Searching historical herbal texts for potential new drugs

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The medicinal uses of plants have been described in herbal texts for thousands of years.[1] This documentation is fortunate, as knowledge of traditional medicine is continually lost, and such knowledge is useful for the discovery of new drugs. Here we show that a treatment for dysentery, identified by "mining" a 400 year old Dutch text on herbal medicines, has antibacterial effects that are specific to the part of the plant described in the historical text.

The search

We used a novel semantic bioinformatics tool[2] to search the text of the *Ambonese Herbal*, which was written nearly 400 years ago by G E Rumphius, an employee of the Dutch East India Company. In this text he described the medicinal uses of plants on the island of Ambon in Indonesia. Our search identified the kernels of the atun tree (fig 1) as a potential source of an antibacterial or antimotility compound.[2 3] About the atun tree he wrote, "... these same kernels ... will halt all kinds of diarrhoea, but very suddenly, forcefully and powerfully, so that one should use them with care in dysentery cases, because that illness or affliction should not be halted too quickly: and some considered this medicament a great secret, and relied on it completely."[4]

We therefore organised an expedition to the Independent State of Samoa to collect botanical specimens, so that we could examine extracts of this plant for potential antibacterial properties. The leaves and fruit of the atun tree were collected (*Atuna racemosa* Raf, originally incorrectly identified as *Parinari glaberrima* Hassk), and voucher specimens were deposited in the National Tropical Botanical Gardens, Kalaheo, Hawaii, USA. To verify that we had collected the same plant as that described by Rumphius, we compared voucher specimens with original plates from the Rumphius text (courtesy of the Wangensteen Historical Library, University of Minnesota, Minneapolis, USA).

Laboratory confirmation of the antibacterial properties

We preserved the leaves and kernels of *A racemosa* collected in the Independent State of Samoa in 70% ethanol and prepared alcohol extracts according to standard protocol. Various concentrations of kernel extract and leaf extract were added to samples of two Gram positive bacteria (*Staphylococcus aureus* and *Enterococcus faecalis*) and two Gram negative bacteria (*Pseudomonas aeruginosa* and *Escherichia coli*) in a minimal inhibitory concentration assay. This assay was performed in cation adjusted Mueller-Hinton broth according to the standard protocol.[5]

Fig 1 Images from the original *Ambonese Herbal* written by Rumphius in the 1600s, which describes how kernels from the atun tree (*Atuna racemosa*) can be used to treat dysentery

The assay showed that the extracts from *A racemosa* (the atun tree described by Rumphius) had antibacterial activity that was specific for the Gram positive bacteria tested (table). The minimal inhibitory concentrations of the leaf extract were significantly different from those of the kernel extract in both of the Gram positive bacteria (*S aureus* 75-100 *v* 30-35 for the leaf and kernel; *E faecalis* 175-225 *v* 25-30; $P < 0.05$; Mann-Whitney rank sum test). The kernel had a stronger antibacterial effect, which corroborates Rumphius's reports of its use as an antibacterial agent. The minimal inhibitory concentration of kernel extracts for *E faecalis* (25-30 μg/ml) is similar to other antibacterial compounds, such as carbenicillin (16-64 μg/ml).

Minimal inhibitory concentrations (μg/ml) of extracts of the atun tree (*Atuna racemosa*)

	Gram positive bacteria		Gram negative bacteria	
Extract	*Staphylococcus aureus*	*Enterococcus faecalis*	*Pseudomonas aeruginosa*	*Escherichia coli*
Leaf	75-100	175-225	>1000	>1000
Kernel	30-35	25-30	>1000	>1000

Implications

Our findings show that potential drugs can be identified by searching historical herbal texts. Although we will never know the exact disorder that

was treated with the kernel of the atun tree, these kernels were described nearly 400 years ago as a treatment for symptoms that are treated today with modern antibiotics. The current literature has no descriptions of the use of the atun tree to treat any disease similar to dysentery.[6] By searching historical texts on herbal medicine, therefore, we have identified a potential new drug with antibacterial properties and have recovered lost knowledge of traditional medicine.

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Contributors and sources: EJB conceived the study, drafted the manuscript, and helped in its design and coordination. BAB helped design and coordinate the study. HEJ and GT helped in the botanical field work and creation of the voucher specimens. EMB translated the historical text and helped draft the manuscript. KLF assisted with the minimal inhibitory concentration assays. CLH helped in study design and statistical analyses. All authors read and approved the final manuscript. EJB is guarantor.

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Competing interests: Since this manuscript was accepted, Mayo Clinic has applied to patent the antibacterial properties of the atun tree. BAB and EJB are on the patent. The patent was only recently submitted so we do not know its status.

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The life of G E Rumphius

Georg Everhard Rumpf (fig 2)—who Latinised his name to "Rumphius" after he achieved renown as a naturalist—enlisted as a soldier in 1652 with the first multinational corporation of the modern era, the Dutch East India Company. In 1657 Rumphius was discharged from the military to the civilian branch of the company, and he started to collect, describe, and draw the plants for his monumental *Ambonese Herbal*.

It is amazing that Rumphius's work was ever published. In 1670 he went blind, and four years later his wife and daughter were killed in an earthquake. Thirteen years later, in 1687, a fire levelled the capital of Ambon's European quarter, and his manuscripts and the botanical illustrations that he had drawn himself were burnt. Yet Rumphius took this opportunity to begin the herbal again; he dictated a new and revised text in Dutch to scribes, and he commissioned draftsmen to do the illustrations.

Finally, in 1692, the first half of the *Ambonese Herbal* was finished, and the governor general at the time ordered the manuscript and the illustrations to be copied. This order was fortunate, as the original herbal text was destroyed on the way to Holland when the transport ship was sunk by a hostile French naval squadron. Again, upon notification of the disaster Rumphius did not surrender to despair. Rather, he took the opportunity to augment and correct the first half of his text while he completed the six volumes of the second half. Rumphius added new material (to make volume seven) only a few months before his death at the age of 74.

Fig 2 G E Rumphius, who spent most of his life documenting the medicinal uses of plants on the island of Ambon in Indonesia

Getting new drugs to market: how individuals could do this without leaving their desks

Joe Collier

At one time, all of the products that came out of a pharmaceutical company were researched, devised, developed, and manufactured within its four walls; the company offered the complete package. Now, although vast amounts of money, intellectual property, and management capacity remain within the imposing headquarters of the multinationals, much of the real work is done elsewhere—by start-up companies, contract houses, university departments, and public bodies.

One way or another, the work of big drug companies has changed, and inevitably this change, which will continue and probably accelerate, will lead to the collapse of the monolithic system and its replacement by smaller, leaner, and more nimble companies. As this process continues, virtual companies, run by individuals working from their desks in cyberspace, could well develop.

Developing drugs

The development of medicines for human use is a tricky business and one that is continually evolving as new technologies, such as genetic engineering, emerge. At its simplest, the process involves finding "new" molecules, purifying them, checking that they do what they are designed to do, showing that they work in

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