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NegEnt: Cannabidiol-based Aromatherapy

Theoretical Aspects, Pharmacology, Clinical and Research Perspectives, Economic and Social Implications

Abstract

The article describes a research project that included the conception, development, testing and dissemination of a new drug, based on cannabidiol and called *NegEnt* (registered name and trademark).

In this contribution, the author fully describes a new product for Aromatherapy that was developed and how it can be used for significant progress on various treatments for different conditions in psychiatry, neurology, and medicine. It also presents completed work for new *herbal medicines* at affordable costs worldwide.

The clinical research program launched and the organizational and legal solutions identified are described to scientifically evaluate in accordance with a *single case research study* design. *NegEnt*'s pharmacokinetics, bioavailability, pharmacodynamics, therapeutic efficacy, and tolerability is examined.

In the last part of the article there is an outline of the project formulated for the development in Sicily in the province of Enna where *NegEnt* is produced in accordance with an innovative project of regional social promotion and based on the cultivation of *cannabis Sativa Light*, otherwise known as *Progetto Demetra*.

This project established an operational module that is managed by a non-profit social enterprise called the *Higher Institute for Cognitive Sciences*, the *ALETEIA LAB for Therapeutic cannabis*, and as an *ethical enterprise*, which is called *Herbal Neurocare* (registered name and trademark). It contributes to improved health as well as promoting the economic and social development of this economically depressed area.

Keywords: therapeutic cannabis; cannabidiol; aromatherapy; NegEnt; Herbal Neurocare

Introduction

This article illustrates a five-year research project, which achieved some success early on, but currently remains in a development phase. In fact, we are currently completing Phase 1, Phase 2 is underway, and Phase 3 is the planning stage for the marketing of a new pharmaceutical product.

When a new pharmacological unit in medicine is developed, it is important to demonstrate its unequivocal efficacy, efficiency, and tolerability to allow it be widely available and at low prices to treat as many patients as possible (Backes, 2017).

Penicillin, for example, one of the most important drugs in human history, was discovered by Alexander Fleming in his microbiology laboratory in 1928. However, years of study and investment were subsequently required to make it accessible worldwide. In fact, it took until 1941 for a series production process to be finally implemented, and only in the 1950s did penicillin become available on a large scale worldwide (Fleming, 1929; Gaynes, 2017).

The therapeutic effects of cannabis sativa and cannabidiol (CBD) have been known for several millennia, but today it is still not an approved drug with exclusive cannabidiol composition with the sole exception of *Epidiolex*. *Epidiolex* has been registered in the United States by the Food and Drugs Administration for a limited and specific neurological indication: Lennox-Gastaut epilepsy (Sekar, 2019).

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Cannabidiol (CBD) is an important cannabinoid compound that is extracted from cannabis sativa. CBD was isolated and described in 1940, but its chemical-physical structure was not determined until 1963 (Pertwee, 2016).

A growing number of studies and increasing research has tended to identify CBD as a new, interesting, and promising pharmaceutical resource that has potential use in psychiatry, neurology, and medicine to treat things like pain, inflammation, and systemic oxidative stress.

To date, as previously mentioned *Epidiolex* has received approval from the American FDA but for narrow set of indications for Lennox-Gastaut epilepsy. Therefore, this clinical research project that was developed immediately met with a serious difficulties. The only form of pharmaceutical CBD that can be prescribed in Italy was and is the *galenic* type and is prepared by pharmacists.

Considering a dosage of 200 mg of galenic CBD per day for anxiety disorders and 800 mg for schizophrenic psychosis, the monthly cost of therapy in Italy today fluctuates between €300 and €1,000. This expenditure is obviously not sustainable for most patients, especially when it comes to long-term treatments.

To obtain a formulation based on CBD that is economically sustainable and easily practicable for long periods of treatment, we developed a research program known as *NegEnt Project*.

The name *NegEnt* is a portmanteau of *Negative Entropy* that refers to an innovative model for treating schizophrenia that the author of this paper developed in the 1990s. (Scrimali T.: Entropy of Mind and Negative Entropy. A Cognitive and Complex Approach to Schizophrenia and its Therapy. Karnac Books, London, 2008).

The author have defined schizophrenia and any psychic disorder, in general, as *Entropy of the Mind*, with reference to Thermodynamics, to indicate a condition of disorder of the brain and mind (i.e. any psychiatric disorder). Every treatment in psychiatry, be it pharmacological, psychotherapeutic, or rehabilitative must aim to promote *Negative Entropy* (shortened to *NegEnt).*

The *NegEnt Project* involves a series of steps described as follows:

- Identifying and putting into production a pharmaceutical formulation, based on CBD, which can be easily used on a large scale that are effective , efficient, and affordable;
- Studying a possible intermediate legal solutions for clinical trials and the large-scale sale of this new product in Italy, Europe, and, eventually, worldwide;
- Collecting adequate case studies on the use of CBD in psychiatry, neurology, and medicine starting with *single case study* protocols and subsequently in accordance with the methodologies of controlled clinical studies;
- Implementing the procedure for submitting this new pharmaceutical product to the Italian Medicines Agency as a *Traditional Herbal Medicinal Product*;
- Developing a production chain for NegEnt in Sicily, near the city of Enna, with the establishment of an *ALETEIA cannabis Farm*;
- To develop a pharmaceutical laboratory in Sicily that is specialized in the extraction of CBD and the production of *NegEnt*.

Finally, the above is form part of larger project known as the *Demetra Project*, which is in the planning stages.

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Materials and Methods

Setting

The settings that have made it possible to achieve *NegEnt* and its availability to patients on a large scale were the *ALETEIA Lab for Therapeutic cannabis* and *Herbal Neurocare*, which were both founded and directed by the author of this article.

ALETEIA Lab for Therapeutic cannabis is at the *ALETEIA Clinical Centre in Enna and* constitutes an operational module of the *Higher Institute for Cognitive Sciences*, which has been a non-profit social enterprise for the last 30 years in scientific research and professional training in applied neuroscience, psychiatry, psychotherapy, and psychosomatic medicine.

The *ALETEIA Lab for Applied Neuroscience* is fully equipped and is capable of evaluating, through specific software, quantitative analysis, various psychophysiological parameters such as quantitative electroencephalography (QEEG), heart rate variability (HRV), and electrodermal activity (EDA). It also has a *Laboratory of Clinical Psychology and Neuropsychology* for computerized testing of many parameters and processes of the human mind (Scrimali, 2012).

Herbal Neurocare is an innovative start-up with a statute built around ESG operational logic, i.e. it is based on ethical management of the **e**nvironment, **s**ocial inclusion, good rules of administration, and **g**overnance.

At the *ALETEIA Lab for Therapeutic cannabis* and within the *ALETEIA Clinical Centre*, the author conducts clinical research on the effectiveness of therapeutic cannabis, while Herbal Neurocare was created to produce and disseminate *NegEnt*. The profits eventually generated will mainly serve to finance research and innovation in the field of CBD pharmacotherapy.

NegEnt

NegEnt is a CBD-based product prepared from cannabis sativa plant varieties with a low tetrahydrocannabinol (THC) content (0.2% maximum), legally cultivable in Italy, in compliance with Law No. 242 of 2 December 2016, in accordance with Circular No. 70 of 22 May 2018 of the Ministry of Agricultural, Food, Forestry and Tourism Policies, and in compliance with the Ruling of the Court of Cassation with Judgment No. 4929/2019 (Benvenuto, 2018).

The CBD contained in *NegEnt* is prepared using the supercritical carbon dioxide extraction method that allows *CBD isolate powder* to be obtained. This method ensures that the CBD, the active ingredient in *NegEnt*, is of pharmaceutical quality. CBD is subsequently made *water soluble* through the use of *nanostabilization* technology, followed by *ultrasonic nanoemulsion*, implemented by the procedure described elsewhere.

A specific and unique characteristic of *NegEnt* is that it is a water-soluble product that is extracted from cannabis sativa light that cultivable in Sicily. The author focused on achieving palatability and comfortable intake. This aspect seemed of crucial importance in consideration that NegEnt has been studied for prolonged treatments in uncooperative patients such as those afflicted by mental and neurological discomfort.

The product's palatability has not been neglected, in consideration of its use in pediatric patients, especially if afflicted by neurodevelopmental disorders. Hours of work in the laboratory and the full use of my skills as a sommelier, qualified after three years of study, have allowed the lab to develop an orodispersible product in powder form with a flavor that is light and balanced with bitter and sweet components. It is not too 'mouth-puckering', it is without a persistent negative aftertaste, and is non-irritating even after weeks of prolonged use.

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The author came to the formulation of *NegEnt* as follows: 25, 50, or 100 mg of CBD and some safe plant excipients, mainly gum Arabic and triglycerides that were derived from coconuts.

A serious problem to be addressed and resolved for the dissemination of NegEnt, has been in identifying a method of production, conservation, sale, and clinical experimentation in Italy and in Europe. This region in that the author currently operates in is capable of compliance with stringent regulations for new drugs and also guarantees that it is scientifically valid and a reliable product capable available via electronic commerce.

In a recent review article, Specchio, Pietrafusa, and Cross carried out a review of a large amount of data available on CBD-based products for sale worldwide. Within the European Union, CBD does not currently constitute a substance subject to strict controls for marketing purposes (Specchio, Pietrafusa, Cross, 2020).

In fact, there are numerous companies in Europe that distribute CBD-based products that were obtained from the extraction of dried inflorescences of industrial cannabis (cannabis light). Unfortunately, since the sale of these products is currently unregulated and there is no data or a guarantee of scientific and commercial correctness. For example, important data such as any health and clinical indications, daily dosage, tolerability, pharmacokinetics, and/or bioavailability are almost never given to consumer and neither are the contents of the preparation analytically reported.

The poor reliability that Specchio, Pietrafusa, and Cross have identified in commercial CBD preparations that are widely available in the European Union have been observed by the author as galenic preparations prepared by pharmacists. The level of standardization recorded was rather low and significant differences were found between samples set up in different phases. In particular Specchio, Pietrafusa, and Cross identified the following crucial indications were not provided:

- Indication of accurate origin of the raw material and the method of preparation
- Comprehensive chemical and physical analysis of the product
- Daily dosage
- Pharmacokinetics
- Bioavailability
- elimination
- Tolerability
- Route of administration
- Maximum recommended dose per day in the various, different indications
- Packaging characteristics
- Expiration date
- Conservation method
- Product stability

NegEnt as a magistral galenic preparation

The first solution, that the author identified and used for several years to be able to conduct clinical research in Italy with *NegEnt* before it underwent large-scale preparation and sale, was to develop, in collaboration with pharmacists, equipped with galenic laboratories, the form of *NegEnt* that constitutes a *magistral galenic preparation* in accordance with Italian drug legislation.

According to the Italian legislation, magistral galenic preparations are medicaments prepared by the pharmacist on the specific indications and instructions of a doctor and this doctor must decide which substances and relative dosages to include in the galenic preparation in question.

Thanks to prescriptions for individual patients of *NegEnt* that were prepared by a pharmacist as a *magistral galenic drug*, the author was able to submit a request to the Ethics Committee of the local Healthcare Authority to authorize some clinical trials of *NegEnt* according to design of Single Case Research Study (Rubin, Bellamy, 2012).

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NegEnt as an *aromatherapy product*

After the positive and encouraging results of experimentation with *NegEnt* as a *magistral galenic preparation*, the author tried to identify a method of large-scale production and sale of *NegEnt* to the Italian public as well as in Europe by no longer using a *magistral galenic drug*, but as a *product for aromatherapy*, under that label it is now offered and sold at www.herbalneurocare.it. In fact, given the low bioavailability of CBD, it was administered as a magistral galenic preparation in capsules that led to high dosages. For example, 800–1000 mg/day in the treatment of psychosis, i.e. 3 capsules of 300 mg, entailed a treatment cost of approximately €1000.00 per month.

Contrary to what the name might suggest, *aromatherapy* involves the use of aromatic substances that can be introduced into the body by inhalation and/or through oral mucosa. The term *aromatherapy* does not refer to the method of use that should only be inhalation; however, to describe the compounds that are used and come from essential oils that are aromatic (Price, Price, 2012).

Perry and Perry suggested that the term *aromatherapy* should be replaced by *essential oil therapy* or *phyto essential pharmacotherapy*. In this study, the term *essential* must refer to a plant essences from the products (Perry, Perry, 2006). *NegEnt* is not ingested and does not constitute a *food*, which, consequently, makes it not even a *novel food* but an *aromatherapy product*.

Although the foundations of *aromatherapy* were already known and described more than 5000 years ago by the Egyptians who used oils and balms to treat wounds and in the process of mummification of corpses. Scientific *aromatherapy* began between the end of the nineteenth and the beginning of the twentieth century with the work of René-Maurice Gattefossé who is considered the father of modern *aromatherapy*, a term coined by him in in *Aromathérapie - Les Huiles essentielles - hormones végétales*. (Gattefossé, 1937).

Nowadays, in Europe, *aromatherapy* is practiced mainly in England, where a great deal of activity has been developed in this field by many aromatherapists, even if the discipline is unregulated by the government. In the United States, *aromatherapy* began to become popular during the 1980s (Cooke, Ernst, 2000).

Currently, we are witnessing the attempt to develop scientific *aromatherapy* that is evidence-based. To date, there is a limited amount of scientific literature on the subject. In this regard, Koo carried out a bibliometric analysis from 1995–2014 (Koo, 2017) and identified 549 articles by 1888 authors. The largest number of articles were found to have been published in the United States and the most representative journal, with the largest number of articles was the *Journal of Alternative and Complementary Medicine*. Koo's bibliometric research has shown that most of the research cited does not exhibit robust experimental designs. The author identifies that clinical research of aromatherapy products need further development by adopting valid and robust experimental designs.

In Italy, the sale of *aromatherapy* products, obtained from essential oils and their derivatives, is not currently regulated. In fact, the European Union and the Italian government have not yet defined a regulatory framework that confers legal recognition on bio-natural disciplines and the sale of aromatherapy products. *NegEnt* is currently sold to the adult public via e-commerce using the website www.herbalneurocare.it.

NegEnt as a Traditional Herbal Medicinal Product

Although up to now it has been proposed, provisionally and for reasons of greater rapidity and economic efficiency, in accordance with Italian regulations, as a *mainstream galenic preparation* and an *aromatherapy product*, *NegEnt* still exhibits all the characteristics necessary to be submitted for registration by the Italian Medicines Agency (AIFA) as a *herbal medicinal product* or *traditional phytotherapeutic product*, pursuant to Article 1ii of Legislative Decree 291/06. In accordance with the

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aforementioned legislation, the definition *Herbal Medicinal Product* applies to: any medicine that contains exclusively, as active substances, one or more *herbal substances* or one or more *herbal preparations*. *Herbal preparations* are considered those obtained by subjecting herbal substances to treatments such as extraction, distillation, squeezing, fractionation, purification, concentration, or fermentation. *NegEnt* is a *herbal preparation* that is obtained by distillation using supercritical carbon dioxide from the dried inflorescences of *cannabis sativa light* with the addition of some herbal excipients.

The registration procedure for a traditional herbal medicinal products is simpler, shorter, and cheaper than for a drug. It is necessary, to demonstrate the safety and efficacy of a new product to be registered and to document a period of medicinal use in a European Union territory of more than 15 years and more than 15 years in countries outside Europe. These parameters are amply fulfilled by CBD (De Hoop, Heerdink, Hazecamp , 2018).

This procedure is underway and could make *NegEnt* the first cannabidiol product, registered in Europe, as a *traditional medicinal of plant origin*.

***NegEnt*: Pharmacodynamics**

CBD increases the activity of the endocannabinoid mediator anandamide, inhibiting its metabolic degradation, regulated by the hydrolase enzyme, of fatty acids, and improving its bioavailability (Mechoulam, Fride, 1995).

In this way, CBD exhibits an effect on the central nervous system that is not stimulating but rather inhibiting and tranquilizing. CBD exerts this pharmacodynamic effect through a mechanism defined as *allosteric*. That is, it does not act directly on the CB1 receptor, but, instead, powerfully conditions the way the CB1 receptor will interact with the CBD. It is a *morphological modulation* exercised on the receptor, modulating its physical structure, and blocking its interaction with its specific mediator (Debra, Kendall, Yudowski, 2017). .

CBD is psychoactive in a tranquilizing sense and, depending on the dose, exerts an anxiolytic pharmacodynamic action at low dosages (in this case we can define it as a *minor tranquilizer*, or also with a more modern term, *anxiolytic*) and a *major tranquilizer* at higher dosages. This case assumes the characteristics of an *antipsychotic* with a pharmacological profile similar to second generation neuroleptics such as clozapine, but without any of the heavy, potential side effects of this family of drugs (Blessing, Steenkamp, Manzanares, Marmar, 2015).

Therefore, CBD already appears to be a perfect candidate for the role of a therapeutic substance highly useful for human health.

To complete the description of *NegEnt*'s pharmacodynamic profile, it is necessary to talk about the anti-inflammatory, antioxidant, and anti-ageing activities carried out primarily by the interaction with the CB2 receptor, on the liver, pancreas and intestines; and on cells of the immune system of spleen, tonsils, and bloodstream. It is also present in the central nervous system (Mackie,2008).

The aforementioned pharmacodynamic, antioxidative, and anti-inflammatory actions are also within the central nervous system for an overall improvement in neuronal functioning and in the brain's immune cells of the microglia (Martin-Moreno, Reigada, Ramirez, Mechoulam, Innamorato, Cuadrado, De Ceballos, 2011).

Various diseases of the nervous system, such as Parkinson's disease, Alzheimer's disease, Huntington's chorea, amyotrophic lateral sclerosis, and multiple sclerosis have been linked to the brain cells of the microglia producing substances involved in the inflammatory and degenerative cellular process. These include cytokines and a series of harmful free radicals that lead to serious oxidative stress that CBD

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could intervene due it antioxidative and anti-inflammatory pharmacodynamic activities (Stampanoni, Bassi, Sancesario, Morace, Centonze, Iezzi, 2017).

CBD's pharmacodynamic, antioxidative, and anti-inflammatory actions are exercised through its interaction with the CB2 receptor and through activities that are not attributable to receptor modulation, but rather to the interaction with different biochemical processes that are positively modified by CBD (Pertwee, 2016).

These pharmacodynamic actions can be used in the treatment of many diseases, attributable to autoimmune etiopathogenetic processes, such as rheumatoid arthritis, ulcerative rectocolitis, and some forms of hepatitis.

NegEnt: Bioavailability and Pharmacokinetics

Although there is considerable interest in the therapeutic potential of CBD today, in many clinical indications there is often little scientific data available on the pharmacokinetics and pharmacodynamics of this compound (Lucas, Gallettis, Schneider, 2018).

Yet bioavailability and pharmacokinetics are crucial variables for designing a CBD-based treatment that is effective, efficient, and low cost. Therefore, as part of *NegEnt's* development work, many efforts were used to identify the method of intake that could optimize the bioavailability of CBD.

Oral use

Research in laboratory animals and humans has shown that the bioavailability of CBD taken orally is rather low, at around 13–19% of an ingested dose (Mechoulam, Parker, 2012).

This data is attributable to a marked effect of metabolization and hepatic inactivation of the molecule with the formation of inactive metabolites that are excreted via the kidneys (Huestis, 2007). Oral administration of CBD entails limited bioavailability and a prolonged time to reach the plasma peaks necessary to exhibit the pharmacodynamic potential of the molecule (Grotenhermen, 2003).

A dose of 10 mg of CBD showed a maximum plasma concentration of 2.47 nanograms per milliliter after one and a half hours after intake by healthy volunteers. A high CBD dose of 800 milligrams (i.e. eighty times higher than that considered in the previous study) made it possible to appreciate a maximum blood concentration of 77.9 nanograms per milliliter after three hours with the collaboration of healthy volunteers in another study. The maximum concentration reached was only 31 times greater than that obtained in the first study. (Millar, Stone, Yates, Saoirse, and Sullivan, 2018)

This data, together with other research, compared different maximum plasma concentrations achievable in healthy volunteers after oral intake of 400 or 800 mg of CBD showed that they do not differ much and led to a *saturation effect*. This means that, with oral intake, the highest plasma concentration is reached with certain dosages and that much higher doses do not increase the maximum achievable plasma concentration (Guy, Flint, 2004).

Based on the above, with reference to the high inactivation index of the CBD molecule, after the first hepatic passage, the saturation effect and the slowness that the pharmacodynamic action is manifested, the oral route of administration for CBD does not appear convenient, although it may appear at first sight to be what is the most comfortable for the patient.

Intake by inhalation

The method of inhalation, after combustion, is vaporization and this appears rather promising based above all on pharmacokinetics and bioavailability available.

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However, during the development of *NegEnt*, the author excluded a priori data in consideration of various solutions of inhalation generated by combustion as this poses a threat to human health from the inhalation of hydrocarbons and other lung irritants. The hypothesis of vaporization of CBD crystals remains to be considered for the formulation of *NegEnt*. Indeed, several studies have shown that the bioavailability of CBD, vaporized, by heating to about 220 degrees in small portable vaporizers, is quite high and is around 31–36% pure vaporized CBD (Hartman, Brown, Milavetz, Spurgin, Gorelick, Gaffney, Huestis, 2015).

As you can see, the bioavailability of CBD, taken through small portable vaporizers, equipped with a special burner, designed to obtain the powder, made up of pure CBD crystals, appears high, i.e. more than double compared to oral ingestion.

The author decided to experiment with the possibility of producing *NegEnt* as a product to be inhaled after vaporization. A series of experiments, carried out with healthy volunteers, however, allowed me to identify some critical issues. The most important and injurious was the irritating effect of CBD vapor on the mucous membrane of the pharynx, trachea, and bronchi, with the establishment of a dry, intense, and disturbing cough. Other negative aspects of this route of administration were the difficulty of dosing the powder to be inserted into the burner and the difficult maintenance of this device. In fact, the CBD residues, that remain after each use, once cooled, turn into a hard resinous material that is difficult to remove. It is necessary immediately after taking an established dose of CBD to scrupulously clean the burner with alcohol-based substances that can leave residual traces and be inhaled during subsequent use.

Considering that the Author developed *NegEnt* for use in chronic diseases, for long-lasting treatments, and that psychiatric, neurological, developmental, and elderly patients did not appear compliant with the use of the vaporizer, the author decided to abandon this as a possible solution.

Oromucosal intake

Oral transmucosal administration, has numerous advantages compared to preparations to be ingested, such as capsules, tablets, or syrups. In fact, it guarantees better compliance in psychiatric, neurological, pediatric, elderly patients, or those in any way afflicted by difficulty swallowing, due to dysphagia, nausea, or following a stroke, Parkinson’s, or Alzheimer's disease, multiple sclerosis, or other neurological disorders.

It can also allow a greater bioavailability for many substances. In fact, the entire buccal mucosa and the sublingual mucosa, thinner and more vascularized, are excellent access routes to systemic circulation for many molecules and is not easily bioavailable by intestinal absorption.

Furthermore, drugs that access the bloodstream through the vascular plexuses of the oral mucosa are significantly less exposed to any neutralization in the acidic environment of the stomach, to the first pass through the liver, and to degradation by enterocytes.

Some studies show that bioavailability, i.e. the quantity of CBD that reaches the target organs and receptors, after oral intake, reaches up to double what happens after oral ingestion. The sublingual administration of 20 ml CBD in drops made it possible to appreciate a maximum plasma concentration of 3.3 nanograms per milliliter that entails a high bioavailability index, reaches 35%, and is superimposable to what was exhibited by inhaled CBD after being vaporized (Atsmon, Cherniakov, Izgelov, Hoffman, Domb, Deutsch, Deutsch, Heffetz, Sacks, 2018).

After choosing to adopt the option of formulating *NegEnt*, as a product to be taken sublingually, the author became interested in the possibility of increasing the bioavailability of CBD, using the formulations obtained with new methodologies based on the technology called *pro-nano dispersion*.

To be able to make the best use of the sublingual route of administration, the author decided to adopt a formulation of CBD that was water soluble (water soluble CBD). In fact, during recent years, new

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technologies have been developed that can improve the water solubility of CBD based on the use of lipids with that CBD is bound by a process of emulsification.

The water solubility of CBD, contained in *NegEnt* has been achieved by using a technology that uses liposomal nanovectors bound to the CBD molecule through the use of a nanoemulsion procedure, which was implemented with an ultrasonic processor.

Literature data from the laboratories of ALETEIA Institute for Therapeutic Cannabis show that the water-soluble formulation of CBD when administered sublingually exhibits the ability to produce maximum blood CBD concentrations up to four times higher than those achievable with oromucosal administration of non-water-soluble CBD preparations.

The adoption of a water-soluble formulation confers a high level of bioavailability for the CBD contained in *NegEnt* through the sub-lingual intake and the consequent absorption by the oromucosal route. The CBD droplets that are obtained are about 30 nanometers, which ensures excellent solubility in water and prolonged stability. The *NanoStabilizer* was used as a stabilizing complex and LSP-600 instrumentation was used as an ultrasonic processor, both from the US company *Industrial Sonomechanics*.

Thanks to the adoption of these measures, it has been calculated that the bioavailability of CBD contained in *NegEnt* reaches up to three times that exhibited by the CBD taken orally. This means, for example, that 50 mg of CBD, contained in NegEnt, performs a pharmacodynamic action compatible with that exhibited by 150 mg of CBD, formulated in capsules, and taken orally.

Half-life of CBD contained in *NegEnt*

At *ALETEIA Institute for Therapeutic Cannabis*, studies are underway on healthy volunteers to document the half-life of CBD contained in *NegEnt*. The preliminary data, obtained in our laboratory, after administration of *NegEnt*, as well as reported in the literature, relating to water-soluble CBD, taken oromucosally, indicate a half-life of about 5 hours, after administration of 25 mg of CBD. This results in a duration of action of *NegEnt* of approximately 6 hours.

***NegEnt* formulation**

NegEnt is offered in packs, containing 30 disposable sachets each, filled with a single dose, consisting, depending on the case, of 0.5, 1, and 1.5 grams of orodispersible powder containing 25 mg, 50 mg, and 100 mg of *water-soluble liposomal CBD*.

Conservation method

NegEnt has been tested as stable and active for at least a year, if stored in a cool environment and not exposed to intense light.

Instructions for intake

The contents of the sachet must be placed on the buccal mucosa under the tongue. You have to wait a minute (mentally count to 50.) before swallowing. The positive effects begin to manifest themselves within 15 mins from intake, is fully revealed within half an hour, and remains for 4–6 hours.

Doses

The indicated dosages of *NegEnt*, in various clinical conditions, have been identified through studying the literature and through original experiments the author conducted.

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To improve well-being and hinder oxidative processes, and for anti-ageing in the elderly:
One or two 500 mg sachets once or twice a day. Typically, a single intake a day, in the morning, appreciably improves the sense of well-being, both physical and mental. If no appreciable positive effects are felt after four days, try adding a second sachet in the evening.

For psychic and neurological discomfort:
Initially, a sachet of 1.5 grams per day, to be taken in the morning, before moving on to two a day, one in the morning and one in the evening if there is an insufficient response. In severe conditions (manic and schizophrenic psychosis), use three sachets a day: in the morning, at lunch and in the evening.

In conditions characterized by inflammation and pain:

One or two 1 gram sachets a day. As already mentioned for the previous indications, start with a sachet in the morning and eventually, after four days, move on to two, one in the morning and one in the evening.

Maximum dosage studied

CBD is safe even though considering high dosages up to 1200 mg per day in adults. NegEnt has been proved to be safe and did not cause any problems at a dosage of 800 mg/day that was administered to some psychotic patients for two months.

Side effects and adverse reactions

No side effects or adverse reactions have ever been reported after CBD administration; *NegEnt* must be considered a handy and safe product. *NegEnt* has been taken for months by volunteers without detecting any toxicological problems or registering any intolerance. The values of liver transaminases have never changed.

Bergamaschi et al were the first to conduct an accurate meta-analysis study of the literature on the safety and possible side effects of cannabidiol (2011).

Most research, taken into consideration by Bergamaschi et al suggested that CBD is not toxic to humans in any way and that its consumption does not induce catalepsy, i.e. muscle stiffness or other motor disorders, it does not affect the main physiological parameters (heart rate, blood count, body pressure, and body temperature), does not influence gastrointestinal transit, and does not alter psychomotor or psychological functions. It does not interfere with the ability to operate a motor vehicle. Furthermore, chronic use, even at high doses, up to 1,500 mg/day of cannabidiol, according to several studies conducted and taken into consideration by Bergamaschi et al was well tolerated in humans.

In 2017, Iffland and Grotenhermen updated and extended the meta-analysis study by Bergamaschi et al. and concluded that the most frequently reported side effects were feeling tired and diarrhoea although these were still rare (Iffland and Grotenhermen, 2017). They formulated a final evaluation of cannabidiol as a substance with a favorable safety profile.

In order to consider the registration of a traditional herbal medicinal product, to ascertain its tolerability, the European Medicines Agency (EMA) requires a long-term and well-documented use, which has been documented for CBD. In particular, the EMA requires that a period of traditional use of at least 30 years within the European Union or at least 15 years in the European Union and at least 15 years outside the European Union be demonstrated.

For cannabidiol (CBD), legislation in Holland has also indicated the same data and as a member state of the European Union that promulgated medicinal cannabis legislation in 2003, and the introduction of the legal use of medical cannabis in 1996 in the state of California in the USA to show its traditional use is verified both inside and outside the EU.

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De Hoop, Heerdink, and Hazekamp (2018) considered the use of cannabinoids in the Netherlands from 2003–2016. Data were analyzed for 16,427 subjects who had taken cannabinoids for several months (3–10). No habituation phenomenon was observed with increased doses and nor were any side effects.

As for use outside Europe, history shows that way back in 1978 in New Mexico USA, cannabis was legally recognized as a medicinal substance. California was then the first state in the USA to legalize prescription use of cannabis as a medicine in 1996. So, there is at least a 42-year history for New Mexico and 22 years in California (Rasmusson, 2014).

Another important piece of data that demonstrates the exceptional tolerability of cannabidiol, is the fact that the United States Government patented a cannabidiol-based drug (US Patent No. 6,630,507) way back in 2003.

In conclusion, in terms of cannabidiol tolerability, consider all of the studies conducted for the registration of Epidiolex, which is an approved drug in the United States and will soon be present in pharmacies in Europe as well. Clinical studies that led to the registration of Epidiolex in the United States by the Food and Drug Administration have amply demonstrated its tolerability and safety (Silvestro et al 2019).

In light of this, NegEnt must also be considered a safe and manageable product. As such, NegEnt, has been taken, for months by healthy volunteers (including the author, for more than a year), without any detection of any toxicological problems or registering any intolerance. Liver transaminase levels have never changed And there was some slight side effects, which were rarely observed, such as a possible slight drop in blood pressure, a dry mouth, mild asthenia, and the feeling of light-headedness.

The drop in blood pressure, which is sometimes observed, could be useful for patients with hypertension, as a positive therapeutic effect that can be combined with that of any anti-hypertensive treatment. This is the case for the author who, since taking 25 mg of CBD per day in the form of NegEnt, in the morning, has seen for the first time in 25 years systolic pressure return to 120 mm/hg and diastolic to 80 mm/hg, which are figures that had not been seen since forty years of age, when hypertension was diagnosed and began to take beta-blockers and calcium channel blockers.

Use during pregnancy and when breastfeeding.

Some literature documents how CBD passes through the placenta and reaches the fetal circulation (Grant, Petroff, Isoherranen, Stella, Burbacher, 2017). There is also evidence that demonstrates the passage of CBD into breast milk and how it can be absorbed by the infant during breastfeeding (Ryan, S.A., Ammerman, S.D., O'Connor, M.E., 2018). On the contrary, there is not enough data to rule out that CBD could be harmful to the fetus and newborns (Davis, Lee, Weber, Bugden, 2020). For these reasons, *NegEnt* should not be taken by pregnant women and breastfeeding women.

Clinical uses

The most important and best-documented uses, from a large scientific literature, and based on clinical trials conducted by the author in the form of *single case studies* on the positive effects of CBD on human health are:

As an anxiolytic and neuroleptic (Khan, R., Naveed, S., Mian, N., Raafey M.A., Aedma K.K., 2020).

- Sleep disorders
- Agoraphobia
- Panic disorder
- Obsessive compulsive disorder
- Post-traumatic stress disorder

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- Eating disorders
- Dependence on substances and behaviors (compulsive gambling, above all)
- Borderline personality disorder
- Schizophrenia and bipolar psychosis

As anti-ageing (Wedman-St Louis, B. (Ed.), 2018).

In the preventive treatment of physiological cognitive decline due to the senescence process.

As an activator of brain metabolic processes and as a substance capable of reducing neuroinflammatory and neurodegenerative processes (Booz, G.W., 2011)

- Neurocognitive disorders (dementias)
- Neurodevelopmental disorders (including Autism Spectrum Disorders)
- Parkinson's Disease and Parkinsonisms
- Multiple sclerosis

As an anti-inflammatory, pain reliever and antispasmodic (Nagarkatti, P., Pandey, R., Rieder S.A., Hegde, V.L., and Nagarkatt, M., 2010).

- Irritable bowel syndrome
- Ulcerative rectocolitis and Crohn's disease
- Inflammatory and degenerative diseases of the osteoarticular system like arthritis and arthrosis
- Fibromyalgia
- Premenstrual syndrome
- Treatment of chronic pain

In sports (Saugy, Avois, Saudan, Robinson, Giroud, Mangin, Dvorak, 2006)**.**

The anti-inflammatory and antioxidant effect of CBD proves invaluable for sports, during which microtraumas can be produced in the joints and muscles as well as free radicals and lactic acid with negative metabolic consequences.

***NegEnt* research and clinical trials**

A series of clinical trials of *NegEnt* in psychiatry, neurology, and medicine have already been carried out and are planned for the next few years. Such research will be carried out according to the *single case study* and *single case series* methodology. The *single case study* describes a clinical situation observed in a single individual to provide information to recognize, identify, and describe the therapeutic actions of new drug and non-drug treatments.

Numerous *single case studies* have been carried out, are in progress, or have been planned for the following months for the following pathologies:

- Generalized anxiety disorder
- Panic disorder
- Post-traumatic stress disorder
- Obsessive compulsive disorder
- Eating disorders
- Substance use addictions (alcohol, cocaine, cannabis, tobacco)
- Borderline personality disorder
- Schizophrenia and bipolar psychosis
- Neurocognitive disorders (dementias)
- Autism Spectrum Disorders
- Parkinson's disease and Parkinsonisms

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- Irritable bowel syndrome
- Ulcerative rectocolitis and Crohn's disease
- Inflammatory and degenerative diseases of the osteoarticular system such as arthritis and arthrosis
- Fibromyalgia
- Premenstrual syndrome
- Treatment of chronic pain

Demetra Project

The possibility of developing the cultivation of *cannabis sativa light* in Italy began with Law No. 242 of 2 December 2016, that came into force at the beginning of 2017. With this law, in fact, for the first time in Italy, production and marketing began of industrial hemp inflorescences, sealed bearing the words "for technical and research use".

Subsequent acts concerning the standardization of the production and sale of products derived from cannabis sativa with a low THC content also commonly known as *cannabis light*, are Circular No. 70 of 22 May 2018 of the Ministry of Agricultural, Food, Forestry and Tourism Policies and the Ruling of the Court of Cassation with Judgment No. 4929/2019.

As it stands, the Italian regulatory scenario for the cultivation of cannabis sativa with a low THC content and the production of pure CBD is not fully defined and a clear and comprehensive framework of rules is expected to be issued (Benvenuto, 2018).

At the moment, however, some production possibilities have opened up in Italy for CBD obtained from the inflorescences of cannabis sativa varieties with high CBD content and low THC content (< 0.2%) commonly called *cannabis light*. In Italy, there is a principle of constitutional law according to whatever is not explicitly prohibited can be considered implicitly lawful.

Based on this new regulatory situation, after working for years, preparing *NegEnt* with the use of a *CBD water-soluble powder* base from the United States, the author decided to formulate a project for cultivating cannabis sativa light and preparing *NegEnt* in a factory to be created in Sicily.

Thus was born the *Demetra Project*, named after the Greek goddess (Demeter) of agriculture and crops. By virtue of my passion for classical Greek culture (the author studied ancient Greek at the Liceo Classico Napoleone Colajanni in

Enna), the author wanted to name my project to produce CBD starting from local cultivations in Sicily in the Province of Enna after Demetra, the Greek goddess of agriculture and crops.

Indeed, in Enna, the city where the author grew up in the heart of Sicily, the myth and cult of Demeter and Kore were deeply felt in the classical Greek period. Dionigi d'Alicarnasso informs us that already in 552 BC, Enna was inhabited by the Greeks and that the ancient city occupied a natural fortress located right in the centre of Sicily. Today, in my city of Enna, you can still visit the so-called *Rocca di Cerere*.

The *Demetra Project* is aimed at promoting the production of *cannabis sativa light* in inland Sicily, potentially perfect from a pedoclimatic point of view for cultivating the cannabis varieties allowed with a low THC content and a high CBD content according to the Italian legislation in force. This applied research program is divided into the following points:

Establishing an *ALETEIA Cannabis Farm* for producing *cannabis sativa light*. The cultivation will be done according to current legislation for cultivating food, nutraceutical, and pharmaceutical ingredients, i.e., organic culture without pesticides, in soil free from pollutants, especially heavy metals;

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Obtaining dried, handpicked, and dehydrated female inflorescences from the *ALETEIA Cannabis Farm* according to good practices that avoid any pollution.

Developing, in Sicily, a pharmaceutical laboratory specialized in the production of *NegEnt*, starting from the dry inflorescences of *cannabis sativa light* and able to carry out distillation in supercritical carbon dioxide and ultrasonic nano-emulsification to make the CBD water soluble.

The procedures used in this laboratory will mainly consist of extraction from CBD by means of a supercritical carbon dioxide method and by promoting the water solubility of CBD through ultrasonic emulsification nanotechnologies.

The development of the *Demetra Project* is inspired by the economic and social promotion of one of the poorest and currently most underdeveloped areas of Europe, the Province of Enna. The cultivation of cannabis is an activity that requires the use of a lot of manpower, not necessarily qualified or specialized. In addition, the work will be carried out in a rural environment, in a relaxing and sustainable manner and at a relaxed and sustainable pace. These considerations serve to introduce the fact that the workers who work at *ALETEIA Cannabis Farm* will consist of former psychiatric patients, treated, rehabilitated, and healed at the *ALETEIA Clinical Centre*. To this end, years ago in Enna, the author founded a *Social Cooperative called ALETEIA*.

The *Demetra Project* is in perfect synthesis with the *NegEnt Project*, aiming to promote the economic and social conditions of an underdeveloped area of Europe and to encourage the employment and social integration of socially and economically disadvantaged people, such as those who have suffered a serious psychiatric illness.

In this way, the term *NegEnt* takes on a wider value to lower the *entropy of the mind*, for the patients to whom *NegEnt* will be administered and to reduce the social and economic discomfort of the Enna province.

Discussion and Conclusions

In light of the data reported in this article, *NegEnt* promises to be a potentially significant contribution to improving human health and could also play an important new role in the development of pharmacotherapy in psychiatry, neurology, and medicine.

For these premises to materialize, however, considerable organizational and procedural effort is required to move from encouraging laboratory and clinical research data on individual cases to large-scale applications and robust research based on controlled experimental studies, including with a blind and double-blind design.

After developing a new therapeutic product based on CBD, the author also plans to implement a project for the cultivation of *cannabis sativa light* and large-scale production of *NegEnt* in Central Sicily, with the aim of helping to promote the well-being of one of the currently most economically depressed areas in the entire European Union.

The research lines, methodologies, and epistemology called upon in the topics covered in the article are articulated in a complex and integrated perspective that sees the intertwining of scientific, anthropological, economic, and social themes.

At the *ALETEIA Institute for Therapeutic Cannabis* and within the *ALETEIA Clinical Centre* in Enna, in-depth studies on the pharmacokinetics and bioavailability of *NegEnt* are underway with the collaboration of healthy volunteers and clinical studies carried out on the basis of single-case research on *NegEnt* therapeutic efficacy in numerous psychiatric, neurological, and medical pathologies.

The expected results are improvements to human health and economic promotion of an internal area of Sicily, pursued with ecological, ethical, and sustainable methodologies.

NegEnt appears to be a perfect product of postmodern complexity with its roots in the ancient Enna districts, lands of Demeter, thanks to the cultivation of a plant whose domestication and cultivation has been around for millennia. In other ways, *NegEnt* is part of the most advanced stream of contemporary science between neuroscience, psychiatry, and molecular nanotechnology.

Only in the next few years will we be able to fully evaluate whether the encouraging premises that manifest themselves today, while NegEnt's Phase 2 and Phase 3 trials are *underway* will be maintained. We shall see if my plan to provide a small contribution to the goal of improving human health, and promoting the economic development of Sicily, constitutes an ***utopia of reality*** to quote my great Master, Franco Basaglia (Basaglia, 2005) and also remembering a great Italian entrepreneur, Adriano Olivetti (Communitas, 2008), finally a ***reality of utopia***.

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Declarations

Submission

The article has been submitted, on June, 07, 2020 at the ***Journal of Cannabis Research***.

List of abbreviations

Just two abbreviations are used in the article as follows:

CBD: cannabidiol
THC: tetrahydrocannabinol

Ethics approval and consent to participate

The manuscript quotes some clinical studies, carried out by the author, involving human participants. For this reason it includes a statement on ethics approval and consent, include the name of the ethics committee that approved the study. The preliminary approval was request and obtained by the Ethics Committee of the local Healthcare Authority (City of Enna, Italy).

Competing interests

I declare a possible competing interest.
In fact, until now, I carried out all the work described in the article working for a no profit company I have founded many years ago, the Istituto Superiore per le Scienze Cognitive the owner of both the ALETEIA Lab for Therapeutic Cannabis and of the ALETEIA Clinical Center.

Recently I founded a Company for profit named Herbal Neurocare (www.herbalneurocare.it) that will sell the product that I developed and named NegEnt. I am the founder, the Director and I am the majority shareholder of such a Company.

Funding

The sources of funding the research, described in the article, is the no profit company Istituto Superiore per le Scienze Cognitive, located in Enna, Via Duca D'Aosta 25, Italy (for more information: www.issco.org).

Authors' information

Family name: Scrimali; First name: Tullio; Second Name: Michele Researcher unique identifier: orcid.org/0000-002-1880-1856

Catania, Italy, on June 03, 1952 and actually he is resident in Enna, Sicily. Physician, he reached is "laurea" "cum laude" in Medicine at the University of Catania and he specialized in Psychiatry at the University of Milan. Tullio Scrimali is founding fellow and therapy certified trainer consultant of the Academy of Cognitive Therapy (ACT of Philadelphia). He was one of the pioneers in the development of Cognitive Psychotherapy in Italy, publishing his first research in 1976 and obtaining the first Chair, even set in Italy of Cognitive Therapy, at University of Catania, in 1980.

He is official teacher of the Italian Association of Behavioural and Cognitive Therapy (SITCC) and also Member and Teacher of the European Association for Behavioural and Cognitive Therapies (EABCT).

Tullio Scrimali teaches this subject both at the ALETEIA International, European School of Cognitive Therapy (www.aleteiainternational.it), of which he is the Director (and which was founded by him in 1990) and at the University of Catania, where he is a Professor of Clinical Psychology.

He has been carrying out and still carries out research and didactic activities in several foreign countries, among which the United States, Canada, Mexico, Columbia, Argentina, Uruguay, Brazil, Morocco, Egypt, China, Korea, Japan, Taiwan, Moscow and various European Community countries. He organized and directed the first Training in Cognitive Psychotherapy ever organized in Poland. He is the author of 165 scientific articles and several monographs written in six languages.

His recent book: Neuroscience-Based Cognitive Therapy, published by Wiley, is a huge international success.

He also developed and patented a new device designed for integrating Applied Psychophysiology and Biofeedback into CBT. This device is called MindLAB Set and it is disseminated by Psychotech (www.psychotech.it).

As CEO of Psychotech Tullio Scrimali developed a great experience in the field of medical marketing. He also has been, during Eighties, Medical Director of Takeda Italia and responsible of the new drug named Esilgan (Estazolam).

He founded and he is the Director, at the Department of Psychiatry, University of Catania, of the first Laboratory of Cognitive Psychophysiology and Biofeedback started in Italy. He describes this experience in the monograph he wrote, together with Grimaldi "On the Traces of Mind" (Angeli Editore, Milano 1991).

He has been concerned for more than thirty years about the cognitive approach to the Therapy and Rehabilitation of schizophrenic patients. He published several scientific contributions on the issue of schizophrenia, among which the first controlled study ever carried out in Italy on a cognitively inspired protocol for the treatment of schizophrenia. His book on this topic, Entropy of Mind and Negative Entropy. A Cognitive and Complex Approach to Schizophrenia and its Therapy, published in London, by Karnac Books, on 2008 is a great international success. This book was officially presented in New York in March 2008, during the Congress of the International Society for Psychological and Social Approaches to Psychosis.

He was the Chair of the Scientific Committee and of the Organizing Committee of the first International conference of the International Association for Cognitive Psychotherapy “Cognitive Psychotherapy Towards a New Millennium” to be held in Catania in June 2000.

He is Chair of two International Conferences: Volcanic Mind and The Mind in the Clouds, held every year in Catania and in Enna (Sicily).

During 2001he was an invited speaker at the World Congress of Behaviour and Cognitive Therapy in Vancouver and at the annual meeting of the European Association for Cognitive Therapy in Istanbul. Tullio Scrimali presented in occasion of the EABCT of Prague on September 2003 an invited keynote lecture, a one-day workshop and three symposia.

In Kobe (Japan), during the World Congress of Behavioural and Cognitive Therapies, held in July 2004, he has been an invited lecturer ad also he held a very successful one day workshop on Schizophrenia (the workshop was overbooked and 46 participant attended).

During the 2005, 2006 and 2007, 2008, 2009, 2010 he has been invited lecturer and workshop leader in Serbia, Sweden, Finland, Greece, Brazil, Poland, Spain, Argentina, Uruguay, Romania, Lithuania, Croatia, Serbia, Slovakia and Russia.

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He also lectured in England, France, Germany, Spain, Denmark, and Mexico.

During 2006 he presented, as an invited speaker, at ALAPCO of Buenos Aires and then in 2008 at the ALAPCO held in Montevideo, at the EABCT of Helsinki and in New York during the ISPS Congress. He his invited speaker and workshop leader at the EABCT 2009 in Dubrovnik.

In June 2010, Tullio Scrimali has been chair of a Round table in Boston for the WCBCT and in October, he held a workshop in Milan for the EABCT Congress.

In February 2011, Professor Scrimali lectured in Columbia and has been and invited speaker at the ICCP Congress of Istanbul. In July 2011, he also served as an invited speaker and workshop leader during the third Asian Congress of CBT, held in Seoul. Actually, he is Chairing Professor at Asia University of Taichung in Taiwan.

During 2012, Professor Scrimali lectured and held workshops in New York and in Boston at the Boston University, School of Social Work, in Geneva at the EABCT, in Hong Kong and in Taichung (Taiwan) at Asia University.

On August 2013, he served as an invited speaker at the Fourth Asian CBT Congress in Tokyo and in September 2013 as a workshop leader at the EABCT Congress of Marrakesh.

During 2014, Professor Scrimali has been among the founders of the Egyptian Association for CBT and served as an invited speaker at the first National Congress organized by this newborn scientific society. In August, he has been Invited speaker and workshop leader in Beijing, China where he has been charged of training some psychiatrists and psychologists in CBT for Schizophrenic Patients.

During 2015 and 2016, he lectured and held workshops, as an invited speaker, in Cairo City, Pittsburgh, Athens and Stockolm.

During 2017, he served as an invited speaker at the ICCP of Cluj-Napoca and at the EABCT 2017 in Ljubljana.

During 2018, he lectured and held workshop in Egypt, Poland, Russia and Bulgaria.

In June 2019, I took part as a lecturer and as a workshop leader at the World Congress of Cognitive and Behavioral, held in Berlin.

In Italy, during last 40 years, he always took part, as speaker and invited speaker at the national conferences organize by the Italian Association for Behavioural and Cognitive Therapy (SITCC).
Tullio Scrimali speaks fluently English and French and he is a journalist, member of the Italian Association of Journalists. He founded and directed an international scientific journal named Complexity and Change and still direct the scientific bulletin: ISSCo & ALETEIA News.