Status of natural product sciences in Ethiopia

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ABSTRACT

This brief review summarizes important episodes in the plant chemistry research undertaken over two centuries from and within Ethiopia. Ethiopia is endowed with a substantial plant and animal genetic resources, some of which were tapped for food or medicine throughout the generations, albeit traditionally. In order to fully realize the benefits of these resources, their chemical contents need to be investigated with state-of-the-art chemical analysis. Chemistry's vital role to do this was greatly facilitated by the opening of graduate programs in Addis Ababa University, and later in other universities, which led to a steady stream of research undertaken mostly on native plants that were expected to have some potency as medicine or food additives. These include among others, coffee, *khat, khoso, endod,* civetone, *mettere, kebericho, gesho,* etc. The challenge with regard to using natural products is the miniscule amounts of the active ingredients, which will not allow the full range of evaluations in terms of benefits, toxicity, etc. to be done before application. Genome editing and synthetic biology are expected to enhance the production of these active compounds in the near future.

Keywords: Organic chemistry; Ethiopian medicinal plants; Indigenous knowledge; Biological products chemical analysis; Active ingredients

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INTRODUCTION

The first Department of Chemistry in Ethiopia was within Addis Ababa University and as a full-fledged academic department it graduated only one student in its first batch 55 years ago in 1968. I was in the second batch of 16 students who received the BSc in chemistry a year later. I did my senior research project on the psychoactive plant *Catha edulis* Forsk (known as ጫት). I isolated a simple ephedrine alkaloid but although this finding may not have been great; symbolically the exercise I did, supervised by R.O. Whipple may very well have been the beginning of natural products chemistry research in Ethiopia. *Chat* is a well-known plant and is widely used in Ethiopia, initially among the Muslim communities, but is now used all over. The UN sponsored a study on chat and concluded that it should be classified as a narcotic. Although as many as sixty

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or so alkaloids, terpenes, flavonoids and tannins have been found the psychoactive principles are believed to be simple phenyl alkyl amines particularly the unstable cathinone and to a lesser effect cathine (Wabe, 2011).

HISTORICAL BEGINNINGS OF NATURAL PRODUCTS SCIENCE FROM ETHIOPIAN SOURCES

One of the earliest records of structural elucidation of natural products from Ethiopian sources may be associated with the constituents of the stimulant plant *Coffea arabica* (Rubiaceae). Caffeine was first isolated as a white crystalline substance in 1819 by a German scientist, Friedlieb Ferdinand Runge (1820). But it was the Nobel laureate (1902) Emil Fischer of the University of Erlangen, Germany who studied the active principles of tea, coffee and cocoa, namely, caffeine and theobromine, and established the constitution of a series of compounds in this field, eventually synthesizing them. Caffeine is a stimulant found principally in coffee, tea and the cola nut, but it is known to occur in the seeds, nuts and leaves of as many as 60 other plant species or varieties. Although coffee is traded among all nations of the world, it is produced only by a few countries in Africa, South America, and Asia. The origin of coffee, *Coffea arabica*, is believed to be in the Kaffa region of Ethiopia, the only place in the world where the coffee plant is found growing in the wild. Coffee is consumed primarily for two reasons: to overcome drowsiness and be alert as well as to improve physical performance. Traditionally, coffee is a socializing process particularly in Wollo region where they drink the first coffee extract (አቦል), then the second (ቶና) and finally the third extract (በረካ). Caffeine has an additional use in medicine to assist infants with respiration. Caffeine has a chemical structure with striking resemblance to adenine and guanine, which are components of DNA. Caffeine has a remarkable solubility in both water (hot) as well as non-polar media and hence the ease with which it crosses the lipid barrier to get to the brain. Its stimulant properties are a result of its ability to reversibly block the action of adenosine by binding on its receptors. Coffee is also regarded as a diuretic, but this is probably due to the theobromine which is a metabolic product of caffeine and thus is present in the body arising from the caffeine that is consumed.

A second plant of significant history going back over 200 years is *Hagenia abyssinica* Gmel, a plant (ኮሶ in Amharic) whose female flower-extract was widely (and may still be) used as a taenicide in Ethiopia. There was a time when Europe was plagued with this parasite and the story goes that a physician (Brayer) was at a barber's shop in Constantinople (ca 1820). Once you sit on a barber's chair you are a victim listener and Dr. Brayer heard of the miraculous taenicidal effects of the Ethiopian plant which may be obtained by chance encounter with travelers passing along the Red Sea who then took it to Europe for its medicinal uses. The doctor even managed to get a sample from his barber whom he took and administered to a lady who had taenia and meticulously recorded her heart beat, blood pressure, temperature, etc., thereby documenting the first effects of a patient treated with *Hagenia abyssinica*. The doctor was happy with the results of the medication and took two important actions. The first was to show the flowers to a botanist (Kunth) who identified it as belonging to the family Rosaceae and called it *Brayera antihelimintica* Kunth; and secondly, he presented a paper at the French Society meeting of 1820. There is a lot of history written about the Kosso plant and significantly in 1874 the German company Merck marketed the structurally unidentified white substance called "kosins" as an anthelmintic (Fluckiger and Buri, 1874). The chemical structure of kossotixin was published a century later (1974) by a Finnish chemist (Lounasmaa *et al*., 1973). Previously, famous chemists like Birch and Todd (1952) failed in their attempt to elucidate the structure of the active ingredient.

There is no taenicidal drug in the market derived from an Ethiopian plant at the present time although there are many plants that are sold in the traditional market for use against tapeworm infestation. A former colleague in our faculty who was a traditional doctor once revealed to us that there are as many as 147 plants in Ethiopia which he knows to be taenicidal. Our natural product scientists should be disappointed for this failure to have a drug in the market and this may be an important topic for the leaders including policy makers to investigate the reasons and seek corrective measures for the future.

The third example of a natural product is of animal origin called civetone which was identified by Leopold Ruzicka (Ruzicka, 1926), a Czech chemist who worked on civet material that was exported from Ethiopia to London and then shipped to him in Czechoslovakia. He elucidated the structure of civetone as a 17 carbon -ring macrocyclic ketone. Ruzicka got the Nobel Prize for chemistry in 1939. Large carbocyclic rings were not known at the time, and curiously were thought unlikely to exist. In the first Peeler Lecture delivered before the Chemical Society in London in 1929, W.H. Perkin Jr. I described "the early history of the synthesis of closed carbon chains". He dealt not only with the reactions which led to the synthesis of small carbon rings during the period 1881-1883, but also with the pessimistic views of the leading chemists of that time regarding the possible existence of carbocycles other than the 5- and 6-membered rings. Adolf von Baeyer, Emil Fischer, and Viktor Meyer advised Perkin not to waste his time on attempts to prepare such compounds, which could hardly be capable of existence. Civetone is highly valued as a component of expensive perfumes and is attributed with fixative values of the sensual and erotic constituents of the perfumes.

A fourth example and one that involved an Ethiopian scientist is *Phytolaca dodecandra* or otherwise known as *endod* እንዶድ in Amharic or soapberry in

English. An Ethiopian scientist - Aklilu Lemma - discovered that Endod possessed molluscicidal properties by noticing a lot of dead snails along the banks of the Adwa River where people used the berries of the plant for washing their clothes. Endod was shown to reduce the incidence of Bilharziasis in a field study conducted in Adwa, Tigrai (Lemma, 1990). Aklilu was interested to know the active ingredients of this plant and work conducted in California revealed that saponins were responsible for the biological activities of the plant (Parkhurst *et al*., 1974). It is a pity that Aklilu did not reach out to compatriot chemists to elucidate the structures of the endod active principles. But in all honesty, the facilities in Ethiopia were not as developed as they are now and it is understandable that he preferred quick results that scientists in California were able to deliver.

MODERN NATURAL PRODUCT SCIENCE FROM ETHIOPIAN SOURCES

About half a dozen of the best and the brightest graduates of the first two batches from the Department were sent for graduate education in the UK and the US. Most of these students returned to the country in 1972 and 73 and constituted themselves as a group to develop a chemistry program of training and research in the country. The first publication based on work conducted, partly in Addis and partly in Ibadan (Nigeria) was the structure elucidation of a bidesmosidic saponin from the Ethiopian medicinal plant *Glinus lotoides* (ሙቱሬ) (Abegaz and Tecle, 1980). Work in natural products by Ethiopian scientists began since then and continues until today. It must be recognized that the progress in the science of natural products was heavily facilitated by the previous publications on traditional medicinal uses of plants in Ethiopia and the SAREC supported project to write the Flora of Ethiopia. One of the earliest papers (Baxter, 1987) published in Volume 1 of the *Bulletin of the Chemical Society of Ethiopia* is entitled: Some thoughts on traditional Ethiopian chemistry. In this article Bob Baxter reflected on the subject and began his article by saying: The story of indigenous Ethiopian Science and technology remains to be written. It appears however, Ethiopian Scholars of the past were men of letters, chiefly interested in such matters as poetry, history, theology, law and magic and frequently displayed much depth and ingenuity in their discussions of these topics. Robert M. Baxter was a Canadian biochemist and the 2nd head of the Department of Chemistry of the then Haile Selassie I University from 1961-1973. Baxter considered our decision to launch this first journal of chemistry and remarked: the establishment of the *Bulletin of the Chemical Society of Ethiopia* can be thought of as marking the emergence of a distinct and productive Ethiopian community within the framework of world science. It seems that Baxter was right in recognizing the advent of the appearance of a series of papers on natural products that came from the dissertation research of postgraduate students in the Department of Chemistry, the School of Pharmacy and subsequently from the many higher education establishments that were established in various administrative regions of the country. Many highly prominent medicinal plants that have been used culturally in the country were investigated and hundreds of papers published in peer reviewed journals. Some of the highly popular medicinal plants addressed in this period include *Echniops kebericho* Mesfin (Compositae) (Abegaz *et al*., 1991), *Taverneria abyssinica* ድንገተኛ (Duddeck *et al*., 1987), *Rumex abyssinicus* (Fasil *et al*., 1985), *Kniphofia foliosa* (የጅብ ሽንኩርት) (Dagne and Steglich, 1984) and many more.

Another culturally important plant is *Rhamnus prinoides* or otherwise known in Amharic as *Gesho* (ጌሾ). MSc student Teshome Kebede studied this plant and identified several secondary metabolites. But perhaps the most interesting result was the identification of the bitter principle of the leaves and stems of the plant which turned out to be a new natural product called Geshoidin (Abegaz and Kebede, 1995). An informal panel was set up to taste an aqueous solution of Geshoidin and concluded that the characteristic taste of *tella* was in the aqueous solution of the glycoside. The gesho plant produces abundant quantities of this substance and can be considered as a viable source should it be needed in large quantities. Gesho is an important ingredient in the locally brewed domestic beverages of *tella* and *tej*. The plant is known to occur in many countries from Ethiopia to South Africa, but it is only in Ethiopia where it has been domesticated, cultivated and sold in traditional markets. Two areas famous for the production and cultivation of Gesho are the Kara Kore area in northern Shoa and also in Tigrai region. A recent study to determine the acute and sub-acute toxicity of the leaves on rats resulted in no significant damage to various organs (Abebe, 2023). Hence it is important to know that gesho leaves do not have any toxicity to worry about.

WHAT BROUGHT ABOUT THE GROWTH AND DEVELOPMENT OF NATURAL PRODUCTS IN ETHIOPIA?

The most critical contribution in any endeavor comes from knowledgeable and skilled people. But the growth and development of natural products in Ethiopia was due to a multitude of factors and an effort will be made here to include the important ones. These include people at various levels in terms of not only the scientists to undertake the work but also the institutions that promoted and allowed such work to be undertaken; those in policy that endorsed and supported the project including funding it. Much of the work was done in the process of teaching postgraduate studies as dissertation research for the students. Chemistry is a molecular science and requires the availability of sophisticated instrumentation which is very expensive and demands special supplies and highly skilled technicians. Cryogenic liquids such as liquid helium, nitrogen and inert gases require special arrangements to acquire.

In the early 70s, the New Science Complex was constructed using a loan from the World Bank long before decisions were made in the university to initiate graduate programs. The loan also had provisions to acquire equipment for the center. The briefing given to the committee to plan for what was to be the new science center did not make any reference to a future graduate program that the center would be likely to house. The author of this paper was a member of this committee and it was his personal vision that sooner or later there would be graduate programs and he felt that facilities for such should be included. But there was no evidence to indicate if this was a view held by all committee members across all disciplines. So, for chemistry items like NMR, MS, etc. were included. In the late 70s, some graduate programs were initiated- during a decade that also saw the great Ethiopian famine, the downfall of the Haile Selassie I Regime, the bitter Ethiopia war against the Somali expansionist regime and the ascent to power of young military officers with socialist leanings. The prevailing attitude with the hunger, responding to the needs of the proletariat did not make vertical expansion of the higher education a priority at the time. The author clearly remembers the fear in the minds of Addis Ababa University authorities who were convinced that the Government would not approve the launching of postgraduate studies especially if the funds for it were to be requested from internal sources. As a result, they were happy to state that the proposal to launch postgraduate education would not require the allocation of significant resources. So, we forged ahead with MS programs in the 70s and PhD programs in the 80s. Luckily, the Swedish SAREC supported the postgraduate program and every dissertation and thesis had to express gratitude to Sweden for financial support to the graduate program. It was at this time that the concept of the sandwich program was launched. Post graduate students were able to travel to countries like Sweden and Germany to get access to better instrumentation and literature to be able to compose scholarly writings. Hence the graduate program was developed in an atmosphere of scarcity. Deeper knowledge was acquired through the graduate research programs but interdisciplinary knowledge and skills were minimal. Papers were published but patents and efforts to develop products and services were more or less avoided. So, it is possible to conclude that we were able to explore the chemistry of natural products and also get a little bit of understanding and appreciation of the culture of traditional medicine. But very little effort was done successfully to either develop any products or services.

THE FUTURE OF NATURAL PRODUCTS RESEARCH, CHALLENGES AND SOLUTIONS

There is no doubt that the success of natural products research must be judged by the benefits that accrue to the population. One of the aspects to consider in natural products work especially in linking the ingredients to benefits is the quantity of the desired substance in the source plants. If the active substance is in microgram or milligram amounts then not much testing can be done. Bulk plant materials are sometimes not feasible to isolate large quantities if the extraction and purification protocols are complex. Though rare, some natural products are present in abundance while the generally accepted norm is that others are present only in minute quantities. For example, dehydrocostus lactone is a sesquiterpenoid natural product that is found in abundance in ቀበርቾ (*Echinops kebericho* Mesfin). Likewise, Geshoidin can also be isolated in large quantities from the stems and leaves of ጌሾ (*Rhamnus prinoides*), and the oil of *Carum copticum* is almost technically pure carvacrol. The three plants mentioned above give good quantities of natural products and of these; carvacrol is the only one that is commercially produced from plant sources such as oregano (*Origanum vulgare*), thyme (*Thymus vulgaris*), pepperwort (*Lepidium flavum*), and wild bergamot (*Citrus aurantium* Bergamia). Carvacrol is effective against food-borne pathogens, including *Escherichia coli*, *Salmonella*, and *Bacillus cereus*. It is not possible to make any conclusions regarding the clinical importance of carvacrol because of the absence of human trials.

One of the most outstanding examples of natural products from natural sources is the antimalarial compound artemisnin isolated from the Chinese medicinal plant *Artemisia annua*. This plant has been used to treat malaria in Chinese traditional practice for hundreds of years. Today the WHO recommended treatment for malaria is Artemisia Combination Therapy called ACT. This guideline is intended to avoid the emergence of resistant parasites to the drug. A major global concern has been to meet the global demand for the supply of artemisnin for treatment of malaria. The 2015 Nobel Prize in physiology and medicine was awarded to a Chinese scientist, Youyou Tu, for her work on the plant *Artemesia annua*, sweet wormwood, and showing substantial inhibition of rodent malaria parasites (Liu *et al*., 2016). Although the effect of this substance in curing patients was spectacular it was realized that neither the plant nor the results of chemical synthesis would be able to meet the global demand for the natural product. But recent advances in recombinant DNA technology (Khan *et al*., 2016) and synthetic biology (Martin *et al*., 2003; Voigt, 2020; Song *et al*., 2021)) have provided possibilities to get bacteria to produce sufficient quantities of artemisnin. For example, Song *et al*. (2021) were able to establish in *Bacillus subtilis* a CRISPR-Cas9 system that enabled them to do precise and efficient genome editing. This led to a strain which increased extracellular amorphadiene production from 81 to 116 mg/L after 48 h flask fermentation without optimization (Song *et al*., 2021). A recent article by Chris Voigt (Voigt, 2020) states: Products from synthetic biology are rapidly permeating society and by 2030, it is highly likely that you will have eaten, worn, used or been treated with one (Martin *et al*., 2003). Amorphadiene is a known precursor of artemisnin and can be synthetically converted to the target molecule in four steps. The lesson to learn from this paragraph is the need to embrace genomics and genome editing as a path to maximizing the benefits of natural products to society.

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