Chapter 1: The Foundations of Herbal Chemistry

In order to really understand what we read about herbal constituents, the structures and properties of molecules, phytochemical synergy, constituent solubility, and other chemistry-based information, we need to know a few basic concepts. If you have studied (and retained!) general, organic, and biochemistry, you are likely to already know these; but some of us don’t have an extensive academic background in the sciences, and not a few others have blissfully allowed themselves to forget the tedious convolutions and complexities of chemistry-as-taught-in-school. This book will give you the gist of practical phytochemistry for practitioners, in the context of widely-used medicinal plants, and without going into unnecessary or mathematical detail.

Visualizing Phytochemicals

Whenever I teach class, I begin by showing the students a remarkable image called an electromagnetic flow visualization. This colorful diagram depicts the intricate, symmetrical flow patterns created by the various arrangements of electrons which vibrate around atoms in a molecule. I ask the students to imagine this image coming alive: humming and sparkling in three dimensions as it vibrates, rotates, and drifts along through the tiny realms of intermolecular space. Conventionally, we’re not taught to think about it this way; but if we could actually ‘see’ a molecule, we might be surprised by how exotically and curiously beautiful it is. We might see colorful, blooming, interlaced patterns of perpetually moving energy which nevertheless retain a stable spatial relationship with each other. I like to say that rather than thinking of molecules as tiny objects, we might better conceptualize them as being patterns of energy in relationship. This way of visualizing phytochemicals introduces the intriguing possibility of perceiving them as fluid expressions of a plant’s energy or spirit. We might also realize that these phytomolecular entities can interact with the entities/energies/molecules of the human system to bring about biological change — potential healing in the case of medicinal molecules.

In most books and academic programs, however, phytochemicals are depicted in a much more pedestrian manner. We use simple line drawings to suggest which kinds and numbers of atoms are present and how they are bonded together to form the overall pattern of a molecule. I think of these chemical structure drawings as being like hieroglyphs: rather esoteric, minimalist markings that can nevertheless convey significant information to those who learn how to interpret their symbolic visual language. When we dig into the details of molecular structure drawings in the rest of this handbook, keep in mind that we are examining the map and not the territory. The territory — the actual living, changing molecule itself — is far more weird and wonderful than we could ever depict with lines and letters on paper. I also like to keep in mind that the medicinal herbs really do make these phytochemicals — they’re not something we invented in the lab. In addition, consider the implications of the fact that these compounds are very often the original inspiration for many of those synthetic imitations we call drugs.

The Basic Structure of Phytochemicals

The foundation of phytochemical architecture is made up of the tiny entities we call atoms. Each chemical element (carbon, hydrogen, sulfur, magnesium, etc.) is composed of countless atoms that are almost identical. Atoms are mostly empty space, containing a tiny nucleus surrounded by organized ‘clouds’ of electrons. Each different kind of atom contains a unique number and pattern of electrons. Electrons are the basis of electrical charge; when they flow, we have electricity. Although electrons are invisible, we can observe their effects. They are named after the Greek word for amber, elektron, perhaps because when amber is rubbed with silk, static electricity builds up. All electrons have a negative charge.

Inside an atom’s nucleus, the protons have a positive charge and the neutrons have no charge. The attraction between opposites (positive protons and negative electrons) holds the atom together. When an atom contains an equal number of protons and electrons, it has no overall electrical charge; the positives and negatives balance each other out. However, if the atom has one more electron than protons, it has an overall negative charge of –1 and it’s called an ion (specifically, an anion). Anions can also have charges of –2, –3, etc., depending on how many extra electrons they have. If the atom has somehow lost one or more electrons, the opposite situation occurs: it will have an overall positive charge (+1, +2, +3, etc.), and it is then a type of ion called a cation.
The larger atoms contain different layers of electrons. The inner layers generally don’t get involved in chemical bonding and reactions, but the outer electrons (called the valence electrons) do. The energetic valence electrons are quite important, because they determine which sorts of bonds and reactions the atom can be involved with. The activities of the electrons also determine the polarity of a molecule – we’ll get to that a bit later. Suffice it to say that polarity is one of the major features determining the solubility of a molecule and the types of bonds it can form, as well as how it relates to other molecules in its environment.

There are many different chemical elements that occur in Nature, but only a relative few are found in phytochemicals. The most common ones are carbon, hydrogen, oxygen, nitrogen, sulfur, and phosphorus. Sometimes elements and ions like calcium, magnesium, iron, copper, selenium, or fluorine are associated with particular phytochemicals. Although I am trained in science, I am aware that contemporary science is only one of many valid perspectives for understanding the world in which we live. Because of this, I also cultivate a somewhat mystical view of elements and chemical compounds. In the paragraphs that follow, I discuss the elements as belonging to Earth, Air, Fire, or Water – the ancient system of four elements used by Western herbalists and healers for generations. This is a way to conceptualize the nature of elements so that we can have a closer relationship with them; so that they can make more sense to us in our nonlinear world of experience.

Elements in Phytochemicals

Carbon

All phytochemicals contain carbon (C). I think of carbon as the quintessential Earth element in living systems. Graphite (pencil ‘lead’), coal, and diamonds are examples of nearly pure carbon in Nature. From an organic perspective, it forms the stable basis for all of the elaborate structural variations that life creates. When a carbon atom makes four single bonds, the electrons are naturally arranged in the form of a tetrahedron. This illustration shows how a carbon atom (in the center) can use those electrons to bond to four other atoms. If you draw lines connecting each of the outer atoms (in this case they are hydrogens), you’ll see a tetrahedron. Students of sacred geometry take note.

Carbon forms the backbone or skeleton of most organic molecules. You can see this in the illustration below, which depicts three different ways to draw a molecule of catechin (a type of flavonoid found in plants such as Green Tea).

The first way of representing catechin shows the location of each atom in the molecule with a letter symbol. C stands for carbon, H stands for hydrogen, and O stands for oxygen. The straight lines between the letter symbols tell us that there is a chemical bond between each of those atoms. In phytomolecules, these bonds are almost always what we call covalent bonds, which means that they are formed when atoms share pairs of electrons. If a single electron pair is being shared, we have a single bond, which is represented by a single straight line. If two pairs of electrons are being shared, we have a double bond, which is represented by a pair of parallel lines. Sometimes carbon atoms even share three pairs of electrons in a triple bond; we’ll see an example of that later. You might also notice that one of the bonds is drawn as a dashed line, and another is shown as a dark wedge.

This is done in an attempt to give us some three-dimensional information in a two-dimensional format. A plain line indicates that the bond should be visualized as lying on the surface of the paper; the dashed line means that the bond pokes backward behind the paper; the dark wedge means that the bond pokes forward out of the paper, towards us. In the compact
structure drawing, the letter symbols for the carbons (C) have been removed, and we see angles connected by straight lines. We are supposed to assume that there is a carbon atom at every angle. Also, this compact drawing leaves out the hydrogen atoms that were attached to the carbon atoms. This is done because we know that every carbon atom likes to form four bonds with other atoms (four single bonds, two double bonds, two singles and one double, or one single and one triple). So, for the sake of an uncluttered drawing, we are supposed to remember but not draw the hydrogens that are really there, ensuring that every carbon has a total of four bonds on it.

The third drawing depicts the carbon backbone of catechin, with all of the hydrogens and oxygens left off. It shows you the basic shape of the molecule. Since plants are very efficient, they can use this basic shape as a framework to construct not only catechin, but numerous other closely-related compounds — molecular variations on a theme. For example, hundreds of different flavonoid molecules might contain the same basic skeleton as catechin, but will have different kinds and numbers of additional atoms or groups of atoms attached in different places. They might also have slightly different three-dimensional shapes or electrical charges. Structurally similar molecules are grouped together into categories. Each category might belong to several larger, more encompassing categories. Sometimes we classify phytochemicals according to which biosynthetic pathways make them or by the types of plants in which they occur.

For example, catechin is most specifically classified as a flavan-3-ol. The next larger group it belongs in is the called the flavanols. The next level up is the flavonoids, the next is the polyphenols, and the highest is the phenolic compounds. So if you called catechin a flavan-3-ol, or a flavanol, or a flavonoid, or a polyphenol, or a phenolic compound, you would be right every time. This possibility of correctly referring to a single molecule by several different names is often a source of confusion. Learning the hierarchy of phytochemical relationships can be very helpful for understanding this sort of thing.

From: Functional Groups

**Acetate group**

The acetate group is a specialized type of ester. It is formed when acetic acid (a type of carboxylic acid) reacts with a hydroxyl group on a molecule to form an ester bond. Molecules containing an acetate group often begin with the prefix acetyl- or end with -acetate. The drawing of salicylic acid and acetylsalicylic acid to the left illustrates the concept. During the invention of aspirin, the acetate group was added to the salicylic acid molecule to make it less damaging to the stomach. Acetylsalicylic acid is the chemical name for aspirin. Can you identify the other functional group on the aspirin molecule?

Another common acetate compound is ethyl acetate. It’s made when ethanol reacts with acetic acid to form an ester. Small amounts of ethyl acetate occur naturally in various fruits and in vinegar. Like many other small esters, it has a fruity aroma. It is also sometimes used as a low-polarity solvent to make concentrated herbal extracts.

Many essential oils contain molecules bearing ester or acetate functional groups; in the language of aromatherapy, these are often classified and discussed as esters, while compounds having carboxyl groups are referred to as acids and those with hydroxyl groups are called alcohols. Like other ester groups, the acetate group is only mildly polar.
Chapter 2: Solubility and Extraction of Herbal Constituents

There are plenty of other good books giving instructions on how to make herbal extracts, so I will focus on explaining the principles behind the solubility of particular kinds of constituents, the choice of solvent mixtures, and the stability or reactivity of various constituents in extracts and formulas. Understanding these principles will help you to know which constituents are favored by which solvents; to decide which sorts of solvents and extraction methods are best for individual herbs and applications; and to understand which extracts are compatible or incompatible in formulas. A solvent, by the way, is pretty much anything that will dissolve another thing; we tend to think of solvents as referring to nasty chemicals, but water and ethanol are solvents too.

The solubility of any phytochemical in a given solvent is influenced by many factors, including whether or not the compound is in the glycoside or aglycone format; the polarity of its skeleton and functional groups; the overall size of the compound (also called its molecular weight); any other molecules with which it might be associated (complexed); whether or not it’s oxidized or reduced; the particular matrix of the plant it’s in; the temperature of the extraction solvent/s; and the pH of the solution (which influences whether or not the compound is ionized).

It’s possible to look up the solubility of most phytochemicals in reference works like the Merck Index®, but keep in mind that this information applies to the isolated phytochemical compound, and usually to only one particular form of it. Such information is useful, but once you have a phytochemical inside the matrix of any individual plant, along with all of its synergistic and companion compounds, the solubility may change significantly. In fact, the situation can be so complex that it is often difficult to predict what the solubility of a compound (from a given plant with a given extraction method) will be. Analyzing the finished extract to see how much of the compound actually did dissolve is often necessary to determine the compound’s solubility under any specific set of conditions.

Keep in mind that because of these factors, some of the information in this section about solubility and extraction should be thought of as a reasonable generalization or estimation. There will always be exceptions. The general principle, however, is like dissolves like. Highly polar compounds tend to dissolve in highly polar solvents; compounds with low overall polarity tend to dissolve in low-polarity solvents. Solvents with polarities similar to one another will mix (e.g., ethanol and water); solvents with very different polarities will not mix (e.g., oil and water), except in the presence of emulsifiers ...

Chapter 3: Synergy and Variability in Herbs and Formulas

The Origins of Phytochemical Synergy

Many herbalists acknowledge that one of the main differences between whole herbs and traditional extracts on the one hand, versus individual vitamins, minerals, isolated phytochemicals, or conventional single-molecule drugs on the other hand, is the principle of synergy. Synergy can be defined in a number of ways, but the underlying idea is that complex interactions among the many constituents of an herb give rise to its unique characteristics, personality, and healing properties. To borrow a concept from physics, the very complexity of a living plant – which contains perhaps thousands of interacting chemicals – gives rise to emergent behavior: activities and effects which could not have been predicted from what is known about the individual components of the system. In other words, the whole herb is far more than the sum of its constituents.

Since we humans also have very complex physiological systems, it seems to be common sense that we would respond to plants as healing entities. Tradition expresses this idea as the ‘wisdom of Nature’: since humans and plants are made from the same elemental substances, and share a number of fundamental biochemical and energetic similarities, we should respond in a more ‘natural’ way to whole plants than to isolated chemicals. From a scientific perspective, the theory of co-evolution provides a modern explanation for this intuitive concept.

Co-evolutionary theory

The co-evolutionary theory points out that the various organisms within any ecosystem have continually evolved and adapted to one another over a long period of time. For example, medicinal herbs have developed their particular array of constituents as a response to the pathogens (bacteria, viruses, fungi), predators (insects, herbivores), and symbiotic organisms (mycorrhizae, beneficial insects, pollinators)
that share their environment. In other words, plants have not evolved in isolation, but rather in responsive and adaptive relationships with their companion organisms.

As an illustration of the co-evolutionary principle, imagine the case of a plant species which is routinely infected by a particular kind of bacteria. Over time, mutations naturally arise within the plant species which cause it to produce a higher concentration of a phytochemical compound, X, that kills the bacteria. As a result, the X-producing mutants survive and reproduce while the plants lacking this compound gradually die off. This is the process of natural selection: the bacteria which share the environment with the plant selects for the survival of the high-X strain of the species. However, bacteria are even more genetically nimble than plants, and so they would rather quickly develop resistance to compound X. The X-resistant bacteria could then infect the plant species again, and once again become significant pathogens. And so, in order to prosper, the plant must come up with a new antibacterial compound.

This cycle repeats over thousands of years of co-evolution, until the plant has developed a whole bag of tricks – a complex mixture of synergistic antibacterial phytochemicals – to deal with the continual evolution of resistance in the bacteria. Now consider that the plant has been adapting not just to one species of bacteria, but to many other organisms as well; it is not difficult to see how this would lead to the development of numerous different phytochemical constituents with various physiological activities. In essence, the plant species has invented the strategy of synergy as a way of maintaining its place in its environment. Fortunately for us, many phytochemical substances developed as ‘medicines’ for the plants themselves are active for humans as well; and so we reap the benefits of phytochemical co-evolution in our medicinal herbs.¹ ...

Chapter 4: Herbal Constituents Outline

This outline demonstrates how the different types of medicinal plant constituents are related to one another, and gives a few examples from each category. The following chapters explore the characteristics and therapeutic uses of individual constituents, and discuss the most commonly used herbs in which they may be found.

Major categories:

1. Carbohydrates
2. Lipids
3. Amino acids and derivatives
4. Phenolic compounds
5. Terpenes
6. Steroids
7. Alkaloids

Categories, subcategories, representative constituents:

1. Carbohydrates
   a. Monosaccharides
      i. glucose: human blood sugar, first product of photosynthesis
      ii. fructose: fruit sugar; does not trigger insulin release, but is metabolized into fat in the body & disrupts the function of satiety hormones
      iii. arabinose, xylose, galactose, mannose, & rhamnose: generally found as part of heteropolysaccharides or as sugar units on glycosides
   b. Disaccharides
      i. sucrose: universal transport sugar in plants; made of glucose + fructose
      ii. maltose: comes from the degradation of starch
      iii. lactose: milk sugar; not a plant product; important because some people are lactose-intolerant
   c. Oligosaccharides
      i. inulins: fructose polymers, part of soluble dietary fiber
      ii. inulins are found in Chicory, Dandelion, Burdock, Sunflower (Jerusalem Artichoke) roots; Onions & Garlic
iii. FOS (fructooligosaccharides) contain various inulins
iv. inulins are prebiotics: food for probiotic organisms; help balance blood sugar & blood lipids; help prevent colon cancer
d. Polysaccharides
   i. starch: major dietary energy source; metabolized into glucose; triggers insulin release, raises blood sugar levels
   ii. cellulose: indigestible; serves as insoluble dietary fiber (roughage)
   iii. gums, pectins, mucilages are water-soluble heteropolysaccharides; emollient, soothing, cooling, healing to skin & mucous membranes
   iv. mucilaginous herbs: Marshmallow, Comfrey, Flaxseed, Borage
   v. immunomodulating polysaccharides
      1. arabinogalactans found in Echinacea spp.
      2. beta-1,3-glucans found in tonic mushrooms (Reishi, Maitake, Shiitake) & brewer’s yeast
      3. many adaptogens contain immunomodulating polysaccharides: Eleuthero, Ginseng, Baptisia, Calendula
e. Organic acids
   i. the organic acids are derived directly from carbohydrates & include such compounds as the fruit acids (e.g., citric acid, malic acid) & other acids including formic acid, oxalic acid, & ascorbic acid (vitamin C) ...

Chapter 5: Carbohydrates in Medicinal Plants

Many of us are familiar with carbohydrates in general from studying nutrition and biochemistry; basic information on the topic is available in any undergraduate-level textbook. Here we will focus on the most interesting carbohydrate constituents that contribute to the medicinal characteristics of various herbs and their extracts. For a brief definition of carbohydrate, see the Glossary. As a group, the carbohydrates tend to be water-soluble and are mostly found in whole herb powders and water-based extracts such as teas, infusions, and decoctions. Some carbohydrates may be preserved in hydroethanolic fluid extracts if the ethanol percentage is around 30% or less.

The major subcategories of the carbohydrates include:

- Monosaccharides
  - amino sugars
  - uronic acids
- Disaccharides
- Oligosaccharides
- Polysaccharides
  - homopolysaccharides
  - heteropolysaccharides
    - gums, mucilages, pectins
    - immunomodulating polysaccharides
- Organic acids (derived from small carbohydrate precursors)

Monosaccharides

Monosaccharides are often called simple sugars; their names end in the suffix –ose. The prefixes D- or L- designate stereoisomers of the molecule when it is in a linear (non-cyclized) format. Most naturally occurring sugars occur as the D- forms. Monosaccharides generally form ring structures in aqueous solution; sugars with five-membered rings are called furanoses; those with six-membered rings are pyranoses. Recall that a furan ring is an oxygen heterocycle with one oxygen atom and four carbon atoms in the ring, and a pyran ring is an oxygen heterocycle with one oxygen atom and five carbon atoms in the ring. All of the monosaccharides are small, highly water-soluble compounds.
This diagram of fructose illustrates a further stereoisomeric designation, that of the alpha- and beta- forms. These two isomers differ only in the spatial arrangement of the \(-\text{OH}\) and \(-\text{CH}_2\text{-OH}\) groups attached to carbon #1 (the anomeric carbon) of the ring. A more detailed name for these two forms of the monosaccharide would be alpha-D-fructofuranose and beta-D-fructofuranose, referring to the five-membered ring structure. The next illustration depicts alpha-D-glucopyranose and beta-D-glucopyranose, two forms of the simple sugar, glucose. As you can see, these molecules also only differ in the arrangement of the atoms around the anomeric carbon: in this case, an \(-\text{OH}\) group and a hydrogen atom. Sugar isomers like this are called anomers.

The consequences of this difference, as we discussed earlier, arise from the way these different anomers can bond together to form polymers. A very common polymer of alpha-D-glucose units is called starch (amylose and amylopectin), while the most abundant polymer of beta-D-glucose units is known as cellulose (see p. 37). Since we can digest starch (the salivary glands and pancreas produce enzymes such as amylase, which hydrolyze the \(\alpha\)-glycosidic bonds between the glucose units in the polymer), it is an important nutrient substance for us. Cellulose, however, remains indigestible because we do not produce cellulase enzymes capable of breaking the \(\beta\)-glycosidic bonds in the cellulose polymer. Consequently, cellulose serves us as insoluble dietary fiber, sometimes called \textit{roughage}; it is not a nutrient \textit{per se}, but does nonetheless contribute to the health of the colon.

\section*{Chapter 6: Lipids in Medicinal Foods and Herbs}

Familiar dietary lipids include the fatty acids and the triglycerides, which make up the majority of constituents in our edible oils. Fatty acids, in the form of phospholipids, are found in the cell membranes of all living plant and animal cells. Some roots, fruits (e.g., Palm berries, Avocados, and Olives), and most seeds and nuts (e.g., Flaxseed, Hempseed, and Walnuts) accumulate lipids as high-energy food storage compounds. In general, they are low-polarity molecules; the phospholipids, however, are amphiphilic. Most lipids are readily extracted from plant material with fixed oils, supercritical carbon dioxide, or organic solvents such as hexane, ethyl acetate, or acetone. Nitrogenous lipid derivatives (e.g., the alkamides in herbs like Echinacea) are somewhat polar and can be extracted with hydroethanolic solvents having a moderate-to-high ethanol content. For a brief definition of \textit{lipid}, see the \textit{Glossary}.

Essential oil constituents are not considered to be lipids, but rather are classified with the terpenoids because of their structures and biosynthetic origins. However, most of them will readily dissolve within plant oils, as will other oil-soluble compounds including larger terpenes, carotenoids, steroids, fat-soluble vitamins, etc. Consequently, unrefined oils (e.g., cold-pressed Olive oil) generally contain not only fatty acids and triglycerides, but numerous other types of oil-soluble phytochemicals.

The major subcategories of the lipids and their derivatives include:

\begin{itemize}
  \item Fatty acids (FAs)
\end{itemize}
Fatty Acids

Fatty acid structure

Fatty acids are composed of hydrocarbon tails with a single carboxyl group on one end, called the delta (Δ) end of the molecule. A methyl group is found at the opposite (omega or ω) end. Most fatty acids have from 12 to 18 carbon atoms in the tail, but others with as few as four or as many as 36 carbons are known. For the most part, they occur in plants either free or bonded to glycerol in the form of non-polar triacylglycerols (triglycerides). Sometimes they are esterified (ester-bonded) to other molecules. Fatty acids may be either saturated (SFAs) or unsaturated (UFAs).

Naming fatty acids

Most fatty acids are known by their common names or initials (e.g., linoleic acid is LA). In addition, they can be referred to by specific abbreviations. There are several ways of doing this; for detailed descriptions of unsaturated fatty acids, I prefer to use the delta designation, where the format is [carbon chain length:number of double bonds (position of double bond)]. For example, LA has 18 carbons and 2 double bonds between C9 and C10 (C1 is the carbonyl carbon of the carboxyl group) and between C12 and C13; this is abbreviated as: 18:2(Δ9,12). See the illustration below. Another example of this format is the symbol for alpha-linolenic acid (ALA), which is 18:3(Δ6,12,15). This tells us that ALA has eighteen carbons and three double bonds, between C9 – C10, C12 – C13, and C15 – C16.

Another way to describe fatty acids is to use the omega classification, which tells us the location of the first double bond when counting from the methyl end of the tail, rather than the carboxyl end. Our example, linoleic acid, is an omega-6 molecule because the first double bond is between the 6th and 7th carbons when you start counting from the methyl end (in other words, at C12 to C13 in the delta system). This kind of abbreviation reads 18:2 ω-6 which is sometimes expressed as 18:2 n-6. Although this only tells you where the first double bond is, you can figure out the location of the other one/s based on the fact that you know how many there are all together, and that the double bonds are always separated by a single carbon atom.

Saturated fatty acids (SFAs)

A saturated fatty acid has no double bonds in its hydrocarbon tail; visualize every carbon atom being saturated with hydrogen atoms – in other words, bonded to as many hydrogens as possible. Semi-solid and tropical plant oils such as Coconut and Palm, and Cocoa
Chapter 7: Amino Acids and Derivatives

Individual amino acid structures and functions are adequately covered in general biochemistry and nutrition texts. In this chapter we'll focus on some of the more important physiologically active amino acid derivatives in medicinal plants. In general, free amino acids are water-soluble, with the exception of the aromatic ones (phenylalanine, tryptophan, and tyrosine) which are only sparingly soluble in water. Plant and animal proteins are made from the ‘standard’ amino acids. We used to think there were twenty of them, but now we count twenty-two: selenocysteine and selenomethionine (with selenium replacing the sulfur in regular cysteine and methionine) are the ‘new’ standard amino acids found in some enzymes of the immune system. ‘Nonstandard’ amino acids, of which there are hundreds, play other physiological roles in both plants and animals. These include ornithine, 5-hydroxytryptophan (5-HTP), betaine, theanine, and many others.

In plants, amino acids serve as precursors to many other classes of molecules including peptides, proteins, enzymes, amines, most alkaloids, the cyanogenic glycosides, the pungent Allium compounds and glucosinolates, and some of the polyphenols. In this section we’ll look at a few of the more direct derivatives of amino acids; the polyphenols and alkaloids form their own major categories and will be discussed later.

The major subcategories of the amino acids and derivatives include:

- Amino acids
- Amines
- Glucosinolates
- Sulfur compounds from Allium spp.
- Cyanogenic glycosides
- Peptides, proteins, enzymes

L-Theanine

L-theanine is an amino acid found in and named after Tea leaves. In the body, it is a precursor of neuroactive amines and can cross the blood-brain barrier. Research indicates that this and other alkylamines prime the response of certain immune system cells known as γδ T cells (gamma delta T cells), thereby enhancing ‘immunosurveillance’ against pathogenic microbes and tumor cells. Presumably because of this effect, supplementation with L-theanine and catechins can bring about a decrease in cold and flu symptoms. In addition, animal studies have demonstrated that L-theanine has a relaxant effect on blood pressure and acts as an anxiolytic and stress-reducer by favorably altering concentrations of neurotransmitters including dopamine and GABA. This unique amino acid may mitigate some of the stimulating effects of caffeine, giving Tea a more relaxing ‘personality’ than Coffee.

5-Hydroxytryptophan

This amino acid is extracted from the seeds of Griffonia simplicifolia, a West African medicinal vine. Its structure is simply that of tryptophan with a hydroxyl group added to C5 of the aromatic ring. In the body, 5-HTP is easily absorbed and is able to cross the blood-brain barrier, after which it is metabolized directly into serotonin (5-hydroxytryptamine). As a dietary supplement, it has been used to treat fibromyalgia, insomnia, depression, migraine, over-eating, and other conditions associated with low serotonin levels. Studies have found that 5-HTP is as effective as certain antidepressant pharmaceuticals for some people; it also works synergistically with SSRIs.
Chapter 8: Polyphenols

Polyphenols are often referred to as ‘phenolic compounds.’ They form a very large and diverse category of physiologically active molecules in medicinal plants. All polyphenols have one thing in common, which is an aromatic ring structure bearing two or more hydroxyl groups. This explains the name polyphenol, which is short for *poly-hydroxylated phenol*. Some authors have written that the defining feature of a polyphenol is two or more phenolic rings, but technically this isn’t correct. Some of the polyphenolic derivatives are modified, having other functional groups substituted for one or more of the original hydroxyl groups. Phenolic and polyphenolic rings are illustrated on p. 15. You may recall that phenol simply consists of an aromatic ring with one hydroxyl group attached.

Biosynthetically, the polyphenols have various origins, arising from either or both the *shikimic acid (shikimate) pathway* and the *acetate pathway*. Some have isoprenoid side chains synthesized via the *mevalonic acid pathway*. In the shikimic acid pathway, simple carbohydrate precursors are transformed into the aromatic amino acids; these then provide the aromatic ring structure of many polyphenols (e.g., the phenolic acids and the phenylpropanoids). The acetate pathway produces polyketides, which can cyclize to form phenolic rings (e.g., in the anthraquinones and the benzofurans). The flavonoids, a large and therapeutically important subclass of polyphenols, have moieties synthesized by both the shikimate and acetate pathways. Many polyphenols can polymerize with each other or various other types of compounds (usually bonding via hydroxyl groups) to form larger and more complex ‘hybrid’ molecules; the flavonolignans from Milk Thistle, collectively known as silymarin, are a good example.

Many of the polyphenols exist in plants as both glycosides and aglycones. The glycosidic forms are typically water-soluble while the aglycones tend to have quite limited solubility in water but are generally soluble in hydroethanolic solutions. For details, see p. 45.

The major subcategories of the polyphenols include:

- Phenolic acids
- Phenylpropanoids
- Coumarins
- Furanocoumarins (furocoumarins)
- Lignans
- Phenylpropanoid derivatives
- Stilbenoids
- Xanthones
- Styrylpyrones
- Flavonoids
- Hydrolyzable tannins
- Proanthocyanidins & condensed tannins
- Isoflavones (isoflavonoids)
- Benzofurans
- Chromones
- Quinones
- Phloroglucinol derivatives
- Phenolic resins
Phenolic Acids

A phenolic acid (synonym: hydroxybenzoic acid) is a molecule containing at least one phenolic ring along with an acidic carboxyl group (in other words, they are phenolic carboxylic acids). All green plants contain phenolic acids, although some accumulate more of these compounds than others do. Phenolic acids can exist as free entities or can be attached to other types of polyphenols (e.g., gallic acid versus gallate groups attached to a flavonoid such as epicatechin). Most of them are antioxidant and anti-inflammatory compounds.

One of the most widely-known phenolic acids is salicylic acid, derived from the naturally-occurring salicylate glycosides (e.g., salicin, populin) in plants such as Meadowsweet (Filipendula ulmaria), Willow (Salix spp.), Wintergreen (Gaultheria spp.), Sweet Birch (Betula lenta), and various Poplars including Aspen (Populus tremuloides) and Cottonwood. Salicylic acid was originally named ‘spiric acid’ because it was extracted from Meadowsweet which was at that time called Spiraea ulmaria. By adding an acetyl group to spiric acid, early pharmaceutical chemists created the drug a-spirin: acetylsalicylic acid. Both the natural salicylates and aspirin share analgesic, anti-inflammatory, and antipyretic properties; but only aspirin with its extra acetyl group has significant antiplatelet (blood-thinning) properties. This common drug also has the added side-effect of sometimes inducing serious gastric bleeding; it is said to be responsible for several thousand deaths per year in the U.S. alone.1,2

Other common phenolic acids include ellagic acid, a dimeric compound which occurs in many edible plants including Grapes (and wine), Strawberries (Fragaria spp.), Blackberries and Raspberries (Rubus spp.), and Pomegranates (Punica granatum); it is also a structural component of the ellagitannins (more on these below) and is released when they are catabolized. Ellagic acid has been studied for its potent antioxidant and anticancer properties. A recent study found that it can induce apoptosis in human pancreatic cancer cells via inhibition of nuclear transcription factor κB (NF-κB).3 Similar activities have been found with other types of cancer cell lines including colon,4 prostate,5 and leukemia (synergistically with quercetin).6 In addition, ellagic acid has been found to inhibit the development of atherosclerosis by suppressing the aortic smooth muscle cell proliferation induced by oxidized LDL.7

Gallic acid is found in Grapes and wine, Walnuts and other nuts, and numerous berries; it also frequently occurs as an added moiety (i.e., a gallate unit) on many other types of polyphenols including catechins (e.g., EGCG – epigallocatechin gallate), OPCs, and tannins. When these types of molecules are broken down in the body, the gallate units (phenolic rings with three hydroxyl groups) are usually released. Gallic acid has anti-inflammatory, antioxidant, and anticarcinogenic properties;6,9,10 can modulate hepatic detoxification enzymes;11 and is well-absorbed and readily bioavailable.12 Historically, it was used by the Eclectics as a systemic astringent for conditions of the gastrointestinal and urinary systems and as a topical application for ‘purulent conjunctivitis.’13

Chapter 9: Terpenoids

The terpenoids (terpenes) take their name from compounds first identified in turpentine (distilled Pine oleoresin). Formerly called isoprenoids, these diverse molecules were once considered to have been constructed from various numbers of 5-carbon isoprene units. In reality, they are biosynthesized from similar 5-carbon phosphorylated precursors called dimethylallyl pyrophosphate (DMAPP) and isopentenyl pyrophosphate (IPP); we now know that isoprene is a breakdown product of terpenoids discovered in early organic chemistry laboratories. Nonetheless, use of the term persists in the literature to some degree.

The major subcategories of the terpenoids include:
Chapter 10: Alkaloids

The alkaloids are a large and structurally diverse group of compounds; some of them are not entirely distinguishable from amines (e.g., ephedrine). The names of these molecules tend to end in the suffixes –ine or –in. Many are derived from amino acids, but others result from modification of various classes of molecules including polyphenols, terpenes, or steroids. With a few notable exceptions, alkaloids are most soluble in hydroethanolic media (this also depends on pH; see p. 46); they generally occur as salts (e.g., chlorides or sulfates) and/or as N-oxides in the plants. Most of them have a heterocyclic nitrogenous ring or ring system and a basic (alkaline) character. They are often dramatic compounds, having noticeable physiological effects – whether therapeutic or detrimental. Among the alkaloids we find potent medicinal molecules as well as toxic or even potentially fatal ones.

There are many different ways of classifying alkaloids; here we use a system based mainly on either the type of ring structure or the botanical taxa in which the alkaloids are found. By this method, there are some sixteen major groups of alkaloids; eighteen if you include the methylxanthines (e.g., caffeine) and phenethylamines. Some of these, like the indole or the isoquinoline alkaloids, contain several subcategories and a large number of therapeutic compounds; others have only a few molecules of interest to botanical medicine. In alphabetical order, these are:

- Amaryllidaceae alkaloids
- Betalain alkaloids
- Diterpenoid alkaloids
- Imidazole alkaloids
- Indole alkaloids
- Isoquinoline alkaloids
- Methylxanthines
- Monoterpenoid alkaloids
- Peptide alkaloids
- Phenyethylamines
- Piperidine alkaloids
- Pyridine alkaloids
- Pyrrolidine alkaloids
- Pyrrolizidine alkaloids
- Quinoline alkaloids
- Quinolizidine alkaloids
- Steroidal alkaloids
- Tropane alkaloids

In this chapter we'll discuss only a few of the more common alkaloids found in medicinal plants. For an outline of the other subcategories, see pp. 70-72. As with all compounds, new alkaloids and activities are being discovered daily; this is by no means a comprehensive listing. There is also the case of the nitrogenous ‘pseudoalkaloids’ – compounds which have some characteristics of alkaloids, but for various reasons don't entirely qualify to be classified as such. Two of these, allantoin and capsicain, are important to herbal medicine.

Allantoin

Allantoin is an odd compound, arising biosynthetically from purine metabolism (the purines include two of the nitrogenous bases in DNA: adenine and guanine; the methylxanthines and uric acid are also purine derivatives). Allantoin is slightly soluble in hydroethanolic solutions, and very soluble in alkaline or hot water; but it can be made
to dissolve in oily media by using an emulsifier. It is best known as a potent cell proliferant (stimulates the growth of healthy tissue in wound-healing) and anti-scarring emollient.1,2 Because of its soothing and healing properties, along with the fact that it helps the skin to slough off dead or damaged cells, synthetic allantoin is also high in pyrrolizidine alkaloids (PA).

Rich natural sources of allantoin include Comfrey (Symphytum officinale), especially the root; Houndstongue (Cynoglossum officinale), a common weed of temperate climates which is also called Wild Comfrey; and another Boraginaceae family plant, Lungwort (Pulmonaria officinalis). Notice that all of the Latin names of these plants end in either officinale or officinalis, indicating that they were once officially included in the pharmacopoeias of either Britain or the U.S. Be aware that while Houndstongue is a good source of allantoin, it is also high in pyrrolizidine alkaloids (PA – see p. 157); it is probably best to limit it to external use only (e.g., as a poultice). Lungwort, in contrast, is PA-free.

Capsaicin is another nitrogenous compound, but it is totally unrelated to allantoin biosynthetically. It is discussed under 'phenylpropanoid derivatives' on p. 114; it might, however, be thought of as an oil-soluble pseudoalkaloid or even as a fatty acid derivative. The aromatic ring of the molecule originates from a phenylpropanoid precursor; the nitrogenous part from an amino acid; and the hydrocarbon tail from a fatty acid.

References: Alkaloids

Acetate This word can refer to the functional group (CH₃COO⁻) derived from acetic acid (CH₃COOH), the negatively-charged acetate ion, or a compound containing an acetate group. Another name for acetate group is acetyl group, and a molecule containing one will often start with the prefix acetyl-. It can be considered to be a type of ester group or a type of acyl group. Acetate groups are mildly polar.

Acetate pathway A major biosynthetic pathway in plants that produces the polyketides: the fatty acids and their derivatives (including alkamides), and the aromatic polyketides (including anthraquinones); it also provides part of the structure of many other phenolic compounds including the flavonoids. It is sometimes referred to as the malonaldehyde pathway. For other biosynthetic pathways, see shikimic acid pathway and malonate pathway.
**Acetone**  An amphiphilic ketone, CH$_3$C=OCH$_3$, used as a solvent in some laboratory procedures to extract botanical constituents. Acetone will dissolve numerous substances with a variety of polarities. The smell of nail polish remover is primarily due to its acetone content. Acetone is sometimes used to extract herbal materials such as Kava.

**Acetyl**  A prefix indicating that a molecule has an acetate group attached. For example, acetylsalicylic acid is salicylic acid with an acetate group attached; acetylcholine is choline with an acetate group. An acetyl group is a type of **ester group** or **acyl group**.

**Achiral**  The opposite of chiral. A carbon atom not having four different atoms or groups attached (i.e., two of them are the same) is achiral. See **chiral**.

**Acid**  Chemically, an acid can be defined as a 'hydrogen donor,' a molecule capable of donating a **proton**, which is a hydrogen nucleus without its single electron. For example, hydrochloric acid (HCl: a strong acid) comes apart in water (**dissociates**) to give positively charged hydrogen ions/protons (H$^+$) and negatively charged chlorine ions (Cl$^-$). In plants, we find only 'weak' acids (**carboxylic acids**). A phytomolecule is an acid if it has one or more –COOH groups (**carboxyl groups**; example: citric acid); or it can be weakly acidic if it can lose a hydrogen atom from, for example, a **hydroxyl group** (–OH group). Generally, when a molecule acts as an acid and loses a hydrogen atom, it becomes negatively charged. Its name then changes like this: citric acid becomes citrate; malic acid becomes malate, etc. So a name like 'magnesium malate' means a molecule consisting of a positive magnesium ion associating with a negatively charged malate ion. The illustration depicts malic acid.

**Acidic**  A solution is acidic if its pH is less than 7.0. A molecule is acidic if it is capable of acting as an acid (donating a proton).

**Acyl group**  A functional group consisting of a carbon atom double-bonded to an oxygen atom, and also single-bonded to an R group. Types of acyl groups include **acetyl**, **malonyl**, and **benzoyl**. Acyl groups are derived from the corresponding carboxylic acids which have lost the –OH from their carboxyl groups. You see this term as part of the word 'triacylglycerol' which is another word for triglyceride. It indicates that three fatty acids are bonded to a molecule of glycerol with acyl type linkages.