INSIGHTS INTO EVOLUTIONARY SYSTEMS *VIA* CHEMOBIOLOGICAL DATA

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Summary

Nowadays, a large part of knowledge and technology is being privatized, generating an unprecedented dispute among the diverse levels of our society, such as consumers, environmentalists, scientists, traditional societies, governments, politicians, economists, business managers, and pharmaceutical companies. To the next generations remain the consequences, good or bad, of the actual eco-socio-economic conflicts. Hence, the

major challenge for our generation is trying to reconcile economic interests and the well-being of humanity and planet Earth. Dream or reality?

Meanwhile, our battle for survival continues. Human health care requires that the ever-increasing resistance of pathogens be confronted by a correspondingly fast rate of discovery of novel drugs, in other words, speeding up the search for bioactive phytochemicals. This, however, will remain a distant dream unless the mechanisms responsible for plant bioactivity may be recognized, alleviating the heavy burden of random selection of plants. Unfortunately, little is known about the relationships of natural products with morphology, ecology and evolution of their plant source.

This chapter resumes the efforts of our group to develop a new multidisciplinary field of study, Quantitative Chemo-Biology. This new approach demonstrates that traditional knowledge, when considered by an adequate methodology based on a scientific point of view, possesses systematic and evolutionary relevance. Our procedure indicated that the choice of plants for medicinal and food purposes involves their polyphenolic content. Thus, plant metabolic cycles are regulated via gallate/caffeate feedback loops and constitute a powerful tool to elucidate evolutionary mechanism regulators of bioactivity. The immediate consequence is the recognition that both dualistic systems (medicine/food and gallate/caffeate), jointly with a wide range of physical, chemical, biological and social systems, constitute one more, important demonstration of the universality of antagonistic forces. Hopefully, Quantitative Chemo-Biology will provide new insights into the mechanisms of the functioning of nature.

1. The Phytochemical Discovery of Brazil

"Traziã alguũns deles huũs ourjços verdes de arvores que na cor querjam parecer de castinheiros se nõ quanto herã mais e mais pequenos e aqueles herã cheos de huũs grãos vermelhos pequenos. que esmagandoos entre os dedos fazia tintura muito vermelha da que eles andavam tintos e quanto se mais molhava tanto mais vermelhos ficavam./"

"Some of them brought spiny green balls like hedge-hogs (sea urchins), from trees, that in colour seemed to resemble chestnuts, but much, much smaller. And they were full of small red grains, which, when crushed between the fingers, left a very red dye, with which they painted their skins and the more they got wet, the redder they got."

Letter from Pero Vaz de Caminha to El-Rey Dom Manuel, April, 1500

This first official report on the arrival of the Portuguese navigators at the new South American territories did not spare enthusiastic words to describe, in a poetic prose, the great enchantment caused by the tropical Brazilian flora. However, even without their knowledge, this amazement was indeed due to the incredible diversity of chemical compounds responsible for the most diverse uses and actions of this exuberant vegetation. After all, the biological functions of plants are also due to their diverse chemical arsenal.

The astonishing reddish color from seeds of the tropical annatto tree (urucu or roucou), *Bixa orellana* L. (Bixaceae), was caused by a pigment with an atypical structure, bixin (see Plate 1 and Figure 1). This natural coloring matter, identified as a diapocarotenoid with a chain of 24 carbon atoms and a double bond with *cis* configuration, is responsible for the vast use of this seed to color foods, such as margarines and cheeses, as well as cosmetics. Many biological actions are also attributed to the annatto seeds, from digestive and expectorant, to aphrodisiac and insect repellent. Probably, this latter activity should be the true reason for the indigenous use of this natural pigment.

Plate 1. *Bixa orellana* L. (Bixaceae), urucu, roucou, or “lipstick tree”

The use of plants by men for the most diverse ends, i.e. for foods, for cures of illnesses or even for festivities and rituals, goes hand in hand with the evolutionary history proper and the development of human civilization.

Since the Stone Age, humans have tried to obtain the maximum advantage from nature! In the sixteenth and seventeenth centuries the European forests were ferociously devastated to allow progress of agriculture and production of raw material for heating and construction of houses and ships. Those same “civilized” European men, utilizing vessels built at the expense of their own trees, were completely fascinated by the exuberant flora and fauna of the new lands. Did this paradox ever change?

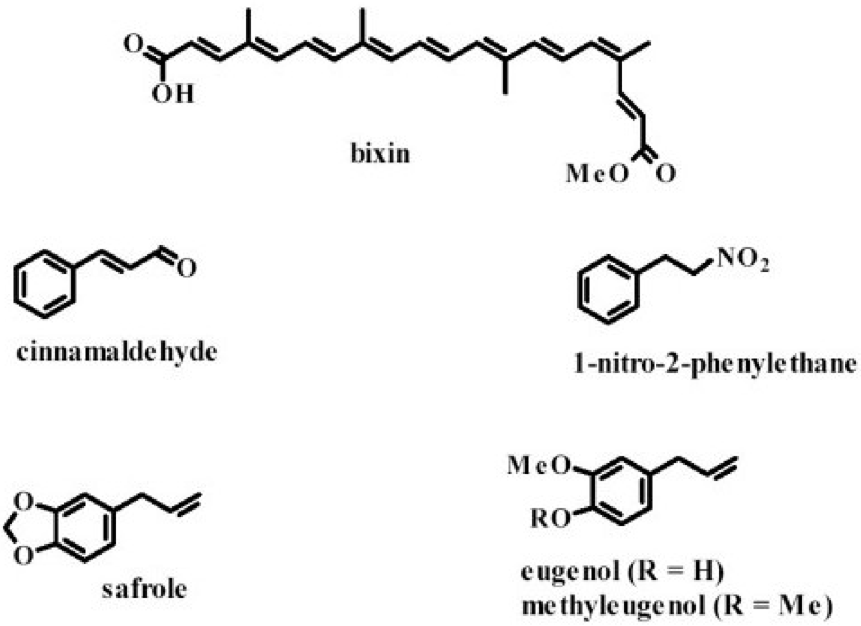

Figure 1. Structure of annatto (*Bixa orellana*) pigment (bixin) and some constituents of essential oils isolated from species of cinnamon and sassafras (Lauraceae).

2. Chemical Variability: Puzzles of the Lauraceae

2.1. The Puzzle of Cinnamon (The Discovery of Amazonia)

In about 1541 the Pizarro brothers, saturated with blood and precious metals, came to hear about a fantastic legend: on the oriental slope of the Andes a land of cinnamon was supposed to exist. In an age when spices were as alluring as gold, there was magic in the word. Spices, valued not only for their culinary applications but for medicinal properties, we are only now starting to rediscover, played an unexpectedly pivotal role in the exploration of the world. Cinnamon is an antiseptic, a powerful digestive and a respiratory stimulant.

Thus, immediately, Gonzalo Pizarro, with three hundred and fifty conquerors, two hundred horses, two thousand ferocious dogs trained to attack Indians and four thousand Indians, marched out of Quito (Peru) down the Andes to look for that precious spice. They did indeed find cinnamon, but the tree was not abundant in any particular place. Slowly the troop, famished and decimated by illness, lost interest.

Finally, a group headed by Francisco Orellana, built a vessel, with which it initially descended the Napo river in search of provisions. Being incapable of returning because of the strength of the river currents, or wishing to escape the oppression of the Pizarros, Orellana continued down the Amazon river until he reached the Atlantic Ocean and returned to Europe. Thus, he became the first navigator to complete this fantastic journey on the rivers of the Amazon. It had taken eight months to get from the Andes to the Atlantic. Meanwhile, Gonzalo Pizarro, with no sign of Orellana, staggered back to Quito on foot with eighty fellow Spaniards. Not one Indian, horse or dog had survived.

This disastrous expedition, the first one of the white man to Amazonas, did not find the land of cinnamon. The curiosity that was aroused by their fight against the legendary tribe of the Amazons and by their search for the dream of Eldorado, obscured another relevant question: Which could have been the species of tree that motivated this first journey of the white man down the Amazon river? The true cinnamon, *Cinnamomum zeylanicum* Blume, is an Asiatic species of Lauraceae and is not native to the American continent.

Only in 1800 the famous naturalists Humboldt and Bonpland reached the Amazon by the Orinoco and discovered, on a hill which they called Monte Canelillo, the probable land of Amazonic cinnamon. There they found the Orinoco cinnamon (“canela do Orinoco”) or precious bark (“casca preciosa”), which they denominated *Aniba canelilla* (H.B.K.) Mez (Lauraceae). This is the only one among the South American cinnamon species with an ample geographic distribution throughout the entire Amazon region capable of motivating the extensive Spanish expedition through inhospitable and unknown territory.

Thus, after resolving the biological part of this mystery, there remained the task of clarifying the chemical composition of *Aniba canelilla* (H.B.K.) Mez. After nearly one hundred years, in 1893, chemists of the German industry Schimmel & Co studied the essential oil of that species. To their great surprise they did not isolate the expected cinnamic aldehyde (Figure 1) responsible for the aroma of cinnamon found in Asiatic species. They tried, as did other chemists, to determine the structure of the mysterious odoriferous component, but remained unsuccessful. Indeed, what after all is that substance?

The answer to this question appeared only in 1959 when the Brazilian researchers, Gottlieb and Magalhães, isolated from this essential oil methyleugenol, and, finally, the compound responsible for the cinnamon odour, 1-nitro-2-phenylethane (Figure 1). This is the first register of a nitro-derivative in essential oils, one of the few natural compounds containing this functional group (Table 1).

Species	Popular name	Geographic localization	Aroma	Odoriferous compound	Obs.
Cinnamomum zeylanicum Blume	Asiatic cinnamon	Asia	cinnamon	cinnamaldehyde	Absence of 1-nitro-2-phenylethane
Aniba canelilla (H.B.K.) Mez	Amazonian cinnamon (“canela do Orinoco”or “casca preciosa”)	Amazonia (Brazil)	cinnamon	1-nitro-2-phenylethane	Absence of cinnamaldehyde
Ocotea quixos Lam.	“ishpingo”	Ecuador	cinnamon	cinnamaldehyde	Absence of 1-nitro-2-phenylethane
Sassafras albidum (Nutt.) Nees	North American officinal sassafras oil	North America	safrole	safrole	—
*Ocotea pretiosa** (Nees) Mez	Brazilian sassafras oil (“canela	Santa Catarina (Brazil)	safrole	safrole (more than 84%)	—

	sassafrás")				
*Ocotea pretiosa** (Nees) Mez	Brazilian sassafras oil ("canela sassafrás")	São Paulo, Rio de Janeiro, Minas Gerais (Brazil)	cinnamon	1-nitro-2-phenylethane	Predominance of methyleugenol and absence of safrole

* First example of physiological variation observed for Brazilian plant species.

Table 1. Essential oils from some species of Lauraceae. See Figure 1 for compounds structures.

2.2. The Puzzle of Sassafras

The North American officinal sassafras oil, produced by distillation of *Sassafras albidum* (Nutt.) Nees, a species of Lauraceae which does not occur in South America, is rich in safrole (Figure 1). This compound was used in the aromatization of North American dental products. Brazilian sassafras oil, extracted from *Ocotea pretiosa* (Nees) Mez (Lauraceae) localised in the Itajaí valley (state of Santa Catarina) has a similar chemical composition to the North American sassafras. For several years, since 1939, it was exported from Brazil to supply the international demand. This unleashed an intense search for this species in other regions of the country.

At this stage serious problems started to appear, since it was discovered with surprise that wood samples collected in other Brazilian states (São Paulo, Rio de Janeiro and Minas Gerais) did not possess the characteristic aroma of safrole (Figure 1) but that of cinnamon. Study of the chemical composition of these essential oils revealed that methyleugenol (Figure 1) was their chief component, while safrole was absent. However, according to morphological analysis (including the anatomy of the wood) all the samples belonged to the same species, *Ocotea pretiosa* (Nees) Mez.

Up to 1924, there had been the concept of chemical invariability of a species, i.e. all individuals of one species should possess the same chemical composition. It was the pioneering work of A.R. Penfold and F.R. Morrison (1924), studying the essential oils of different individuals of the Australian *Eucalyptus dives* Schauer (Myrtaceae), that originated the concept of "forms or physiological varieties". It seemed evident that Brazilian sassafras oil was a case of this type. This was the first report of chemical variation for a Brazilian species distributed through different regions.

Although this part of the puzzle of sassafras had been deciphered, one question was still open: What was the odoriferous principle of the cinnamon smelling variety of *Ocotea pretiosa* (Nees) Mez found in the Brazilian states of São Paulo, Rio de Janeiro and Minas Gerais? Analogous to *Aniba canelilla* (H.B.K.) Mez, this principle was again the nitro-derivative, 1-nitro-2-phenylethane (Figure 1).

Several years later, the odoriferous fraction of another American cinnamon from Ecuador, *Ocotea quixos* Lam. ("ishpingo") was studied. Surprisingly here, as well as in the traditional Asiatic spice, *Cinnamomum zeylanicum* Blume, the presence of cinnamaldehyde (Figure 1) was detected (Table 1). This was good news for past and future consumers of "ishpingo". As early as Incaic times, this plant was known as medicine and as a spice. Its aromatizing properties, rather than any hallucinogenic effect probably due to another plant, motivated its addition to ritual beverages. Even now it is still being used in traditional medicine (appetizer, eupeptic, antidiarrheal, disinfectant and local anaesthetic) and as a valuable spice in Ecuador.

At this point a very relevant question should be asked: Why, even today, when chemistry, evolution, systematics, ecology and pharmacology are seen to have made such ample progress, should ethnomedical (and ethnobotanical) information still be considered a decisive factor for the rational search of bioactive principles in plants?

3. A Plant is no Factory

A plant is not a factory mounted specifically for a certain production. It is a living being subject to stress of varying environments, such as soil fertility, humidity, solar radiation, wind, temperature, herbivory, associated biota, atmospheric and soil pollution. These factors could influence and alter the chemical composition of the plant, which is also determined by the phase of the vegetative cycle of the plant at its time of harvest. The adaptation to environmental conditions is variable and frequently adverse. Hence all plants are somewhat toxic.

The production of chemical compounds by plants may not have been the primary reason resulting in the biosynthesis of these toxins, but it is surely the reason for their survival in nature. According to T. Swain (1974) animals act, plants produce. Animals defend themselves by behaviour; plants, being unable to flee, defend themselves by chemistry. Plants used as foods are practically innocuous because the agriculturist, a long time ago, eliminated the major part of their toxic load by genetic selection. For this reason, as is well known, food plants do not survive without permanent human protection.

There are so many intrinsic and extrinsic factors involved in the biosynthesis of natural products that, with our present knowledge, it is a hard task to rationalize all of them. Therefore, looking for new bioactive compounds will continue to be a subjective matter while the fundamental mechanisms responsible for the production, accumulation and expression of natural substances yet remain unknown. But, how to fill this gap?

4. How does Nature Work?

It is surprising that “at the threshold of what is widely regarded as the Century of Biology, with the life sciences undergoing a profound transformation” fundamental questions continue to lack an appropriate answer. “Man goes to the Moon, a rocket goes to Jupiter, but we cannot even count the plant species on the planet.” (O.R. Gottlieb, 1994).

Up to the present time it is impossible to know if there are 5, 30 or even 100 million species of living organisms, nor why a certain species occurs in a certain area, and what its fate will be year after year. In fact, with the present knowledge it is not even possible to determine the value of a region with respect to its biological potential, invalidating serious proposals of controlled preservation and exploration (sustainable use). Unless scientific efforts are made to urgently provide answers to these questions, many of our natural resources could be lost forever, endangering future generations.

Meanwhile, an enigmatic new organization, the All Species Foundation (http://www.all-species.org/), have announced the lofty goal of recording all 7 million to 100 million species on Earth within 25 years. This, dismissed by some as a quixotic purpose, represents an effort equivalent (maybe more complex) to the human genome project; it has over a million dollars in start-up money. The importance of this enormous attempt resides in the great possibility of training new taxonomists to bridge the dangerous lack of professionals in this field .

But, to make an inventory of all living species, even if it is successful, is only the first step towards a better understanding of how nature works. Actually, this complex question can only be answered by trying to understand general rules capable of explaining the mechanisms responsible for the origin and operation of all living systems. On the other hand, general rules applied to any biological system would only emerge if different types of information on the organisms, were considered. Our efforts to this intent are resumed in this chapter, showing some concepts relevant to discussion of fundamental questions about the functioning of nature and life. Finally, only a “coherent language” can achieve the integration of chemical (structural) and biological (functional) terms capable of explaining the properties of organisms.

According to C. Sagan (1997): “If you know a thing only qualitatively, you know it no more than vaguely. If you know it quantitatively—grasping some numerical measure that distinguishes it from an infinite number of other possibilities—you are beginning to know it deeply. You comprehend some of its beauty and you gain access to its power and the understanding it provides. Being afraid of quantification is tantamount to disenfranchising yourself, giving up on one of the most potent prospects for understanding and changing the world.”

Thus, the major challenge consists in the replacement of the traditional and narrative approach, by a holistic and quantitative methodology. But, how?

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Biographical Sketches

Otto R. Gottlieb was born in Brno (Czechoslovakia) in 1920, but he opted for Brazilian nationality in 1941. After his graduation, in industrial chemistry (Universidade do Brasil, 1945), he worked in the production of pure chemicals from Brazilian essential oils. Ten years later, he moved to the Instituto de Química Agrícola (Rio de Janeiro, 1955-1963). He obtained a PhD and “livre-docente” at the Universidade Federal Rural do Rio de Janeiro (1966) and a full professorship at the Universidade de Brasília (1964) and the Universidade de São Paulo (1967). Fascinated by the diversity of the chemical composition of the Brazilian flora, one of the last biological frontiers, he pioneered the introduction in this country of natural products chemistry concomitantly with modern organic chemistry. Gottlieb founded and directed research groups in several Brazilian institutions, directly supervised 120 theses (52 M.Sc. and 68 Ph.D) and taught 147 disciplines, several based on his own research. He acted as visiting professor at Sheffield University, England (1964), Weizmann Institute of Science, Israel (1959-1960), Indiana University, USA (1964), Hamburg University, Germany (1985, 1986, 1991) and presently at the Universidade Federal Fluminense (Niterói). He was awarded honorary degrees of professor and doctor *honoris causa* by 11 universities (10 in Brazil and by the University of Hamburg), received 29 national and international awards and several other honors. He is a member of the Academia Brasileira de Ciências and The Third World Academy of Sciences among other scientific academies. He has organized and chaired scientific meetings and participated in the editorial boards of the major scientific journals of this research area. His contributions in plant evolution, systematics and ecology include 660 papers (articles, book chapters, books and patents), more than 1180 communications and 655 invited lectures. He was responsible for the elucidation of chemical and pharmacological potentialities of many plant species, primarily from the Brazilian Amazonia and Cerrado, discovering new categories of compounds. Seeking to explain life on Earth through chemistry, he proposed original principles and developed methods for quantitative chemo-biology, a new discipline based on integration of chemistry, morphology, biogeography and bioactivity. At present, after nearly 50 years dedicated to the study and teaching of biodiversity, Gottlieb concentrates his efforts on the search for unifying concepts for the understanding of how nature works.

Maria Renata de M.B. Borin was born in Santos (São Paulo, Brazil) in 1961, and graduated in industrial pharmacy at the Universidade Federal Fluminense, Niterói (1983). She obtained her MSc degree (1988) and PhD (1993) in natural products chemistry at the Universidade de São Paulo, under the supervision of Prof. Otto Gottlieb. She acted as visiting researcher at the Instituto Oswaldo Cruz, Rio de Janeiro (1993-2001), as visiting professor at the Universidade do Estado do Rio de Janeiro (2001-2002), and presently at the Universidade Federal Fluminense. During all these years of intense collaboration with Prof. Gottlieb, she has been dedicated to the development of quantitative chemo-biology, a new scientific discipline created in Brazil by Prof. Gottlieb. Her studies on plant evolution, systematics and ecology are based on the rationalization of the evolutionary-ecology mechanisms and processes responsible for the production and expression of the secondary metabolism of plants. Her work has focused on the understanding of biodiversity and plant bioactivity seeking to unify concepts responsible for the functioning of nature.