

Goat's rue – French lilac – Italian fitch – Spanish sainfoin: *gallega officinalis* and metformin: The Edinburgh connection

DR Hadden
Hon. Consultant Physician, Royal Victoria Hospital Belfast, Ireland

ABSTRACT The hypoglycaemic drug metformin is derived from galegine, which is found naturally in Goat's rue (*gallega officinalis*). This plant is spreading northwards in the UK.

KEYWORDS metformin

DECLARATION OF INTERESTS No conflict of interest to declare.

Correspondence to Professor DR Hadden, Royal Victoria Hospital, Grosvenor Road, Belfast, BT12 6BA Northern Ireland

tel. +44 (0)2890 667110

fax. +44 (0)2890 310111

e-mail
david.hadden@royalhospitals.n-i.nhs.uk

If you need a good reference book on eighteenth century botany, it is worth consulting a series of large volumes in the College library. When Sir John Hill produced his magnum opus on *The Vegetable System* in 26 volumes, between 1759 and 1775, he was partially financed by the then Earl of Bute, who subsequently (after Hill died penniless in 1775) presented them to the College, of which he was an Honorary Fellow. John Dallas, the College rare books librarian, identified Goat's Rue in Volume XXI, page 54, as a full page colour plate.

Although Linnaeus had admired the plates he also is said to have wept at the lack of science, nevertheless Hill's

brief description of Goat's Rue as *galegus officinalis* under genus 10 (leguminosae) still stands today.

'This is a perennial, native of Spain, and Italy; of Greece and Africa. A specious plant, of a yard high, that flowers in August. The stalk is juicy, and green: the leaves are of a fine fresh green: the flowers are purple; sometimes white.' (Figures 2A, 2B).

Goat's Rue, also known as French Lilac or Italian Fitch, is the natural source of galegine which is a precursor of metformin, now a very widely used oral antidiabetic agent. The story of its discovery, dismissal and rediscovery on

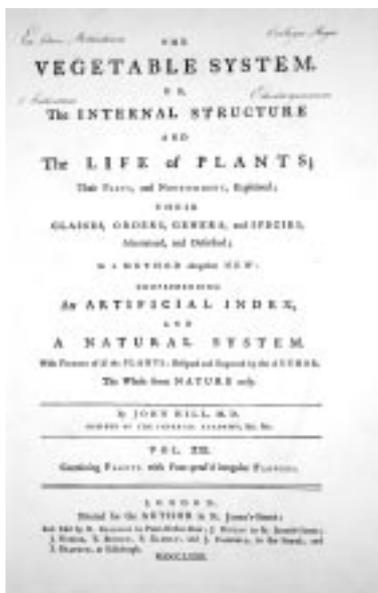


FIGURE 1A Title page of *The vegetable system*.¹³



FIGURE 1B Page 54 of Volume XXI, *The vegetable system*.¹³



FIGURE 2A *Galegus officinalis* growing in the Chelsea Physic Garden in London, June 2004. (Reproduced by kind permission.)



FIGURE 2B Goat's Rue. Plate 54, *The Vegetable System*.¹³ (Reproduced from the copy in the Library of the RCPE by kind permission.)

two occasions makes a useful comment on the problems of the pharmaceutical industry, with some Edinburgh connections.

METFORMIN – THE ROAD TO ACCEPTANCE

Pharmaceutically, metformin is an interesting substance, and at times those working on it might have diverted into the antimicrobial actions of the biguanides – germicidal, antiviral and antimalarial – the most widely used of these compounds is hexamethyl bischlorophenyl biguanide, or chlorhexidine, a useful germicide and disinfectant.¹ The history of the early researchers has been extensively reviewed under the auspices of the pharmaceutical firms Liplha and Merck, who now with Bristol-Myers Squibb continue to produce metformin for use as an oral hypoglycaemic agent.² This continues under the watchful scientific eye of Dr H Howlett, who served his time in the ethical pharmaceutical industry with metformin, and after many years of involvement in clinical research studies was elected a Fellow of the Royal College of Physicians of Edinburgh in 2002.

Metformin first became available in the UK National Formulary in 1958, and the earliest clinical reports of its effectiveness in maturity-onset (now Type 2) diabetes date to that time – including one in French from the Royal Victoria Hospital, Belfast.³ The small French company, Aron, which marketed metformin under an even smaller UK subsidiary, Rona, was at a commercial disadvantage, and I well remember as a junior doctor the difference in the sales pitch between that of the large international company with pharmaceutical representatives who supported phenformin (another

biguanide), and the friendly approach of the only representative of the Rona organisation, who was also the managing director of the UK company. Perhaps for that reason, metformin found an understanding reception in Belfast and in Edinburgh, and our clinical experience gradually supported the rather meagre scientific background to the drug. (One suggested explanation of its action was biophysical rather than biochemical – it was a mild cell poison that made holes in the cell membrane and allowed glucose to enter without the need for insulin!) In the south of England it was not widely used, and it was never marketed in the USA at that time. A number of clinical studies by Dr B Clarke and Dr L Duncan at the Royal Infirmary of Edinburgh, and others in Belfast, demonstrated the efficacy and safety of metformin over the next decade.^{4, 5, 6} Professor I Campbell and Dr H Howlett more recently produced an important meta-analysis at a time when the use of metformin in Type 2 diabetes was becoming less popular and other types of drugs were being widely promoted.⁷

All this has changed in the past decade since the outcome of the UK Prospective Diabetes Study, where metformin had been included as a primary randomisation (although only for the obese sub-group).⁸ Metformin (also known by its trade name Glucophage) is now the most widely prescribed oral antidiabetic medication throughout the world, with a new understanding of its mode of action as an insulin sensitiser.

GOAT'S RUE IN THE UK

Traditional plant medicines have been recorded as treatments for diabetes since the Ebers papyrus in 1550

BC, which recommended a high fibre diet of wheat grains and ochre.⁹ Goat's Rue, as *galega officinalis* is known in the UK, is now becoming increasingly common as a wild flower in this country. Look out for this member of the pea family (leguminosae) 'a medium-tall, erect, often hairless perennial to 1.5 m. Flowers pinkish-lilac or white, 12–15 mm with five bristle-like sepal-teeth, in stalked spikes June–September. Pods rounded, short to 3 cm. Increasingly naturalised in waste, usually grassy, places'.¹⁰ The new atlas of 10 km squares of botanical distribution in the UK indicates that the spread of this species is very recent. Although introduced into cultivation in England in 1568, and first recorded in the wild in 1640, it was not mapped at all in 1962. Now, it is found in 75% of the 10 km squares in London, and is widely distributed in the home counties. It has even been officially recorded in Edinburgh, but not yet in Ireland (see figure 3).¹¹ So watch out for this tall lilac pea-like flower on your walks: if you or your patient mislay your metformin tablets, remember the galegine-containing seeds of Goat's Rue – but beware of the side effects, which might even be hypoglycaemic!

The final irony has been pointed out by Clifford Bailey in Birmingham,¹² that *galega officinalis* is classed as a class A Federal Noxious Weed in 35 states of the USA, and appears on the database of poisonous plants, recalling the observation of Paracelsus (1493–1541) that 'the right dose differentiates a poison from a useful medicine'.

ACKNOWLEDGEMENTS

I am grateful to the staff of the Chelsea Physic Garden in London for their interest and enthusiasm in cultivating this plant and for the photograph taken in June 2004.

REFERENCES

- Bell PM, Hadden DR. Metformin. *Endocrinol Metab Clin North Am*. 1997; **26**(3):523–537.
- Pasik C (editor). *Glucophage (1957–1997): Serving diabetology for 40 years*. Paris: Media Memoire; 1997;78.
- Allen GE, Montgomery DAD, Weaver JA. Dimethyl biguanidine dans le traitement du diabete sucre. *Rev Francaise d'Endocrinol Clin* 1960; **2**:1.
- Clarke BF, Duncan LJP. Comparison of chlorpropamide and metformin treatment on weight and blood glucose response of uncontrolled obese diabetics. *Lancet* 1968; **1**:123.
- Clarke B, Campbell I. Comparison of metformin and chlorpropamide in non-obese, maturity-onset diabetics uncontrolled by diet. *BMJ* 1977; **2**:1576–8.
- Rigas AN, Bittles AH, Hadden DR, Montgomery DAD. Circadian variation of glucose, insulin and free fatty acids during long-term use of oral hypoglycaemic agents in diabetes mellitus. *BMJ* 1968;



FIGURE 3 Distribution of *galega officinalis* in the British Isles (2002), from the New Atlas 10 km Census Dataset.¹¹

John Dallas, rare books librarian at the College kindly provided the reproduction from the large volumes of Sir John Hill (1772). Clifford Bailey has done more than most to reveal the interesting botanical background to this plant, originally prized in the English garden but now becoming a weed. It has invaded Scotland, and I await its first sighting across the Irish sea.

- 4:25–8.
- Campbell I, Howlett H. Worldwide experience of metformin as an effective glucose-lowering agent: a meta-analysis. *Diabetes Metab Rev* 1995; **11**:557–62.
- UKPDS group. Effects of intensive blood glucose control with metformin on complications in overweight patients with type 2 diabetes. *The Lancet* 1998; **352**:854–65.
- Bailey CJ, Day C. Traditional plant medicines as treatments for diabetes. *Diabetes Care* 1989; **12**:553–61.
- Blamey M, Fitter R, Fitter A. *Wild Flowers of Britain and Ireland*. London: A & C Black; 2003;154.
- Preston CD, Pearman DA, Dures TD. *New Atlas of the British and Irish Flora*. Oxford: Oxford University Press 2002;CD-ROM.
- Bailey CJ, Day C. Metformin: its botanical background. *Practical Diabetes International* 2004; **21**:115–17.
- Hill J. *The Vegetable System, or the Internal Structure and the Life of Plants*. 1772;Volume XXI.

4. Hadden DR. Goat's rue " French lilac " Italian fitch " Spanish sainfoin: gallega officinalis and metformin: The Edinburgh connection. J R Coll Physicians Edinb 2005, 35, 258-60. 5. Galega officinalis. https://en.wikipedia.org/wiki/Galega_officinalis accessed 27 February 2017. 6. Glucophage 1957-1997: serving diabetology for 40 years. Pasik C (Ed). Galega officinalis. Common name: Goat's Rue, French Lilac, Italian Fitch, Professor-weed, x'xœx'x" x"xqx"xTMx^a. Family: Fabaceae (Peaheqxqx"xqx"x xTMxTMx (x\$x~x xTMx^axTMxTMx)). Locations. 1: Europe: Central european deciduous foresthexxTMx"xqxqx": xTMxçx" xŽxŽx•x-x' x©xTMx" x©xœ xŽx"x>x- xxTMx"xqxqx" (EST3) â€¢ Accession: 2017-0474/2 â€¢ Provenance: Garden. Area. Individual. Share. Hadden DR (2005) Goat's rue"French lilac " Italian fitch " Spanish sainfoin: gallega officinalis and metformin: the Edinburgh connection. J R Coll Physicians Edinb 35:258â€"260. CAS PubMed Google Scholar. 5. Galega officinalis. Available from https://en.wikipedia.org/wiki/Galega_officinalis. Accessed 27 Feb 2017.