Phytocannabinoids as an anti-tumor tool

Preclinical evidence has confirmed that cannabis induces cancer cells to commit suicide. Whole plant extracts are better therapeutic tools than isolated compounds.

By Cristina Sanchez

Cancer is a word that we use to define many different diseases—more than 200 diseases, according to the World Health Organization. They all have something in common and present challenges to oncology. We need to improve our tools for the early diagnosis of patients. We need new treatments for those patients who have no effective therapy. And for those patients who are treated, we need therapies with less toxicity.

We have more than enough evidence to say that we can use cannabis to help address these three issues. Early diagnosis requires a political solution—public investment in health care. Where you live requires a political solution—public investment in health care. Where you live requires a political solution.

We don’t speak about this today because I am not a politician, I am a scientist. I am going to present data supporting the use of cannabis to improve oncologic treatments.

It is important to bear in mind that cancer patients have to deal with many things that are related to the pathology indirectly. The side effects of the anti-tumor therapies we use include nausea and vomiting, lack of appetite, and pain. There are also psychological effects of the disease that impact in a negative way. When someone has cancer, not only the patients but the families suffer anxiety. We have trouble sleeping, too.

We have known for many years that we can use cannabis as a palliative agent. It has been demonstrated in the preclinical setting and also in the clinical setting that we can treat or prevent the nausea and vomiting induced by chemotherapy with cannabis. We can use it as an analgesic to reduce and endure pain, as a tool to stimulate appetite, decrease anxiety, and help improve sleep.

Our research has been focused not on the palliative aspects of cannabis but on its potential as an anti-tumor agent. As with any other anti-tumor compounds, with cannabinoids we have to prove two things: one, that this tool is efficacious, that cannabis is actually an antitumor agent, and second, that this tool is safe.

In the late 1990s we conducted a series of experiments confirming that cannabinoids induce the death of cancer cells. We cultivated human glioblastoma cells and treated them with THC, which caused them to die. Subsequently we moved on to more physiological models in cancer, and we have seen anti-tumor responses to cannabinoids in glioblastoma (GBM), breast cancer, skin cancer, and many others. In an experiment with MMTV-neu mice, illustrated above, half were treated with THC, and half with vehicle (sesame oil). In mice that did not receive THC treatment, the tumors grew exponentially. In those treated with THC we saw a drastic reduction in tumor growth.

THC, by binding to CB1 and CB2, switches off the regulator of cell survival.

This response occurs when cells detect problems in the folding of their proteins and forms of damage. It usually is the trigger for suicide, so that the cell avoids being a problem for the rest of the organism. The response involves changes in the levels and activities of a number of proteins. All these changes converge in the inactivation of a protein called AKT, which is the master regulator of cell survival.

So THC, by binding to CB1 and CB2, switches off the regulator of cell survival. This triggers a process called autophagy, which means “self-digestion” and leads to apoptosis, which is programmed cell death.

THC dramatically slowed proliferation in experiment involving MMTV-neu mice with HER2+ breast cancer that were separated into two groups. Graph at left shows exponential tumor growth (vertical scale) over 100 days (horizontal scale) in mice treated with vehicle. Graph at right shows reduction in tumor growth following treatment with THC.

THC drastically slowed proliferation in experiment involving MMTV-neu mice with HER2+ breast cancer that were separated into two groups. Graph at left shows exponential tumor growth (vertical scale) over 100 days (horizontal scale) in mice treated with vehicle. Graph at right shows reduction in tumor growth following treatment with THC.

THC drastically slowed proliferation in experiment involving MMTV-neu mice with HER2+ breast cancer that were separated into two groups. Graph at left shows exponential tumor growth (vertical scale) over 100 days (horizontal scale) in mice treated with vehicle. Graph at right shows reduction in tumor growth following treatment with THC.

THC drastically slowed proliferation in experiment involving MMTV-neu mice with HER2+ breast cancer that were separated into two groups. Graph at left shows exponential tumor growth (vertical scale) over 100 days (horizontal scale) in mice treated with vehicle. Graph at right shows reduction in tumor growth following treatment with THC.
**THC blocks angiogenesis by activating CB1 and CB2 receptors in cancer cells.** Modulated as a result are HIF-1, the main regulator of angiogenesis, and VEGF, the main growth factor regulating vessel formation and vessel growth. Proteins involved in endothelial cell migration are also modulated and cease to function.

Research indicates that THC blocks angiogenesis by activating CB1 and CB2 receptors in cancer cells. Among the proteins modulated are HIF-1, the main regulator of angiogenesis, and VEGF, the main growth factor regulating vessel formation and vessel growth. The result of these changes is that vessel formation and vessel growth is impaired.

In addition, cannabinoids block the migration of endothelial cells by inhibiting a family of proteins that break down the extracellular matrix that surrounds the cancer cells.

We also have proof that cannabinoids block the metastasis processes that occur in the later stages of the disease. In an experiment with MMTV-neu mice that developed breast tumors, 70% metastasized in a control group that received no treatment. In the animals that were treated with THC, this number went down to 20%. (See illustration at bottom of page.)

Again, we know the mechanism of action. THC acts by binding and activating CB1 and 2 receptors, and modulates the family of MMPs, and also the activity of other growth factor receptors like EGFR, which trigger migration and invasion. So if cannabinoids block these proteins, they are blocking these processes.

THC also blocks what we call the "Epithelial-Mesenchymal Transition." In our tumors, most of the cells have low-epithelial phenotypes, and show epithelial markers, but when they have to migrate and invade other tissues to generate metastasis, they have to start moving, and to do that, they have to change their shape, their phenotype. They have to acquire mesenchymal markers instead of epithelial markers, so they start to produce mesenchymal phenotypes. They change shape and start moving. Cannabinoids, especially THC, can block these transitions.

In the case of CBD, it seems the main mechanism of anti-metastatic migration is the down-regulation of the ID1 gene, which controls many of the expressions of pro-migration and pro-invasion proteins. By decreasing the levels of these proteins we hamper the invasion capabilities of the tumor.

**Breast cancer types and treatments.**

Cannabinoids, especially THC, modulate proteins involved in cancer cell migration and block the epithelial to mesenchymal transition. CBD down-regulates the ID-1 gene, which controls expression of pro-migration proteins.

Cannabinoids decrease the viability of two hormone-sensitive breast cancer cell lines (vertical scale in both graphs) more potently as dosage increases (horizontal scale). Extract (purple dots) decreased viability more potently than THC (green). Experiments summarized in graphs used T47D cells (left) and MCF7 cells (right).

Breast cancer types include:

- **Hormone-sensitive** cancer, which is characterized by overexpression of the oncogene HER2+. These cancers are usually treated with drugs that block the hormone that stimulates the cancer cells to divide. One example of this kind of drug is trastuzumab, which is directed against the HER2+ subtype.

- **Hormone-resistant** cancer, which is characterized by a reduced response to hormone therapy. These cancers are usually treated with drugs that block the hormone that stimulates the cancer cells to divide. One example of this kind of drug is trastuzumab, which is directed against the HER2+ subtype.

- **Triple-negative** breast cancer, which is characterized by a reduced response to hormone therapy and chemotherapy. These cancers are usually treated with drugs that block the hormone that stimulates the cancer cells to divide. One example of this kind of drug is trastuzumab, which is directed against the HER2+ subtype.
All breast cancer subtypes are sensitive to cannabinoid antipro liferation action.

breast cancer. We started with hormone sensitive tumors, and chose Tamoxifen as the drug of study.

In vitro studies showed that submaximal doses of tamoxifen produced a very small decrease in cell viability, and so did submaximal doses of THC. But when we combined tamoxifen with THC, we could see a synergistic response. This is an example of one plus one is more than two. We see an unexpected decrease in cell viability.

Tamoxifen was also a decrease in cell viability when we combined tamoxifen with the whole plant extract. When we tried this in vivo, we found that the extract we were using was more potent than pure THC and as potent as tamoxifen, which is the drug that most patients are using nowadays. Disappointingly, when combining tamoxifen and the extract, we didn’t observe the synergistic response that we observed in vitro.

We did the same studies in HER2+ breast cancer cells using Lapatinib as the drug combined with cannabinoids. And we observed the same thing: The extract is as potent as the current treatment that these patients receive. But again we observed no statistically significant improvement of efficacy when the extract and Lapatinib were combined.

In triple negative breast tumors we used cisplatin as the chemotherapeutic agent, and we observed no synergy in vitro. THC added to cisplatin produces the same effect as cisplatin alone. Adding the extract in combination with cisplatin is more effective.

When we move to the animal setting we observe that cisplatin seems to be slightly more potent than the extract. When we combine the extract with the cisplatin, we see a slightly higher antitumor response, but it’s not statistically significant either.

The take-home message is that the extract is as potent as standard therapies, and that the extract is more potent than the pure THC compound in vivo, which is important. Often you see in vivo experiments do not reproduce the in vitro results, but in this case the extract is more potent in both cell cultures and test animals.

A second conclusion is that the THC extract was as potent as the standard therapies tested in this study. Also, the combination of cannabinoids with the tested anticancer therapies tested did not improve the potency of the individual treatments.

We would like to repeat these experiments with lower doses of the treatments. The dose of cisplatin we used was so high and produced such a strong effect, that it left very little room for improvement from the extract. So we would like to repeat this experiment with a dose of cisplatin that would produce less of an effect.

fact that it doesn’t express either estrogen receptors or progesterone receptors, or HER2+. Unfortunately, this is the most aggres sive phenotype, and we don’t have any targeted therapy because we don’t have any molecules or markers that we can spec ifically target. The only therapy that these patients can receive now is standard chem otherapy, which indiscriminately targets all cells in the body that are undergoing proliferation.

We started by comparing and analyzing the anti-tumor effects of pure THC versus a whole plant preparation in the cell model of hormone-sensitive breast cancer, using a cell line called T47D. Both the THC and the extract decreased the viability of the cells. The effect of the extract was more potent.

We next ran the same experiments in other hormone-sensitive cell line (MCF7). The differences were not statistically significant: both pure THC and the extract served the same thing: THC does not reproduce the in vitro results, but in this case the extract is more potent than the pure compound.

When we replicated the experiment with an HER2+ cell line, we saw the same pattern. Both pure THC and the extract decreased cancer cell viability, and the extract was more potent than the pure compound.

We completed this series of experiments in models of triple negative breast cancer. And in this case again, we used two different cell lines in culture, and we saw the same thing. Both cultures decreased the viability of the cancer cells, and the extract was more potent than the pure compound.

So we concluded that all breast cancer subtypes are sensitive to cannabinoid anti proliferation action. It’s important to point out this conclusion, because there are comments out there that hormone sensitive-tu