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Spring 2019

Discovering
Nature's
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Potential

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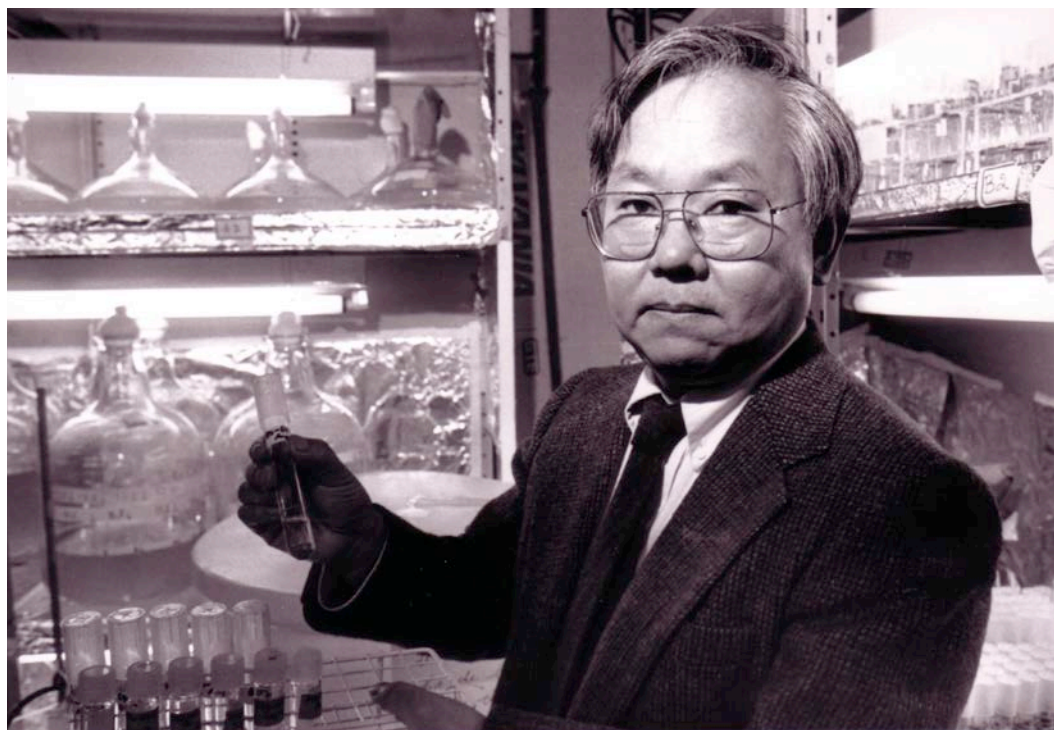
In Memoriam: Yuzuru Shimizu

By Dr. David Rowley

ASP Fellow and former ASP President Dr. Yuzuru Shimizu, Omar-Youngken Distinguished Chair Emeritus of Natural Product Chemistry at the University of Rhode Island (URI), passed away on January 8, 2019 at the age of 83 in Kingston, Rhode Island. His storied career spanned more than 40 years, and he will long be remembered as a pioneer in marine natural products chemistry, especially for his groundbreaking work on aquatic toxins.

"It is with great sadness that we note the passing of our colleague Professor Yuzuru Shimizu," stated current ASP President Dr. Susan Mooberry. "He made significant contributions to the field of marine natural products and to the ASP and will be sorely missed."

Born in Gifu, Japan, Dr. Shimizu attended Hokkaido University in Sapporo, Japan where he earned a baccalaureate degree in pharmaceutical sciences (1958) followed by MS (1960) and PhD (1963) *continued on page 3*



Dr. Yuzuru Shimizu ca. 1988 at the University of Rhode Island College of Pharmacy with microbial cultures.

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EDITOR'S CORNER



I begin this with a reflection on a story that the *Newsletter* is NOT running this time, the partial shutdown of the federal government that began December 22, 2018. As we approached our spring deadline, the federal government was still shutdown, and I began to wonder if and how this may impact ASP members, like those who work directly or indirectly for the federal government. I received a startling e-mail from the president of the City University of New York (CUNY) Graduate Center saying the shutdown was impacting research at CUNY campuses, especially those projects funded through the National Science Foundation, Food and Drug Administration, and Environmental Protection Agency, to name a few that seem most relevant to ASP members.

This CUNY president went on to make this strong recommendation, "If the shutdown continues until the end of January, payroll and all other expenses covered by the affected sponsors will be suspended; if the shutdown lasts beyond that date, payroll for these projects will eventually be terminated. The RF [Research Foundation of CUNY] advises PIs and supervisors to notify employees on affected federally funded projects that layoffs may begin as soon as February 17."

Fortunately, the partial shutdown ended on January 25, 2019. By that time, I had reached out to about a half dozen ASP members for comment, but there was reluctance to say much due to ties with these agencies that obviously run deep. Several government employees I communicated with likened this to the cost of doing business, and one even noted keeping a stack of draft manuscripts handy on days that going to the office is forbidden. Certainly, this budget brinkmanship is bad for scientific productivity and places some postdocs and graduate students at great unease and confusion. One of my own graduate students, supported through private funding, was uncertain how to react to the CUNY president's closing paragraph where she warned everyone may eventually feel the pain: "Currently, these emergency courses of actions apply only to funds from agencies affected by the shutdown as well as federal pass through grants from State and City agencies. Eventually, these steps may affect all sponsored projects." Such unnecessary worrying is counterproductive. I wonder how many more shutdowns I will live through.

In other somber news, ASP lost Professor Yuzuru Shimizu, one of its great early members, past ASP President, and ASP Fellow. ASP member Dr. David Rowley, a colleague of Dr. Shimizu at the University of Rhode Island, has contributed a beautifully written and comprehensive remembrance as the cover story for this issue of the *Newsletter*. In December, the *New York Times* published a belated obituary for Dr. James Duke, a botanist who worked for many years at the USDA and was well-known to many members of the ASP, including Dr. Kurt Reynertson who contributed his memories of Jim and his wife Peggy to the current *Newsletter*. Finally, right before going to press, we learned about the death of ASP member Dr. Judy Bolton, who for many years was a leader at University of Illinois at Chicago's NIH-sponsored botanical center. We plan to publish an article about her in the summer *ASP Newsletter*.

The 60th Annual Meeting of the ASP will be held in Madison, Wisconsin on July 13-17. Abstract and early registration deadlines are coming up soon. Please take time to look over the article about this meeting and make plans to attend this exciting conference.

I am writing this on St. Patrick's Day, and spring is definitely in the air here in New York City. Have a wonderful spring!

Dr. Edward J. Kennelly

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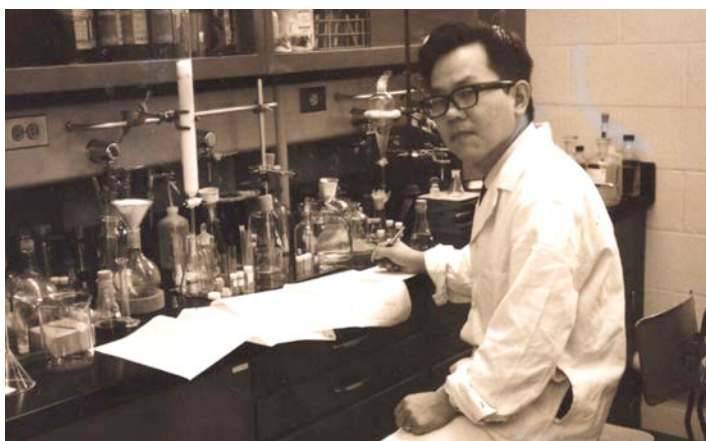


In Memoriam: Yuzuru Shimizu

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grees in natural product chemistry. He then traveled to the United States, first to the Worcester Foundation for Experimental Biology where he worked on steroid chemistry with Dr. Eliahu Caspi from 1963-1964, and then to the department of chemistry at the University of Georgia, conducting research on saponins produced by the medicinal plant *Polygala senega* with Professor S.W. Pelletier from 1964-1965. Dr. Shimizu returned to Hokkaido University as an assistant professor in the faculty of pharmaceutical sciences in 1965 where he worked primarily on steroids and secondary metabolites from terrestrial plants.

In 1969, Dr. Heber Youngken, then Dean of the URI College of Pharmacy, recruited Dr. Shimizu. Youngken believed the marine environment to be the next frontier for natural products drug discovery, and he set his eyes upon Shimizu to lead the effort at URI. It proved to be a momentous decision, and over the next 36 years, Professor Shimizu became one of the leading world experts on the chemistry of marine toxins. He will be especially remembered for his seminal work on the structures and biosynthesis of paralytic shellfish poisons and polyether toxins, including brevetoxin A. There is little doubt that his work helped inspire a generation of natural products chemists and provided enormous benefit to scientists across diverse disciplines, including toxicologists, synthetic chemists, and environmental scientists.



Dr. Shimizu in his laboratory at URI in 1969.

Youngken believed the marine environment to be the next frontier for natural products drug discovery, and he set his eyes upon Shimizu to lead the effort at URI.

Dr. Shimizu was a tenacious researcher who tackled tough scientific challenges and succeeded. His studies on the chemistry of dinoflagellates are especially notable due to the superb skill and expertise required for the isolation and culture of microal-

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Dr. Shimizu delivering a lecture.

gae, the purification of exceedingly trace quantities of water-soluble metabolites from vast volumes of media, and the structure elucidation of exquisitely complex molecules. Each culture would begin with a single cell, delicately collected by mouth pipetting while observing the organisms through a microscope. Over the course of months, the cells would be painstakingly nurtured into

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cultures reaching the tens of liters. Considering the time intensive nature of dinoflagellate isolation and culture, it is remarkable that he published nearly 200 papers in his career. Visitors to his laboratory witnessed the staggering amount of ongoing culture work. (Marine algae cannot be cryogenically preserved and must be kept in continuous culture.) He was truly a versatile, dedicated and gifted scientist who elected to work on challenging problems.

Professor Shimizu will be warmly remembered also for his highly engaging lectures, always punctuated with his special brand of wonderfully dry wit. This renowned talent held his audi-

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In Memoriam: Yuzuru Shimizu

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Dr. Shimizu's career was remarkable in terms of his service to the natural products community. Working together with Dr. Paul Scheuer in the early 1970s, he was a driving force in creating the Gordon Research Conference on Marine Natural Products. He was the primary organizer for the first GRC-MNP meeting in 1974, acting as vice chairman, and then served as chairman for the next meeting in 1976. Today, the GRC continues to be one of the most important conferences for convening international scholars to discuss advancements in marine natural products. As a world expert on aquatic toxins, Dr. Shimizu served as a consultant to organizations such as the World Health Organization and National Marine Fisheries, and as a reviewer for numerous granting agencies, including the NIH, NSF, NOAA, and EPA. He was the ASP president from 1997-1998 and was elected an ASP fellow in 2009.

I am personally indebted to Professor Shimizu for the kindheartedness that



Dr. Shimizu examining one of his cultures under the microscope.



Dr. Shimizu conducting fieldwork from a boat in Japan.

As a world expert on aquatic toxins, Dr. Shimizu served as a consultant to organizations such as the World Health Organization and National Marine Fisheries, and as a reviewer for numerous granting agencies, including the NIH, NSF, NOAA, and EPA.

he and his wife, Hiroko, extended to my family when we arrived in Rhode Island. We instantly felt part of their family. Over the years, this was the case for many dozens of other families and individuals from around the world, each arriving in Rhode Island to work alongside a giant in the field of natural products chemistry.

After retiring in 2006, Professor Shimizu maintained a presence at the URI College of Pharmacy as a volunteer in the Heber W. Youngken Jr. Medicinal Garden. While he was truly knowledgeable on the cultivation and uses of medicinal plants, some might speculate that this position also allowed him to keep a close eye on the ongoing pursuits in natural products research at URI. The garden will not be the same without his presence.

Professor Shimizu is survived by his wife of 55 years, Hiroko, his children Ken and Keiko, and three grandchildren. He will be dearly missed by the countless many scientists that he mentored and inspired with his contributions to the field of natural products. ■

In Memoriam: James Duke

By Dr. Kurt A. Reynertson

Editor's Note: Dr. James A. Duke, a person well-known to many ASP members, died on December 10, 2017. Even though his death was over a year ago, his obituary appeared only recently in The New York Times. Dr. Duke, critic of pharmaceutical companies and the overuse of modern drugs, promoted the use of healing plants as an alternative, becoming a pioneer in the field of natural medicine.

One of the first times I met Jim Duke was when Sheila, now my wife, and I were invited to housesit for him and his wife Peggy while they traveled to South America. Sheila had met Jim while studying herbalism in Virginia, and I had subsequently struck up a correspondence because I was planning to enter graduate school to study phytochemistry.

Jim had recently retired and was in the beginning stages of planting his Green Farmacy Garden. As we toured the garden, he pointed out certain favorite plants and had a story for each one. He talked about the chemistry, the historical uses, interesting anecdotes, or the provenance of cutting or seeds. He liked to walk barefoot through the garden to be closer to the ground, which in retrospect is indicative of how he did so many things, grounded: grounded in science, humanity, and humility.

In the garden, he was like an excited kid, eager to show you a new toy. I remember his wry smile as he pointed out an *Arisaema* that he called “dog’s dick” rather than “Jack-in-the-pulpit” because of the spiked inflorescence. I have called it that, in my head at least, ever since. As dusk set in, we sat on the ground to watch the amazing, magical timing of evening primrose blooming, each flower bud untwisting with a spring-loaded pop.

Later that evening, Sheila and I sat on the porch with him and Peggy and drank gin and tonics with a sprig of some fragrant herb from the garden while he played guitar and sang herbal folk songs to entertain us all. He had a wonderful ability to weave the magical and the concrete, to keep a sense of wondrous amazement towards nature without losing the structured, rational, scientific side.

During our time at their place, we kept the garden watered and took on the task of organizing his library, which he had earlier described as being in complete disarray. He had a basement study of two or three rooms filled, wall-to-wall and floor-to-ceiling, with printed matter. It was an amazing collection: floras, pharmacopeias, medicinal plant texts, and plant chemistry books from around the world, as well as manuals, handbooks, and stacks of journals and pages of half-written manuscripts. Many were inscribed by the books’ authors with dedications to him as a cherished mentor. Going through those books was a huge undertaking, one we dove into with gusto. I always wondered if he kept our categorization.



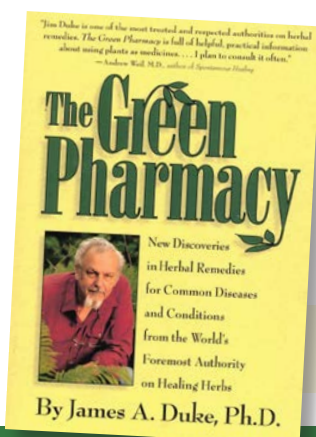
Peggy and Jim Duke

I was afraid to ask if he ever had trouble finding something.

Back then, internet research was almost non-existent. “Research” still meant spending time in a library, bookshop, or browsing a friend’s collection. To have access to this treasure trove, as I was first entering the field, was a real gift; and before they left on their journey, he told us to take home any duplicates we wanted. There turned out to be boxes of duplicate books and journals, and I still have many to this day.

I do not think Jim was particularly interested in leaving his garden for places like New York City, but true to his generous nature, he came up on Amtrak for my first dissertation committee meeting. I always felt like he was a sort of guardian angel over my career. We stayed in sporadic contact over the years; I would occasionally see Jim at conferences, and sometimes reach out to ask career advice. Once or twice he would e-mail me to ask about anthocyanins or the tropical fruits I studied, thrilling me to be treated as an equal.

To this day, I am amazed that he trusted a couple of scruffy youngsters with his garden, library, and home. However, I think it shows how important passing on knowledge was to him. I do not have to tell ASP members about his prolific publishing in the literature, his popular books, and creation of the USDA Phytochemical and Ethnobotanical databases. We have all read his writing or used his online database. For Jim, learning, discovering, and experiencing life went hand-in-hand with teaching and sharing. I am not sure if he ever knew how important his support and accessibility was to me. Over time, his example showed me that being a real scientist and mentor meant more than just research and publishing. It also meant being a storyteller and caring about people and the world we live in. It meant being a real person with true heart. So long, Jim. ■



<https://phytochem.nal.usda.gov/phytochem/search/list>

<https://thegreenfarmacygarden.com>



By Dr. James B. McAlpine

Author's Note: *At my first ASP Fellows meeting in Lexington, I learned that "silence is golden." After waxing on about the problem of "predatory" journals, I found myself volunteered (yes, despite what the dictionary says, it is used as a transitive verb) to write an article for the Newsletter on "Integrity."*

According to that all important source of trusted information, Google, the word "integrity" has two meanings:

- 1. the quality of being honest and having strong moral principles; moral uprightness.**
- 2. the state of being whole and undivided.**

Both of these apply directly to pharmacognosy, the science and the practitioners.

The former applies most specifically to the practitioners and the latter to the science itself. I have often claimed that there can be no such thing as a dishonest scientist, on the grounds that the essence of science is a search for the truth, and the moment an individual becomes dishonest he/she ceases to be

a scientist. Alas we have many examples in recent years of blatant dishonesty from claimed scientists. Perhaps the most infamous example of this is Andrew Wakefield et al.'s paper in *The Lancet* in 1998 implying a link between measles, mumps and rubella (MMR) vaccination and colitis/autism.¹ The lay press gave considerable coverage to this throughout the world, and parents of autistic children, anxious for a cause for this symptom, joined already existing anti-vaccination groups, and these advocated avoidance of MMR vaccinations. This resulted in an increase in cases of measles and the concomitant increase in childhood deaths from this totally preventable disease.

Several large-scale studies failed to find any association between MMR vaccination and autism, and investigations revealed that Wakefield had: 1. an undisclosed conflict of interest (He had accepted £55,000 from a legal defense fund needing evidence in support of claims centered on immunizations against pharmaceutical companies.) 2. selected carefully his 12 patients (the total!) for the study, and 3. falsified some of the histological data. It was not until 2007 before *The Lancet* fully retracted the paper. By that time the damage was done, both to families of thousands of lost children and to the

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The resulting publications in these predatory journals are effectively prostituting science, and the journal's publishers are clogging one's email with requests for manuscripts and invitations to editorial board membership.

reputation of medical science. Even today some parents refuse to have their children vaccinated with MMR. Wakefield and one of his co-authors lost their licenses to practice medicine in the UK in 2011.

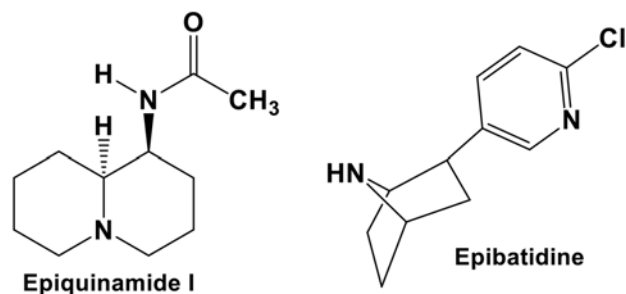
"The love of money is the root of all evil." In 2017 *The Guardian* published an article on the incredible profitability of scientific publishing and the fact that scientific *research* institutions are virtually obliged to purchase journals and books reporting on scientific "advances." This fact has sparked the birth of literally hundreds of new "predatory" journals which usually advertise "open access and rapid publication," simultaneously claiming "peer review." Those of us with any editorial duties realize that rapid publication and peer review are incompatible. These journals will publish almost anything for a fee. When I questioned in our research group, "Who in their right mind would pay \$2,000 to publish a paper?" I was to receive some education on Asian academic advancement. One of our Korean colleagues replied, "I know people who will pay \$3,000!" In several Asian countries including Indonesia, Korea and China, an academic's advancement is heavily tied to numerical formulae including number of publications. In Korea it is via points awarded per publication divided by the number of co-authors (thereby discouraging collaborative research!), and with no account of the quality. In China it is modified by impact factor, but also accompanied by significant cash payments to the senior authors. This obviously leads to squabbles about author sequence. In Indonesia it has been tied to number of citations leading to massive self-citing and clubs of cross-citers, thereby creating a system originally intended to encourage science but actually doing the reverse. The resulting publications in these predatory journals are effectively prostituting science, and the journal's publishers are clogging one's email with requests for manuscripts and invitations to editorial board membership. A similar situation has arisen with scientific conferences where one's "confirmed position as a speaker, chairperson, plenary lecturer" (choose one) in a very reasonably titled conference in some exciting part of the world is at least a daily occurrence. When will this nonsense stop?

Retraction of a published paper may not be an indication of a lack of integrity. It can be the very opposite. Most science projects today involve collaboration between several scientists, and an honest mistake by one can easily throw the conclusions

into error. Discovering such an error and immediately retracting the publication is the honest course of action. However, when a single author has several retractions, the verdict has to be that the author has been publishing fiction rather than science. The Retraction Watch, <https://retractionwatch.com>, publishes a list, which they admit may have some inaccuracies, of no less than 32 individuals, each with more than 20 papers retracted. One author is listed with a staggering 183 retractions. One must admire the hard work and pity the fact that it is not science.

In the second definition of "integrity," pharmacognosy has a definite problem with "natural products," and the problem comes in two forms, adulteration and residual complexity. Adulteration can be economically motivated or accidental. The advertisements for natural preparations to treat ED are a direct give-away for contamination of some innocuous plant extract spiked with a synthetic analogue of sildenafil, if not that drug itself. It will usually be the former in an attempt to hinder rapid identification, which will commonly comprise only HPLC-UV-MS against standards. Such a case clearly represents a lack of both personal and substance integrity. A common example of accidental substance integrity is the contamination of black cohosh (an extract of the roots/rhizomes of *Actaea racemosa*) with extracts of the analogous parts of *A. podocarpa*.² These two species look alike and grow in the same locations, hence this adulteration can be the result of negligence rather than intention.

Most of the examples of residual complexity are sad stories. The problem of epiquinamide, isolated from the skin of an *Ecua-*
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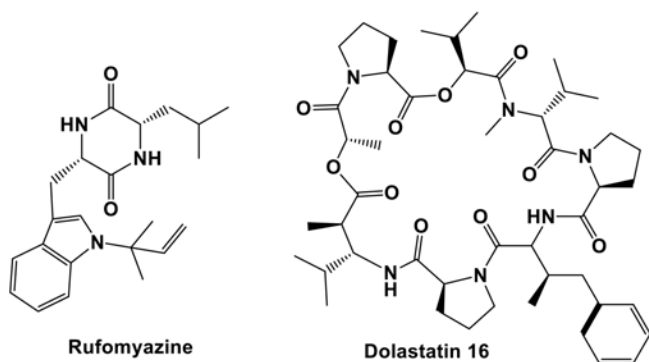
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The integrity of a natural product can be very difficult to authenticate but very necessary. Contamination by a small quantity of a very potent bioactive is always a possibility.

dorian frog and attributed $\beta 2$ -selective nicotinic acetylcholine receptor agonist activity, was solved by virtue of its rarity. Insufficient material to assign one of four diastereomers to the active principle led to synthesis of all four, none of which had the activity of the original isolate. The activity was eventually assigned to the congeneric epibatidine and ascribed to splash over from adjacent wells in a microtiter plate used to collect fractions from an HPLC purification.³

The integrity of a natural product can be very difficult to authenticate but very necessary. Contamination by a small quantity of a very potent bioactive is always a possibility. Another example of this was the presence of rufomyacin at 0.24% in rufomyazine.⁴ Here the relatively simple and small diketopiperazine structure of the dipeptide was appealing from a medicinal chemistry point of view despite appearing to be 400 fold less potent than the congeneric rufomyacin heptapeptide. Again synthetic material was inactive and tracking down the exceedingly minor impurity would have been very difficult were it not that



pure rufomyacin was available.

Perhaps the saddest case of residual complexity is that of dolastatin 16. This is the last of several peptides, isolated for their potent activity against human cancer cells, from the sea hare *Dolabella auricularia*, by the Pettit group. From a metric

ton (wet weight) of the sea hare (these little fellows are less than the size of an average adult fist) 3.1 mg were isolated, the structure elucidated and the activity against several human cancer cell lines determined as GI_{50} s of approximately 1 nanogram/mL.⁵ Subsequent isolation of dolastatin 16 from the cyanobacterium *Symploca cf. hydnooides* by Luesch et al.⁶ and synthesis by several groups including Pettit's⁷ indicated that the activity seen in the "purified" natural product did not belong to this structure. The sad part of this is that we will never know what the exceedingly potent impurity in dolastatin 16 was, as no material is in existence nor is the raw NMR data which may have permitted a full spin analysis subtraction approach, as was used by Gao in the determination of the structures of minor components in the ecumicin-producing fermentation.⁸

Integrity to the pharmacognosist means, among other things, that samples sent for biological evaluations must have gone through a thorough purity analysis, and this should be documented in any reports of the compound and its biological activity. Moreover HPLC-UV/MS, as most commonly used, is hardly adequate as any highly polar, UV-transparent impurity will "fly under the radar." It is also a lack of integrity to expect a manuscript reviewer to do your literature search for you. A recent article claimed that rufomyacins were discovered by Eli Lilly scientists on the basis of their patents filed in 2000.⁹ In fact this antibiotic complex was discovered by Takeda Chemical Industries and first patented in Japan in 1960, with a US equivalent patent 3,336,725 issuing in 1972.

I recently reviewed a manuscript which made the claim that no structurally novel antibacterial had been discovered and approved by the US FDA since 1962. Variations of this lie appear frequently. Two completely novel structures with novel modes of action, mupirocin (Bactroban) and fidaxomicin (Tiacumicin B), are currently in use, albeit for somewhat specialized indications. Oxazolidinones, on the other hand, have broad antibacterial applications. Fluoroquinolones, carbapenems, and monobactams, all may have modes of actions known for earlier analogues, but each represents a major jump in therapy. Integrity also implies avoiding dishonest statements. ■

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ASP 2019 Annual Meeting: Innovations in Natural Products Chemistry

By Drs. Melany P. Puglisi and Tim Bugni

On behalf of the organizing committee we invite you to attend the 2019 Annual Meeting in Madison, Wisconsin! 2019 marks the 60th Anniversary of the American Society of Pharmacognosy. Registration and abstract submission are now open! Register by **May 8, 2019** so you don't miss out on early registration (aspmeetings.pharmacognosy.us/registration/rates/). The submission deadline for abstracts is **April 29, 2019** (more information can be found at aspmeetings.pharmacognosy.us/abstracts/). Attendees will be notified of acceptance no later than **May 31, 2019** and must register by **June 10, 2019** to be included in the program. Rooms have been reserved at the Madison Concourse Hotel (aspmeetings.pharmacognosy.us/accommodations/) located in the center of Madison within steps of the Wisconsin State Capitol and surrounded by "farm to table" restaurants. You will be able to step outside the hotel and experience the thriving city of Madison. Plan to arrive early to experience the Dane County Farmer's Market, Saturday on the Square, open until 1:45 PM. The concourse is located only a short walk from the Monona Terrace on Lake Monona.

The **program** is comprised of a diverse group of dynamic speakers and includes three special sessions sponsored by the American Chemical Society (ACS), the National Institutes of Health National Center for Complementary and Integrative Health (NIH/NCCIH) and the ASP Foundation. Dr. Tawnya McKee will moderate a session on "Breaking the Bias Habit" on Monday. Saturday evening will feature an open-air reception on the roof of the Monona Terrace with live music entertainment (www.mononaterrace.com). Monday evening attendees will gather at the Wisconsin In-



Madison, Wisconsin, downtown

stitutes of Discovery (discovery.wisc.edu). These events will feature local foods and brews. The Younger Members Event will be held at the SETT on the campus of the University of Wisconsin at Madison (union.wisc.edu/visit/union-south/the-sett-at-union-south) featuring bowling, pool and table games. Tuesday afternoon excursions include Build a Wisconsin Cheese Board, Bitters Boot Camp and a Stroll Down State Street (aspmeetings.pharmacognosy.us/registration/optional-tours-excursion/). Individuals and groups can also participate in the Dine Around on Sunday evening. Reservations can be made upon arrival.

Two **workshops** are scheduled. Dr. Pieter Dorrestein of the University of California at San Diego will conduct a workshop entitled, "A Hands-on Global Natural Product Social Molecular Networking Workshop for Beginners and Advanced Users," and Dr. Thomas Williamson from UNC Wilmington will conduct a workshop called, "Expanding the Structure Elucidation Toolbox with Anisotropic NMR Parameters." Additional workshops may be added in the next few months.

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The program is comprised of a diverse group of dynamic speakers and includes three special sessions sponsored by the American Chemical Society (ACS), the National Institutes of Health National Center for Complementary and Integrative Health (NIH/NCCIH) and the ASP Foundation.

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Sunday features the *Journal of Natural Products* Symposium, “Heroes of the *Journal of Natural Products*,” celebrating the careers of Drs. Gordon Cragg, David Kingston, Rachel Mata and David J. Newman.

Our **plenary speakers** feature Drs. Nancy Keller from the University of Wisconsin at Madison, Nadja Cech from the University of North Carolina at Greensboro, Pieter Dorrestein from the University of California at San Diego, John Beutler from the National Cancer Institute, National Institutes of Health, Sarah E. Reisman from the California Institute of Technology, Helen Blackwell from the University of Wisconsin at Madison and Jairo Kenupp Bastos from the Faculdade de Ciências Farmacêuticas de Ribeirão Preto-USP.

Sunday features the *Journal of Natural Products* **Symposium**, “Heroes of the *Journal of Natural Products*,” celebrating the careers of Drs. Gordon Cragg, David Kingston, Rachel Mata and David J. Newman. These distinguished members of the Society will participate in a panel discussion following brief introductions. Monday morning will feature an NCI/NCCIH symposium, “Diet and Gut Interactions.” Speakers include Drs. Michael P. Snyder of Stanford University, Annadora J. Bruce-Keller of the Louisiana State University Biomedical Research Center, Diana E. Roopchand of Rutgers University, Hang Xiao of the University of Massachusetts at Amherst and Jan F. Stevens of Oregon State University.

Tuesday morning will include a **young members’ symposium** in memory of our long-time ASP Treasurer Dr. David Slatkin, sponsored by the ASP Foundation. This symposium will feature contributed lectures from postdocs and graduate students. Participants in this symposium will also be eligible for one of two Bruker Awards to be awarded for excellence in NMR spectroscopy.

Students and postdocs can also participate in the 2019 **Poster Competition** sponsored by the ACS. Interested attendees need to indicate that they will enter the competition by checking the correct box when submitting their abstracts. Posters in pdf format must be submitted to the link provided on the meeting website by midnight on **June 13, 2019** for preliminary judging. Fifteen (15) finalists will be contacted prior to the conference opening. Final judging will be at the poster during the poster sessions by members of the editorial board of the *Journal of Natural Products*. Three prizes will be awarded for the best posters during the banquet.

TRAVEL INFORMATION

Two hotel venues have been reserved for attendees – The Madison Concourse Hotel located on the square in downtown Madison (www.concoursehotel.com) and the Hilton adjacent to the Monona Terrace (www3.hilton.com/en/hotels/wisconsin/hilton-madison-monona-terrace-MS-NMHHF/index.html). The hotels are located 5 miles from Dane County Regional Airport. Attendees can also fly into the General Mitchell International Airport in Milwaukee, WI or O’Hare Airport in Chicago, IL. Shuttle service to Madison can be arranged from both airports.

SPEAKER SPOTLIGHT

Liva Rakotondraibe

Dr. Liva Rakotondraibe, assistant professor of medicinal chemistry and pharmacognosy of the College of Pharmacy at The Ohio State University, will deliver a talk entitled, “Mining new and antiproliferative compounds from untapped natural product sources.” Dr. Rakotondraibe is a native of Madagascar and attended the Université d’Antananarivo for his Diplome d’Etude Approfondie (DEA, equivalent to MS degree, 1998) in organic chemistry, option: natural products. He pursued his graduate studies in pharmaceutical sciences, natural product chemistry at Hiroshima University, Japan (PhD 2003 with



Dr. Liva Rakotondraibe

Dr. Kazuo Yamasaki). After four years of postdoctoral research on new and biologically active compounds from liverworts at Tokushima Bunri University, Japan (Advisor, Dr. Yoshinori Asakawa), he went back to Hiroshima University to be an assistant professor (2007-2009) in the Graduate School of Biomedical & Health Sciences. Dr. Rakotondraibe moved to Virginia Polytechnic Institute and State University, Department of Chemistry as senior

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Rakotondraibe leads the NIH sponsored project, “Development of plant-derived, resistance-breaking mosquitocides for controlling vectors of Zika virus.”

research scientist in 2009 to work on antiproliferative and antimalarial compounds from Malagasy plants, soil microbes, marine organisms and their microbial associates, for the ICBG/Madagascar project (PI and Advisor, Dr. David Kingston). He has been at The Ohio State University since September 2013 where he currently holds a diversity supplement in the NIH funded program projects entitled: Anticancer Agents from Diverse Natural Origins (PI, Dr. A. Douglas Kinghorn). He also leads the NIH sponsored project, “Development of plant-derived, resistance-breaking mosquitocides for controlling vectors of Zika virus.” The broad goals of his research are to: develop NMR-based dereplication methods, discover new and bioactive compounds from untapped natural product sources, and understand and optimize the production of bioactive microbial secondary metabolites.

Jan F. Stevens

Dr. Jan Frederik (‘Fred’) Stevens received his MS in pharmacy (1988), PharmD (1990), and PhD in pharmaceutical chemistry (1995) from the University of Groningen, The Netherlands. His doctoral research aimed to determine the evolutionary relationships among species within the Eurasian Sedoideae and Sempervivoideae (stonecrop family, Crassulaceae), using plant metabolomics approaches. He received postdoctoral training at Oregon State University (1995-1999), the Free University of Amsterdam (1999-2000), and the Leibniz Institute for Plant Biochemistry, Halle/Saale, Germany (2000-2002). In 2002, he joined the faculty at Oregon State University (OSU), Corvallis, where he is professor of pharmaceutical sciences in the College of Pharmacy and principal investigator at the Linus Pauling Institute. He has authored or co-authored 129 articles in peer-review journals (Web of Science h-index 36). He received five awards for excellence in teaching at the OSU College of Pharmacy. He has mentored >66 postdoctoral fellows, graduate students, undergraduate students, visiting scholars, and foreign exchange students. He holds a guest professorship at the University of Antwerp, Belgium, where he has taught a

course on medicinal natural products every fall since 2008. He is a member of the Executive Editorial Board of Molecular Nutrition & Food Research and serves as an editor for *Scientific Reports*. He served the Phytochemical Society of North America (PSNA) as president (2013-2014) and vice president (2012-2013). He chaired the organizing committee for the 2013 Meeting of the PSNA in Corvallis, Oregon and co-organized two annual meetings of the American Society of Pharmacognosy (ASP), held in Corvallis (2005) and Portland (2017), Oregon. His research aims to determine the role and function of vitamins and dietary phytochemicals in human health and disease. His research relies heavily on mass spectrometry-based metabolomics for the discovery of biological effects of natural products in cultured cells, animal models of disease, and in humans. ■



Dr. Jan Frederik (‘Fred’) Stevens

His research aims to determine the role and function of vitamins and dietary phytochemicals in human health and disease.



Hot Topics in Pharmacognosy: Obtaining Novel Microbial Metabolites Other Than by Whole Genome Analysis



By Dr. David Newman

A few columns ago, I mentioned the work of the Lewis group at Northeastern and the Brady group at Rockefeller and had previously mentioned the Cichewicz group at Oklahoma. Another group has now come to the fore by using “a single activator to multiple activators to persuade recalcitrant microbes to yield up their previously unknown treasures.”

This group is the one from Princeton led by Dr. Mohammad (Mo) Seyedsayamdost. He has just been named by the Royal Society of Chemistry *Natural Product Reports* Editorial Board as the 2019 *Natural Product Reports* Emerging Investigator Lecturer; and, as the RSC-NPR states, “His lab is interested in the discovery, structure, function, and biosynthesis of natural products from microbial sources, with an emphasis on bioactive cryptic metabolites.”

In these studies, as will be shown with a few examples, his lab blends microbiology, bacterial genetics, natural product chemistry, and enzymology to “persuade” microbes to produce previously unknown metabolites.

In 2014, his lab developed a method for identifying inducers of silent gene clusters¹ known as the HiTES system. Then in 2016, a seminal paper came from his laboratory demonstrating that by using the well-known antibiotic, trimethoprim, the secondary metabolome of *Burkholderia thailandensis*, a well-known model organism for the *Pseudomallei* group pathogens that had previously been shown to have a significant number of silent gene clusters,² could be “activated.”¹ Rather than use “customary phenotypic

screening” they used a *lacZ* translational fusion to the *mal* gene cluster which produced the cryptic virulence factor, malleilactone, which potently inhibits the growth of *Caenorhabditis elegans*. Using a 640 member library of bioactive small molecules (including antibiotics and antitumor agents), and monitoring the *lacZ* activity induced by each member of the library tested in 96 well plates, nine elicitors were identified that upregulated expression of the *mal* cluster. Intriguingly all nine were clinically used antibiotics, trimethoprim, piperacillin, cefotaxime and five different fluoroquinolones. All were potent activators at sub-inhibitory concentrations (when compared to their MICs), with the two best being trimethoprim and piperacillin with at optimal concentration; trimethoprim produced an approximately 150-fold induction of malleilactone.

Following on from this work, in 2016 Okada et al. reported a fuller-scale analysis for the trimethoprim activation, demonstration of over 100 compounds that were not observable under standard growth conditions.³ By using MS/MS networking coupled to high-field NMR they were able to assign structures to over 40 of the compounds elicited, including a previously unknown series that they called the acybolins (**1**) which are part antibiotic, part quorum sensing agent. In addition, they found extra members of a previously reported quinoline family, and two further analogues of the previously reported capistruin family, which had only been observed after heterologous expression of the relevant gene cluster in *E. coli* at the elevated temperature of 42 °C.

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Then in January 2019 came the *pièce de résistance* when Xu et al.⁶ reported “removing the genetic constructs” from such studies by linking elicitor screening using 502 small molecules to induce the secondary metabolome of a given strain, followed by substituting imaging mass spectrometry (thus visualizing the resulting metabolome) in place of the challenging genetic, cloning, or culturing procedures necessary for “normal procedures.” As a result, the method can be used with both sequenced and unsequenced bacteria.

A fuller discussion of the work described above was published by Okada and Seyedsayamdost in *FEMS Microbiology Reviews* in 2017, which should be consulted for further details of the trimethoprim/HiTES system.⁴

Then later in 2017, Xu et al. demonstrated that the system could function in a Gram-positive organism, in this case, *Streptomyces albus* J1074.⁵ Their high-throughput transcriptional assay in *S. albus* used eGFP deliberately inserted at both a neutral site and inside the biosynthetic cluster of interest, as a read-out for secondary metabolite synthesis. Using this approach and a 500 natural product based HiTES assay, a silent gene cluster in *Streptomyces albus* J1074 was activated after use of etoposide and ivermectin as inducers. This system allowed the group to isolate and structurally characterize 14 novel small molecule products of the chosen cluster. One of these molecules is a novel antifungal, acylsurugamide A (**2**) related to the surugamides, some of which had been previously reported from a marine streptomycete, while several others in the same structural family inhibit cathepsin B, a cysteine protease which has been implicated in cancer.

Then in January 2019 came the *pièce de résistance* when Xu et al.⁶ reported “removing the genetic constructs” from such studies by linking elicitor screening using 502 small molecules to induce the secondary metabolome of a given strain, followed by substituting imaging mass spectrometry (thus visualizing the resulting metabolome) in place of the challenging genetic, cloning, or culturing procedures necessary for “normal procedures.” As a result, the method can be used with both sequenced and unsequenced bacteria.

Xu et al. then proceeded to demonstrate the utility of this approach by applying it to diverse bacteria including *P. protegens* and, in particular, to *Streptomyces canus* NRRL B3980, which is reported to contain more than 20 BGCs that have not been linked to a natural product. Using the 502-membered natural product library, they induced a third compound family with m/z in the 1563 and 1579 range.

The inducer in this case was “kenpaullone, a CDK inhibitor” (though the claim to use 502 natural products was not quite accurate as “kenpaullone” is a synthetic compound, based upon a natural product, and would be classified as an S* in the standard Newman/Cragg system). They then moved to “interrogate” *Amycolatopsis keratiniphila* NRRL B24117, whose genome had not been sequenced prior to this work, but PCR reports had demonstrated a vancomycin-like BGC. Compounds in the m/z ranges from 1,286 to 1,811 were found when inducers with indole-bearing alkaloids were used. From this work seven analogs were subsequently identified, the keratinimicins and keratinicyclins (structures not shown) all containing a chlorine atom. Shotgun sequencing then enabled the group to identify the relevant GPA cluster, *but it needs to be emphasized, the sequencing was to find and use the BGC after identifying the compounds, not the reverse, which is the norm.* Although the antimicrobial activities of the two chemotypes were not better than vancomycin, what is of interest is that one compound in the cluster, keratinicyclin B (structure not shown), demonstrated significantly better activity against respiratory syncytial virus (RSV) being 16 fold better than the usual treatment of ribivarin, and was inactive against the bacterial strains tested for the other compounds in the cluster, and was also inactive against influenza A.

Thus, the group demonstrated the potential of this method by applying it to diverse bacteria, identifying nine cryptic metabolites with potentially therapeutic bioactivities, including a new glycopeptide chemotype that demonstrated significant inhibition of the pathogenic RSV.

It will be very interesting to see if any commercial enterprise picks up on this methodology, as from the descriptions the avoidance of having to use genetic constructs and/or heterologous expression, etc., and with a direct identification of the new(er) compounds, a major time-consuming operation appears to have been bypassed. ■

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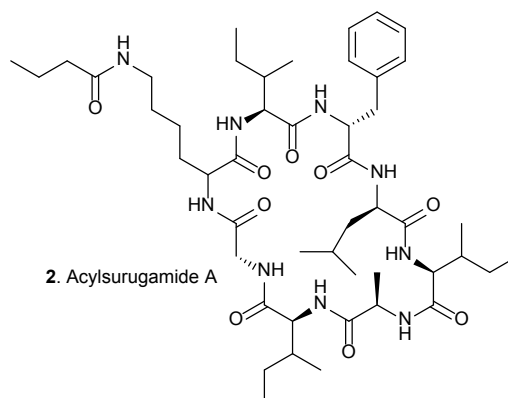
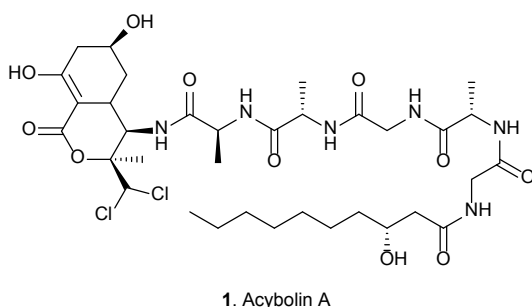
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Structures



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Meet a New ASP Member

Dr. Vitor H. Pomin is our featured new member in this issue of the Newsletter. Since April 2018, he has served as an assistant professor of pharmacognosy in the Department of BioMolecular Sciences and a research assistant professor at the Research Institute of Pharmaceutical Sciences in the School of Pharmacy at the University of Mississippi. He has published over 60 articles in peer-reviewed journals and 15 book chapters and is highly active as an editor and reviewer in the area of glycobiology. We are pleased to be able to officially welcome Dr. Pomin to ASP.

By Dr. James Fuchs

What is your scientific background?

I received my teaching licensing as an undergraduate from the Institute of Biological Sciences, Federal University of Rio de Janeiro (UFRJ), Brazil. I also pursued graduate studies at UFRJ in Biological Chemistry at the Institute of Medical Biochemistry Leopoldo de Meis (IBqM), receiving my Diploma of Licentiate, MS, and PhD degrees in 2003, 2005, and 2008, respectively. At that point, I then pursued post-doctoral studies in the United States at the Complex Carbohydrate Research Center at the University of Georgia. In 2011, I went back to IBqM/UFRJ as an assistant professor of biological chemistry, biochemistry, glycobiology, and NMR spectroscopy and stayed there until moving to my current position at the University of Mississippi in 2018.

What are your research interests?

My research interests are in the areas of glycobiology (mostly sulfated polysaccharides), structural (glyco)biology, NMR spectroscopy and marine medicinal glycomics. All of these fields fall directly or indirectly into the classical concept of pharmacognosy. Specifically, my laboratory seeks to understand the structural and functional details of biomedically active carbohydrates in some pathophysiological events such as coagulation, thrombosis, inflammation, cancer, angiogenesis and viral and microbial infections. We are dedicated to the application of NMR technologies on biomolecules not only for the elucidation of the primary structures of new sugars, but also for the assessment of their conformational and dynamical properties in solution, and the atomic details in interactions with functional



Dr. Vitor H. Pomin

PHOTO BY FRANK WIGGERS

binding proteins. Current investigations of my laboratory focus on the structure-active relationship analysis of sulfated glycans of marine origins such as unique glycosaminoglycans, sulfated fucans and sulfated galactans.

How did you hear about the ASP?

My colleague from the Division of Pharmacognosy at the BioMolecular Sciences Department at the University of Mississippi, Dr. Dale Nagle, recommended this society to me as a good platform based on my professional skills, research interests, and achievements.

Why did you ultimately decide to join ASP?

After becoming a faculty member in an American research institution, becoming a member of the ASP was a very natural step. This society discusses the general aspects of drugs or potential drugs from natural sources, which are closely related to my research interests

in the marine-derived biomedically-active carbohydrates.

What do you hope to achieve through your membership?

I hope to be able to increase my professional network, enlarge the potential number of scientific collaborations, share my research results with the scientific community, improve the visibility of my work and achievements, be involved with conferences and scientific meetings related to my research field, and be updated with news related to pharmacognosy.

What other scientific societies do you belong to?

The Brazilian Society for Biochemistry and Molecular Biology, the Nuclear Magnetic Resonance Users Association, the Brazilian Society for the Advancement of Science, the American Association of Colleges of Pharmacy and the American Heart Association.

What do you like doing in your spare time?

I like to play chess, swim, hang out with family and friends, travel to other countries, listen to music, read books, watch movies and enjoy a good coffee.

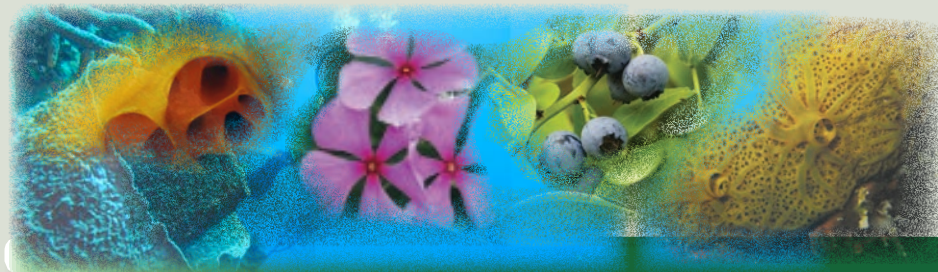
Based on that response, what are you currently reading?

The Universe in a Nutshell by Stephen Hawking.

What are your favorite movies?

I actually have a few - *Back to the Future*, *Forrest Gump* and *Star Wars*. ■

New Members of ASP Spring 2019



ASP would like to welcome our new members. The Society's main objectives are to provide the opportunity for association among the workers in pharmacognosy and related sciences, to provide opportunities for presentation of research achievements, and to promote the publication of meritorious research.

New members include 6 full members and 3 associate members.

We look forward to meeting you and learning more about you and your work.

FULL MEMBERS

Ms. Adeyoyin Adeniji
Operation Manager
PhytoCare Health Services
Lagos State, Nigeria

Dr. Thomas Giagou
Research Chemist
Constellation Brands, Inc.
Madera, California

Prof. Kyo Bin Kang
Assistant Professor
Sookmyung Women's University
Seoul, Republic of Korea

Prof. Vitor Pomin
Assistant Professor
The University of Mississippi
Oxford, Mississippi

Mr. Priyabrata Sahoo
Senior Director
MetricStream, Inc.
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Prof. Makio Shibano
Lecturer
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Pharmaceutical Sciences
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Chicago, Illinois

Ms. Mirielle Nauman
PhD Student
University of Illinois at Chicago
Chicago, Illinois

Ms. Andrea Rague
Graduate Student
Duquesne University
Pittsburgh, Pennsylvania



Pharmacognosy Field Notes: Ugandan Rain Forest Dreams

By Mr. Fabien Schultz

As a child, I admired Jane Goodall, Dian Fossey and other hero-explorers. I dreamed of exploring remote places and wildlife. I grew up in Germany, where virtually everybody always tells you to get a regular job and stop dreaming about being an explorer and discovering nature's secrets. Indeed, soon enough reality set in and I had to focus on getting good grades in school rather than pursuing my dreams. Sadly, most school systems are not meant for dreamers, and so my ambitions ended up getting as dusty as my childhood books about the jungle. In the blink of an eye I was at the top of my university class in bioproduct technology, majoring in applied chemistry. I even landed my first big job as an intern in the industry at a large German research center, where I worked on development of a skin care cream for the NIVEA brand. My future seemed to settle, and I envisioned a path to a well-paying career with a nine-to-five-job behind a desk, just what my teachers and parents always advised. However, in the summer of 2012, all of my future career plans and later even my field of expertise changed drastically. What had happened? East Africa happened!

My girlfriend Inken and I decided to go to Uganda and begin studies at Kampala University. It turned out to be a journey of a lifetime, and also one into the unknown. At least to us it felt like this, as everything came together quickly. When we arrived at Entebbe Airport, we had no place to stay, no study program, no reliable contacts in the country, no contact address, no appropriate clothing and no experience with travelling outside Europe. The final nail in the coffin of our Western comfort zone: we were on a tight budget. We were apprehensive about what to do next in case the university did not send somebody to pick us up as promised. When exiting the airport, though, there stood a middle-aged Ugandan man with a worn-down "Back to the Future" cap from the 80s, happily waving at us. His name was Dan, and this is when our deep and relentless love for Uganda, its people, culture and nature, began.

Uganda is a tropical country north of Lake Victoria and bordered by the Democratic Republic of Congo, South Sudan, Ke-



Photos by Inken Dworak.

Along a first expedition deep into the Ugandan rain forest in 2012, this photo of Fabien Schultz with a wild mountain gorilla, was taken at Bwindi Impenetrable Forest, near the border with the Democratic Republic of Congo.

nya, Rwanda and Tanzania, and is one of the poorest countries in the world. Yet, due to the hospitality of its people and its natural splendor, Uganda is often referred to as the Pearl of Africa.

Our first week was exhausting and at the same time amazing, getting to know a culture so different from our own. An Ebola outbreak occurred, and we were frightened by the rapid spread of the horrible disease. We read the news constantly, watching the World Health Organization work tirelessly to stop the epidemic.

As the weeks passed, we relished living in Uganda more and more. We found a home away from home with an amazing Ugandan family, who we still visit each time we return to the country. Today, seven years later, this is still our starting point before leaving for our fieldwork expeditions to all parts of the country.

We were the first non-African students at the university, and locals and fellow students often watched in surprise as we climbed clumsily onto the backs of boda-bodas (motorcycle taxis), squeezed ourselves into the fully loaded tiny buses for public transport or simply walked along the road to get water. We began

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Uganda is a tropical country north of Lake Victoria and bordered by the Democratic Republic of Congo, South Sudan, Kenya, Rwanda and Tanzania, and is one of the poorest countries in the world. Yet, due to the hospitality of its people and its natural splendor, Uganda is often referred to as the Pearl of Africa.

Pharmacognosy Field Notes: Ugandan Rain Forest Dreams

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learning bits and pieces of the local language, Luganda, which served as an effective ice-breaker at the markets and still uplifts the atmosphere when entering remote villages during fieldwork. Most Ugandans speak English, but by at least trying to greet and exchange some phrases in the local language, we aimed to show our respect and love for Uganda and its people.

My study program, biotechnology, was technically regarded as agriculture in Uganda, which is why we were actively involved in fieldwork from the very beginning of our stay. We were called “muzungu” countless times, and the further our fieldwork took us into the villages, the louder we would hear the term being excitedly called out by the children to greet us. The Bantu language term “muzungu” refers back to the European explorers of the 18th century and literally translated means “someone who roams around (sometimes: like a crazy person).” Today, it is commonly used to refer to “someone with white skin.”

Although locals were usually happy with our visits, we were surprised by the reaction our arrival caused in one village. A group of young children crossed our path, and they were absolutely terrified. Instead of happily shouting, they all started crying out of fright, and our smiles and local greetings could not convince them of our good intentions. We were later told that the reason for their behavior was that they had never seen light-skinned people and possibly even a car before.

After 6 months, Inken and I left Africa to continue our studies in Germany; and just 8 months later, we returned back to our second home again for one month and co-founded our own charity, “ARUDEVO,” in rural Lwengo District in South-Central Uganda. Since then, we have been actively engaged as scientific advisors to various NGO projects (www.arudevo.com).

After graduating with my master’s degree in Germany, I de-



This year Inken and I are going back for a research expedition to investigate self-medication in wild chimpanzees and mountain gorillas while collaborating with renowned primatologists in the field (see *planned expedition route*). Being that this is a zoopharmacognosy project, it will be crucial to collect plants and insects used by the Great Apes and then test their extracts for antinematodal and antimalarial activity.

ecided to continue doing fieldwork, and I developed a passionate interest in East African traditional medicine and ethnopharmacology. Essentially, without a related university degree or mentoring/supervision, it was solely my personal experience in the field that drove me to become a field researcher. During my stays there, I realized that the indigenous traditional healers by far outnumber the western trained physicians. In the tropical rainforest ecosystems of Western Uganda and Eastern Democratic Republic of Congo, I expected that a substantial proportion of plants and insects had not yet been discovered. More than 99 percent of the total species have not been investigated for bioactivity yet. I teamed up with Godwin Anywar, a Ugandan PhD student and ethnobotanist, with whom I now work on surveying the indigenous peoples. Godwin’s expertise is crucial as he translates local plant names and identifies specimens. After collecting 16 species and creating a plant extract library of 86 different extracts, I confirmed traditional uses of the medicinal species through pharmacological bioassays in Germany. I got accepted into a PhD program at the Technical University of

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[We] co-founded our own charity, “ARUDEVO,” in rural Lwengo District in South-Central Uganda. Since then, we have been actively engaged as scientific advisors to various NGO projects (www.arudevo.com)

After collecting 16 species and creating a plant extract library of 86 different extracts, I confirmed traditional uses of the medicinal species through pharmacological bioassays in Germany.



Above: Situated along the Great Rift Valley, the country is Africa's hotspot for biodiversity, boasting 6 of Africa's 18 plant phytochoria or phytogeographical regions. This picture of the Murchison Falls was taken from the Nile shore of the Budongo Forest.

Below left: By organizing workshops, we are trying to transfer knowledge bidirectionally. Locals of rural villages, here in Lwengo District, get to decide on workshop topics that they find helpful so that we can transfer our lab results back to them or bring in experts, and traditional healers share their knowledge with us at www.arudevo.com.

Below right: To identify medicinal plant species, we conduct surveys with local healers in relatively isolated tribes. Over generations, their knowledge about the effects of plants has only passed through oral record. As a result of resettlement, drift to the cities and deforestation, traditional knowledge is being lost.



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Berlin and, to my great fortune, met my supervisor Dr. Leif-Alexander Garbe, who enthusiastically supported my independent research approach.

Today, Inken and I are happily married. We still like to visit unusual places, but our lives have become far more settled with her working as a journalist and me as a third-year PhD student in the lab. Having just returned from a Fulbright-sponsored stay with the research group of Dr. Cassandra Quave at Emory University, I am very happy with how everything has developed.

Looking at old photos and fieldwork notes always brings back a flood of memories. They range from lovely and nostalgic to weird and funny in a uniquely Ugandan-muzunguian kind of way. Some also bring back recollections of very dangerous situations, mostly involving the wildlife or military. Once I was attacked and dragged deep into the forest by a frustrated chimpanzee. That chimpanzee, in fact, had gotten chased away by the alpha male and decided to validate his superiority by picking a fight with me! Yet even such fierce dangers do not diminish in the slightest my passion and desire for being right there, in the wild, to conduct fieldwork. This year, one of our goals in returning to Uganda is to study self-medicating behavior and plant/insect use of the same chimpanzee group.

Field research has been one of the most enchanting and deep experiences of my academic education. It also contributed immensely to my professional development, instilling in me a great sense of responsibility, igniting my creativity, and refining my self-organization and independence. Although my parents and peers advised me against field research, step by step I managed to shift my research towards fieldwork, harmoniously connecting my laboratory activities to my research with the people and natural resources of Uganda. ■



Conference Calendar

The *Newsletter* is pleased to announce the following upcoming conferences and meetings. The events portrayed here reflect what listings and notices the *Newsletter* has specifically received. For a more extensive calendar, please visit the ASP website at www.pharmacognosy.us. If you have a conference or event you would like mentioned, please send us relevant information, including any graphics or appropriate fliers, at asp.newsletter@lehman.cuny.edu.

16th Annual Conference of the Natural Health Products Research Society

May 26 – 29, 2019

Edmonton, Alberta, Canada

events.eply.com/2019ConferenceandMembership2795115

Natural Products in Drug Discovery and Health (NatProDDH), organized by Phytochemical Society of Europe (PSE)

July 28 - 31, 2019

University of Lisbon, Lisbon, Portugal

www.emedevents.com/c/medical-conferences-2019/natural-products-in-drug-discovery-and-health-natproddh-2019-1

19th International Congress of the International Society for Ethnopharmacology

June 12 – 14, 2019

Technische Universität Dresden, Germany

tu-dresden.de/mn/internationales/veranstaltungen/symposien-kolloquien/2019-international-ethnopharmacological-congress

18th Meeting of the Consortium for Globalization of Chinese Medicine (CGCM)

August 8 – 10, 2019

Shanghai University of Traditional Chinese Medicine, Shanghai

www.tcmedicine.org

3rd International Conference of Marine Fungal Natural Products (MafNap 2019)

June 26 - 28, 2019

Athens, Greece

docs.wixstatic.com/ugd/a5860a_f0f3102c38294d488621b056b236824e.pdf

67th Annual Meeting of the Society for Medicinal Plant and Natural Product Research

September 1 – 5, 2019 Innsbruck, Austria

www.ga2019.at/

7th Annual Meeting of the Good Practice Traditional Chinese Medicine Research Association (GP-TCM RA)

July 9 – 10, 2019

Daegu Haany University, Daegu City, Republic of Korea

www.gp-tcm.org

XVI International Symposium on Marine Natural Products & XI European Conference on Marine Natural Products, 2019

September 1-5, 2019

Peniche, Portugal

wmnp2019.ipleiria.pt/

60th Annual Meeting of the American Society of Pharmacognosy

July 13 – 17, 2019

Madison, Wisconsin

aspmeetings.pharmacognosy.us



12th International Congress on Natural Products Research

July 25 – 30, 2020

San Francisco, California

icnpr2020.org



Brief News from Washington

By Dr. Georgia Perdue

- **President Trump, in his State of the Union speech, said he wanted to end the HIV epidemic in the United States.** On February 7, NIAID sent out a press release entitled: **Ending the HIV Epidemic: A Plan for the United States.** “The initiative will target our resources to the 48 highest burden counties, Washington DC, San Juan Puerto Rico, and 7 states with a substantial rural HIV burden.” Stay tuned!
- **The Food and Drug Administration approved 59 new drugs in 2018,** 34 of which are “novel drugs for rare diseases.” Fourteen were designated as “breakthrough therapies.”
- A report on February 13 noted that **two addiction experts,** Keith Humphreys PhD, Stanford University, and Richard Saitz MD, Boston University School of Public Health, argue that **“substituting cannabis for opioid addiction treatment is potentially harmful.”** (see *Medscape MD*).
- **Dietary supplement companies,** considered very lucrative, are in the cross hairs of FDA. **In mid-February the agency identified 17 companies selling products “with improper claims” for preventing, curing or treating diseases.** They were given two weeks to reply with corrections. A Harvard Medical School professor noted such companies get away with their claims and people believe them. Stay tuned.
- **Dr. Francis Collins talked about two new interesting members of Congress at the December 13, 2018 NIH Advisory Committee to the Director (ACD). Rep. Sean Casten (D-IL),** born in Dublin, Ireland, has a bachelor’s degree in **molecular biology and biochemistry** from Middlebury College. He worked for two years at Tufts University School of Medicine, investigating **dietary impacts on colon and breast cancer,** and he holds two master’s degrees: a master of engineering management and a master of **science** in biochemical engineering from Thayer School of Engineering. The second addition to Capitol Hill is **Congressman Earl L. Carter, former owner of Carter’s Pharmacy in South Georgia.** He is the only pharmacist in Congress! He earned his bachelor of science degree in pharmacy from the University of Georgia.
- At the same **ACD meeting, Dr. Collins mentioned that Johns Hopkins University East Baltimore campus will have a new building by 2022 named after Henrietta Lacks.** Cancer cells, named HeLa, were unwittingly taken from Henrietta and subsequently used in cancer research with some success. She left a legacy. A book, *The Immortal Life of Henrietta Lacks* by Rebecca Skloot, tells the story. [There is a back story: at one point at NCI, HeLa cells had contaminated KB cell cultures. While it was vehemently denied by NCI, it was confirmed within a year as being true and helped explain certain research findings.]
- **On November 26 Dr. Helene Langevin was sworn in as the new Director for the National Center for Complementary and Integrative Health (NCCIH).** (see Winter 2018 *ASP Newsletter* for more details about her) Her thoughts include: “... it has been my longstanding con-

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(see *Medscape MD*).

Since Dr. Langevin's arrival at NCCIH, at least five articles on specific plants and their "medical" usefulness have been posted online: bilberry for cardiovascular conditions, diarrhea, UTIs and more; cinnamon, GI problems, diabetes...; pomegranate, of which it was said "there isn't a lot of strong scientific evidence on [its] health effects"; peppermint oil used for irritable bowel syndrome; and passion flower with many uses including anxiety and sleep problems.

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viction that integrative health care is more than just the sum of conventional and complementary health approaches...." **"I am thrilled to be leading NCCIH in its continued exploration of this frontier...."** She acknowledged her predecessors which included **the late Dr. Stephen Straus, who at one Council meeting did not mince his words re: the pros and cons of alternative medicine which had to be "scientifically proven effective!"** And, he emphasized that "the public would have to accept the findings"! **Dr. Langevin also noted the role NCCIH has in "finding solutions to the current opioid crisis with research on non-drug approaches."**

- Since Dr. Langevin's arrival at NCCIH, at least five articles on specific plants and their "medical" usefulness have been posted online: **bilberry** for cardiovascular conditions, diarrhea, UTIs and more; **cinnamon**, GI problems, diabetes...; **pomegranate**, of which it was said "there isn't a lot of strong scientific evidence on [its] health effects"; **peppermint oil** used for irritable bowel syndrome; and **passion flower** with many uses including anxiety and sleep problems. Also mentioned was **cupping**, "used in traditional medicine in several parts of the world."

(A personal note: My parents were Greek immigrants. My mom was an expert in using the technique of dry cupping on my father's back, which believe it or not, helped greatly to relieve pain! Dry cupping is putting a flame in the cup until it is hot and placing it on the skin's surface.)

- Last December 4 **NCI Director Dr. Norman Sharpless shared news at the combined National Cancer Advisory Board and Board of Scientific Advisors meeting. In FY 2018 NCI received its largest funding increase**

since FY 2003. Early stage Investigators received 25% more. And, **the total number of new RPGs was up from 2017.** For FY 2019 NCI received a \$180 million increase; \$100 million was earmarked for the Moonshot effort. **There has been a 30% increase of grant applications since 2013: 2000 R01 applications.** "It is a very exciting time for NCI," noted Dr. Sharpless. "It is testimony to NCI from the applicants." Nevertheless going forward, there will be an across the board funding cut –grants will be funded at the 2018 rate; a 3% cut to non-competing awards; no cuts to Moonshot or cancer centers; R21s are the "hardest to get from NCI." Good news is there has been an overall decrease in mortalities, but an increase in liver cancer and a few other cancers. **On March 2019 the debt ceiling is reinstated and budget caps return starting in October 2019.**

- A private company, **Steba Biotech**, with headquarters in Luxembourg, received **FDA approval for its cancer drug, Tookad, to treat prostate cancer.** The name is from the *Torah*. The company's medical/regulatory team is in France and its research and manufacturing centers are in Rehovot, Israel. The scientists say they will have a cure for cancer in a year! Stay tuned.
- On April 27, the National Cancer Research Foundation will be awarding the **Szent-Györgyi Prize to NCI's Dr. Steven A. Rosenberg, MD, PhD.** The prize "recognizes Dr. Rosenberg's pioneering role in the development of adoptive immunotherapy to treat cancer." **"Dr. Rosenberg's groundbreaking work has changed cancer research and what we know about treatment...his findings have also immeasurably changed patients' lives,"** said NCI Director Dr. Norman Sharpless. ■

There has been a 30% increase of grant applications since 2013: 2000 R01 applications. "It is a very exciting time for NCI," noted Dr. Sharpless. "It is testimony to NCI from the applicants."

From the Archives: Pharmacognosy in the War against Adulteration

By Ms. Devhra BennettJones

The Society's members are integral advocates in promoting the growth and development of natural products. By advancing the visibility of pharmacognosy and increasing public awareness, these scientists are notable authorities on the adulteration of plant products. Contamination raises a host of issues about the quality of herbal ingredients found in dietary supplements.¹ In the United States the Food and Drug Administration regulates dietary supplements under law established by the Dietary Supplement Health and Education Act of 1994 (DSHEA). Those that manufacture and sell these products are required to accurately label and use good manufacturing practices. The FDA is tasked with proceeding against any mislabeled or adulterated dietary supplement product.² Adulteration lawsuits have serious consequences for the defendants. Convictions can result in FDA fines, probation, and jail time. Judgements for plaintiffs can reach in the millions of dollars, for individuals and in class-action lawsuits. Defendants can even be convicted of racketeering in some cases.

On February 11, 2019 FDA Commissioner Scott Gottlieb, MD, issued a statement dedicating vigorous resolve to protect the American consumer from adulterated dietary supplements. He professed,

Making healthy choices about diets can have a significant and positive impact on Americans' health. To be able to make those choices with respect to dietary supplements, consumers need to have access to safe, well-manufactured, and appropriately labeled products. One of my top goals is ensuring that we achieve the right balance between preserving consumers' access to lawful supplements, while still upholding our solemn obligation to protect the public from unsafe and unlawful products, and holding accountable those actors who are unable or unwilling to comply with the requirements of the law.

Today, we're announcing new steps we intend to advance to achieve these twin goals. These steps include communicating to the public as soon as possible when there is a concern about a dietary supplement on the

market, ensuring that our regulatory framework is flexible enough to adequately evaluate product safety while also promoting innovation, continuing to work closely with our industry partners, developing new enforcement strategies and continuing to engage in a public dialogue to get valuable feedback from dietary supplement stakeholders.³

Legal regulation of herbal products can extend the pharmacognosists' responsibilities into the court room. Throughout his career, the ASP's charter member Dr. Norman Farnsworth served as an expert pharmacognosist witness in multiple dietary supplement adulteration litigation cases. Regardless of whether he was hired by the plaintiff or the defendant, Dr. Farnsworth adhered to pharmacognosy integrity; he was forever faithful to the science. He had a specific process of investigation into alleged adulterated dietary supplements:

- Acquire samples of the dietary supplements under investigation;
- Inquire about the genus of each plant utilized in the manufacture of the dietary supplement;
- Inquire about the quality control procedures in the plant(s) acquisition, transport, storage, and the manufacture of the dietary supplement;
- Collect all the information of a pharmacologic and a chemical nature that is available in computerized information series on the plants;
- Investigate the textbook literature about the plants that did not appear in computer databases, such as NAPRALERT;
- Collect information on the chemical constituents in each of the plants contained in the dietary supplement;
- Analyze the legal position of the plants under investigation that are being sold as foods according to the US Food and Drug Administration;

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Making healthy choices about diets can have a significant and positive impact on Americans' health. To be able to make those choices with respect to dietary supplements, consumers need to have access to safe, well-manufactured, and appropriately labeled products.

From the Archives: Pharmacognosy in the War against Adulteration

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- Determine whether the specific plants are on the FDA GRAS list as plants that are generally accepted as safe;
- Review the plants status in the pharmacopeia of the US and the pharmacopeias of the nations of Europe, China, Japan, Latin America, Britain, and Canada;
- Scrutinize World Health Organization drug information circulars about the constituents in each of the plants contained in the dietary supplement;
- Contract with at least three independent chemistry laboratories for heavy metal analysis, cytotoxic materials, and plant chemical constituents of the dietary supplement;
- Quarantine and trace the handling, storage and transport of the dietary supplement samples sent to each laboratory;
- Confirm that each of the independent chemistry laboratories adheres to state and federal Environmental Protection Agency accepted chemistry analysis methodologies;
- Confirm that each of the independent chemistry laboratories is certified by the state's Environmental Protection Agency;
- Investigate the status of the heavy metals, cytotoxic materials, and plant chemical constituents found by the independent laboratories and their affects upon human health;
- Analyze the concentration of the chemical constituents of the dietary supplements and their affects upon human health; and,
- Establish a quality control trail of his own investigation, with documented steps and the results of each stage.⁴

Dr. Farnsworth's quality control methods of establishing a paper trail, record-keeping, and residual samples gave his investigations high credibility in depositions and in the court room. His expert testimony did not always bolster the case of the litigant that hired him. He adhered to the same standards regardless of his employer and whichever side benefitted from his testimony. Even though Dr. Farnsworth's expertise as a consulting chemist was a source of income, his scientific opinion was not for sale.

Pharmacognosists' dedication to providing safe and effective plant products are firmly aligned with the goals recently avowed by FDA Commissioner Scott Gottlieb.

Our first priority for dietary supplements is ensuring safety. Above all else, the FDA's duty is to protect consumers from harmful products. Our second priority is maintaining product integrity: we want to ensure that dietary supplements contain the ingredients that they're labeled to contain, and nothing else, and that those products are consistently manufactured according to quality standards. Our third priority is informed decision-making. We want to foster an environment where consumers and health care professionals are able to make informed decisions before recommending, purchasing or using dietary supplements.^{3,5} ■

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Attention of: **NORMAN R. FARNSWORTH**
Company: **UNIVERSITY OF ILLINOIS - CHICAGO**
Address: **BOX 6998**
City/State/Zip: **CHICAGO, ILLINOIS 60680**

ARRO NO.	SAMPLE DESCRIPTION
131623	EXHIBIT 5
131624	EXHIBIT 8
131625	EXHIBIT 7
131626	EXHIBIT 8
131627	EXHIBIT 9

ANALYSIS	131623	131624	131625
ARSENIC	<1	3	4
BARIIUM	<1	<1	<1
CHROMIUM, TOTAL	<5	8	7
LEAD	13	12	47
MERCURY, ppb	287	1639	4827
SELENIUM	<5	<5	<5
SILVER	<1	<1	<1
TITANIUM	<3	<3	<3

CHICAGO SPECTRO SERVICE LABORATORY, INC.
Spectrographic and Chemical Analysts
Metallurgists
6245 S. OAK PARK AVE. - CHICAGO, ILL. 60638
AREA CODE 312-229-0099
FAX 229-0313

ANALYSIS REPORT FOR:
University of Illinois @ Chicago
Box 6998
Chicago, IL 60680
Attn: Norman R. Farnsworth, Ph.D. (MC877)

PURCHASE ORDER NO. _____
DATE: 2/24/90
Report Number: 3268

Sample Number: EXHIBIT 5
Lead _____
Mercury _____

Rec'd 4/25/90
net

DA Daily Analytical Laboratories
1621 W. Cassidette Drive Peoria, Illinois 61614
Tel. (309) 692-5252

Univ. of Illinois at Chicago
College of Pharmacy-Box 6998
Chicago, IL 60680
Attn: Dr. Norman R. Farnsworth
Work ID: Exhibit 5
P O # 1

Date Received: 04/04/90
Date of Report: 04/17/90
Work Order: 90-04-081
Job Number:
of Samples: 1

Test	Units	Exhibit 5
Silver, Total	mg/kg	<0.17
Arsenic, Total	mg/kg	<1.7
Barium, Total	mg/kg	3.4
Cadmium, Total	mg/kg	<0.08
Chromium, Total	mg/kg	0.13
Mercury, Total	mg/kg	<0.02
Lead, Total	mg/kg	43000
Selenium, Total	mg/kg	<1.7
Thallium, Total	mg/kg	<0.20
Metals Digest, nonsuspensious	mg/kg	04/04/90

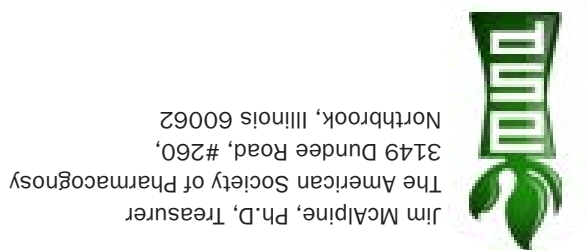
with D.C. Arc excitation
with Nitric Acid with Lead additions to

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LITERATURE CITED

- ¹ *American Botanical Council*, The ABC-AHP-NCNPR Botanical Adulterants Program is a long-term, multi-party coalition of herb quality and identity experts in university research groups, third-party analytical laboratories, government agencies, trade associations, and industry companies to examine the extent of suspected adulteration of herbal materials, particularly adulteration that is economically motivated. The intention is to confirm the extent of adulteration in the United States and global markets, determine which official or unofficial analytical methods are currently available to help detect the presence (or absence) of a suspected or known adulterant, and to provide comment and guidance on the relative strengths and/or weaknesses of differing analytical methods. The results of this investigation will be published in a series of reports (white papers) and will be made available on the ABC website. [American Botanical Council (ABC), the American Herbal Pharmacopoeia (AHP), and University of Mississippi's National Center for Natural Products Research (NCNPR)] **2016**. cms.herbalgram.org/BAP/About_Adulterants_Program.html
- ² *United States Food & Drug Administration*, FDA regulates both finished dietary supplement products and dietary ingredients. FDA regulates dietary supplements under a different set of regulations than those covering "conventional" foods and drug products. Under the Dietary Supplement Health and Education Act of 1994 (DSHEA), 16 November **2018**. www.fda.gov/Food/DietarySupplements/
- ³ Gottlieb, S. *FDA Statement: Statement from FDA Commissioner Scott Gottlieb, MD, on the agency's new efforts to strengthen regulation of dietary supplements by modernizing and reforming FDA's oversight*. February 11, **2019**. www.fda.gov/NewsEvents/Newsroom/PressAnnouncements/UCM631065.htm
- ⁴ *Norman R. Farnsworth Papers*, Lloyd Library & Museum, Boxes 16-21, **1990-1992**.
- ⁵ Gottlieb, S. submitted his resignation as FDA Commissioner. His tenure concluded March 31, **2019**. www.nytimes.com/2019/03/05/health/scott-gottlieb-resigns-fda.html





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Full membership is open to any scientist interested in the study of natural products.

Current membership dues and *Journal of Natural Products* subscription rates can be found at www.pharmacognosy.us.

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