Researchers at Oregon State University have identified chemical compounds found in hemp that appear to prevent the coronavirus from entering human cells. Richard van Breemen is a professor of medicinal chemistry at OSU and a faculty member at the university's Global Hemp Innovation Center. He says these hemp compounds have the potential to prevent as well as treat COVID-19 infections. Read details of the discovery from van Breemen.

The following transcript was created by a computer and edited by a volunteer.

Dave Miller: *Social media was abuzz last week with breathless and often completely inaccurate claims about COVID. That's obviously nothing new. What was new is that research that came out of Oregon State University was the reason for many of those claims. Researchers announced unexciting but limited initial findings. It has to do with two compounds found in hemp plants. We're going to sort out fact from fiction right now with the lead author of the paper. Richard van Breemen is a professor of medicinal chemistry at Oregon State University and a principal investigator at OSU's Linus Pauling Institute. What did you set out to find in the big picture? What were you looking for?*

Richard van Breemen: When the COVID pandemic began we turned our attention from looking for natural products as potential therapeutic agents to other targets - to natural products that could help prevent COVID or treat COVID infection.

Miller: *And how did you go about doing that?*

van Breemen: We turned to the very first step in the process by which the SARS Coronavirus-2 that causes COVID infects human cells, the cell entry step. Now one could address any step in that cycle after infection, by which the virus replicates itself and then goes out to infect other cells. But we started at the very first step at which the Coronavirus spike protein, that's that large spike protruding from the surface of the virus particle that we've seen in electron micrographs and illustrations on the news. But that spike protein interacts with the human cell and binds to a very specific target on that cell. So we looked for small molecules. And we screened a variety of botanical natural products sources and found molecules in hemp that could bind to just the right place on that spike protein to prevent it from interacting with the human cell.

Miller: *Is the basic idea here that if you attach something to the part of the spike protein that attaches to a human cell, then that particular virus, it can't do that. It can't attach to a human cell and then it can't replicate itself. You're trying to prevent it from attaching to human cells, right?*

van Breemen: This is correct. It's essentially the same process by which the antibodies that are induced by vaccines help prevent infection by COVID. The vaccine induces the human body to make antibodies which are large molecular-weight proteins that bind with great selectivity and affinity to the spike protein. And then the spike protein can no longer interact with the human cell and infect it. So we reasoned that small molecules, if they bind to the right place and in the right manner with the right affinity, could do the same thing.

Miller: *Just in terms of size, this is a curious piece here. You're talking about small molecules. How much smaller would the hemp compounds that we're talking about here, and we'll learn a lot more about them as we go, but how much smaller are they than an antibody that we learned to make from a vaccine or that we learned to make because we actually get infected?*

van Breemen: Antibodies are proteins that weigh approximately 150,000 mass units. Natural products like cannabinoids weigh less than 500. So that's a huge difference. Several orders of magnitude and size.

Miller: *Is that significant medicinally, the gigantic order of difference in terms of size, or is it just a curiosity?*

van Breemen: Well, there's an important distinction here. Antibodies cannot be absorbed if given orally as drugs. They cannot reach the bloodstream if given as pills. They must be injected intravenously. And that's the basis for what's called antibody therapy. For people who are infected and get extremely sick, get hospitalized and then need intravenous therapy, one of those therapies is antibody therapy which will do just this process. The antibodies will bind to the spike protein and stop it from infecting new cells and invading new tissues. But antibodies are limited to the bloodstream. If an infection is in a compartment like the brain, the antibodies do not penetrate the blood brain barrier. But small molecule drugs can and that's one of the exciting aspects of cannabinoid therapy because cannabinoids as we know, have the ability to cross the blood brain barrier and reach compartments where antibodies cannot go.

Miller: *Let's turn to how you actually looked for the compounds that did the best job of sticking themselves to the spike protein. Because my understanding is that you use a technique that you and your lab pioneered to actually make this new discovery. Can you describe the technique in ways that we can understand?*

van Breemen: Well, I mentioned molecular weight of the antibody and molecular mass of the small molecules. We use an analytical tool called a mass spectrometer which effectively makes ions out of molecules and weighs them. It can take a beam of ions and separate them into a spectrum of ions of different mass, just the way a beam of light can be separated by a prism into a rainbow of colors, colored light. So we can identify molecules, characterize them by mass spectrometry and this is so selective and informative that we can assay 1,000 molecules at once in a complicated extract of a plant and find just those molecules that interact with the spike protein or any other therapeutic target that we choose. So that's the basis of the analytical screening that we call affinity selection mass spectrometry.

Miller: *So you said you can have 1,000 or more compounds or have them all present at once. And then using this technique you can see which of them did the best job at sticking themselves to the spike protein?*

van Breemen: Correct. So we can find that needle in the haystack. We can use our analytical approach to find the small molecules that interact with the large receptor like a spike protein, characterize it by its molecular mass, isolate it, purify it for additional

spectroscopic characterization if we need to identify it further. And it's very fast. So this was our step one in the drug discovery process.

Miller: *And step one found, if I understand correctly, that there were two compounds found in hemp that most [stuck] onto the spike protein. What are these two compounds?*

van Breemen: We actually found three. They are cannabinoid acids, tetrahydrocannabinol called THC A, cannabidiolcolic acid CBD A, and cannabigerolic acid CBG A. We went on to test two of those in cell culture studies with live virus and those were CBD A and CBG A. So not only do we find three compounds that bind to the spike protein from hemp, but two of them were then tested in live virus culture with human cells and showed that the mechanism of action that we had proposed - the binding to the spike protein - works and it can prevent those cells from getting infected by the virus. And we tested three different strains of the virus too in addition to the original SARS Coronavirus-2 strain.

Miller: *Am I right that you got up to Delta. But this was all before the Omicron so you don't have data about Omicron?*

van Breemen: This was data long before the Omicron variant appeared. It's the nature of viruses to mutate quickly. And we worked as quickly as we could. We identified molecules that could stop the original strain of the virus and then two subsequent strains. And these molecules were about equally effective against all the variants that we tested. So we are hopeful that it would be also effective against more recent variants like Omicron. But we have not yet tested that.

Miller: *A lot of us are used to hearing about CBD or THC but not CBD A or THC A or CBG A. What does that extra A mean?*

van Breemen: Cannabinoid acids have an extra functional group that CBD does not. It's an organic acid group called a carboxylic acid and it makes these molecules more polar, more water soluble than CBD, which is a very hydrophobic and oil soluble molecule. One of the differences is the CBD A and CBG A are also relatively unstable to heat and extremes of temperature or other cell culture conditions. So that if one were to heat it they actually lose that acidic group and can be converted to their less polar analogs. So CBD A, upon heating, converts to CBD, CBG A can be heated to decarboxylate and convert to CBG.

Now we've heard a lot about CBD as a cannabinoid that is effective as an FDA approved drug against certain forms of epilepsy in young people. And we also know that CBD has some anti-inflammation properties and even some other benefits. What's less known are the potential therapeutic applications of CBD A and CBG A and some of the other cannabinoid assets. But in our particular assay, CBD and CBG did not bind to the spike protein of the virus, whereas their acidic analogs did.

Miller: *So to break this down into the most useful information for listener (and the place where I feel like I saw the most erroneous information) when you say that heating can turn CBD or CBG A into CBD and if CBD doesn't work to block the spike protein, then vaping or*

smoking a cannabis product would destroy the spike protein binding properties of these chemicals. Right? I mean that smoking or vaping would make it so everything you're talking about wouldn't work?

van Breemen: So I do not advocate for smoking these products because it definitely would contribute to the degradation of the anti-COVID compound CBD A and CBG A. A more effective approach might be oral administration as a dietary supplement in a pill form for example.

Miller: *We're talking about research that Richard van Breemen and his team recently published, finding that two compounds or really three compounds in cannabis plants prevented the Coronavirus from attaching itself to human cells. So let's turn to that third one, because you mentioned that in the first parts of your experiments, you found that it wasn't just the CB's but also THC A was effective. But then you didn't actually do the further studies on that. Is that because of the federal prohibition on marijuana research?*

van Breemen: Exactly. THC A, like its analog CBD A and CBG A, is unstable to heat. And so it's very easy to convert it to THC. And tetrahydrocannabinol ,THC, is a controlled substance with psychoactivity.

CBG A and CBD A and their analog, CBG and CBD are not psychoactive and are not controlled substances.

Miller: *I want to talk about the next research steps in just a second. But before that, let's just skip ahead. Assuming that a lot of things were to fall into place, how do you imagine that these compounds could be used with respect to COVID. I mean, what's the dream here?*

van Breemen: I would hope that subsequent clinical trials will demonstrate that these compounds prepared from hemp might help prevent COVID infection. They might help shorten the course of a COVID infection. Right now if any of us get exposed to a family member, a colleague at work or at school, for example, who was diagnosed with the COVID infection, we need to self-isolate and hope we don't get sick. The best thing we know is just to take good care of ourselves, drink plenty of fluids and exercise and eat well. But wouldn't it be nice if we could add to that a therapeutic agent that's readily available, like our cannabinoid product, that is active against infection and can prevent that infection from even starting.

Miller: *So let's turn to the next steps. You mentioned clinical trials. What are the series of steps that you have to go through before you could get FDA approval for what you're talking about?*

van Breemen: Typically one needs to carry out, after this initial drug discovery, development experiments to look at how the molecules might be absorbed orally or not, whether they get transformed through drug metabolism which is a process by which the body normally deactivates and eliminates drugs from the body. We'd have to look at the

safety aspects [such as] optimum dosage, what's too much, how it could be delivered to reach the optimum dosage. Fortunately a lot of this information is already known.

People have been consuming cannabinoids which include CBD A and CBG A for quite a long period of time. And we know that these molecules are relatively safe over a wide range of concentrations. And so a lot of the drug toxicity testing which might typically be carried out in animals prior to the clinical trial may not be necessary. We are in a position where we can move relatively quickly to clinical trials to establish the optimum dosage and dosage forms and also evaluate efficacy. And so I think that process could be shortened from years to months.

Miller: *What normally happens when CBG A or CBD A are ingested in humans? I mean what do those molecules normally bind to or do?*

van Breemen: Well we know from what clinical evidence there is that when hemp extracts are administered orally and blood levels are monitored, CBD A [as well as] CBD A does appear. They do reach the bloodstream after oral administration. There's information about how long it lasts in the body before it gets eliminated. That's the half life. It has a relatively long half life, which is a good thing because that means one would not need to administer too many doses a day in order to maintain a therapeutic window of effective concentration.

Miller: *And this is important because if these compounds, when ingested, normally either were expelled or bound to something else and they wouldn't be available to bind to the spike proteins of the virus and thus they wouldn't be helpful. You're saying that based on previous research it seems that it's likely that they could be flowing around and ready to hit the spike protein?*

van Breemen: Absolutely. And this is based on what we already know from clinical studies where complex hemp extracts are being administered and hemp cannabinoids are being monitored and measured in human blood. So often, in our natural products research, we find that a lead compound which works great in our invitro cell culture experiments (meaning in a test tube) doesn't translate very well to the clinic. The human body is designed to detoxify such compounds very often in food. We eat many different plants. We're omnivores and the plants have evolved to produce secondary metabolites which often are designed to stop predators from consuming them.

And so a lot of the things that we recognize as spice are secondary metabolites the plants make to stop it from being consumed by say a caterpillar or a grazing animal. So our livers are designed and other steps of human metabolism say the intestinal absorption step to detoxify plant compounds that were intended to deter us from consuming them. So we know that CBD A and CBG A are absorbable and are not transformed to inactive forms the way so many natural products are in a quick time.

Miller: *Are clinical trials or at least plans for clinical trials underway right now?*

van Breemen: I have talked to quite a few folks in the last few days who are gearing up to carry out the clinical studies of safety and efficacy of cannabidiol CBD A and CBG A, the acid forms. We ourselves are talking with clinicians to design and initiate clinical studies as well. So I hope that before the year is over, some of these studies will have reached a point where at least preliminary data can be published and reported in the peer reviewed literature. And I hope that we'll have evidence that supports our mechanism of action. And I hope that these compounds show efficacy in clinical studies. That's the way we will know for sure if this works.

Miller: *You're obviously talking carefully here and you noted five minutes ago that you don't want people to smoke cannabis or hemp compounds because of everything you're talking about. It would lose whatever efficacy it's already been shown invitro. But nevertheless, in just the last week and a half, there has been so much misinformation flowing around. People, either joking or saying seriously, stuff like 'ah smoking pot prevents COVID. That's why I haven't gotten COVID, I knew it'. And it's hard to tell on social media what's a joke and what's intended seriously. But increasingly that line is being blurred anyway, when things get pinged around the internet. How concerned are you that a lot of people are missing the subtleties of your findings?*

van Breemen: If anyone is taking a dietary supplement made from hemp right now and wants to know if CBD A and CBG A are present, they might be able to find it on the label of the product they use. Or they can look up a certificate of analysis from its manufacturer. In many cases the products that are in use will not contain appreciable quantities of CBD A or CBG A because the emphasis in the market has been to produce a product rich in CBD, which in our mechanism doesn't bind to the spike protein and probably will not prevent cell entry of the virus. But CBD may have other valuable properties. We know it's a good anti-inflammatory agent and helps suppress seizures. So it has pharmacological activity. But as for these wild ideas on the internet, I can't control what people say and do about it. I am delighted that there's a good [amount of] attention about what we're doing. I'm delighted that there's a renewed interest in natural products as sources of therapeutic agents, especially for therapeutic agents against some of these emerging viruses like the SARS Coronavirus Type-2. And I hope that this leads to increased funding and resurgence of research into the drug discovery of compounds from nature.

Miller: *Richard van Breemen is a professor of medicinal chemistry at Oregon State University, a faculty member at OSU'S Global Hemp Innovation Center.*

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