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How To Make Viagra

by Enrico Uva

Science 2.0 / August 28, 2011

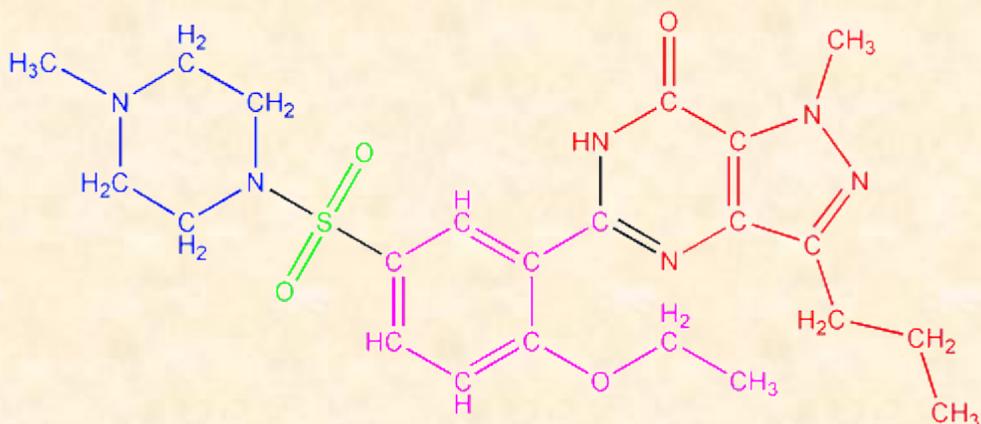
Wizards exist in real life beyond the films and books of Harry Potter. They cook willow bark extract in car battery acid and wood alcohol and convert it into a pleasant-smelling component of candy or of a rubbing compound. In their glassware, petroleum products turn into life-saving medicines.

The vastly underrated wizards that we are referring to are organic chemists who specialize in synthesis. In their quest to create new combinations of atoms or in their attempts to find ways of producing natural compounds, they craft new reactions, constantly combining creativity with the scientific method. Even if somehow we were not interested in creating organic compounds (and in doing so, saying goodbye to pharmaceuticals, plastics, fabrics, oils, and perfumes), synthesis would still be needed to verify chemical structure.

Here's why. When chemists isolate a new compound, they determine its structure using various spectroscopic techniques: mass spectroscopy which identifies the unknown's molecular formula; infrared spectroscopy which identifies key functional groups; and nuclear magnetic resonance which reveals the local chemical environment of each atom within a molecule. From the spectral analysis, a model is constructed. Then a compound is synthesized step-by-step to test the validity of the proposed structure. If the synthesized product and unknown natural product have identical physical, chemical, and spectral properties, the model is in all likelihood valid.

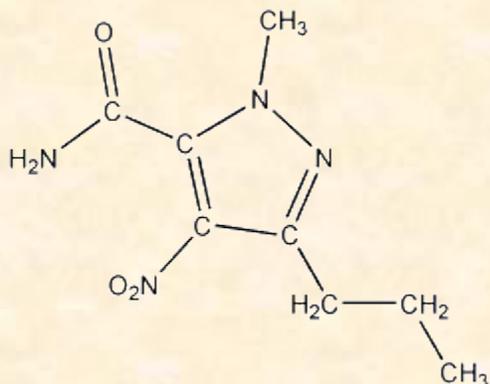
But just exactly how do organic chemists assemble exotic molecules or carbon-copies of evolutionary products? As an example, let's use sildenafil, the key part of sildenafil citrate also known as Viagra. Nitric oxide(NO) is released from the nerve endings of a sexually-stimulated male, leading to the production of cyclic guanosine monophosphate(cGMP) which relaxes penis vessels, allowing blood flow to increase. But enzymes eventually break down the messenger, allowing some blood to flow out of the penis. Viagra (molecular impostors of cGMP) relieve men with erectile dysfunction by competitively binding to the enzyme phosphodiesterase type 5 which then cannot attack its intended prey. The end result is a prolonged erection in the presence of sexual stimulation.

The following is the structure of sildenafil:



The parts I've colored are essentially its 4 basic building blocks. Of course, without knowing the chemistry of the components' precursors, the thermodynamic stability of in-between products, and anticipation of side reactions, they will never come together to give us our target molecule. Even then, because specific conditions such as pH, temperature, and solvent-type are such important factors that it takes a lot of tweaking, luck and lateral thinking to come up with a sequence of reactions that will yield a respectable amount of final product.

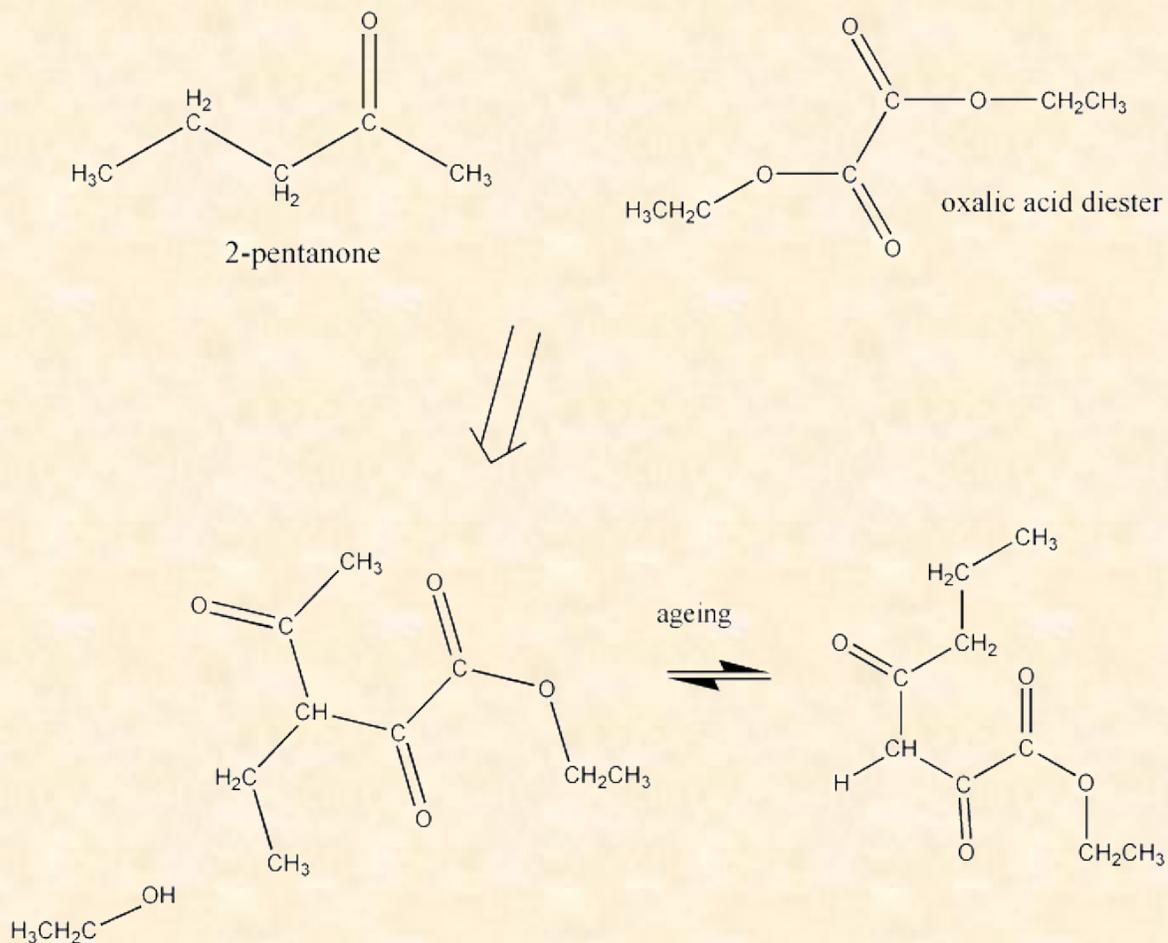
In the synthesis that I've chosen to highlight (it's not the only viable method), there are 9 steps. If each step was only 90% efficient, then the overall process would only have a $0.909 = 39\%$ yield. 61 percent of the original mass of reactants would be wasted. As Peter J Dunn outlines in a few of his review papers, the commercial synthesis of Viagra is highly efficient and also clean environmentally.



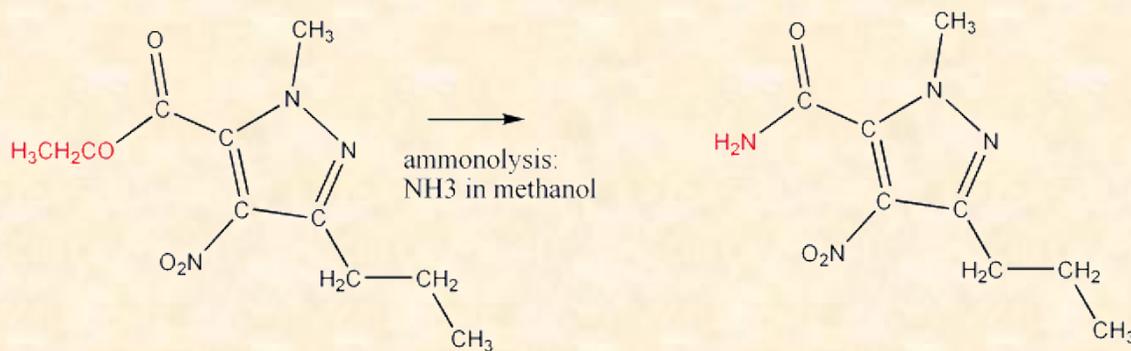
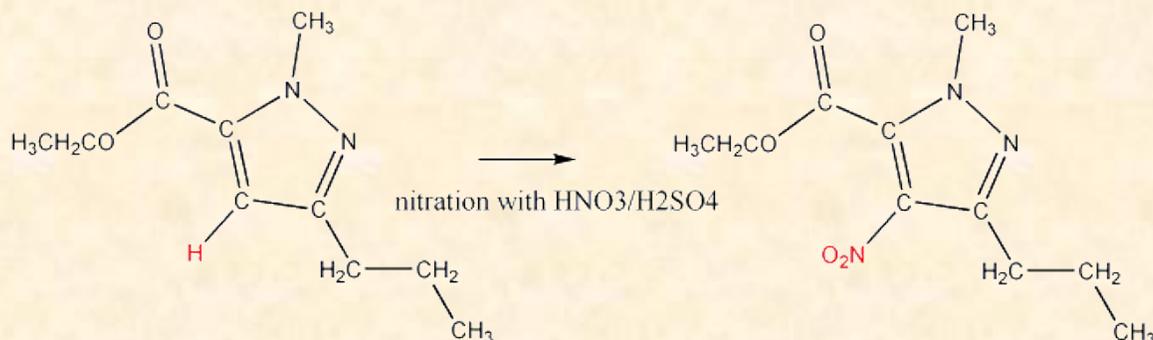
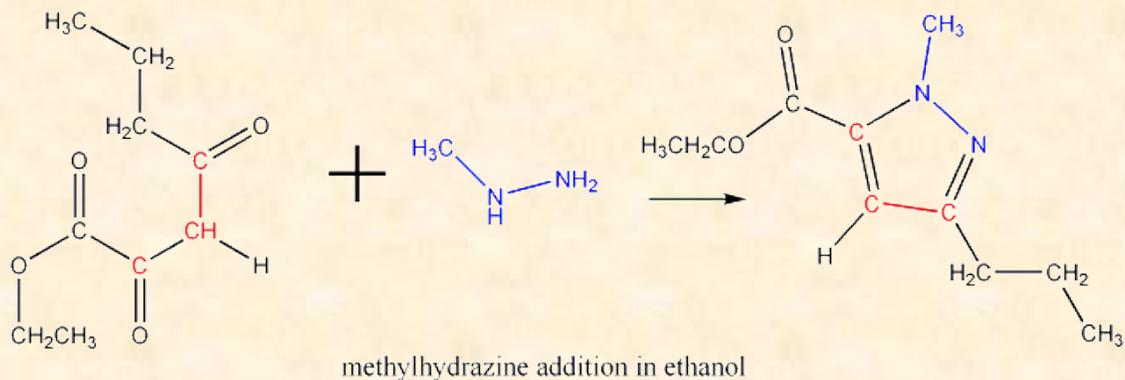
The **red** part of the molecule that features a pentagon-shape with 2 nitrogen atoms and 2 additional nitrogen atoms is a pyrazole-derivative. Before fusing into the final Viagra structure, the reactant (dubbed pyrazole 4) is shown to the left. It is so key to the overall production of Viagra that several pharmaceutical companies have patented unique ways of producing the compound.

In one method, a colorless and rare food additive with a smell like that of nail-polish remover (thanks to alkaline conditions) attacks the electron loving-site of the double-bonded carbon in oxalic acid diester. (Also known as ethyl oxalate, it's sold to academics for \$58/kg.)

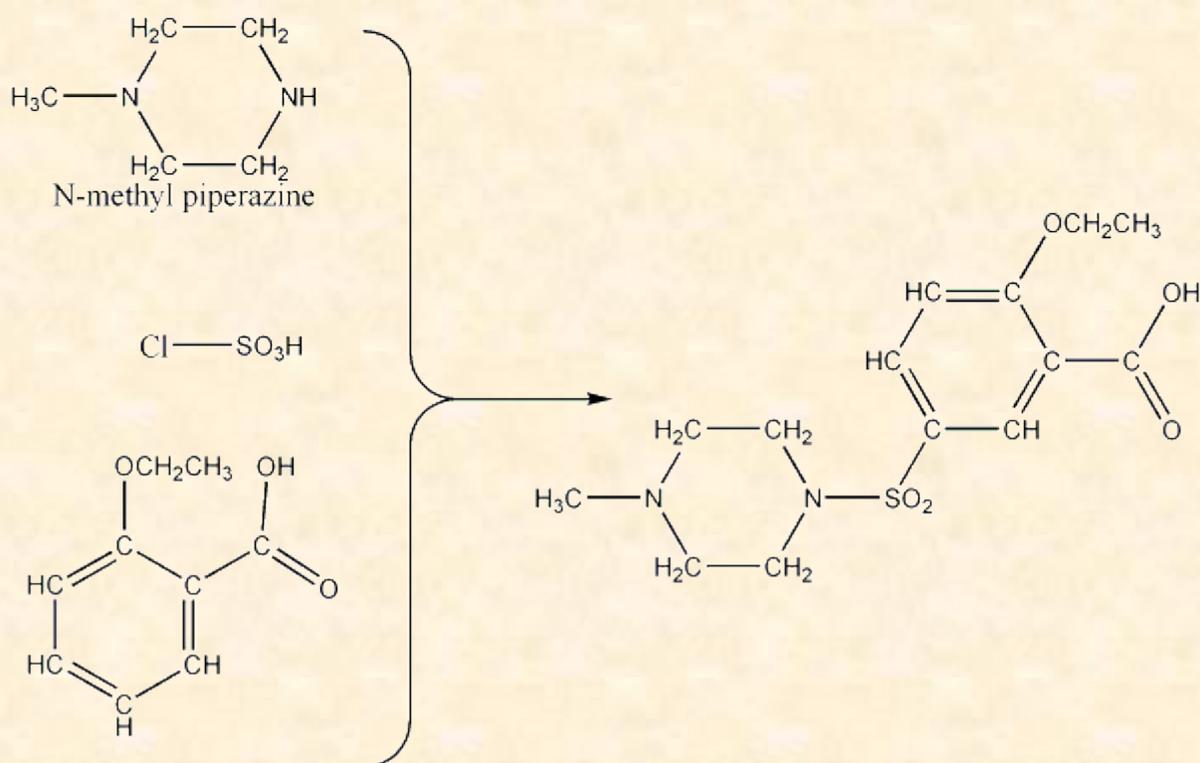
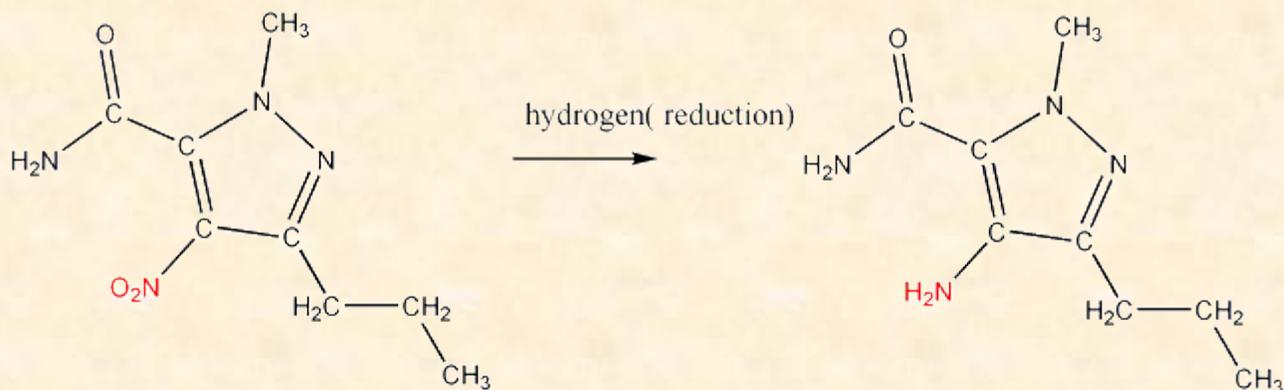
The fused product accompanied by the production of alcohol has to age like certain wines to its more thermodynamically stable product, shown to the right of the equilibrium sign.



The 2 nucleophilic nitrogens of methylhydrazine subsequently attack two C=O groups of the same molecule to create the pyrazole. In the 2 final steps that create pyrazole-4, nitric acid and ammonia add 2 more nitrogen atoms which are needed keys to latch on to the “purple part” of the Viagra molecule.



Pyrazole-4's nitro group(NO₂) is reduced with hydrogen gas to an amino group(NH₂). This will fuse with a molecule created by three common chemicals combining in a chlorosulphonation reaction. What happens essentially is that the chlorine atom gets bumped out by the more basic of the 2 nitrogen atoms in the piperazine ring while the rest of the chlorosulfuric acid (ClSO₃H) molecule attacks the aromatic ring of 2-ethoxybenzoic acid (a molecule sometimes used as a dental cement).



In the second last step, CDI (carbonyldiimidazole or Staab's reagent) is used to link the previously constructed molecule with pyrazole-4. The idea of using CDI comes from the fact that it helps link amino acids (the amino part to the carboxylic part) in creating peptides or simple proteins. Finally we get a similar reaction of an amino group combining with an amino group. But this time the attack is intramolecular, closing a second nitrogen ring to create sildenafil.

Viagra is actually a citrate salt which is water-soluble. This is obtained simply by reacting sildenafil (a base) with citric acid in a reaction that is 100% efficient. The last 3 key steps of the reaction make use of only one solvent, making the process environmentally friendly. Solvents have to be discarded. So by using less, pharmaceutical companies create less waste. The overall environmental impact of Viagra's industrial production is low with just 6 kg of waste per kg of product compared with an industry average of 25 to 100 Kg. In 2003, for their efforts towards the efficient production of Viagra, Pfizer received the United Kingdom Award for Green Chemical Technology ("Best Process" category).

References

- Peter J. Dunn. Synthesis of Commercial Phosphodiesterase(V) Inhibitors. *Organic Process Research&Development* 2005 9, 88-97
- Peter J. Dunn, Stephen Galvin, and Kevin Hettenbach. The development of an environmentally benign synthesis of sildenafil citrate (Viagra™) and its assessment by Green Chemistry metrics. *Green Chem.* , 2004 , 6 , 43 – 48

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Comments

1. Helen Barratt / 08/26/11, 19:05 PM

Why go to so much trouble making this pharmaceutical drug Viagra when there is a perfectly natural alternative with fewer side-effects called horny goat's weed. And what's more, it is an aphrodisiac for women too. Okay, maybe the name is a bit of a worry. According to this [New Scientist article](#):

The soft green heart-shaped leaf of the **horny goat weed** could hold the key to a new drug for treating erectile dysfunction. Researchers say the Viagra alternative could be as effective as the famous **blue** pill but have fewer side-effects.

Mario Dell'Agli of the University of Milan, Italy and colleagues tested 4 plants which are used as natural aphrodisiacs in traditional cultures to establish their potential as alternatives to Viagra. Viagra's active compound sildenafil, works by inhibiting an enzyme called phosphodiesterase-5 (PDE5). Because PDE5 helps control blood flow to the penis, inhibiting PDE5 promotes male erection.

Dell'Agli and his colleagues tested the 4 plants in vitro to see how efficient they were at inhibiting PDE5. **Just one -- Epimedium brevicornum (also known as horny goat weed) and Bishop's Hat -- had an effect.**



This confirmed previous studies showing that icariin (a compound found inside the horny goat weed) is a PDE5 inhibitor. The 5th compound Sildenafil, however, is 80 times more effective at inhibiting PDE5 than icariin. Dell'Agli and his team extracted icariin from the plants and produced 6 modified versions of it which they also tested on PDE5. The most efficient of these -- compound 5 -- "**works as well as Viagra**", says Dell'Agli. A drug made from compound 5 **could also cause fewer side effects than Viagra**.

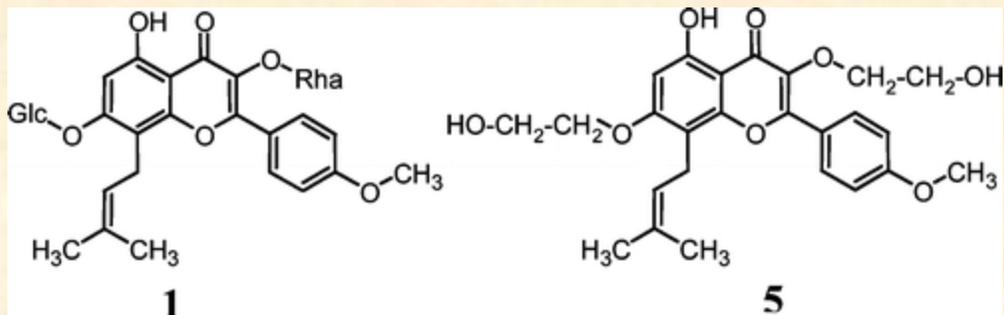
2. Enrico Uva / 08/27/11 , 05:37 AM
Hi Helen,

What you don't mention is that the 5th compound is a lab-created derivative of icariin. They synthesized 3,7-bis(2-hydroxyethyl)icariitin from icariin by substituting the 2 sugar groups. (Rha in diagram is rhamnose and Glc is galactose, also a component of milk sugar) The substitutions were necessary probably because the sugar-side chains are too big to let icariin occupy the enzyme's active site as well as cGMP, structure 5, or Viagra.

From [Potent Inhibition of Human Phosphodiesterase-5 by Icariin Derivatives](#):

Plant extracts traditionally used for male impotence (*Tribulus terrestris*, *Ferula hermonis*, *Epimedium brevicornum*, *Cinnamomum cassia*) and the individual compounds cinnamaldehyde, ferutinin, and icariin were screened against phosphodiesterase-5A1 (PDE5A1) activity. Human recombinant PDE5A1 was used as the enzyme source. Only *E. brevicornum* extract (80% inhibition at 50 µg/mL) and its active principle icariin (1) (IC₅₀ 5.9 µM) were active.

To improve its inhibitory activity, 1(icariin) was subjected to various structural modifications. Thus 3,7-bis(2-hydroxyethyl)icariitin (5) -- where both sugars in 1 were replaced with hydroxyethyl residues -- potently inhibited PDE5A1 with an IC₅₀ very close to that of sildenafil (IC₅₀ 75 vs 74 nM). Thus, 5 was 80 times more potent than 1 and its selectivity versus phosphodiesterase-6 (PDE6) and cyclic adenosine monophosphate-phosphodiesterase (cAMP-PDE) was much higher in comparison with sildenafil. The improved pharmacodynamic profile and lack of cytotoxicity on human fibroblasts make compound 5 a promising candidate for further development.



3. Helen Barratt / 08/27/11 , 07:18 AM

Well, I quoted *New Scientist* who said that they extracted it from these plants. But I think you are saying that they did more than this. That they then did structural modifications in the laboratory and substituted some natural sugars with various other components to synthesize it?

Is this process using herbs more complicated than your completely synthetic method above for making Viagra and do you think it is possible that as they claim, the end-product synthesized from horny goat weed might possibly be less risky than Viagra for people with heart conditions? The [New Scientist article](#) said that:

Compound 5 will now have to go through lengthy clinical trials before it can be approved as a drug. It could be 10 years before it reaches the market. In the meantime, "if people eat horny goat weed, I think it can be beneficial because it contains icariin," says Dell'Agli. "But it will not be as effective as Viagra." Horny goat weed is found in the wild in China, Asia and Europe. The research was supported by private funds. But Dell'Agli declined to provide details.

I have occasionally taken horny goat weed which you can buy in any health food shop here in Australia and it definitely works as a powerful aphrodisiac for me. Personally, I wouldn't feel comfortable about even trying this compound 5 that contains Sildenafil if, as they claim, it is 80 times more effective at inhibiting PDE5 than icariin. But then I'm not a man with erectile dysfunction and fortunately I never will be :) .

4. Enrico Uva | 08/27/11 | 09:24 AM

> "Well, I quoted *New Scientist* who said that they extracted it from these plants. But I think you are saying that they did more than this. That they then did structural modifications in the laboratory and substituted some natural sugars with various other components to synthesize it."

That's right. It's a common strategy. Codeine, for example, is chemically derived from morphine. But it's still more practical to rely on opium plants for morphine. So if it passes clinical tests, compound 5 might be made from icariin which in turn may be extracted from goat weed. It all depends on whether someone comes up with an economically feasible way of synthesizing the drug on a large scale.

> "it definitely works as a powerful aphrodisiac for me."

You can't dismiss the placebo effect -- i.e., the psychological suggestion combining with an already healthy libido may have been responsible for what you experienced.

A long time ago, my wife suggested to me that black licorice was an aphrodisiac. It "worked" well, even though there's nothing in there that could affect the reproductive system.

> "Personally, I wouldn't feel comfortable about even trying this compound 5 that contains Sildenafil"

I wouldn't either. Same goes with Viagra. But then again, I enjoy the luxury of not needing it (at least not yet!).- If I was on a different boat, my feelings could very well adapt.

5. Helen Barratt / 08/27/11 , 17:51 PM

> "You can't dismiss the placebo effect -- i.e., the psychological suggestion combining with an already healthy libido may have been responsible for what you experienced."

Sorry if this seems pedantic. But according to the Merriam-Webster dictionary, the definition of 'placebo' is :

1a: usually pharmacologically inert preparation prescribed more for the mental relief of the patient than for its actual effect on a disorder

1b: an inert or innocuous substance used especially in controlled experiments testing the efficacy of another substance (as a drug)

2: something tending to soothe.

Origin of PLACEBO Latin, I shall please First Known Use: 1785

Enrico, I feel confident that I can dismiss the placebo effect because the only connection between the horny goat aphrodisiac effect and the placebo effect that could be drawn in my case is from the Latin origin of its meaning "I shall please". This is because I was taking it for recreational use and I was not in any way taking it for mental relief from the effect of a disorder. Also there is scientific evidence that horny goat weed is definitely not an inert substance. And for the record, it is not noticeably soothing (rather the opposite!).

> "A long time ago, my wife suggested to me that black licorice was an aphrodisiac. It 'worked' well even though there's nothing in there that could affect the reproductive system."

Now there's another interesting herb with a similar chemical structure to cortisone. I don't see how you can say that there's nothing in there that could affect the reproductive system. Wiki has several articles about liquorice's [many endocrine effects as it contains isoflavones \(phytoestrogens\)](#). It might lower the amount of serum testosterone slightly.

6. Gerhard Adam / 08/27/11 , 18:20 PM

> "I feel confident that I can dismiss the placebo effect..."

You can't dismiss it because that's what makes it the "placebo effect" in the first place. The point being that our mental attitude (positive or negative) will create a correlation to anticipated results. So it isn't an "effect" that you can simply ignore.

7. Helen Barratt / 08/27/11 , 20:17 PM

"I feel confident that I can dismiss the placebo effect..."

I should have said in this particular case. So are you saying that the Merriam-Webster definition of placebo is wrong?

8. Gerhard Adam / 08/27/11 , 22:15 PM

Merriam-Webster isn't a scientific journal so it's only describing a common word usage. Since Science doesn't have a good explanation for the placebo effect yet, then it would be presumptuous to use the dictionary as a source.

9. Helen Barratt / 08/28/11 , 03:16 AM

Well in that case, any pharmaceutical or herbal drug or medicine that anyone ever takes thinking it might have a positive effect on them (including Viagra) must be subject to the placebo effect, not just me taking horny goat weed for recreational purposes.

10. Gerhard Adam / 08/28/11 , 11:56 AM

That's precisely the point. .

11. Enrico Uva / 08/28/11 , 16:05 PM

When drugs go to clinical trials, if they don't work significantly better than sugar pills(placebos) then they don't get on the market. But yes -- once they are on the market, the placebo effect continues to work in harmony with the pill's direct chemical effects.

12. Gerhard Adam / 08/28/11 , 16:26 PM

That's true. But a concern that has also been raised is whether or not some of the clinical trials also work better because of the "positive" placebo effect. Since the effect can work in both directions, it can also be misleading regarding the effectiveness of a drug.

In short, it's a complex affair in which even the attitudes of the attending medical staff can make a difference in results.

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