



REVOLUTION IN HEALTH

**Research and new treatments
connect Brazil and Canada**



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4 A NEW WORLD IS OPENING

10 Technological Exchange

12 GENE THERAPY ALREADY OFFERS CURE FOR A NUMBER OF DISEASES

19 New Frontier

20 CANNABIS: A THRIVING MARKET

25 Multiple applications

27 Handling care

28 Medicinal or recreational

29 Countless recommendations

throughout history

30 A MATTER OF REGULATION



A NEW WORLD IS OPENING

Gene therapy, research and development of treatments, medicinal use of Cannabis, phytotherapy and supplements: Brazil and Canada evolve and innovate in the field of public health

By Estela Cangerana

A silent revolution has taken place in research labs, universities and hospitals: people recovering vision, treatments preventing the evolution of degenerative diseases, significant reduction of epilepsy crises in children who suffered with dozens of them a week and that now spend months without any episodes, effective treatments for chronic pain, cancer, Parkinson's disease and many other diseases. It seems utopian, but this is an increasingly frequent reality in Brazil and in Canada, as a result of the work of doctors and researchers from both countries, often working together.

One of the greatest examples is the exchange of information and the research conducted by the University of Laval (ULaval), Quebec, in partnership with Brazilian centers, led by Canada Gene Therapy Group. One of the most prominent names in gene therapy in the world and director of the Department of Molecular Medicine at ULaval, Dr. Jacques P. Tremblay, who leads research in the field, has been to Brazil several times in recent years for lectures and discussions with the Brazilian scientific community. There is also a successful partnership between ULaval and Santa Casa de Misericórdia of Rio de Janeiro, for binational research.

The Canada Gene Therapy Group is headed by Brazilian physicians Patricia Schlinkert and Marcello Bossois. According to Bossois, who is assistant to Tremblay in Canada, the gene therapy project has established

Laboratory in Brazil will bring gains in technology transfer and binational protocols.



connections so mature and advanced in the country that the operation may be expanded in Brazil with the opening of a dedicated laboratory. We expect that such initiative brings gains in technology transfer and the implementation of binational protocols. In late February, he presented the results of the work during an event of the CCBC Health Innovation Commission, one of the supporting partners of the project.



Discoveries in the field of genetic research point to the path of curing a number of diseases through techniques such as CRISPR-CAS9, which allows the programming of a protein with the ability to interact with any segment of the genetic code of human cells, bacteria or viruses. According to the experts, it is a matter of time before the use of this treatment is extended and reaches scale.

In another field of research, the number of patients treated with medicinal substances extracted from the controversial Cannabis plant grows. Labeled as a narcotic and banned from being manipulated in Brazil, the plant known as marijuana, actually has numerous uses and benefits, whether in industry, cooking or health care.

In Canada, both the medicinal and recreational use of the plant has already been authorized, thus opening the door to a huge market. In Brazil, the pressure for liberation grows, based on the expressive increase of its medicinal use. The excellent results in the treatments of several diseases reinforce the arguments in favor of such initiative.

The list of symptoms and diseases that can be proven cured or at least relieved by the components of the plant keeps rising. Likewise, the quantity and variety of products derived from cannabis also increase exponentially. In addition to the controlled use medications, there are several Natural Health Products (NHP) cosmetics, as the items known as herbal medicines in Brazil are called in Canada.

TECHNOLOGICAL EXCHANGE

The manner in which types of substances, medicines and natural products are assessed and classified is, however, very different in the two countries. Understanding these differences is essential when it comes to taking advantage of a number of opportunities that may come from the bilateral approach in the health area, according to the Coordinator of the CCBC Health Innovation Commission, Luis Sergio Castro e Silva, who is also the CEO of GCS consulting and co-founder of GC5 trading “The exchange between countries offers many possibilities, with great gains for both sides, either in the area of medicines, raw materials for pharmaceutical manipulation or in technology transfer and joint research development,” he says. He highlights Canada’s great know-how in the industry and the growing interest of the country’s pharmaceutical industry in the Brazilian market. On the other hand, Brazil can be a great supplier of ingredients and substances for this industry, forming a successful commercial partnership.

At the same time, the rapprochement between scientists from universities, research centers

“Our intention (...) is to reveal the advances to more people and open the door to new opportunities.”

Luis Sergio Castro e Silva



and hospitals from both countries is also very interesting for both. The exchanges of experiences and the shared knowledge enrich the work and also benefit the populations, which can have greater access to new treatments.

“There is already a lot going on in both these ways. Our intention with the CCBC Health Innovation Commission is to reveal these advances to more people and open the door to new opportunities”, he says.

A hand in a white lab coat holds a glowing white DNA double helix structure. The background is a deep blue with a faint, larger DNA structure on the left. A bright light emanates from the point where the hand touches the DNA.

GENE THERAPY ALREADY OFFERS CURE FOR A NUMBER OF DISEASES

Advances in DNA manipulation allow replacement of defective parts

If just over 20 years ago, the Human Genome Project united researchers from all over the world to begin to unravel the unknown world of our genes, today one can state with certainty that this journey takes place on well-known terrain. So much so that there are several techniques for correcting defective genes: the so-called gene therapy. The advances obtained after decades of study indicate, according to experts, that the treatment and cure of various diseases of genetic motivation is closer to being achieved than is imagined.

From nucleotide sequencing (association of three molecules present in cells and in the formation of DNA and RNA) it is possible to identify mutant genes that cause nonconformities. "It is now possible to sequence 100,000 nucleotides per second and identify

7,000 hereditary diseases," says Dr. Marcello Bossois, director of the Canada Gene Therapy Group and a member of the research group of the Department of Molecular Medicine of the University of Laval (ULaval), in Canada.

Upon identification of the problem, interventions are made for replacement or fault-correcting action. An associated adenovirus, with the corrected gene, is introduced into the patient's cells.

The treatment has already been successfully carried out, for example, by The Children's Hospital of Philadelphia for Leber's Congenital Amaurosis (ACL), a hereditary retinal

The treatment and cure of various diseases of genetic motivation is closer to being achieved than is imagined.





degenerative disease that causes severe loss of vision from birth. It is caused by a mutant gene and the body does not produce the protein necessary for the proper functioning of the eye. "In that case, an associated adenovirus is injected into the patient's eye which transmits the correct gene for the production of that protein," explains Bossois.

Positive results are also being achieved by the ULAVAL team for Friedreich's ataxia (correction of the gene that produces Frataxin), Alzheimer's (correction of the gene that produces the amyloid body) and Duchenne Muscular Dystrophy (transplantation of genetically modified myoblasts).

Commercially, they are already approved by the competent agencies, and treatments like Glybera, for the correction of repetitive pancreatitis, and the therapy with CAR T cells for the sanguine leukemia, are in use. In addition, there are several lines of studies for other applications, such as for large solid tumors.

"The development of CRISP will bring about so great revolution in medicine as the discovery of penicillin."

Marcelo Bossois



NEW FRONTIER

One of the greatest discoveries in recent years, however, is the CRISP/CAS9 technique, according to Bossois. The difference in this technique, as compared to the others, is that it enables the reprogramming of the protein for the correction of a huge variety of types of diseases. "The development of CRISP will bring about so great a revolution in medicine as the discovery of penicillin," says the expert.

The technique has been used experimentally in the immunological treatment of cancer, but it is possible to combine it with the DNA from various types of viruses, including influenza, HIV and others. It allows adaptation according to the mutation of each virus.

A reprogrammable protein for a wide array of inherited diseases, at a low cost (since it has many applications with the same technology) must involve a huge community of patients. Between 7% and 8% of the world's population suffers from some form of hereditary disease. There are more than 560 million people affected, says Bossois.

Clinical studies using CRISP/CAS9 are advanced and the sale of the technique for the treatment and cure of a significant number of diseases is expected to take place within a few years. It seems that there is a revolution in medicine.

A photograph showing a vibrant green cannabis leaf with serrated edges and a central vein, resting on a rustic wooden surface. To the left of the leaf is a small, clear glass bottle containing a golden-yellow liquid, likely cannabis oil, with a black screw cap. The background is a blurred wooden surface.

CANNABIS: A THRIVING MARKET

From miracle plant to illicit drug, the cannabis market is expected to move billions of dollars in the world in the next years

A huge market is expected to emerge in the coming years: the use of cannabis, the plant known as marijuana, which also offers numerous medicinal gains in various treatments. According to a study by Euromonitor, the consumption of cannabis, both legal and illegal, moves around USD 150 billion in the world today. In 2025, legal sales are expected to have increased to USD 166 billion a year. Of that total, 77% will be from legal sales.

According to the report, "in the next decade, some form of cannabis will be part of everyday consumer routines, whether as a functional ingredient in food, beverages or beauty products, or as a mood or well-being enhancer."

The estimate is based on the growth of the legalization trend towards the use of the plant, both recreational and medicinal. Euromonitor points out that North America is at the forefront of liberalization for recreational consumption. It is authorized in Canada and in ten US states. For medical use there are already 33 US states where it is legal, paving the way for recreational cannabis in the next ten years to be legal throughout the country. In the rest of the world, according to Euromonitor, medicinal use advances with a stronger perspective, especially in markets such as Germany, the Czech Republic and Australia.

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Scientific and practical evidence of the efficacy of cannabis in treatments of various diseases has reignited in recent years the discussion about the use of the plant. After years of criminalization around the world, a movement has emerged in several countries to review its legal classification. In Brazil, the discussion on the topic keeps growing.

The plant remains illegal in the country, but since 2006 carrying and cultivating small quantities for personal use stopped being punished by imprisonment. From the Resolution RDC 17/2015, the Brazilian Sanitary Surveillance Agency (Anvisa) started to allow individuals to import products containing cannabidiol (CBD) and/or tetrahydrocannabinol (THC), as long as these products are intended for such individuals' own use and under medical prescription.

CANNABIS AND YOUR HEALTH

Known indications

BODY

- Autoimmune Diseases
- Cancer
- Cerebrovascular Accident - CVA
- Chronic Pain
- Diabetes
- Fibromyalgia
- HIV
- Irritable Bowel Syndrome
- Metabolic Disorders
- Nausea
- Neuropathy

MIND

- Alzheimer
- Anxiety
- Attention Deficit Hyperactivity Disorder (ADHD)
- Autism
- Depression
- Epilepsy
- Neurodegenerative Diseases
- Obsessive-compulsive Disorder (OCD)
- Post-traumatic Stress Disorder (PTSD)

However, the history of the regulation was different from all others in the history of the agency, according to the director of Anvisa at that time and current consultant Ivo Bucaresky, partner of Orplavi Consultorias and business associate of XLR8 Brazil. "It was not the pharmaceutical industry or the doctor who called for the regulation of cannabis, but civil society. There was high pressure from families, including the media, to release the product for the treatment of epilepsy," he says. The need to create specific rules for this purchase led to RDC 17, which deliberates about the controlled importation. The initiative revealed a huge demand and paved the way for the expansion of the use of medical cannabis in Brazil.

MULTIPLE APPLICATIONS

Data collected by medical cannabis specialist Paula Dall Stella indicate that today there are 6,000 patients in Brazil legally authorized to use drugs with components from the plant. Since 2014, about 78 thousand units of medicines have been legally brought to the country. Statistics also show a significant increase in prescriptions. In 2015, 321 doctors prescribed cannabis. Three years later, in 2018, the number of professionals prescribing it rose to 911.

According to Stella, 34 medical specialties prescribe these medications. Some of the main

Fonte: Dra. Paula Dall Stella

ones are neurology, psychiatry, neuro-pediatrics, radiology, general practice, neurosurgery, pediatrics, rheumatology, orthopedics and general surgery. "Cannabis has been most commonly recommended for epilepsy, autism, Parkinson's disease, chronic pain, malignant neoplasm, anxiety, soft tissue disorder, cerebral palsy, multiple sclerosis and depressive disorder," she says.

Latin America has a potential of 68 million patients for treatments with substances from the plant and Brazil is the largest market in the region. Stella believes that "medical cannabis is rapidly emerging in Latin America as the next stage in the global expansion of the world's leading cannabis companies."

A report produced by New Frontier Data in partnership with the accelerator specialized in the sector The Green Hub confirms the significant numbers of the Brazilian participation. "With a population of more than 200 million people, the medical cannabis market in Brazil can become substantial even in the context of a relatively restrictive regulation," the report states.

The "restrictive regulation" pointed out by the study was the alleged exclusion of chronic pain from a possible list of diseases approved for treatment with cannabis. In this case, the number of patients in the country could reach 959 thousand in the first 36 months of legal sale. If the list also allowed use for clinical symptoms such as chronic pain, that number could reach 3.4 million people. This would represent a market with annual revenues of BRL 4.4 billion, according to the report.

HANDLING CARE

The prohibitions and difficulties of access to cannabis medicines for chronic diseases in Brazil can cause a dangerous reality. The alert is from Thiago Callado, executive director of XLR8 Brazil, a business development consultancy. According to him, the great ignorance of these possibilities of use generates misleading opinions and initiatives such as that of patients seeking authorizations to plant and make teas for treatment at home. Incorrect handling and imprecision in the chemical dosage of plant elements can create health risks.

A similar concern worries the medical specialist in medicinal Cannabis, Paula Dall Stella. "There are several families illegally planting Cannabis without any quality control," says Stella. "Homemade oils can contain bacteria, fungi and heavy metals," she warned.

The study notes that according to the 2016 Global Health Disease Study, one out of five Brazilian adults suffer from back and neck pain, "which means that the decision whether or not to include chronic pain as a clinical condition in a future medical cannabis program could be a determinant in the size and increase of the patient population."

According to the CGO and co-founder of The Green Hub, Marcelo Grecco, the

report brings important findings, such as the fact that commercial transactions involving cannabis will increasingly take place in Latin America and Brazil in a variety of manners. He believes that the relationship with Canadian players will be critical in this process. "The wide array of regulation in the region will require foreign companies to invest heavily in understanding the specific dynamics of each country. Significant investment by Canadian companies with available capital could accelerate the assignment and professionalization of Latin American operators," he says. For him, Latin cannabis prices could even be lower than those of the North American and Canadian ones.

MEDICINAL OR RECREATIONAL

The findings are shared by other industry development experts, such as XLR8 Brazil. According to the company's CEO, Thiago Callado, the expansion extends to a broad range of businesses involving the plant. "One thing is certain and very clear: it's not just medical cannabis that will be extremely profitable. This is an expanding market globally, with pre-existing demand," he says. "The segment has created opportunities for commercial ventures of all sizes and natures. Other related sectors will also benefit."

COUNTLESS RECOMMENDATIONS THROUGHOUT HISTORY

There are currently more than 25,000 published scientific papers on the possibilities of use and effects of cannabis on the human body, according to Dr. Mario Grieco, president for Brazil and Latin America of Knox Medical, a medical cannabis company. "It's a long-established relationship. There are records of successful use of the plant for treating various diseases for thousands of years," he says.

One of the more remote records dates from 2,737 BC, when Chinese emperor ShenNeng allegedly used marijuana tea as a solution for gout, rheumatism, malaria, and even weak memory. The fame of the benefits of the plant is believed to have then spread through Asia, the Middle East and Africa. Later, in Antiquity, prescriptions of cannabis were already as diverse as possible, from headache to epilepsy.

The plant's bad name, as recalled by Grieco, is recent. Not only as medicine, but also for other uses, cannabis has already been very common. "From the flowers medicines are made, from the seeds, food, from the fibers, ship ropes and sails are made, which are very resilient, and even cannabis oil has already been widely used in public lighting in the past," he says. "cannabis já foi muito usado na iluminação pública no passado", diz.



A MATTER OF REGULATION

Herbal medicines, natural products and supplements: the differences in design and use in Brazil and Canada



Pharmacy shelves are suffering an invasion that seems irreversible: that of products that promise health benefits in the form of phytopharmaceuticals, supplements, herbal medicine. In Brazil and Canada, these goods have fallen into consumer tastes and are an interesting niche for industry and laboratories. However, attention needs to be paid to differences in how these items are classified and allowed in both countries. Both went through changes in 2018.

In Canada, the category of Natural Health Products (NHP) encompasses what in Brazil is called herbal medicine, as well as products of Chinese, Indian, probiotic and homeopathic medicine, according to the specialist in regulatory

affairs at GC5 Trading Karoline Calin. "They are what we call complementary or alternative medicines, which claim therapeutic benefits, no prescription required, are subject to quality standards for registration more complex than food, but with less rigor than medicines," she says.

The regulations that separated drug and food product classification within Health Canada (an entity equivalent to the Brazilian Sanitary Surveillance Agency - Anvisa) date from 2004, but last year the rules were revised. At the center of the changes are the permits and prohibitions on the use of cannabis and its substances. Although legalized for recreational use, the plant cannot be sold in the form of NHPs, except in very specific situations, such as the use of seeds and fibers that have concentrations insignificant of the substance tetrahydrocannabinol (THC). Products containing phytochemicals (THC and CBD), in turn, can be sold with prescription, like medicines.

In Canada, isolated substances from plants are used to create Health Products, which is not allowed in Brazil, according to Margarete Akemi Kishi, the pharmacist who coordinates the working group of the phytotherapeutics of the Federal Council of Pharmacy and director of HGSM Consulting. "*Digitalis purpurea*, for example, is a plant popularly known for its positive effects for treating heart failure. An herb tea can be classified as phytotherapy, but if we use its substance alone in a product, it will be a medicine," she explains.

Kishi clarifies that in Brazil, registering a product with cannabis in the category of

drug is allowed, provided that all regulatory requirements are met. "There are no restrictions on the plant as a medicine, but no open doors either." The rule that governs the entire sector is Law 6360/1976, followed by several Resolutions of Anvisa's Board of Directors (RDC).

In 2018, five new RDCs established a new regulatory framework in the herbal and supplements sector in the country. "Anvisa noticed the need to discuss this issue and the differences in the classifications of these products, in addition to the new food situation," explains pharmacist Priscila Dejuste, advisor to the Regional Council of Pharmacy of São Paulo.

The Resolutions were published in July last year when the five-year deadline for rule transition and market adaptation started running. They deal with various topics, from additives to probiotics. "Vitamin C, for example, which used to be just a drug without a prescription, can now be a supplement as well," he says.

In 2018, the supplement market moved BRL 2 billion in Brazil, and the industry's estimate is that, in five years, this amount will increase to BRL 10 billion per year. "More than 54% of Brazilians use or have already used supplements," says Dejuste. In Canada, about 71% of the population adopt some type of Health Products and more than 99 thousand items had been registered in this category until 2016.

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