From Fever Dreams to Pharma Queens: *How Plants Influenced Modern Medicine*

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A suffocating, burning sensation floods your body as your head pounds relentlessly and the world blurs in front of you—*a fever.* If you came down with one of these in the ancient days, the treatment suggested would vary across civilizations. In the 4th millennium BCE, Egyptian, Mesopotamian, Chinese, and Indian cultures may have thought you became the host of an evil spirit and used extreme methods to rid you of its possession to relieve the fever. Concurrently, in Greece, people considered the fever as beneficial to the affected and often recommended "fever therapy" to treat other diseases such as syphilis, gonorrhoea, and epilepsy. Around 400 BCE, Hippocrates recommended chewing on willow-tree bark to those suffering from fever to deal with the pain; this was supported in 100 CE by Dioscorides, who used it in his prescriptions as an anti-inflammatory agent.[1]

Many ancient civilizations successfully sought treatments from nature, although they often lacked a functional or mechanistic understanding of these medications. For example, it was not until the early 1800s—thousands of years after the first recorded use of willow bark to treat fever—that it was discovered that the tannins of willow bark contained salicin (derived from the Latin word for willow), a precursor molecule to salicylic acid, which is now known to treat fever and pain. As technology and scientific knowledge advanced, acetylsalicylic acid (a derivative of salicylic acid) became the active ingredient in aspirin, responsible for its anti-inflammatory, antipyretic (fever-reducing), and analgesic (pain-relieving) effects.

PHYTOCHEMICALS: NATURE'S SECRET AGENTS

'Phytochemical' is a collective term for naturally occurring chemicals in plants. Typically, they serve as secondary metabolites, which provide non-primary survival needs, such as color and flavor production, or protection from pests and environmental stress. In pharmacology, phytochemicals are the compounds active in many herbal medicines due to their ability to influence the activity of key proteins and enzymes in regulating cellular processes that are implicated in various disorders.[2] Consistent with historical records, these compounds have garnered attention for their ability to decrease the risk of several types of chronic diseases, including cardiovascular diseases, diabetes, and cancers.[3]

Although over 10,000 phytochemicals have been identified, a large percentage remains unknown, and only a small fraction of currently known phytochemicals has been studied extensively. With their various functional roles and structural complexities, phytochemicals have yet to receive strict classifications. However, in practice, phytochemicals are classified into major categories by their chemical structures or biosynthetic pathways as researchers deem fit. Biosynthetic pathways are the series of chemical reactions through metabolic pathways derived from primary metabolic pathways that plants usform specialized compounds.[4]

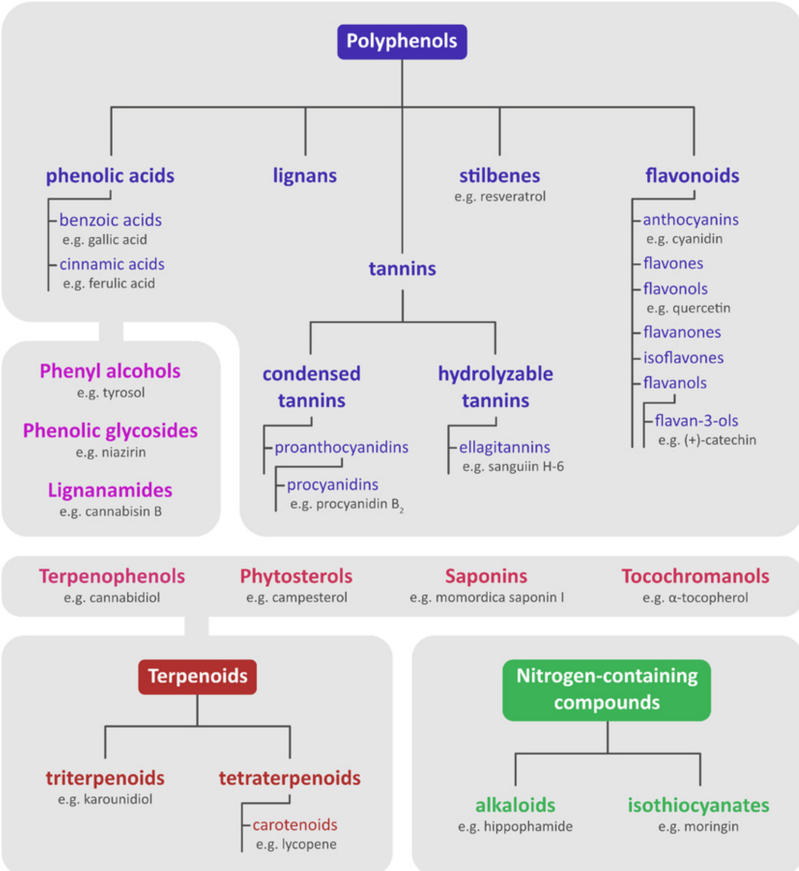

Figure 1: One classification of different types of phytochemicals. Areas conjoined by a grey background share similar structural similarities or involvement/synthesis in the precursors of others.

MALARIA MEETS ITS MATCH: ARTEMISININ (SWEET WORMWOOD)

Artemisinin is the medically active component derived from sweet wormwood. With artemisinin-based combination therapies (ACTs) recommended by the World Health Organization as the first- and second-line treatment for malaria, artemisinin is perhaps the most famous drug with literal roots in plant-based medication. Artemisinin was discovered by Professor Tu You You in the 1970s when she was selected to lead a research team that focused on screening traditional Chinese medicine (TCM)—an ancient system of healthcare—for novel antimalarial drugs. After narrowing down the various methods recorded in TCM to have been used to treat malaria to approximately 200 herbs, she returned to the earliest record of the use of sweet wormwood to treat malarial symptoms in Ge Hong's Zhouhou Beiji Fang (Handbook of Prescriptions for Emergency). Drawing from this literature and her own knowledge of the herb, Tu determined how to extract artemisinin and was awarded the Nobel Prize in Physiology or Medicine in 2015 for her work.[5]

Artemisinin is one of the most abundant secondary metabolites in the genus Artemisia. All artemisinin derivatives have a bitter taste and strong characteristic aromas caused by the presence of terpenes and sesquiterpenes lactones containing an endoperoxide 1,2,4-trioxane ring, which is responsible for its antimalarial properties.[6] It mainly targets malaria parasites by disrupting the parasite in the blood stage, where the parasites replicate within a blood cell. Since artemisinin has a short half-life, staying intact in the body only for a few hours, it is typically paired with another drug that eliminates the remaining parasites over a long period of time to improve the medicine's efficacy.[7]

LIMITATIONS AND FUTURE POSSIBILITIES

While phytochemicals are considerably accessible in that they are provided by nature, their existence still depends on the availability of their parent plants. As such, an issue lies in the complexity and variability in phytochemical compositions, which are inconsistent and dependent on factors like climate, compositions, which are inconsistent and dependent on factors like climate, geographical location, and soil quality. This makes it difficult to standardize the extraction of specific phytochemicals. Furthermore, several phytochemicals have low bioavailability (the proportion of the chemical found in plants), creating difficulties in the extraction process and resulting in very low yields. This, in turn, affects the pharmacological studies and development of medicines.

Despite these challenges, ongoing research and technological advancements in fields such as synthetic biology, chemical synthesis, and genetic engineering are helping to gradually overcome and address these limitations.8 For example, researchers from University of Washington have found a way to use plant biomass to synthetically produce

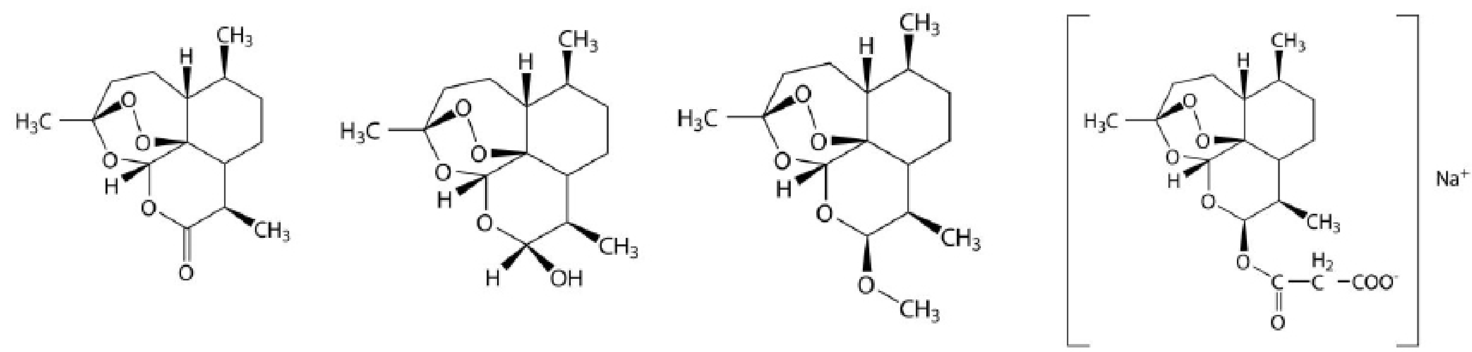

Figure 2: Artemisinin and its common derivatives. From left to right, Artemisinin, Dihydroartemisinin, Artemether, and Artesunate.

Contemporary research validates what our ancestors knew through experience: that nature's chemistry, as found in plants, holds remarkable therapeutic powers. Our ancestors started paving the way, and in following their steps, we can take advantage of their work and use modern technology to explore and refine these ancient remedies for modern applications.

acetaminophen, the active ingredient in the popular pain-reliever, Tylenol.[9,10] The researchers were able to obtain p-hydroxybenzamide (pHB), a chemical derived from the clipoffs of lignin, a phenolic compound found in the cell walls of plants, and break it down into a more useful component. This component could then be converted into paracetamol, the chemical compound for acetaminophen.[10] Since acetaminophen is originally derived from coal tar—a dark liquid that is formed from the byproduct of coke (a solid fuel mostly containing carbon) and coal gas drawn from a finite supply of fossil fuels—their synthetic derivation provides an environmentally friendly alternative for the production of acetaminophen.

Ultimately, the structural relevance and complexity of phytochemicals are established through the development of pharmaceuticals as well as in synthetic chemistry. Contemporary research validates what our ancestors knew through experience: that nature's chemistry, as found in plants, holds remarkable therapeutic powers. Our ancestors started paving the way, and by following their steps, we can take advantage of their work and use modern technology to explore and refine these ancient remedies for modern applications.

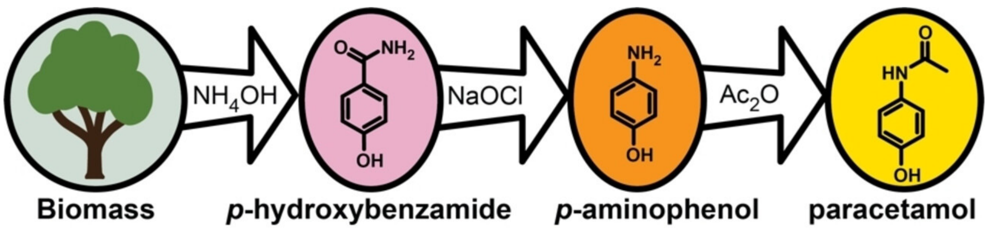

Figure 3: P-hydroxybenzoate is extracted from poplar trees and then converted to its useful component, p-hydroxybenzamide (pHBA). From there, a continuous reaction process converts pHBA to p-aminophenol and then acetylates the p-aminophenol to paracetamol.

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