What Are Natural Products?

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Abstract and Keywords

All organisms are made up of chemicals. There is a common collection of several hundreds of substances that are produced by all living organisms. However, hundreds of thousands of different chemicals are also produced by plants and microbes, with each species producing its own characteristic mix. This much larger class of chemicals, often called Natural Products (NPs), are clearly not essential for life, but their production must bring some benefit to the producer. This chapter begins with a discussion of the difference between NPs and natural products. It then considers the development of studies on NPs from the 19th century onwards, and describes the organisms (microbes and plants) that make NPs.

Keywords: Natural Products, NPs, living organisms, plants, microbes, chemistry

“When I use a word”, Humpty Dumpty said, in rather a scornful tone, “it means just what I choose it to mean—neither more nor less.”

—Lewis Carroll
Summary
All organisms are made up of chemicals. There is a common collection of several hundreds of substances that are produced by all living organisms. However, hundreds of thousands of different chemicals are also produced by plants and microbes, with each species producing its own characteristic mix. This much larger class of chemicals, often called Natural Products (NPs), are clearly not essential for life, but their production must bring some benefit to the producer. The different NP composition of pears and apples, for example, explains why these two fruits taste different. The difference in NP composition of lemons and roses gives each species its characteristic smell. Even within a species, the NP composition can vary; hence, individual varieties of apples or pears can have distinctive flavours.

In Chapter 2, it is argued that NPs have dominated, and continue to dominate, world economic activity and that these chemicals influence the lives of every individual, every day. Consequently, because NPs are so important, one would expect every child to learn about them but they do not. Why? The answer to this question tells us something about how science is conducted and taught. Although science is firmly compartmentalised (at school, university, bookshop or library) into subject disciplines such as physics, chemistry, zoology and so forth, there are no logical boundaries between subject areas. Scientific boundaries, like national ones, are human constructs and are not always wisely drawn. The subject of NPs became fragmented in the nineteenth century when it was split between chemists and biologists. Neither group nurtured their part of the subject. Biologists fragmented their studies of NPs into more subdisciplines, and the chemists became fixated on the structures of the individual chemicals. It is as if the study of orchestral music gradually became the study of some chords or individual notes.

Natural Products (NPs) and natural products—spot the difference
How sad and frustrating that the first hurdle the author has to clear is to try to explain why a natural product differs from a Natural Product.

Most English-speaking people can readily give examples of products that they consider to be ‘natural’. Common examples would be sugar, butter, wood, honey and
cotton. These *natural* products are considered by many as being somehow different (healthier? safer? more environmentally friendly? better?) from *synthetic* products made by humans, such as plastics, petrol, oil, pesticides and pharmaceutical drugs. As advertising agencies have learned, the term *natural* carries with it many positive associations, and it is ideally suited for misuse. The fact that nearly all natural products are now highly processed and refined by humans before being presented to the consumer is overlooked. So the commonly used term ‘natural product’ is vague, open to too many interpretations and features very little in this book.

Unfortunately, the term ‘natural product’ also passed into scientific usage in the nineteenth century. Scientists in the English-speaking world started to use the term *Natural Product* (sadly not always capitalised) to classify a particular type of chemical made by plants or microbes. At that time scientists were beginning to analyse the chemicals found in different plant species. These analyses revealed that some chemicals (many simple sugars, amino acids, some organic acids) were common to most plants studied. However, every individual plant species also contained a few chemicals that were distinctive, substances that gave the species its characteristic smell or taste. These distinctive chemicals were placed in the general category of Natural Products. So we have this Alice in Wonderland situation where all Natural Products are natural products but not all natural products are Natural Products (Figure 1.1). This was indeed an inauspicious, careless start to the building of a new area of scientific study. Many scientists have been unhappy with the term Natural Product and have suggested alternatives, the commonest being *Secondary Metabolite* (the reasons why this term was proposed,
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(p.3) and the reasons why this term is best consigned to history is explained later. Sadly, no alternative term for Natural Products has gained universal acceptance; hence the author feels that it is time to rid ourselves of this unfortunate legacy. In society and science, abbreviated terms are now widely used. Abbreviations have the advantage of being more easily adopted in other languages, yet they can act as an appropriate link to the past usage. Consequently, it is suggested that readers accept the abbreviated term NPs for Natural Products so that the confusion about the name can be left behind us before we start to explore the subject.

So, at this stage of our journey, the reader needs only to know that NPs are the distinctive chemicals which characterise particular plant and microbial species. Each species of plant produces its own mixture of maybe a few hundred NPs. The difference in NP composition explains why a pear tastes different from an apple or a rose smells different from a carnation. In the plant kingdom, hundreds of thousands of different NPs are being produced. Every human experiences many of these substances daily in the scents and flavours in their food and drink, but they are blissfully unaware of the many more chemically complex NPs that they ingest daily but are not sensed by the human sensing systems. Several chemicals which are well known to most citizens, because they are hugely prized, are NPs—morphine, caffeine, quinine, penicillin, the anticancer drug taxol, the drug vinblastine and so forth. With this brief summary of what NPs are, the reader can move on to subsequent chapters to follow their own

Figure 1.1. What is the difference between a natural product and a Natural Product? To chemists the answer was simple. When a chemist uses the term Natural Product (or sadly, even ‘natural product’ without capitalisation), they refer to a naturally synthesised substance that is not made by all organisms but is made by only a few species. However, the term ‘natural product’ is now much more widely used by the rest of society to mean anything not manufactured. This ambiguity is very unhelpful; consequently, this book will adopt the term NP for Natural Product, the term NP being chosen for its historical association and language independence.
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interests or they can find out why the science of NPs has progressed so hesitantly in the past.

**NPs—the subject forms and then fragments**

**Chemicals from minerals and chemicals from organisms—inorganic and organic chemistry**

At the end of the eighteenth century, chemistry was emerging as an academic subject. It drew on two distinct streams of information from past human endeavours—the study of minerals and plant products. Knowledge of mineral rocks, and the metals that could be obtained from them, had been increasing slowly for thousands of years and was highly valued in all cultures. Likewise, the human experience in the production and processing of plant-derived substances to give food, dyes, fabrics and drugs (both pharmaceutical and recreational) was central to all human civilisations. Within all societies, a few people inevitably 'experimented' with new ways of processing minerals or plant products, guided by thoughts of how to produce something of greater value from the starting substance. Since the days of the ancient Greek philosophers, it had been argued that most substances, whether mineral or derived from plant or animal sources, were made up of other entities. Over the centuries, experimental manipulations, guided by theoretical or empirical motives, had been undertaken to try to separate and identify these entities. In the eighteenth century, deductive reasoning was increasingly used to devise general rules that might be applied to the understanding and manipulation of minerals. By the beginning of the nineteenth century, such studies, undertaken particularly intensively by Swedish and Finnish chemists, had led to the identification of 36 elements (carbon, hydrogen, oxygen, sulphur, nitrogen, etc.). By 1830, the number of known elements had risen to 53, with almost half the elements now known being discovered. The contemporaries studying the chemical properties of plant or animal products knew of old evidence that natural materials might also be composed of simple substances combined in some way. For example, distillation had been widely used since the tenth century to separate alcohol from fermented broths and to produce oil of turpentine from pine resin. A significant advance was made in the years 1769–1785 when the Swedish chemist Scheele isolated a number of different sour substances in plant- or animal-derived products—tartaric acid from grapes, citric acid in citrus, oxalic acid in wood sorrel,
malic acid from apples, gallic acid in galls, lactic acid in sour milk and uric acid in urine. Scheele deduced that

- organisms contained many different substances,
- the amount of any one substance could differ in different organisms,
- different substances could share some properties (e.g., there were many substances that humans perceived on the tongue as sour).

Scheele did not possess the ability to identify the elemental composition or the structures of the substances he had isolated, but others soon developed the techniques needed for the crucial next stage. The French chemist Lavoisier's studies of combustion (1772–7) produced a method of determining the elemental composition of most chemicals made by organisms. When Lavoisier (aided very considerably by his wife, Marie-Anne Pierrette Paulze) burned a natural substance (e.g., sugar, ethyl alcohol and acetic acid) in oxygen (discovered first by Scheele in 1772 and then independently again by Priestley in 1774), he found that the only combustion products were carbon dioxide and water. He deduced that such natural substances contained carbon, hydrogen and, possibly, oxygen. By quantification of both the amounts of the starting materials and the amounts of the products formed by combustion, Lavoisier could determine the relative amounts of each element in the combusted product. Subsequent studies showed that some other chemicals made by organisms (e.g., urea, hippuric acid, morphine) produced carbon dioxide, water and nitrogen when burned in oxygen; hence they must have contained nitrogen as well as carbon and hydrogen. Combustion in oxygen was widely adopted as a simple way of determining the elemental composition of all chemicals that were found in organisms. Soon it was discovered that different substances could share the same elemental composition, and it was proposed that the way in which the carbon, hydrogen and oxygen atoms were joined together must be characteristic of each substance. After the concept of valency was accepted, the location of the carbon–carbon links (bonds) was seen as the key to identifying each chemical, and the concept of the carbon skeleton emerged. A convention as to how such chemical structures could be drawn on paper was adopted and the scene was set for the characterisation of the structures of all naturally made chemicals (Figure 1.2).

It was at this stage of the development of chemistry that the problems of terminology began. In 1807, the influential Swedish chemist Berzelius had proposed (p.5)
that the chemistry of substances made by living organisms should be referred to as *organic chemistry* to distinguish it from the chemical studies of mineral or inorganic substances—*inorganic chemistry*. He reasoned that in contrast to inorganic substances, such as mineral ores or metals, organic substances were sensitive, even delicate, as evidenced by their ease of combustion. In particular, he noted that chemists could make (p.6) inorganic substances, such as various salts, but he argued that chemists could never make organic substances—these substances could only be made by living organisms. Berzelius believed and argued that only living organisms possessed the *vital force* needed to make these delicate organic compounds. At that time the merging of scientific ideas with what we would now regard as a mystical concept such as vitalism was in no way remarkable and Berzelius's view was widely accepted.

The vital force—science to anti-science

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*Figure 1.2.* Scheele isolated a family of naturally occurring sour substances. Subsequently, the elemental composition of each substance was determined using Lavoisier's combustion method and later the different structures were proposed. Each member contains common structural element, a carboxylic acid group which gives each its sour taste. The two-dimensional representation of chemical structures as shown is convenient but can be misleading. Also shown is the structure of urea, the first naturally occurring substance to be made in the laboratory by Wohler (shown), who provided the first experimental challenge to the concept of vitalism.
In 1828, the young German chemist Wöhler, who had studied in Stockholm with Berzelius, showed that Berzelius's postulate, that humans could not make organic molecules, was wrong. Experimenting with the inorganic substance ammonium cyanate, Wöhler made the organic substance urea (Figure 1.2). After repeating the experiment many times, Wöhler finally wrote to Berzelius stating, ‘I must tell you that I can prepare urea without requiring a kidney or animal, either man or dog.’ As often found in science, this simple disproof of the existence of Berzelius’s vital force was not immediately or universally accepted. Berzelius was a scientist of great authority, while Wöhler was only starting to make a reputation. Vitalism, supported by authority, was given the benefit of the doubt and the concept lingered on and eventually took on a new life. However, the majority of the new generation of organic chemists did not need the concept of vitalism to guide them in their attempts to make new chemical structures or to determine the structure of chemicals isolated from plants. However, a new subgroup that emerged from organic chemistry, the physiological chemists, found a new role for the concept of vitalism and, in doing so, broke away from the organic chemists.

Physiological chemists (known as biochemists since the twentieth century) were those chemists who were interested in the chemical transformations that are taking place within organisms—ordinary organic chemists were more interested in the chemical transformations that they could make happen in their flasks, beakers or retorts. Physiological chemists were inspired by the work of Persoz and Payen. In 1833, these two French chemists had reported that an extract of malt (the brown, sweet mixture of sugars derived from the germinating grains of barley) in water could break down insoluble starch to produce soluble sugars. They had discovered the catalytic proteins, later to be called enzymes, which were thought to be unique to living cells. The new slant given to vitalism was that only whole living cells were thought to carry out enzymic transformations. Even Wöhler subscribed to this view as did the very influential German chemist Liebig. The concept of vitalism lived on in this new form until 1897, when Buchner found, by accident, that enzymic activity could be measured in extracts of yeast cells which lacked any living cells.
However, even after all traces of Berzelius's ideas on vitalism had been disproved by experiment, his associated term ‘organic’ survived. After Wöhler had shown that humans as well as organisms could make ‘organic’ chemicals, the term *organic chemistry* became the chemical study of any carbon-based compounds, and that usage remains.
As the subject of organic chemistry grew during the second half of the nineteenth century, specialisms emerged within that subject. Some organic chemists were mainly interested in the generation of new carbon-based molecules (organic); consequently, they developed new or improved methods of synthesising known and novel organic molecules. This branch of organic chemistry became known as Synthetic Organic Chemistry. Other organic chemists were fascinated by the diversity of chemical structures made by organisms, and these chemists developed methods to isolate, purify, characterise and synthesise such naturally occurring substances which they called, in the English-speaking world, Natural Products to distinguish them from the synthetic chemicals of interest to other organic chemists; hence the birth of Natural Products Chemistry and the common usage of the term of Natural Products in the English-speaking world. However, Natural Products Chemistry was soon to fragment further.

As the chemical composition and structures of substances derived from living material was explored, it became clear that many substances were found in the majority of organisms but some substances seemed to occur only in a few species. For example, the 22 common amino acids, glycerol, sucrose or glucose could be found in most animals, plants and fungi. But everyone knew that many plant species produced chemicals, such as scents, that were characteristic of that species—roses, mint, pepper, cloves and so forth. Not surprisingly, by the mid-nineteenth century, the most widely distributed Natural Products, those common to most organisms, were attracting most interest. The chemistry of digestion and assimilation, catalysed by the newly discovered enzymes, was an exciting field of study and the Physiological Chemists increasingly concentrated on these universally important substances. Step by step the sequence of the enzymic conversions which led to the formation of each substance was established. Each new enzymic step was added to a ‘map’ of the inter-conversion routes of the chemicals common to most organisms. As the decades passed, the Physiological Chemists studying the enzymes in these widely shared pathways had less and less in common with those Natural Products Chemists studying the chemical structures of the rarer strange chemicals, each of which occurred in only a few species. The techniques and concepts used by those studying the rare, exotic chemicals
had much more in common with Organic Chemists than Physiological Chemists. Inevitably, the subject of Natural Product Chemistry fragmented. By the early twentieth century, some institutions had created new Physiological Chemistry Departments (or Biochemistry Departments as they were subsequently called) to work alongside the Chemistry Departments. In general, the new Biochemistry Departments concentrated on the biochemistry that was nearly universal to all organisms; consequently, the Natural Product Chemists were usually left in Chemistry Departments where they were more at home. Thus the scope of the subject of Natural Products Chemistry, which had started in the nineteenth century as a study of all naturally produced chemicals, was reduced in the twentieth century to the study of only those chemicals which were often found only in a few organisms. To a chemist, a Natural Product is simply a fascinating naturally occurring carbon-based chemical that is of little interest to most biochemists. To most biochemists, Natural Products are occasional useful tools (because a few have a very powerful ability to perturb cell or enzyme functioning) but not much to do with ‘real’ biochemistry—that is why the subject was left to the chemists.

Figure 1.3. The time scale of fragmentation of the study of NPs—a fragmentation that has resulted in the current unsatisfactory situation where different groups of scientists use their own names for the same class of substances.
To further complicate matters, in 1891, the German Physiological Chemist Albrecht Kössel (who won the 1910 Nobel Prize for Medicine) unknowingly aided this fission of the subject of metabolism when he proposed that plants had two distinct types of metabolism, ‘primary’ and ‘secondary’. He proposed that primary metabolites were involved in basic processes of the cell and were common to many organisms. Secondary metabolites were made by distinct pathways limited to some organisms; hence they served a less vital role. Kössel's primary metabolism was the subject taken over by biochemists, and his secondary metabolites were the Natural Products being studied by chemists. A consequence of Kössel's categorisation is that the terms Natural Products and Secondary Metabolites are still used synonymously (Figure 1.3). The former term is used mainly by chemists and the latter mainly by scientists with a biological background. Could there be a better example of the fragmentation of a scientific subject than one where two different groups have the different names for the same subject?
Time to ‘rebrand’?\(^5\)

The result of this century-old fragmentation of the subject is well illustrated when looking for information about *Natural Products* or *Secondary Metabolism* in current biochemistry textbooks. When the indices of 10 important current biochemistry textbooks were examined in 2000, none contained the words *Secondary Product*, *Secondary Metabolism* or *Natural Product*! While it is understandable that biochemists should concentrate on the few hundred chemicals that are commonly produced by most cells, a sense of fair play or balance would surely demand that some reference be made to the fact that most of the world’s biochemical diversity resides in another type of metabolism.

Many scientists studying *Natural Products* or *Secondary Metabolites* have been participants in debates aimed at ‘rebranding’ their subject but without success. Debates have been held as to which is the preferable term and new terms have been suggested, such as *semiochemicals*. A consistent theme in such debates has been the feeling that the use of the term ‘secondary’ has been unfortunate because there is an implication that such compounds are not really important. The term *semiochemical* (from the Greek word *semeon*, a signal) was inspired by the belief that Natural Products were involved in signalling, but the term tends to be used only by those interested in chemical signalling between some groups of organisms (e.g., between insects—see Chapter 8) but the term is inappropriate because most Natural Products are not involved in signalling. The decision by the author to use the term NP in this book, instead of Natural Product, was taken on the basis of historic precedence, but also because it will be argued in Chapter 9 that Kössel’s alternative term, Secondary Metabolites, was unhelpful and wrong!
Which organisms make NPs?

Although microbes and plants are the organisms that are most commonly exploited for their NPs, it is very hard to draw clear boundaries between organisms that do and do not make NPs. For example, humans make some substances of unknown function. (p.10) However, because digestion and excretion was central to the developing subject of Physiological Chemistry in the nineteenth century, such reactions were considered to be more closely related to ‘normal’ metabolism than NP chemistry; hence the role of animals in generating chemical diversity was largely ignored by those interested in NPs. Such a view makes these ‘degradation compounds’, typically formed in the liver, different from NPs. However, it is now clear that this approach is unhelpful and a broader, more holistic approach will be more productive. There are useful analogies between processes occurring in the liver and processes found in many plants and microbes, and, in later chapters, it will be argued that such links are not fortuitous but a consequence of the fact that organisms have evolved to make and adapt to NPs. However, the chapters that follow will concentrate on the remarkable NPs that plants and microbes make because it is those chemicals that have influenced the history of humans and which continue to drive the world economy.
What does this chapter tell us about the way science works?
Clearly the way in which the study of NPs developed in the nineteenth century has had a profound effect on the study of NPs in the subsequent centuries. For psychological reasons, most people like to gather with people who share their view of the world, but whenever such groups form, schisms always develop and subgroups drift off on their own. When such splits occur, some of the ideas shared with the larger group are retained but the new group always has to have a novel perspective. In this type of group behaviour, scientists are no different from those with religious beliefs. While scientists like to think their groupings are logical, based on some accepted realities, all scientific disciplines are human constructs. Those who form a new scientific discipline establish a way of thinking which persists because those who come to study that discipline are now taught what is virtually a creed. The common ideas that united a larger subject are given less emphasis than the key ideas of interest to the smaller group. With the benefit of hindsight, it is clear that when the study of NPs emerged from the study of chemistry in general, the most important idea needed to understand NPs was simply not one that chemists were seriously interested in—evolution. Maybe because the biological concept of vitalism had not proved productive, when vitalism was finally discarded, the biological concept waiting in the wings, selection based on natural selection, was not seized to provide a conceptual framework to shape the thinking of those interested in NPs. Yet, like all biological phenomena, NPs can only be understood in their evolutionary context. The laws of chemistry and the laws of physics apply to individual NPs, but these laws by themselves cannot provide any perspective on why NPs exist, what they do and why humans are in thrall to these chemicals. It is significant that within the broad subject of biology the study of NPs was closely linked to evolutionary ideas in some areas and not in others. Biologists closest to chemistry, the biochemists, were the least influenced by evolutionary thinking, while those working on NPs and their ecological role were working within a clear evolutionary framework. However, any interaction between organisms occurring at population level are really the result of processes occurring in individuals, and within the individual the processes are about the interactions of molecules, which themselves depend on molecular structures and the laws of physics. Any attempt to understand
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the processes that occur in any hierarchy must be built on an understanding of all the processes occurring at the lowest levels, because everything at the higher levels is governed by the laws that have shaped the outcomes of processes at the lowest levels. Sadly, the few simple rules that govern the natural world tend to get obscured by the increasing large piles of ‘facts’ and nowhere is this better illustrated than in the study of NPs. Traditional books about NPs tend to be full of details (the chemical structures of thousands of substances or the subtle interactions between thousands of organisms), so it is not a lack of ‘facts’ that stops non-NP enthusiasts appreciating them. Consequently, this book tries an alternative approach, bringing to the fore a few simples rules and being very sparing with the ‘facts’. (p.12)

Notes:

(1.) Given that how economically important Natural Products (NPs) are to humans, some readers might be surprised to know that no complete inventory of the NPs of any species has ever been published. The genomes of several species that make NPs are known but the NPs that these organisms can make are unknown. As explained in Chapter 9, many enzymes involved in NP biosynthesis are multifunctional and some NPs can be made by more than one route; hence, to assign individual genes to specific steps in NP biosynthesis might be a challenge.


(3.) Valency is the potential of any element to form multiple links to other elements. For example, hydrogen has a valency of one, oxygen a valency of two and carbon a valency of four.
(4.) It is ironic that the belief in vitalism, once central to the scientific study of naturally occurring chemicals, lives on in the minds of some non-scientists. The term ‘Organic’ is used in some English-speaking countries to identify ‘natural’ or ‘ecological’ products, products that are untainted by the endeavours of chemists. Those who believe in unique properties of ‘Organic’ products are essentially followers of Berzelius's classification of chemistry into inorganic and organic and the belief that living organisms possess some unique properties (the vital force).

(5.) As explained in Chapter 2, it can be argued that the concept of the commercial ‘brand’ was first used successfully to sell NP-rich products, especially cigarettes and soft drinks.

(6.) The concept of a scientific ‘fact’ is a slippery one. ‘Facts’ are a human construct and they have a remarkable way of changing as humans learn, think and experiment. As very well illustrated in the wonderfully readable book, Bryson B. (2003). *A short history of nearly everything*. Doubleday, Canada, each generation thinks that they have discovered the ‘true facts’, yet later generations usually show that previous understanding was not perfect. Consequently, all scientists should always be willing to challenge orthodoxy.