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The Gravity of Weight

Metformin: Rejoicing in the Lost Lilac

The unlikely journey of a medieval herbal remedy.

Posted April 27, 2022

KEY POINTS

- **From French lilac, metformin has been known for centuries to lower blood glucose levels, but only became FDA-approved in the mid-1990s.**
- **Metformin is one of the most commonly prescribed medications worldwide as a first-line pharmacological treatment for Type II diabetes.**
- **Recent research on metformin has gone far beyond its glucose-lowering effects and now includes studies on aging, cancer, and the immune system.**

A mass of Goat's Rue (also known as French Lilac), the medicinal herb that led to metformin.

Source: Caroline Eastwood/Alamy Stock Photo. Used with permission.

French lilac is a perennial plant with white, blue, or purple flowers that was used medicinally in medieval Europe to treat the plague, worms, snake bites, fever, and St. Vitus dance, among many other conditions. Its Latin name is *Galega officinalis,* but other common names are goat's rue and professor-weed. References to its pharmacological effects appear in an herbal compendium in the 17th century (Soukas et al, 2019) and as early as the 18th century, at least one source recommended French lilac to treat excessive thirst and frequent urination, symptoms we now associate with Type I diabetes (Bailey, 2017; Bailey and Day, 2004; Witters, 2001).

Over the centuries, over 400 plants have been tried to eliminate the symptoms of diabetes, a disease described at least since Papyrus recordings in ancient Egypt, though only a few of these plants have received any scientific scrutiny (Bailey and Day, 1989).

Chemists in the 19th century, were able to isolate and manipulate the active ingredient in French lilac, guanidine, and by the early 20th century, researchers knew that guanidine could lower glucose levels in animals. By the 1920s and 30s, derivatives of guanidine were used to treat diabetes but these were ultimately discontinued due to their toxicity and the increased availability of insulin. The information was "disregarded and forgotten" (Bailey, 2017).

How then did French lilac, still classified as a "noxious weed" by the USDA (Lasseigne, 1981), and a derivative of its active ingredient, become the fourth-most-commonly prescribed drug in the U.S., with over 78 million prescriptions written each year (DrugReport, 2021) and on the World Health Organization's list of "essential medications" (Bailey, 2017; WHO, 2021)?

"The awesome voyage of metformin from herbal beginnings to respected therapeutic agent has been turbulent. It was discovered, forgotten, rediscovered, repurposed, rejected, rescued, exonerated..." (Bailey, 2017).

Ultimately, a French researcher, Jean Sterne, began experimenting in the mid-1950s with what he called "Glucophage"—"glucose-eater"—and published his findings in an obscure Moroccan medical journal (Bailey 2017; Justice et al, 2021). The first reference to the word "metformin" (a contraction of methyl and phenformin) occurred in the early 1960s (*Oxford English Dictionary*; Ferguson et al, 1961).

The other guanidine derivatives, as mentioned, similar to metformin (and subsequently removed from the market) produced a toxic and potentially deadly metabolic condition: lactic acidosis. As a result, metformin developed an unjustified "tarnished" reputation (Bailey and Turner, 1996) and only gained FDA approval in the *mid-1990s* (Bailey, 2017; Justice et al).

Metformin, a generic, relatively inexpensive medication, though, has proven to have a remarkable safety and tolerability profile and has become the first-line pharmacological treatment for Type II diabetes (Yerevanian and Soukas, 2019.) What do we know of its effects?

Diabetes insulin samples, 1920s. Once insulin was discovered, metformin was "forgotten." Science Museum, London.

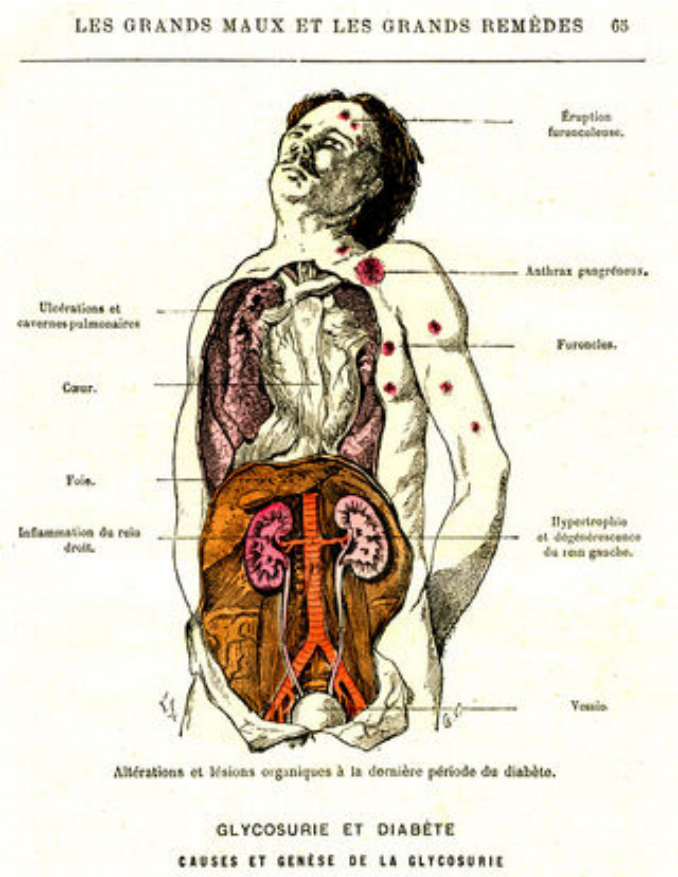
Source: SSPL/UIG/Bridgeman Images. Used with permission.

Effects of metformin

Metformin improves glycemic control in patients with type II diabetes by lowering blood glucose levels, mostly by inhibiting the new production of glucose (gluconeogenesis) in the liver and without causing hypoglycemia. The mechanism responsible, though, is "still hotly debated" despite years of research (LaMoia and Shulman, 2021). Metformin may induce the glucose transporter protein GLUT4 (Herman et al, 2022) as well as may activate AMP-activated protein kinase (AMPK), an important regulator of lipid and glucose metabolism (Zhou et al, 2001). Further, it may affect mitochondrial activity (LaMoia and Shulman; Soukas et al, 2019).

With metformin, glucose and insulin levels decrease, and insulin sensitivity increases (Coll et al, 2020), which is particularly important for those with *insulin resistance,* a condition typical of those with Type II diabetes where insulin levels are high but ineffective. Metformin can even prevent or even possibly delay the onset of Type II diabetes in those who are at high risk (Coll et al.) and those with Type II diabetes who had required insulin may no longer need it or require a much lower dose (Bailey, 2017).

The most important side effects are gastrointestinal, such as nausea, abdominal discomfort, and diarrhea. Titrating the dose slowly as well as taking metformin with food are effective, but about 5% cannot tolerate any dose level (Bailey and Turner). Because of concerns about the rare possibility of lactic acidosis, metformin is not recommended in those with serious renal or hepatic disease. Further, metformin can impair the absorption of vitamin B12 and folic acid (Bailey and Turner).



Diabetes: alterations and organic lesions. Engraving by Jules Rengade, Paris, 1889.

Source: Bridgeman images. Used with permission.

Significantly, unlike other medications used for glucose control, such as sulfonylureas or even insulin, metformin does not cause weight gain. In fact, it may lead to a decrease in weight in many patients, usually by suppressing appetite and decreasing caloric intake (Yerevanian and Soukas). The mechanisms remain unknown (Yerevanian and Soukas) but some researchers speculate that metformin increases levels of GDF15, a peptide hormone that suppresses food intake (Coll et al). Changes in the microbiome may also be involved (Herman et al, 2022; Yerevanian and Soukas; Soukas et al, 2019).

Research on the causal relationship between metformin and weight loss, though, can be compromised if investigators don't include a control group or factor in the possibility of regression to the mean, as noted by Allison and colleagues (Hannon et al, 2019).

Beyond metformin's impact on glucose

In recent years, research on metformin has gone far beyond its impact on glucose. Studies are ongoing on its effect on aging, lifespan, cancer, and the immune system.

Most recently, reports have surfaced about the effects of metformin on sperm production in the months prior to conception and a possible increase in genital defects in male offspring, but researchers call for further study (Wensink et al, 2022; Wadman, 2022; Buck Louis, 2022). I will discuss these topics, including the use of metformin during pregnancy, in subsequent blogs.

Note: Special thanks to Ms. Arlene Shaner, MA, MLS, Historical Collections Librarian at the New York Academy of Medicine, for tracking down two obscure French references about early research on metformin and Robert B. MacArthur, Pharm D, MS, Pharmacy Director, Rockefeller University, for information on metformin prescriptions.

French trading card advertising Brusson Jeune's gluten bread as a cure for diabetes. French School, 19th century.

Source: Look and Learn/Barbara Loe Collection/Bridgeman Images. Used with permission.

English scholars among you will know that my title comes from part VI of T.S. Eliot's poem *Ash Wednesday.*

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