Food that shapes you: how diet can change your epigenome

You are what you eat – quite literally. Our diet can influence the tiny changes in our genome that underlie several diseases, including cancer and obesity.

By Cristina Florean

When you look at yourself in the mirror you may ask, 'How, given that all the cells in my body carry the same DNA, can my organs look so unlike and function so differently?' With the recent progress in epigenetics, we are beginning to understand. We now know that cells use their genetic material in different ways: genes are switched on and off, resulting in the astonishing level of differentiation within our bodies.

Image courtesy of Marcel Theisen / Wikimedia Commons

Fruit market in Spain

REVIEW

- **Biology**
- **Medicine**
- **Ages 14-18**

The article establishes a link between diet during pregnancy and changes in the expression of genes due to the mechanisms of histone acetylation (enhancing transcription) and methylation (reducing transcription). Using examples in humans, mice and honeybees, the article shows that the lack of certain nutrients can affect the development of traits in children. It also deals with dietary effects on epigenetics in adult life, listing a number of foods that are known to have a positive influence on health.

This article could be used as the basis for a discussion about healthy dietary choices compared with junk food, in order to increase students' awareness of the possible consequences of their eating behaviour.

The article could be used in a lesson reviewing some basic topics about gene expression.

Potential questions could include:

- What is the structure and function of histones?
- What are the main mechanisms of regulation of gene expression?
- How does genotype affect phenotype expression?
- How do environmental conditions (internal or external) influence gene expression?
- Diabetes is a good example of a disease that is linked to diet. Can you describe the causes of diabetes?

Monica Menesini, Liceo Scientifico Vallisneri Lucca, Italy

Image courtesy of McKay Savage / Wikimedia Commons

Green tea

Epigenetics describes the cellular processes that determine whether a certain gene will be transcribed and translated into its corresponding protein. The message can be conveyed through small and reversible chemical modifications to chromatin (figure 1). For example, the addition of acetyl groups (acetylation) to DNA scaffold proteins (histones) enhances transcription. In contrast, the addition of methyl groups (methylation) to some regulatory regions of the DNA itself reduces gene transcription. These modifications, together with other regulatory mechanisms, are particularly important during development – when the exact timing of gene activation is crucial to ensure accurate cellular differentiation – but continue to have an effect into adulthood.

Epigenetic modifications can occur in response to environmental stimuli, one of the most important of which is diet. The mechanisms by which diet affects epigenetics are not fully understood, but some clear examples are well known.

During the winter of 1944–1945, the Netherlands suffered a terrible famine as a result of the German

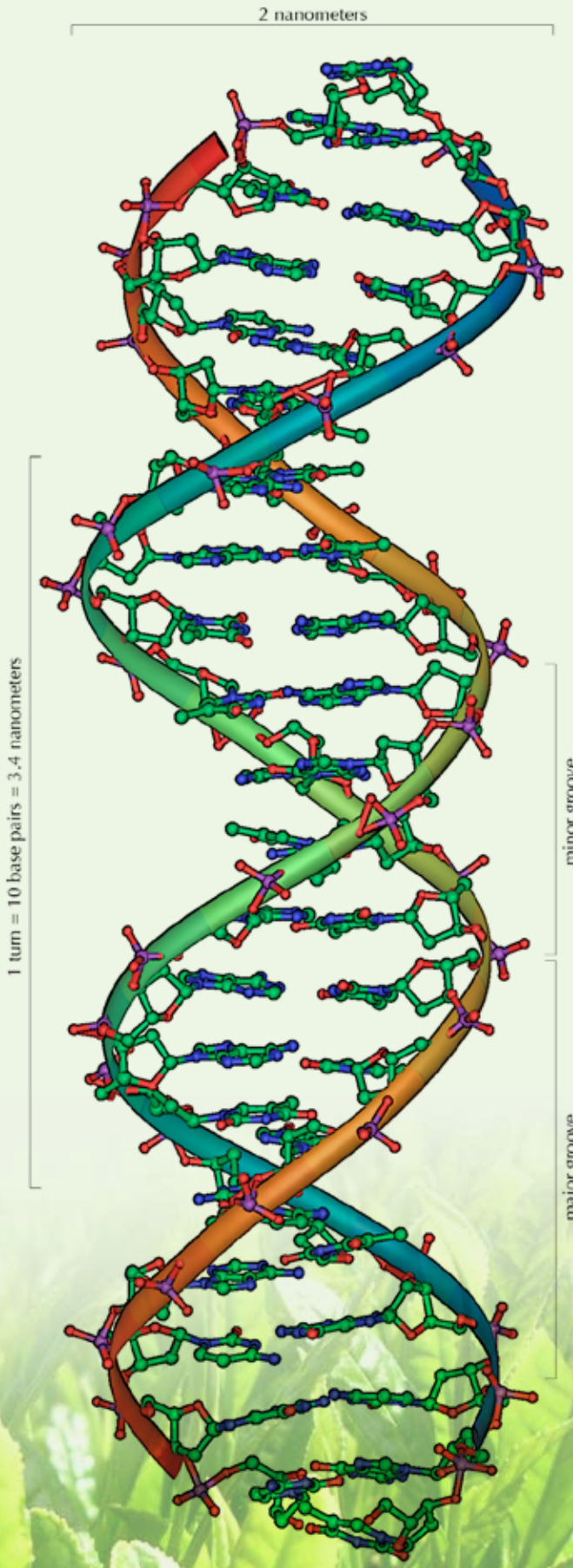

Image courtesy of mstroeck / Wikimedia Commons

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Green tea leaves from Japanese Yabukita tea plant.

Image courtesy of Cristina Florean

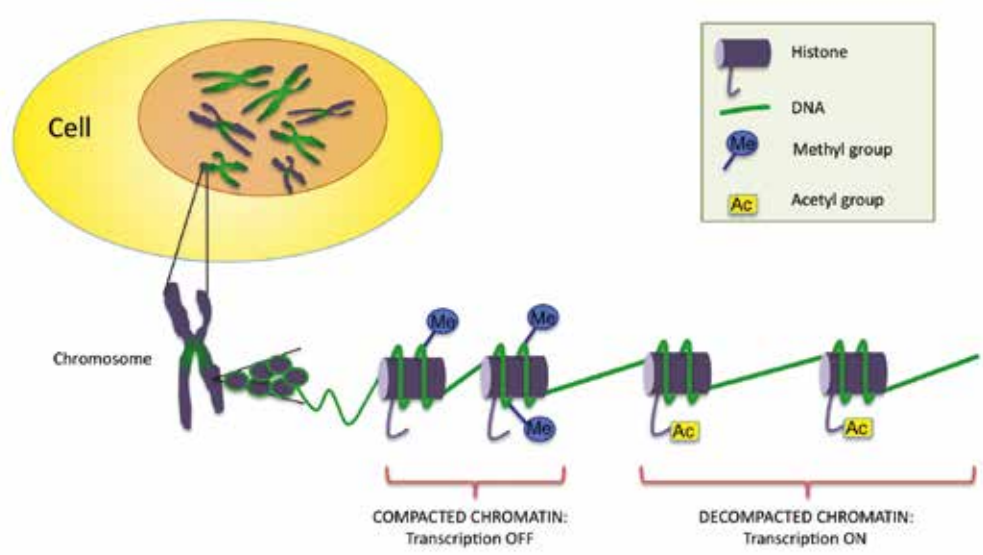


Figure 1: Epigenetic changes to the chromatin structure involve mainly histone acetylation – which enhances transcription – and DNA methylation, whereby methyl groups are covalently bound to cytosine, making the chromatin structure less accessible. These changes are reversible, allowing gene activity to be adapted to changing environmental conditions or signals.

occupation, and the population's nutritional intake dropped to fewer than 1000 calories per day. Women continued to conceive and give birth during these hard times, and these children are now adults in their sixties. Recent studies have revealed that these individuals – exposed to calorie restrictions while in their mother's uterus – have a higher rate of chronic conditions such as diabetes, cardiovascular disease and obesity than their siblings. The first months of pregnancy seem to have had the greatest effect on disease risk.

How can something that happened before you were even born influence your life as much as 60 years later? The answer appears to lie in the epigenetic adaptations made by the foetus in response to the limited supply of nutrients. The exact epigenetic alterations are still not clear, but it was discovered that people who were exposed to famine in utero have a lower degree of methylation of a gene implicated in insulin metabolism (the insulin-like growth factor II gene) than their unexposed siblings (Heijmans et al., 2008). This has some startling implications: although epigenetic changes are in theory reversible, useful changes that take place during embryonic development can nonetheless persist in adult life, even when they are no longer useful and could even be detrimental. Some of these changes may even persist through generations, affecting the grandchildren of the exposed women (Painter et al., 2008).

Image courtesy: Andy Olsen / NWHCM staff / Flickr

Many people in the world depend on international food aid to avoid famine and its many consequences on health and development, like here in Haiti.

The effects of early diet on epigenetics are also clearly visible among honeybees. What differentiates the sterile worker bees from the fertile queen is not genetics, but the diet that they follow as larvae (figure 2). Larvae designated to become queens are fed exclusively with royal jelly, a substance secreted by worker bees, which switches on the gene programme that results in the bee becoming fertile.

Another striking example of how nutrition influences epigenetics

Image courtesy of João Antonio Sarno Bonfim

Broccoli: a healthy diet during pregnancy can positively influence the health of the child after birth.

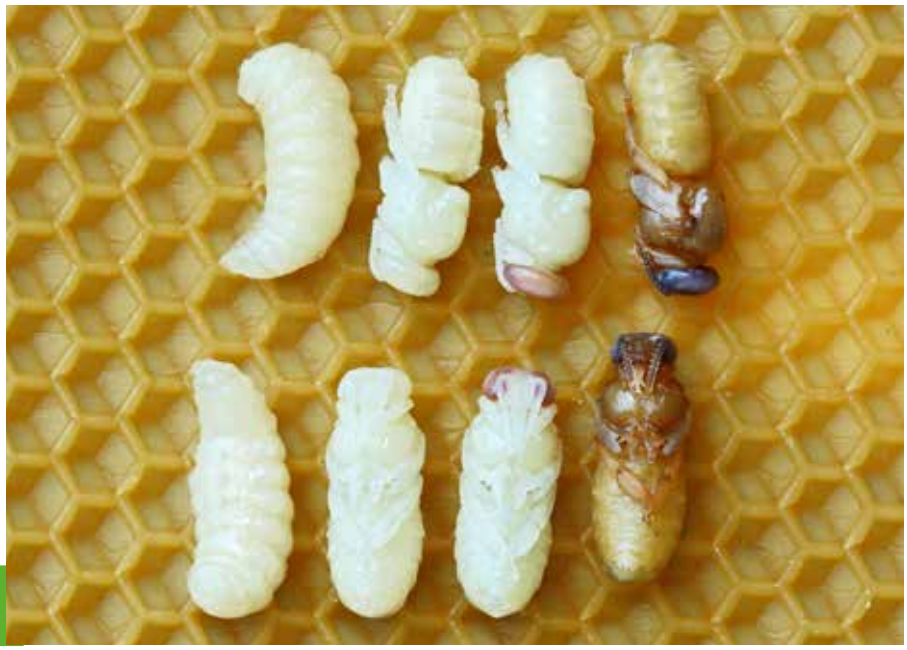
Image courtesy of W. Oelen / Wikimedia Commons

Folic acid

Image courtesy of Waugsberg / Wikimedia Commons

Figure 2: Two queen honeybee larvae floating in royal jelly in their queen cell. Queen larvae are fed exclusively with royal jelly, which triggers the development of the queen phenotype, allowing reproduction.

Image courtesy of Waugsberg / Wikimedia Commons



Larvae of honeybee workers at different stages of development

during development is found in mice. Individuals with an active agouti gene have a yellow coat and a propensity to become obese. This gene, however, can be switched off by DNA methylation. If a pregnant agouti mouse receives dietary supplements that can release methyl groups – such as folic acid or choline – the pups' agouti genes become methylated and thus inactive. These pups still carry the agouti gene but they lose the agouti phenotype: they have brown fur and no increased tendency towards obesity (figure 3). An insufficient uptake of folic acid is also implicated in developmental conditions in humans, such as spina bifida and other neural tube defects. To prevent such problems, folic acid supplements are widely recommended for pregnant women and for those hoping to conceive (see Hayes et al., 2009).

What about the dietary effect on epigenetics in adult life? Many components of food have the potential to cause epigenetic changes in humans. For example, broccoli and other cruciferous vegetables contain isothiocyanates, which are able to increase histone acetylation. Soya, on the other hand, is a source of the isoflavone genistein, which is thought to decrease DNA methylation in certain genes. Found in green tea, the polyphenol compound epigallocatechin-3-gallate has many biological activities, including the inhibition of DNA methylation. Curcumin, a compound found in turmeric (*Curcuma longa*), can have multiple effects on gene activation, because it inhibits DNA methylation but also modulates histone acetylation. Figure 4 shows further examples of epigenetically active molecules.

Image courtesy of Cristina Florean

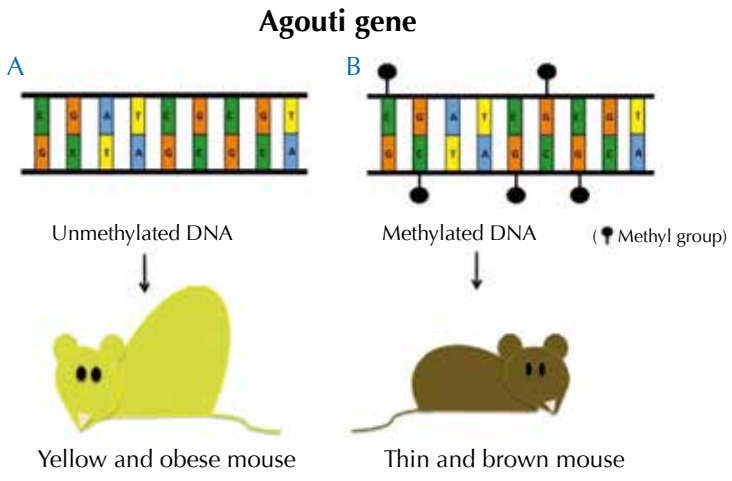


Figure 3: The agouti mouse model. The phenotype depends on the mother's diet during pregnancy. A: Normally, the agouti gene is associated with yellow fur and a tendency towards obesity. B: Mice born to a mother receiving dietary supplements of methyl donors, however, have a methylated and thus inactivated agouti gene, resulting in a thin, brown-fur phenotype.

Image courtesy of Cristina Florean, modified from Wikipedia Commons

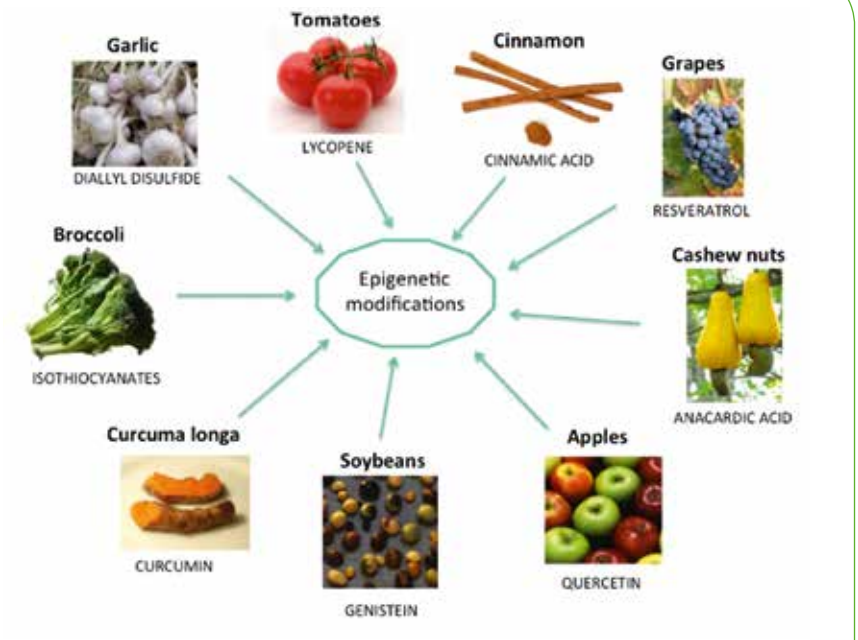


Figure 4: Some epigenetically active ingredients, each with an example of a dietary source.

Most of the data collected so far about these compounds come from in vitro experiments. The purified molecules were tested on cellular lines, and their effects on epigenetic targets were measured. It remains to be proved if eating the corresponding foods has the same detectable effect as has been seen in cellular models (Gerhauser, 2013).

Epidemiological studies, however, suggest that populations that consume large amounts of some of these foods appear to be less prone to certain diseases (Siddiqui et al., 2007). However, most of these compounds not only have epigenetic effects but also affect other biological functions. A food may contain many different biologically active molecules, making it difficult to draw a direct correlation between epigenetic activity and the overall effect on the body. Finally, all foods undergo many transformations in our digestive system, so it is not clear how much of the active compounds actually reach their molecular targets.

As a result of their far-reaching effects, epigenetic changes are involved in the development of many illnesses, including some cancers and neurological diseases. As cells become malignant, or cancerous, epigenetic modifications can deactivate *tumour suppressor genes*, which prevent excessive cell proliferation (Esteller, 2007). Because these epigenetic modifications are reversible, there is great interest in finding molecules – especially dietary sources – that might undo these damaging changes and prevent the development of the tumour.

We all know that a diet rich in fruit and vegetables is healthy for our everyday life, but it is becoming increasingly clear that it might be much more important than that, having significant implications for our long-term health and life expectancy.

Image courtesy of davitydave / Flickr

Purple Cauliflower

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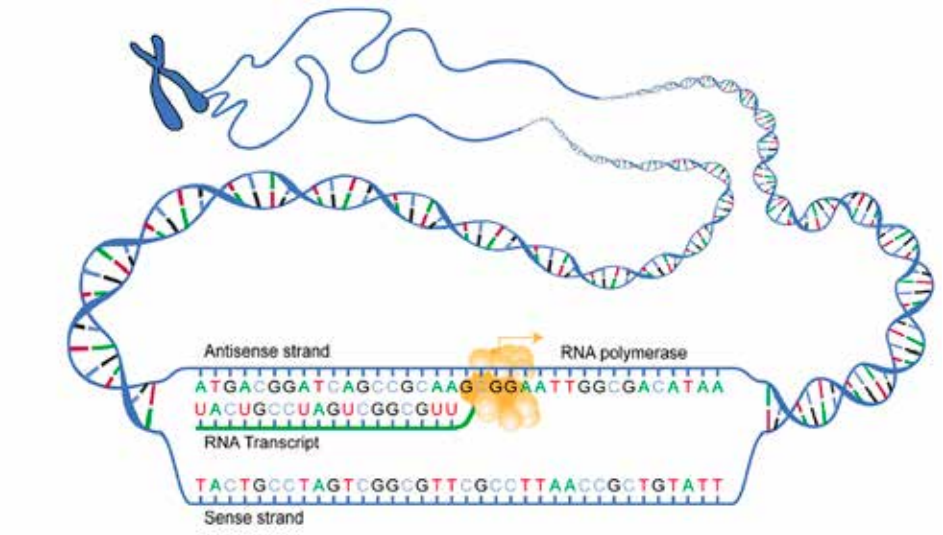

DNA Transcription

Resources

For a simple introduction to epigenetics, see:

McVittie B (2006) Epigentics. *Science in School* **2**: 62-64. www.scienceinschool.org/2006/issue2/epigenetics

To learn more about nutrition and epigenetics, see:

Link A et al. (2010) Cancer chemoprevention by dietary polyphenols: Promising role for epigenetics. *Biochemical Pharmacology* **80(12)**: 1771-1792. doi:10.1016/j.bcp.2010.06.036

The Learn Genetics website: http://learn.genetics.utah.edu/content/epigenetics/nutrition

For more information about the effect of the Dutch famine on adult life and gene methylation, see:

Roseboom TJ et al. (2001) Effects of prenatal exposure to the Dutch famine on adult disease in later life: an overview. *Molecular and Cellular Endocrinology* **185**: 93-8. doi:10.1016/S0303-7207(01)00721-3

The website of the University of Leiden: www.news.leiden.edu/news/dutch-hunger-winter.html

The website of the Dutch Famine Study: www.hongerwinter.nl/item.php?id=32&language=EN

Image courtesy of smith_cl9 / Flickr

We know a healthy diet should have lots of vegetables but we are only just realising how important vegetables are for our well being

For a fascinating and very readable explanation of some recent research into honeybee epigenetics, see:

Chittka A, Chittka L (2010) Epigenetics of royalty. *PLOS Biology* **8(11)**: e1000532. doi:10.1371/journal.pbio.1000532

PLOS Biology is an open-access journal, so this article is freely available online.

For more information about honeybee epigenetics: www.nature.com/scitable/spotlight/epigenetics-26097411

For a simple overview of epigenetics and the agouti gene in mice, see:

Adams J (2008) Obesity, epigenetics, and gene regulation. *Nature Education* **1(1)**. www.nature.com/scitable

To learn how hormone levels during pregnancy can affect the sex of the child, see:

Notman (2012) Intersex: falling outside the norm. *Science in School* **23**: 48-52. www.scienceinschool.org/2012/issue23/intersex

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Cristina Florean received her PhD in biomedical sciences from the universities of Padua and Bordeaux. During her doctorate studies she worked on Alzheimer's disease and drug screening optimisation. She spent one year at the University of Udine working on cancer and epigenetic enzymes, and now works in Luxembourg at the Laboratory of Molecular and Cellular Biology of Cancer *(Laboratoire de Biologie Moleculaire et Cellulaire du Cancer)* as a post-doctoral fellow. Her current research interests are natural compounds displaying epigenetic activity as anti-cancer drug candidates and epige netic events linked to carcinogenesis.

To learn how to use this code, see page 57.

Inspired by nature: modern drugs

Many naturally occurring compounds are useful in medicine – but they can be fabulously expensive to obtain from their natural sources. New scientific methods of synthesis and production are overcoming this problem.

By David Sucunza

The first patient ever treated with penicillin died one month later. The few grams of this antibiotic that were available at the beginning of 1941 were not sufficient to save the life of Albert Alexander, an English police officer who had been unlucky enough to get a bad infection from a scratch on his face. Although Alexander's urine was processed to recover some of the used penicillin, this still did not produce enough. After a few hopeful days, Dr Howard Florey and his team were forced to admit an irrefutable fact: drugs are not truly useful unless there is an adequate supply.

Fortunately, the immense amount of scientific research carried out during the Second World War quickly remedied this situation and

Image courtesy of Nobel Foundation / Wikimedia Commons

Sir Howard Walter Florey (24 September 1898 – 21 February 1968) was an Australian pharmacologist and pathologist who shared the Nobel Prize in Physiology or Medicine in 1945 with Sir Ernst Boris Chain and Sir Alexander Fleming for his role in the making of penicillin.

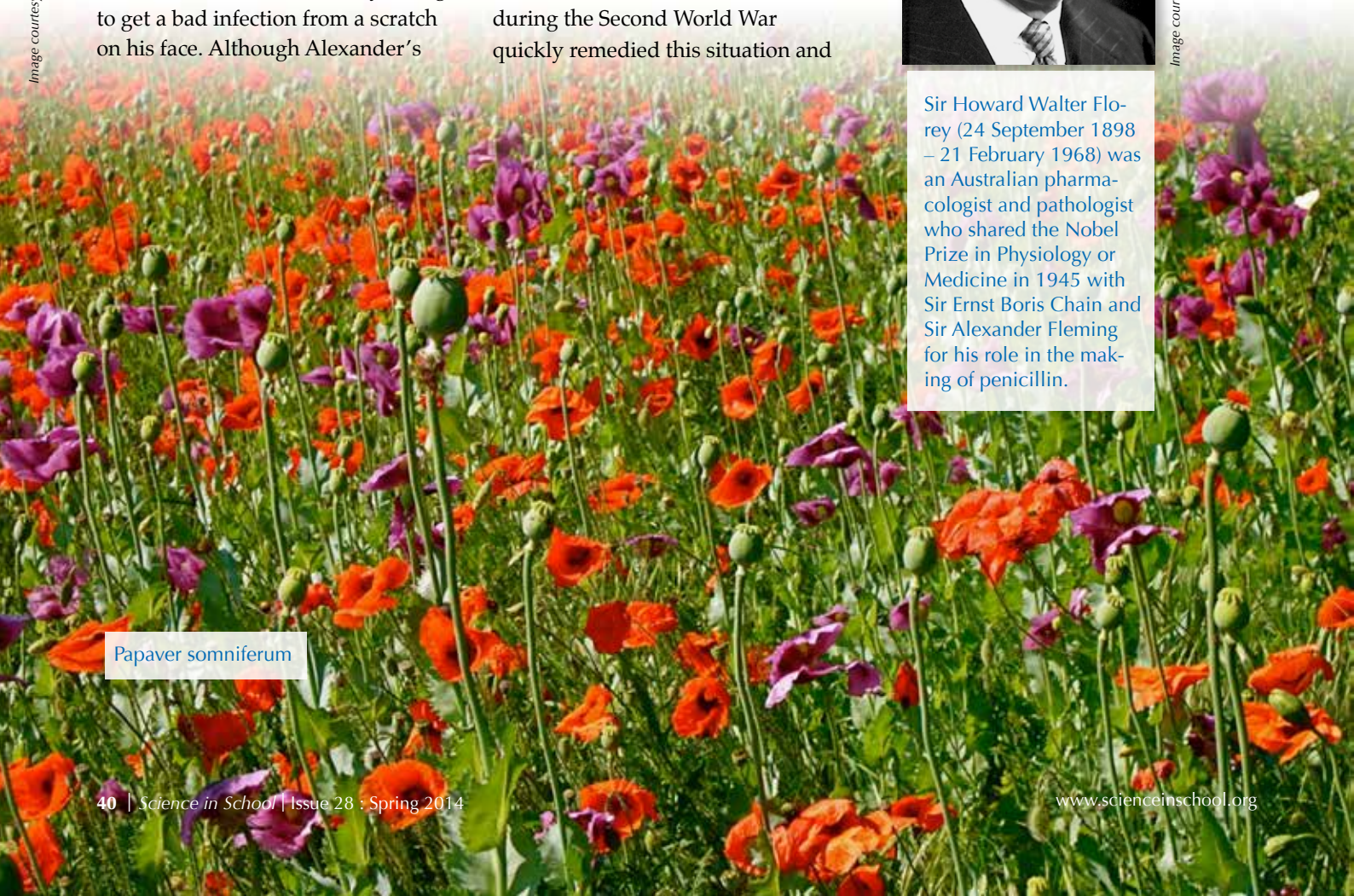


Image courtesy of Nuuuuuuuuuul / Flickr

Papaver somniferum

REVIEW

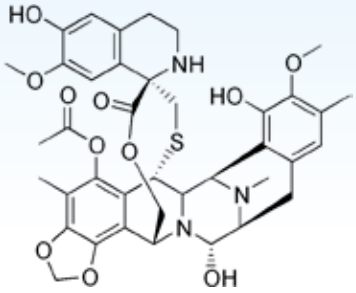
- Chemistry
- Biology
- Organic chemistry
- Ecology
- Conservation
- Ages 15+

The article could be used in chemistry or biology lessons, particularly when teaching organic chemistry, ecology or conservation. For example, it could be used as the basis of a discussion about why natural products have been and still are so important for human health, and whether drugs developed in laboratories are always better than the remedies used by our ancestors. It could also be used as a starting point for a discussion about how chemistry, although often seen as an environmental threat, can in fact help to protect the environment.

Suitable comprehension questions include:

- How have natural products helped to preserve human health in the past?
- How are natural products helping to preserve human health today?
- How can chemistry help to protect endangered species?
- Why is it not possible to obtain all natural products we need from their natural sources?

Mireia Güell Serra, Spain



Chemical structure of trabectedin

Image courtesy of Edgar181 / Wikimedia Commons

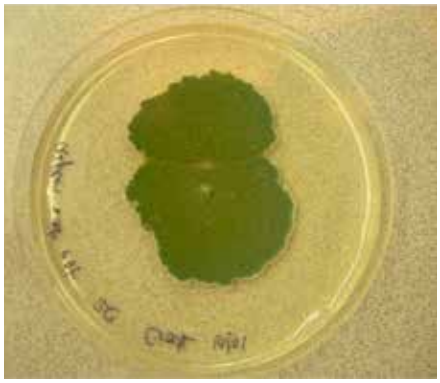


Image courtesy of Ninjatacoshell / Wikimedia Commons

Penicillium growing on a potato dextrose agar plate.

by 1943, an efficient method had been developed for cultivating large quantities of the *Penicillium* fungus and extracting the precious penicillin.

Drug development doesn't always work like this, however. There are many potentially useful natural products that, even today, can be obtained only in minimal amounts from their natural sources. Plants, fungi and sessile marine organisms are particularly promising sources: unable to flee their predators, many of them specialise in chemical defence and this can be exploited to our advantage. One example is bryostatin, which is produced by *Bugula neritina*, a species of tiny marine invertebrates called bryozoans. Bryostatin could prove to be an effective treatment for oesophageal cancer – if it weren't for the fact that it requires several tonnes of the animal to produce a few grams of the pure substance.

Natural compounds and modern medicines

People have used natural products medicinally since ancient times, and some four-fifths of the current world population still do so today. Although these products are traditionally used in the form of medicinal plants or fungi, improved versions of these drugs have more recently become available by isolating the active elements from the plant or fungal source. Since the first natural product (morphine from the opium poppy, *Papaver somniferum*) was isolated in 1804, the use of pure compounds rather than crude plant or fungal preparations soon spread throughout the Western world.

In fact, the application of scientific knowledge and methods has dramatically increased the number of drugs of natural origin that are now at our disposal. By 1990, about 80% of drugs approved in the USA were either natural products or inspired by them (see Li & Vederas, 2009). There are hundreds of examples: antibiotics such as penicillin or erythromycin, anti-tumour drugs such as trabectedin and vinblastine, immunosuppressants such as cyclosporine and rapamycin that facilitate organ transplants, analgesics such as morphine and codeine, and antimalarials such as quinine and artemisinin. These new drugs have become available via two main routes: clinical trials that have proved the effectiveness of some traditional remedies (for example, see Watt & Hayes, 2013); and the discovery of previously unknown, medicinally useful natural substances. Taken together, they have contributed to the success of modern medicine in extending our life expectancy from about 50 years at the beginning of the 20th century to the almost 80 years that it is today.

Among all the sciences, chemistry stands out as having contributed perhaps most to this achievement. Chemical synthesis has made it possible to provide many drugs of natural origin in the dosage required for therapeutic

Image courtesy of Frank Vincentz / Wikimedia Commons

Taxus baccata

Opium poppy (*Papaver somniferum*)

Image courtesy of Chixoy / Wikimedia Commons

Image courtesy of Chixoy / Wikimedia Commons

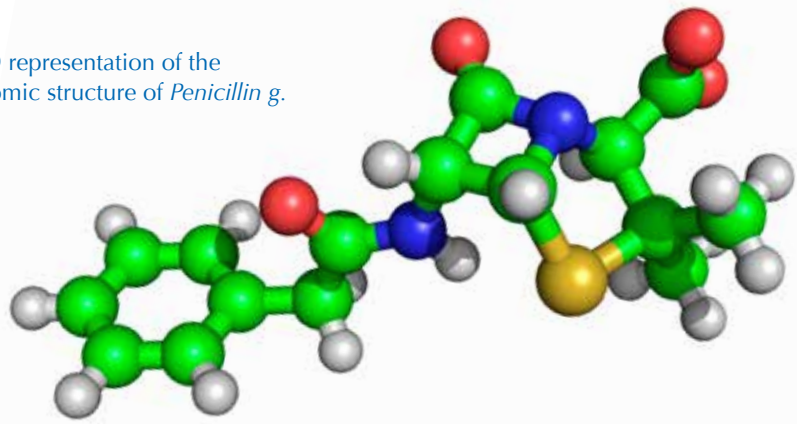
Flower of *Papaver somniferum*

use, despite the often very limited supply from their original sources. This is the case with galantamine, a compound produced by a rare flower from the Caucasus mountains that is proving to be one of the few substances capable of slowing the symptoms of Alzheimer's disease. Despite its complex structure, this natural product is now produced commercially by synthesis from simple chemicals – a method that is much more affordable than its extraction from the *Galanthus caucasicus* flower itself.

In addition, semi-synthetic processes – in which extracts from natural sources and chemical synthesis are combined – are now very common in the development of new drugs. One example of this is Taxol, used to treat patients with ovarian, breast and lung cancers or with advanced forms of Kaposi's sarcoma. Originally isolated from the bark of the Pacific yew tree (*Taxus brevifolia*), clinical use of this source alone would have led to the tree's extinction. As part of semi-synthetic drug development, natural products are categorised into families on the basis of their chemical structure, with members of the same family often sharing many similarities. This process revealed that the compound from the Pacific yew shared a similar structure with a much more accessible initial substance: 10-deacetylbaccatin III, found in the leaves of the European yew (*Taxus baccata*). A pathway to convert 10-deacetylbaccatin III to Taxol via just three simple chemical reactions was developed, providing an affordable and environmentally sustainable source of the drug (see box on page 43)[w1].

Taking this a step further, we now often use natural products as molecular models for potential new drugs, rather than as the actual source or compound to be synthesised. In this strategy, a variety of synthetic compounds, or analogues, are produced with chemical structures that are similar to the original compound but easier to synthesise. The efficacy of each is then investigated, to identify compounds that are sufficiently simple to synthesise on an industrial level, and which also preserve the medicinal properties of the natural substance (see box on page 44). This is being done in the case of bryostatin, and it is very probable that one of these analogues will form the biologically active part of a drug in the near future.

3D representation of the atomic structure of *Penicillin g.*



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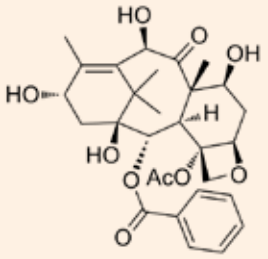
BACKGROUND

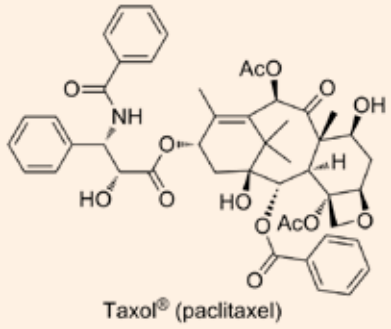
The semi-synthetic synthesis of Taxol

The extraction of Taxol (paclitaxel, figure 1) from the bark of the Pacific yew yields small amounts of the compound: 2000-2500 trees need to be felled to extract 1 kg of Taxol. The semi-synthetic synthesis of Taxol from 10-deacetylbaccatin III (figure 2), a related compound found in the foliage of the European yew, involves three simple chemical reactions (figure 3). Although 3000 kg of leaves from European yew are needed to obtain 1 kg of 10-deacetylbaccatin III, harvesting the leaves does not kill the trees[w1].



10-deacetylbaccatin III

Figure 2: The chemical structure of 10-deacetylbaccatin III. Note the similarity to the structure of Taxol.



Taxol® (paclitaxel)

Figure 1: The chemical structure of Taxol

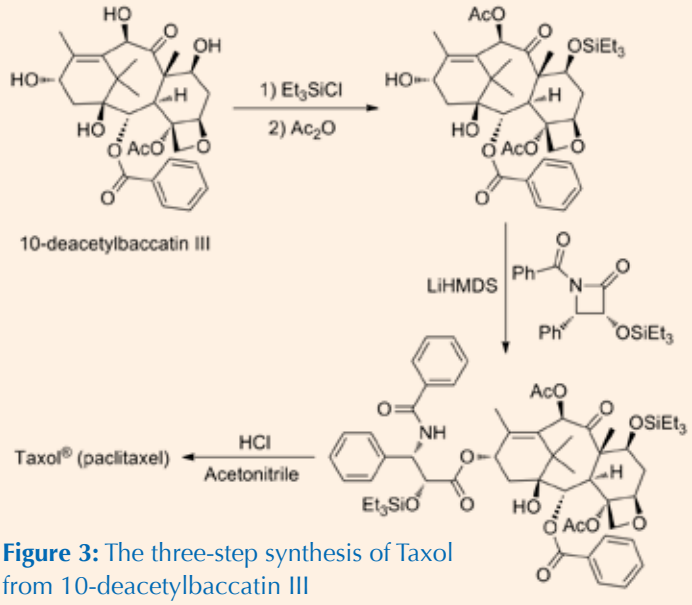


Figure 3: The three-step synthesis of Taxol from 10-deacetylbaccatin III

Images courtesy of David Sucunza

Bioreactors and beyond

Although chemical synthesis methods are often commercially competitive, another even more recent technique is gaining momentum: the artificial cultivation of cells from the natural product source. Growing cells in bioreactors to produce useful substances is now a widespread practice, and designing genetically modified organisms expressly for this purpose is swiftly becoming a more common reality (see box on page 44).

The science of natural medicines continues to evolve. In the search for possible drugs, there are still thousands of plants, marine animals and micro-organisms left to study. This search continues alongside the hunt for new ways of obtaining useful products on a larger scale. After two centuries of intense scientific development, nature is no longer our limit, although it does continue to be our main source of inspiration.

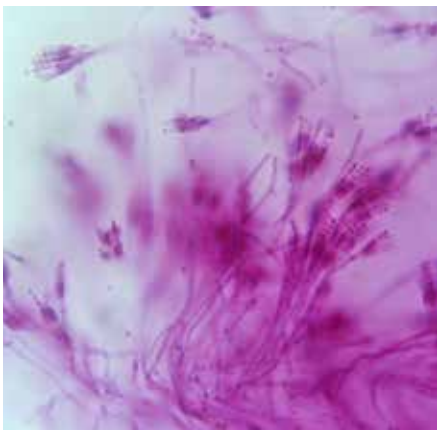


Image courtesy of Peter Halasz / Wikimedia Commons

Penicillium sp. (stained, under the microscope)

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BACKGROUND

Bioreactor synthesis to combat malaria

Malaria remains a major global health problem, killing more than half a million people each year. Currently, the most effective treatment is the natural product artemisinin, in combination with another drug (artemisinin combination treatments or ACTs). Artemisinin is produced by sweet wormwood (*Artemisia annua*) but this plant contains only a tiny fraction of artemisinin (between 0.001% and 0.8%). Supplies from sweet wormwood farms are limited, so ACTs cost US$1-2 per treatment course: too expensive for many patients in malaria-ridden countries.

In 2008, the pharmaceutical company Sanofi licensed a genetically modified yeast (*Saccharomyces cerevisiae*) to mass-produce artemisinic acid, a precursor of artemisinin, in bioreactors[w3, w4]. By 2012, using this method (figure 4), the company has already produced almost 39 tonnes of artemisinic acid, the first industrial-scale deployment of synthetic biology for drug production. The stock could be converted to at least 40 million treatments. Although these treatments are not yet cheaper than the standard ACTs, researchers hope to make the fermentation process more efficient – and less expensive – in the near future.

However, ACT resistance has already been detected in South-East Asia[w5]. As the antimalarial activity of artemisinin comes from its endoperoxide bridge (figure 5), several synthetic analogues based upon the 1,2,4-trioxolane pharmacophore, such as OZ439, are being studied as clinical development candidates.

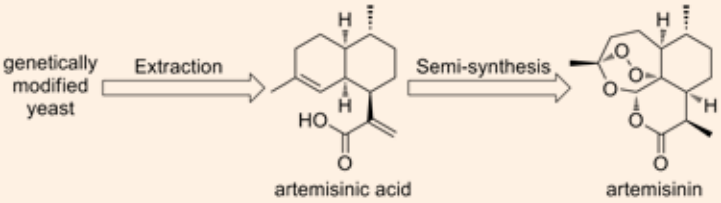

Figure 4: The extraction and semi-synthetic synthesis of artemisinin from genetically modified yeast

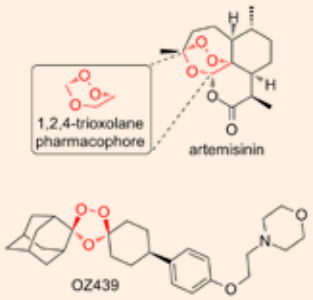

Figure 5: The structure of artemisinin and its synthetic analogue OZ439

Images courtesy of David Sucunza

tier? *Science* **325(5937)**: 161-165. doi: 10.1126/science.1168243

Watt S, Hayes E (2013) Monastic medicine: medieval herbalism meets modern science. *Science in School* **27**: 38-44 - www.scienceinschool.org/2013/issue27/monastic

Web references

w1 – *Research in Review*, published by Florida State University, tells the story of Taxol. See: www.rinr.fsu.edu/fall2002/taxol.html

w2 – The USA's National Library of Medicine's Drug Information Portal provides comprehensive details of Taxol (search for 'paclitaxel'). See: http://druginfo.nlm.nih.gov/drugportal

w3 – *Science Now* describes the synthesis of artemisinin (*Malaria drugmakers see the light*). Search http://news.sciencemag.org/sciencenow or use the direct link: http://tinyurl.com/ppy7ek4

w4 – The website of Path, an international non-profit organisation focusing on global health, describes the organisation's involvement in the development of semi-synthetic artemisinin. See: www.path.org/projects/artemisinin.php

w5 – Nature Education's Scitable website details the problems of ACT resistance (Artemisia annua*: a vital partner in the global fight against malaria*). Search www.nature.com/scitable or use the direct link: http://tinyurl.com/pp9ajw8

Resources

The Plant Cultures website provides easy-to-read information about the roles that plants play in people's

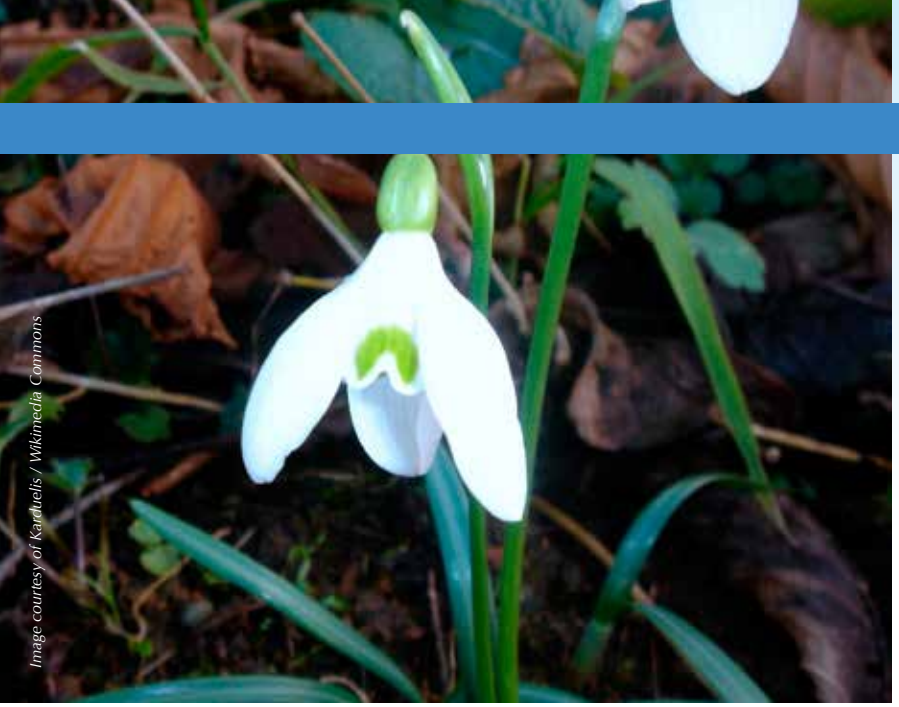

Image courtesy of Kanthuelis / Wikimedia Commons

Galanthus caucasicus – Galantamine is obtained synthetically or from its bulbs and flowers

Image courtesy of Walter Siegmund / Wikimedia Commons

Pacific Yew foliage

Image courtesy of Chixoy / Wikimedia Commons

Artemisia annua

lives all over the world. See: www.kew.org/plant-cultures

The Xplore Health website offers educational resources to teach about drug development. See: www.xplorehealth.eu/en/educators/how-are-drugs-developed

Based on one of the Xplore Health activities, one *Science in School* article explores the genetics of obesity:

McLusky S, Malagrida R, Valverde L (2013) The genetics of obesity: a lab activity. *Science in School* **26**: 25-30. www.scienceinschool.org/2013/issue26/obesity

Nicolaou KC, Montagnon T (2008) *Molecules that Changed the World*. Wiley-VCH: Weinheim, Germany

Raviña Rubira E (2011) *The Evolution of Drug Discovery: From Traditional Medicines to Modern Drugs*. Wiley-VCH: Weinheim, Germany

This book is freely available via Google Books. See: books.google.com

Le Couteur P, Burreson J (2003) *Napoleon's Buttons: How 17 Molecules Changed History*. Jeremy P. Tarcher/Putnam: New York, NY, USA

This book can be freely downloaded from Scribd. See: www.scribd.com/doc/65240357/Napoleon-s-Buttons

A summarised version is available on the Napoleon's Buttons website: http://napoleonsbuttons.blogspot.com.es

Stuart DC (2004) *Dangerous Garden: The Quest for Plants to Change Our Lives*. Harvard University Press: Cambridge, MA, USA

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