaling an area of huge economic potential.

1.2 Types of Drugs

In medicine, drugs are often classified based on their functional use in the human body. In this chapter, four major categories of drugs are explored: cardiovascular, oncologic, neurologic, and pain-suppressants. Pertinent plant-derived medications, including their history, botanical origins, chemical properties, and mechanism of action, will be discussed in each category.

1.2.1 Cardiovascular Drugs

1.2.1.1 Atropine

Imagine a patient feeling lightheaded and confused Drugs, experiencing symptoms Cardiovascular drugs such as fainting and shortness of breath. After visiting the clinician, the patient finds out that he or she has been diagnosed with bradycardia, a medical condition where the electrical impulses in the heart don't fire as normally as they should, resulting in an abnormally low heart rate (Kounis and Chopra 1974). A medication that is used every day in the hospital to revive a patient's abnormally slow heart rate and to treat conditions such as bradycardia is a drug known as atropine (Kounis and Chopra 1974).

Before delving into the specifics of this medication, some foundational human physiology will first be discussed. The human nervous system is broken down into the central nervous system (CNS) and the peripheral nervous system (PNS). The CNS includes the brain and the spinal cord. The PNS contains all other nerves outside of the CNS. More specifically, the PNS can be categorized into the somatic nervous system and the autonomic nervous system. The somatic nervous system controls voluntary muscle movements (e.g., raising an arm, moving a leg), and the autonomic nervous system is in charge of functions that are not consciously controlled (e.g., breathing, heart beat). Within the classification of the autonomic system, there are two main types of nerves which work antagonistically with each other: the sympathetic and parasympathetic nerves (Langley 1921). In simple terms, the sympathetic nerves are activated during times of stress ("fight" response), causing an increase in heart rate and rise in blood pressure (Jänig 2006). The parasympathetic nerves slow down the heart rate and lower the blood pressure ("flight" response). There is a push-pull balance between these nerves to maintain homeostasis.

Atropine works as an anticholinergic or anti-parasympathetic medication through competitive inhibition (Satake et al. 1992), causing decreased activity of the parasympathetic nerves and leading to an increase in sympathetic nerve activity. In the clinical setting, an increase in sympathetic activity coupled with a decrease in parasympathetic activity leads to an elevation in heart rate and a rise in blood pressure (Jänig 2006). For critically ill hospitalized patients, atropine is used to chemically stimulate the heart when the heart rate drops significantly, such as in cases of poisoning (McDonough and Shih 2007). This medication is a crucial aspect of all crash carts in the hospital and ICU settings. Atropine is even on the World Health Organization's List of Essential Medicines, which is a comprehensive compilation of the most safe and effective medicines (WHO 2011).

While atropine is a critical, lifesaving medication, its origins are quite humble. The drug is naturally derived from various plants found in nature, such as the deadly nightshade (*Atropa belladonna*, found mainly in Europe, North Africa, and Western Asia), henbane (*Hyoscyamus niger*, found mainly in Eurasia), thorn apple (*Datura stramonium*, found mainly in Central America), and mandrake (*Mandragora officinarum*, found mainly around the Mediterranean coast) (West and Mika 1957). The medicinal properties of the mandrake plant were first described in fourth century B.C. by Theophrastus, a Greek plant biologist, who described the chemical as an ideal treatment for wounds, sleeplessness, and love (Hamilton and Baskett 2000). Extracts from the henbane plant were used in the last century B.C. by Queen Cleopatra of the Ptolemaic Kingdom of Egypt as a pupil dilation agent to appear more alluring (Hocking 1947). During the Renaissance period of Europe, many women also used the juice of the deadly nightshade plant in order to enlarge their pupils.

These plants contain both hyoscyamine and hyoscine, which are two closely related alkaloid compounds (Pearse 1876). Specifically, atropine is a mixture of two different forms of the hyoscyamine alkaloid. As technology advanced, atropine itself was isolated in the year 1833 (West and Mika 1957). Since that point, through extensive research and scientific testing, atropine is now one of the most widely available generic medicines found in hospitals around the world, with a price tag less than USD $0.50 for 1 mg vials. Derived from plants and first used over 6,000 years ago, atropine has sealed its place as a crucial drug in the modern medical system.

1.2.1.2 Digoxin

There are other cardiac arrhythmias (i.e., abnormal cardiac rhythms) and heart conditions (e.g., congestive heart failure) which can be disabling and sometimes fatal (Domanski et al. 1994). Some of these arrhythmias include atrial fibrillation and atrial flutter. For these conditions, the plant-derived drug digoxin can help regulate the heart rhythm and improve cardiac function during heart failure (Hollman 1996). Digoxin's ability to inhibit the sodium potassium adenosine triphosphatase enzyme (Na/K pump), mainly in the myocardium, helps the heart to beat more regularly and with stronger force (Schwartz et al. 1968).

Like atropine, digoxin is on the World Health Organization's List of Essential Medicines (WHO 2011). Unlike intravenous atropine used in the hospital setting, however, digoxin is used as a cardiac medication consumed daily in the form of a tablet. As of 2019, monthly prescription of digoxin costs less than USD $10. Digoxin was first derived from the foxglove plant, also known as *Digitalis lanata* (Hollman 1996). Digoxin has also been extracted from other plants from the same genus *Digitalis*. The foxglove plant is part of the plantain family, originally coming from the continent of Europe. However, as colonization occurred, the plant was domesticated and brought to North America. The slightly acidic soils of the continent helped foster an environment suitable for optimal plant growth (Allen 1987). The foxglove plant can be found in a wide variety of geographic locations, ranging from woods and cliffs to grassy meadows and wastelands.

In 1785, the English physician William Withering first described the medicinal practicalities of *Digitalis* derivatives in his book, "An Account of the Foxglove and Some of its Medical Uses with Practical Remarks on Dropsy and Other Diseases" (Withering 2014). In his descriptions, Withering talks about *Digitalis* extract's ability to fight dropsy, which is the former name for congestive heart failure and the associated edema (i.e., abnormal accumulation of fluid within certain tissues of the body) (Withering 2014). Based on these accounts, digoxin and digoxin-related substances have been used to treat congestive heart failure for almost 250 years.

1.2.1.3 Warfarin

Warfarin is one of the most popular anticoagulants (i.e., blood thinners) available on the drug market (Pollock 1955). Today, warfarin is commonly used to treat conditions such as blood clots and deep vein thrombosis (i.e., a blood clot in a deep vein, usually within the legs), as well as to prevent strokes in people who have artificial heart valves, atrial fibrillation (i.e., irregular heart rhythm), and valvular heart disease (i.e., damage or defect in one or more of the four heart valves) (Pollock 1955). Warfarin can also help prevent future blood clots and embolism, a condition in which a blood clot migrates through vasculature and physically blocks blood supply to vital organs or tissue.

This drug's origins can be traced back to a very unusual disease that afflicted cattle in the 1920s—one that resulted in sudden and fatal bleeding after minor injuries. Investigation of this mysterious illness concluded that these cattle had consumed a plant known as the sweet clover (*Melilotus alba* and *M. officinalis*) (Kresge et al. 2005). The sweet clover, part of the family Fabaceae, is a part of the common grassland plants and often known as the "weed of cultivated ground." These plants originally are from Asia and Europe, but they are now found all throughout the world. Intrigued by this plant, scientists found that it contained a hemorrhagic factor that reduced the activity of prothrombin, a protein present in the plasma of blood. Researchers were determined to find the identity of this unknown hemorrhagic factor, and eventually identified the active compound as coumarin. These coumarin compounds can also be found in other plants, most notably the sweet-scented bedstraw

(*Galium odoratum*, family Rubiaceae) and lavender (*Lavandula angustifolia*) (Pollock 1955). However, the coumarin compounds themselves do not exert any effect on clotting. Rather, they must be metabolized into compounds such as 4-hydroxycoumarin by various fungi, and then into a compound called dicoumarol, which is the actual active component (Bye and King 1970).

Physiologically, dicoumarol works as an anticoagulant by acting as a vitamin K depleter, functioning to reduce the metabolism of vitamin K in the blood and effectively reduce the clotting of blood cells (Bye and King 1970). Mechanistically, dicoumarol acts to competitively inhibit vitamin K epoxide reductase, the enzyme responsible for vitamin K recycling (Patel et al. 2019). After extensive research into these naturally derived compounds and their medicinal properties, Karl Link and fellow scientists at the University of Wisconsin decided to produce the pharmaceutical drug known today as warfarin (a name which is the combination of the acronym WARF, which stands for the Wisconsin Alumni Research Foundation, and the suffix "-arin" from its coumarin components). Today, warfarin is on the World Health Organization's List of Essential Medicines, yet interestingly, was first approved as a rat poison before its use on humans (WHO 2011).

1.2.2 Oncologic Drugs

1.2.2.1 Paclitaxel

Breast cancer is the second most common type of cancer in the United States (second only to skin cancer). Each year, approximately 266,000 women are diagnosed with invasive breast cancer and an additional 65,000 women are diagnosed with noninvasive breast cancer in situ (Levi et al. 2002). Research into finding effective treatment options for breast cancer has been unrelenting. Currently, treatment options include surgical resection, chemotherapy, radiation therapy, immunotherapy, and hormonal therapy (Levi et al. 2002). One of the more effective chemotherapy options is a medication known as paclitaxel, another member of the World Health Organization's List of Essential Medicines (WHO 2011).

Paclitaxel is a microtubule-stabilizing drug which interferes with the arrangement of microtubules during the process of mitotic cell division, ultimately impeding the proliferation of cancer cells and inducing cell death (Long and Fairchild 1994). As the most well-known naturally derived antitumor drug in the United States, paclitaxel's history is quite unique. In 1962, samples of the Pacific yew tree, also known as *Taxus brevifolia*, were sent by the US Department of Agriculture to the National Cancer Institute (NCI) to aid in their objective of finding natural products that could potentially help treat and cure cancer (Stierle et al. 1994). Scientists from the Research Triangle Institute in North Carolina soon discovered that extracts from the bark actually caused cytotoxic activity on cancer cells (Stierle et al. 1994).

Following this stunning discovery, additional samples of bark were collected and extracts produced for further testing to identify the most bioactive component within

the samples (Stierle and Stierle 2000). After several years, paclitaxel in its pure form was finally discovered as the main bioactive constituent within the Pacific yew tree's bark. Then began the process of testing paclitaxel's biological mechanisms. In-vitro biological mechanistic studies eventually led to in-vivo trials against the mouse melanoma B16 model (Holmes et al. 1991). Finally, paclitaxel was selected to be further developed in the clinical pipeline after extensive testing, both in-vitro and in-vivo.

The wealth of compounds found in an extract such as the bark of the Pacific yew is quite remarkable. Before the evolution of modern paclitaxel, native peoples in North America used the needles and twigs of the tree in order to brew homeopathic teas for various ailments (Wilson and Hooser 2012). However, many traditional shamans were careful in using the tree's medicinal properties, as an excess amount could lead to devastating toxico logical consequences for the human body, including yew poisoning. Interestingly, the yew tree was known as the "tree of death," whose extracts were used to murder ancient kings such as Catuvolcus, the king of the Gallic-Germanic tribe known as the Eburones (Panzeri et al. 2010).

1.2.2.2 Vinblastine

Although some chemotherapeutic agents are used to treat one specific type of cancer, other agents have been used for the treatment of many. An exemplar drug is vinblastine, a common chemotherapeutic used in the field of oncology. Typically utilized as an adjuvant treatment in conjunction with other medications, vinblastine is effective in treating various forms of cancer. For example, the drug is known for its ability to fight non-small cell lung cancer, brain cancer, testicular cancer, melanoma, bladder cancer, and most notably Hodgkin's lymphoma (Ratain et al. 1987). Vinblastine is also used to treat non-malignant conditions, such as histiocytosis and other blood disorders (Tennant Jr 1969).

Currently, vinblastine is on the World Health Organization's List of Essential Medicines and has been recognized as one of the most effective chemotherapeutic substances (WHO 2011). Chemically, vinblastine is an alkaloid compound. It works to inhibit cancer growth by specifically targeting metaphase in the mitotic process. Normally during metaphase, each chromosome lines up in the center of the cell, with every sister chromatid being attached to a respective spindle fiber. Vinblastine binds to tubulin—the protein which is the main constituent of cellular microtubules—in order to prevent the cell from creating spindle fibers in the first place (Jordan et al. 1992). This ultimately interferes with the cell division process and inhibits tumor cell growth by stopping proper mitosis. Vinblastine is similar to paclitaxel in that it interferes with tumor cells during the cell cycle. However, while paclitaxel targets the arrangement of microtubules, vinblastine targets the creation of microtubules altogether (Long and Fairchild 1994).

With all of its intricacies and molecular charm, vinblastine derives its origins from a simple plant known as the Madagascar periwinkle (*Catharanthus roseus*), which is in the dogbane family Apocynaceae (Iskandar and Iriawati 2016). Also

called the "old maid" and the "Cape periwinkle," this plant is native and endemic to Madagascar. However, the periwinkle is grown in various places around the world as a medicinal and ornamental plant. For example, the extract of the roots and shoots of *Madagascar periwinkle* has been used for numerous centuries as an Ayurvedic (i.e., traditional Indian medicine) agent against several diseases (Iskandar and Iriawati 2016). In traditional Chinese medicine, the plant was used to battle various other diseases ranging from malaria to diabetes.

Having such an extensive history of use among various cultures, it was only recently that drug development of vinblastine took place. In 1958, Robert Noble and Charles Thomas Beer at the University of Western Ontario isolated the vinca alkaloid vinblastine from the periwinkle plant (Ratain et al. 1987). Shortly thereafter, vinblastine's potential use as a chemotherapeutic agent was advanced after a successful decrease in infected rabbits' white blood cell count—an indication of the effectiveness of the compound.

1.2.2.3 Etoposide

Besides paclitaxel and vinblastine, another common chemotherapeutic agent is etoposide. Primarily used to treat testicular cancer, leukemia, neuroblastoma, ovarian cancer, lymphoma, and lung cancer, etoposide can either be ingested orally or be injected directly into the bloodstream through an intravenous injection (Van Maanen et al. 1988). The drug is also on the World Health Organization's List of Essential Medicines (WHO 2011).

The mechanism of action of etoposide is very different from other chemotherapeutic substances of its sort. Instead of inhibiting the microtubule processes during mitotic cell division like paclitaxel and vinblastine, etoposide targets the actual DNA strands of the tumor cell. The drug forms a ternary complex with the topoisomerase II enzyme on the DNA (Hande 1998). Topoisomerase II is a protein which helps with DNA unwinding and is crucial for cancer cell function since tumor cells divide so rapidly. When etoposide latches onto the topoisomerase II enzyme, it prevents the DNA strands from religating, ultimately causing errors in DNA synthesis and causing the DNA strands to break (Van Maanen et al. 1988).

While etoposide was approved for medical use in the United States in 1983 and eventually received a designation on the World Health Organization's List of Essential Medicines (WHO 2011), the plant the compound is derived from, known as the wild mandrake (*Podophyllum peltatum*), has a long and extensive history of medicinal use (Hande 1998). Also known as the mayapple, the wild mandrake is a herbaceous perennial plant in the family Berberidaceae, first described as a genus by the Swedish botanist Carl Linnaeus in 1753 (Springob and Kutchan 2009). The wild mandrake is found all across the eastern United States and southeastern Canada. Interestingly, every single part of the plant is poisonous, including its green fruit.

The plant has been used for many centuries by American Indians as an emetic (i.e., vomit inducing), antihelminthic (i.e., expelling parasitic worms), and cathartic

(i.e., psychological relief) agent (Hamilton and Baskett 2000). By boiling the poisonous roots of the wild mandrake, the Native Americans were able to create a natural tonic water in order to treat stomach aches and other gastrointestinal problems. As further research was done into the plant, historians found that the rhizome of the plant was used by settlers in the New World to treat ailments. Creating a semisynthetic derivative of a compound known as podophyllotoxin from the rhizome of the wild mandrake, scientists were able to produce the chemotherapeutic drug known today as etoposide (Hande 1998).

1.2.3 Neurologic Drugs

1.2.3.1 Scopolamine

The brain is regarded as the control center for volitional activities. The brain is also the command module for involuntary activities, such as breathing, heartbeat, bowel and bladder activities, and much more. A critical neurotransmitter, acetylcholine, is involved with the transmission of the brain's signals to the various muscles of the body, both voluntary and involuntary (Perry et al. 1999).

The type of receptor on which acetylcholine interacts is labeled as either muscarinic or nicotinic (Leprince 1986). Nicotinic receptors are usually found on muscles over which the body has volitional control. Muscarinic receptors typically control involuntary function. Chemicals or medications which block the muscarinic receptors prevent acetylcholine from reaching its post-synaptic target site which, in essence, cause malfunction of the end organ (Perry et al. 1999). These chemicals are said to have anticholinergic properties. When one consumes medications or substances with such properties, numerous effects are observed, such as dry mouth, constipation, urine retention, and sleepiness, to name a few.

One commonly used anticholinergic chemical is scopolamine, which is derived from various genuses in the Solanaceae (nightshade) plant family, most notably *Scopolia* and *Hyoscyamus* (Phillipson and Handa 1975). Scopolamine is also found in the secondary metabolites of other plants, such as jimson weed (*Datura stramonium*) and corkwood (*Duboisia myoporoides*) (Phillipson and Handa 1975). For many centuries, the effects of scopolamine were observed and used for various medicinal and divine purposes. Starting from the Neolithic period (from 10,200 to 2,000 BCE), the henbane plant (*Hyoscyamus niger*) has been harnessed for human benefit (Hocking 1947). The ancient Egyptians, Celts, Germans, and Greeks all sought use of the plant as a sacred healing agent as well as an alcoholic enhancer. For example, the Oracle of Delphi inhaled the burning smoke of the henbane plant before forecasting prophecies and divinations (Hocking 1947). After a short period of disappearance from historical records, the drug reappeared during the Middle Ages (4,000–1,400 CE) as a topical ointment. Since strong doses of the medication caused hallucinations and delirium, many regarded topical henbane ointment as the "witch's herb" (Müller 1998).

In the modern era, scopolamine is a common medication in the antimuscarinic family. Used to treat conditions including postoperative nausea, vomiting, motion sickness, and intestinal and bladder cramps, scopolamine can help alleviate the spasmodic pain that is associated with such problems (Hardy and Wakely 1962). Scopolamine is also known for its effects targeting other gastrointestinal problems such as irritable bowel syndrome and diverticular disease. The drug works by blocking the effects of acetylcholine, ultimately reducing the spasmodic contractions of the smooth muscles in the walls of the gastrointestinal tract (Hardy and Wakely 1962).

Interestingly, scopolamine was initially used in conjunction with opioids such as morphine and oxycodone in order to put mothers in labor to a deep sleep (Phillipson and Handa 1975). Scopolamine's analgesic properties when combined with opioids are strong enough to be used as a form of anesthesia. Since scopolamine was first isolated and tested, extensive research has been done on the specific properties of the drug. It is now a key member of the World Health Organization's List of Essential Medicines (WHO 2011).

1.2.3.2 Levodopa (L-Dopa)

Another neurotransmitter, dopamine, is a critical chemical used in the control of body movements, along with many other functions (Hornykiewicz 2010). When there is a loss of dopamine activity in parts of the brain known as the substantia nigra and the basal ganglia, a condition known as Parkinson's Disease (PD) ensues due to impaired neuron-to-neuron communication and firing (Hornykiewicz 2010). This neurodegenerative disorder can be quite disabling without treatment.

A phytochemical compound, levodopa (also known as L-dopa), was first isolated in the years 1910–1913 using the seeds of the broad bean plant (*Vicia faba*) (Tomita-Yokotani et al. 2004). Functionally an amino acid, levodopa is a precursor to dopamine but is not an active compound itself. A few years after the initial discovery of L-dopa, however, scientists discovered in 1938 that an enzyme called dopa-decarboxylase was able to enzymatically convert L-dopa into the neurotransmitter dopamine (Blaschko 1942). This finding set the basis for further research into dopamine replacement therapy, a type of treatment which increases levels of dopamine in affected brain regions to optimal levels for proper neuronal functioning (Kebabian and Calne 1979).

A member of the World Health Organization's List of Essential Medicines (WHO 2011), L-dopa is now a critical component of the modern health system's toolkit to battle CNS diseases including PD (Rodnitzky 1992). In 1967, a levodopa drug regimen was introduced to help treat PD and has been used extensively ever since. Mechanistically, L-dopa crosses the blood-brain barrier—a highly selective and semi-permeable border that serves to separate circulating intravascular blood from cerebrospinal fluid—and is enzymatically decarboxylated into dopamine. The blood-brain barrier is comprised of a close packaging of endothelial cells that line the blood vessels of the CNS, astrocyte end-feet, and pericytes and their basal

lamina (Daneman and Prat 2015). It is also comprised of tight junctions of protein complexes, which serve to bolt the endothelial cells together and restrict movement of ions, molecules, and cells into and out of the CNS (Luissint el al. 2012). Since dopamine itself is too large to cross the blood-brain barrier, levodopa is a smaller, more permeable molecule that is an ideal alternative to get dopamine into the brain (Hornykiewicz 2010). Physiologically, this levodopa-induced spike in dopamine concentrations helps to fight many of the motor symptoms caused by PD, such as bradykinesia, tremors, and impaired gait (Zach et al. 2017).

Historically, levodopa has been used for thousands of years in order to treat PD-like symptoms. For example, ancient civilizations in India used extracts of a therapeutic legume known as the velvet bean (*Mucuna pruriens*) as a psychospiritual and purifying herb in Ayurvedic medicine (Tomita-Yokotani et al. 2004). More specifically, the velvet bean is an annual climbing shrub that is of the family Fabaceae and can grow to over 50 feet in length. Interestingly, in addition to its use as a treatment for neurological diseases, the plant also was used as an antagonist to fight the toxins of various snake bites (Tomita-Yokotani et al. 2004). Other than the velvet bean, L-dopa can also be derived from natural sources such as the broad bean (*Vicia faba*) and plants in the *Cassia*, *Dalbergia*, *Piliostigma*, *Phanera*, and *Canavalia* genera.

1.2.4 Pain Suppressants

1.2.4.1 Aspirin

Fever? Headache? Reach for the aspirin: one of the most widely used medications found in households all over the world (Miners 1989). For everyday aches, aspirin has consistently been the go-to pharmaceutical agent of the past century. A member of the World Health Organization's List of Essential Medicines, aspirin acts in numerous pain suppressant roles and is used immediately after a heart attack in order to reduce the risk of death post-cardiac arrest (WHO 2011). The medication is also used as a preventative medication for ischemic strokes, heart attacks, and blood clotting (Reed 1914). Mechanistically, aspirin inhibits the activity of cyclooxygenase (COX), an enzyme which functions to produce prostaglandins—a specific group of lipids. Physiologically, when aspirin is specifically used as a pain reliever, COX inhibition reduces swelling, inflammation, and pain.

Before the development of the pharmaceutical drug aspirin, its precursor was the medicinal usage of bark from various species of the willow tree family, such as the white willow (*Salix alba*), the black willow (*Salix nigra*), the weeping willow (*Salix babylonica*), and the crack willow (*Salix fragilis*) (Norn et al. 2009). These trees are native to Asia, Europe, and some parts of North America. Since 2,000 B.C., the willow bark's medicinal potential has been recognized and widely used for its anti-inflammatory effects and ability to treat conditions such as headaches, muscle pains, menstrual pains, and arthritis (März and Kemper 2002). For example, about

4,000 years ago, the Sumerian culture described the pain-relieving properties of willow bark on clay tablets (Norn et al. 2009). Ancient Mesopotamian civilizations utilized this willow bark's extracts to treat the daily pains and inflammations of citizens. For more than 2,000 years, traditional Chinese medicine has also made use of willow bark and the bark of the poplar tree in order to help treat colds, goiter, and fever. Additionally, around 400 B.C., during the time of the Greek physician and ancient founder of medicine Hippocrates, citizens were advised to chew on the bark of the willow tree and drink teas derived from the willow tree to relieve fever and pain (Norn et al. 2009).

Despite such long historical usage of the willow bark, it wasn't until 1763 that Edward Stone, member of the Royal Society of London, conducted the first clinical study using an extract of the willow bark on patients affected with ague (i.e., a fever which many believed to be caused by malarial agents) (Stone 1763). By the nineteenth century, many chemists and pharmacists were experimenting with various chemicals found in the willow bark extract. In 1829, a French pharmacist by the name of Henry Leroux isolated a pure crystalline form of a compound known as salicin—one of the primary active components in the willow bark (Norn et al. 2009).

After identifying this salicin compound, in 1853, a French chemist by the name of Frederic Gerhardt combined sodium salicylate (i.e., a sodium salt of salicin) with acetyl chloride to produce the novel compound of acetylsalicylic acid (Norn et al. 2009). Over the next few decades, various chemists worked to determine the exact chemical structure and properties behind this molecule. Eventually, in 1899, scientists at the Bayer company manufactured the drug known as aspirin derived from acetylsalicylic acid (Sneader 2000).

1.2.4.2 Morphine

Morphine is one of the most popular and most commonly used pain medications in the world. Classified as an opiate, morphine works to decrease the feeling of pain by acting directly on the CNS. The drug can be taken for both chronic and acute pain, with morphine being used to treat pain from conditions such as bone fractures, cancer-associated pain, and postsurgical pain (Hamilton and Baskett 2000).

Mechanistically, morphine works by binding to μ-opioid receptors in the CNS. The G-protein in the opioid signaling chain increases the conductivity of potassium channels and inhibits adenylyl cyclase (i.e., the enzyme which synthesizes cyclic AMP from ATP) (Brook et al. 2017). Together, all of these biochemical changes dampen the effect of the nervous system signaling systems which transmit pain.

Morphine is derived from a plant called *Papaver somniferum*, commonly known as the opium or breadseed poppy, which is a species of flowering plant in the family Papaveraceae (Miller et al. 1973). The plant was traditionally grown in the eastern Mediterranean, but is now found all over the world. Primarily, morphine is isolated from the poppy straw portion of the opium poppy. First isolated by the German pharmacist Friedrich Serturner in 1804 (Lockermann 1951), the alkaloid

compound was named after Morpheus, the Greek god of dreams, because of its tendency to cause sleep (Hensel and Zotterman 1951). Before the actual isolation of the compound, the opium plant has had a long and extensive history of use. Traditionally, an opium-based elixir was brewed by alchemists in the Byzantine era as a potent painkiller. In the year 1522, the Swiss physician and astrologer Paracelsus referenced an opium-based pain medication called laudanum (from the Latin "laudare," to praise) in his texts, but stated that it should only be used sparingly (Miller et al. 1973). In the late eighteenth century, laudanum reappeared and became popular among the East India Trading Company, which had a direct interest in the opium trade in India. Fast forward to the nineteenth century—a few years after Friedrich Serturner's isolation of the alkaloid compound of morphine in 1804—the pharmaceutical company Merck began marketing morphine commercially (Brook et al. 2017). Within a few decades, pharmaceutical production of morphine and other opioid-based medications had become a huge industry.

Currently, morphine is classified as a schedule II drug in the United States and is on the World Health Organization's List of Essential Medicines (WHO 2011). However, unfortunately, the abuse of and addiction to prescription opioids such as morphine is one of the most rampant drug epidemics that the United States and other countries have ever seen (Brook et al. 2017).

1.2.4.3 Menthol

Cough drops. Soothing tea. Chapstick. What key ingredient do all three of these day-to-day, winter-time items have in common? The answer is menthol, a drug produced from the mint plant that provides a cooling sensation when ingested or applied. Besides helping to relieve sore throats and chapped lips, menthol is also used to treat minor pains and aches of muscles and joints (Hensel and Zotterman 1951). For example, menthol is commonly used to treat conditions such as arthritis, backache, and sprains.

How exactly does menthol work? The drug has a natural analgesic (i.e., pain relieving) property. Mechanistically, the menthol compound acts as a ligand and binds to the κ-opioid receptor, effectively producing a numbing effect in the target location (Hensel and Zotterman 1951). Additionally, when menthol is applied onto a sore or an aching muscle, the blood vessels in that location are dilated, increasing blood flow to the area and bringing necessary nutrients faster (Hensel and Zotterman 1951). Menthol also acts by stimulating thermoreceptors within the skin cells themselves, tricking the brain into thinking that the temperature in that area has decreased drastically (a process known as counterirritation) (Yosipovitch et al. 1996). In reality, this sense of cooling distracts the brain from the uncomfortable, hot pain at the inflammation site.

For its vast plethora of properties, menthol is derived from a very simple plant: the wild mint, a group of 15-20 species found in the *Mentha* genus (Iqbal et al. 2013). These plants are part of the family Lamiaceae and are found in nature as

perennial herbs. Having originated in the Mediterranean region and Asia, the plant has been known to possess beneficial medicinal effects throughout history. For example, the ancient Greeks added mint into their baths to help stimulate their bodies, and the ancient Romans included mint in certain sauces as a digestive aid and mouth freshener (Iqbal et al. 2013).

Medieval monks also used the mint plant, especially in their cooking, in order to help ward off illnesses. In the seventeenth century, an English traveler by the name of John Josselyn chronicled in his writings that the pilgrims brought mint to the New World and included botanical information on the plant (Josselyn and Tuckerman 1865). Currently, mint has a wide distribution all around the world, including in five continents.

1.3 Conclusion

Although this chapter details just a few of the countless naturally-derived drugs used to treat human ailments, the full list of medications is far more extensive. Mankind has harnessed thousands of compounds, but the wealth of undiscovered medicinal gems in nature is unfathomable. The focus of modern pharmaceutical research has been toward the direction of lab-synthesized drugs and compounds, yet many of these molecules unfortunately have undesirable side effects. Rather, society should look to discover the true potential of phytochemicals in nature—an option that is both scientifically and economically rewarding. Medicinal plants also provide an opportunity to train young minds in the fields of botany, plant conservation, and natural product chemistry (https://www.youtube.com/watch?v=0YqEPDAYsWQ). Time after time, nature has shown to be the master craftsman in creating an inexhaustible array of therapeutic molecules, and carries infinite potential for future drug discovery and treatment of human diseases.

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